



SCIENCE AND TECHNOLOGY SELECT COMMITTEE

Regenerative Medicine

Oral and Written evidence

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Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

Evidence Session No. 4

Heard in Public

Questions 64 - 80

TUESDAY 6 NOVEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
The Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Professor Robin Ali, Professor of Human Molecular Genetics, University College London (UCL), **Professor Graham Lord**, Professor of Medicine and Head of Department of Experimental Immunobiology, and Director of NIHR Biomedical Research Centre, Guy's and St. Thomas' NHS, King's College London, and **Sir John Tooke**, Vice-Provost (Health), Head of the Medical School and Academic Director of the Academic Health Science Centre, UCL, gave evidence.

The Chairman: I should like to welcome our second witness panel this morning. Thank you very much for joining us. As usual, I should remind you that the session is being broadcast and, therefore, sotto voce comments will be picked up by the microphones so please be careful what you say as asides. In a moment, I will invite the three witnesses to introduce themselves for the record, starting with Professor Robin Ali and then working along the row. If you wish to make any brief introductory comments in addition to stating who you are, please feel to do so but please also keep them brief, so that we have time to put or questions to you. Without further ado, may I ask Professor Ali to introduce himself?

Professor Robin Ali: I am Professor Robin Ali. I work at University College London and Moorfields Eye Hospital and my interests are gene and cell therapy for eye disease, retinal disease in particular.

Professor Graham Lord: I am Graham Lord, a professor of medicine. I am an NHS nephrologist—nephrology and transplantation. I am also a clinical academic and director of the NIHR Biomedical Research Centre at Guy's and St Thomas' Hospital.

Sir John Tooke: Good morning. I am John Tooke, a clinician scientist—a diabetologist by background. I am vice-provost (health) at UCL and head of the medical school. I am also academic director of the academic health science centre, UCL Partners. I also have the privilege of being president of the Academy of Medical Sciences at present. As you will all be aware, the academy led a review of the regulatory and governance environment in research. I suppose that in my day job at UCL I see the consequences of the implementation of those processes on a regular basis.

Q64 The Chairman: Thank you. I should like to kick off by asking for your views on the key challenges and barriers to conducting clinical research on regenerative medicine in the NHS and how those barriers might be overcome. Just to give a bit of background, in the written evidence that we have had, people have talked about barriers in terms of recruiting patients, expertise among NHS staff, bureaucracy and securing reliable products that can be used in clinical research. Those are the sorts of barriers that we have heard about but I would be very interested in hearing your views on whether those are the right barriers and how you think they might be overcome. Perhaps Professor Ali would like to kick off.

Professor Robin Ali: I would certainly agree with those previous comments about the specific issues that we face. In particular, there is a burden of regulation, and it is a necessary burden. We need to have regulation in place to protect patients but that generates an additional requirement in resource in terms of managing the bureaucracy that goes with it. So I think there is a need for additional support with regard to regulation. If we think in terms of clinical trials, we cannot carry out those trials efficiently without that support. Some of that needs to be directed to the clinical academic centres—the hospitals—within the research support for the trials, but there is also a need to direct increased support to the teams who carry out the trials. Increased support for just the institutions means additional tiers of regulation that the investigators must then struggle against, rather than having the resource to deal with that regulation. So I would make a specific request for very directed support to the teams in managing that regulation.

Q65 The Chairman: Would that support be in terms of a sort of advice structure—a hotline you could call to help you deal with any regulatory barriers?

Professor Robin Ali: It is the practicality of filling in all the forms and having someone to interface not only with the external regulatory bodies but with the internal hospital and university regulatory departments. There is a huge burden there; clinicians and senior academics just do not have the time to spend filling in huge numbers of forms and the documentation that is required. There is an underestimate of the burden that these necessary regulations put on investigators, particularly those engaged in clinical trials.

Professor Graham Lord: The environment that regenerative medicine, of necessity, operates in is complex. It is complex within the NHS, it is complex within the regulatory environment and it is complex within the academic environment—new science is being discovered every day. It is also complex in the commercial environment. Where is the ongoing funding? How do we make this into realistic treatment for our patients? There are ways of overcoming that complex structure. The models of how we move regenerative medicine through into the clinic, which I think is a tremendous opportunity, require all these

things to develop at the same time. So I think that the partnerships that the previous panel members were discussing, between the NHS, academia and the commercial sector, are absolutely fundamental. Locating all these different stakeholders in the same place, where they can iterate towards a solution, is absolutely fundamental. Getting NHS consultants interested in regenerative medicine is already happening. From my own clinical practice of renal and pancreatic transplantation, we are now running an NHS clinic in which we see patients and discuss with them whether they want a kidney transplant, a pancreas transplant or an islet cell transplant. So cell therapy is going on, albeit in small numbers, as an NHS-commissioned service. Continuing that organisational penetration into the NHS is already happening in exemplar areas. I think the Biomedical Research Centres that the NIHR has funded, which we may come on to in the second question, have been absolutely transformational in forging those partnerships.

Q66 The Chairman: Just as Professor Ali indicated additional support mechanisms in the barrier that he highlighted in relation to the regulatory tangle that one has deal with, are there particular support mechanisms that you would advocate in the area that you have talked about of bringing together clinicians and scientists to deliver patient care?

Professor Graham Lord: Yes, physical collocation of these different areas is a potential solution to this and it is one that we are in the process of putting together. In fact, we have put it together. We have on one floor of Guy's tower—a hospital building next door to the Shard, so it has quite a nice architectural motif next to it—put together clinicians, academics and people who can represent regulatory bodies, together with the R&D departments of the hospital and trial monitors. They are all on the same floor. Essentially, a clinician or academic who wants to perform a cell trial or a regenerative medicine trial can come in the front door, walk around the floor and deal with all the appropriate clinical and academic support structures and the regulatory structures. I am obviously making it sound simpler than it actually is, but given that this is all collocated there is a one-stop shop for the regulatory and governance environment that is necessary to move a regenerative medicine product through into the clinic.

Q67 The Chairman: That is really a matter for the individual institution to organise. It happens that your institution has, from your description, been very proactive and created it—or was it something that you as an individual pressed on your senior colleagues?

Professor Graham Lord: Absolutely. This was the first round of biomedical research centre competition in 2007, which Dame Sally Davies talked about. We made a specific decision to go down that route and build the infrastructure that is required for regenerative medicine, so there is a GMP infrastructure. That is the other complexity of this environment—the clinical research infrastructure that you need is bespoke and very expensive. It also speaks to the lead time required to bring these treatments to the clinic, which has been five years of capital-raising and building. We are now ready to start cell therapy trials in phase 1 and phase 2 clinical trials, but it has taken five years to get to this point.

Sir John Tooke: I would echo many of the previous comments. I start with the generic statement that we all want to see the regulatory burden diminished and the streamlining of processes to make them as efficient as possible. But we must also adhere to the principle of proportionality. Of course, proportionality has two sides to it. We do not want over-rigorous regulation where it is not required because a trial is, for example, of very low risk. On the other hand, the area that we are discussing this morning is at the sharp end of medicine where some of the risks are unknown and many of them are more considerable than the application of a conventional small-molecule pharmaceutical product. So in the rush

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

to get regenerative medicine into practice and into commercial exploitation, we must be aware of some of the risks that are present. That will require close working between academia, the regulators and commercial interests to ensure that that equation is solved appropriately. I also agree with the comments made about the facilities that are necessary to support this area of endeavour. Often it is down to academics to create their own solutions—for example, manufacturing facilities to good medical practice standards. These are often developed by one or two academics. There is not currently the level of infrastructural support to professionalise that activity, if I may put it that way.

Professor Robin Ali: I should like to echo those comments and expand on them a little. We have learnt a lot from our experience of gene therapy, in which the UK is world-leading. To give you some examples, there are four areas in which gene therapy has been shown to provide real clinical benefit to patients: primary immunodeficiencies, B-cell lymphoma, haemophilia B and retinal dystrophy. In three of these areas, the UK is right at the forefront and has done the first clinical trials, so three out of the first four gene therapies have been developed in the UK. We are leading here, yet we have not yet built up in the UK the leading infrastructure to be able to go on to the next phase, to capitalise on the proof of principle and to capitalise really on technologies and the clinical trials that have been done in the UK, because there has not been the long-term investment on a scale that is required to allow us to expand. We see that in the US: many institutions there have invested. In France, too, there are big facilities for GMP manufacture of vectors. These countries are in a much better situation now to really expand and capitalise on the UK's success.

Q68 The Chairman: What has prevented our doing that?

Professor Robin Ali: We and others at UCL, which is the leading centre for gene therapy in the UK, have developed our own GMP manufacturing, rather late, in a very piecemeal fashion, with tiny amounts of funding from different sources that we have cobbled together. So it is just the scale on which the funding is provided, with a very short-term view. There is not the long-term vision or the confidence that the technology will deliver, so the scepticism is much greater here than in other countries. Ironically, we are developing it but others have greater confidence that it will work.

The Chairman: That is very interesting and it is clearly a slightly different perspective from the one that we heard from the funders in the first half of this morning's session. They essentially said that everything is fine except they would like a bit more. I think Lord Willis and Lord Patel would like to come in.

Q69 Lord Willis of Knaresborough: Just as an aside, Professor Lord, I thought your description of the Shard as an architectural motif was quite understated. I am sure the architects and funders will love that. My question is really to Professor Tooke. There is an issue that comes to us every time we talk to researchers on the ground, which is really about regulation. Professor Ali quite rightly said that having strong regulation is what makes us very effective in the long run but going through that morass of regulation is hugely difficult. Indeed, it will get worse because European directives in particular, and some of the court judgments in Europe, will create new problems. Sir John, you were one of the architects of the Academy of Medical Sciences report, which looked at combining regulation, yet you seem to have gone soft, particularly on bringing together the research elements of HFEA and HTA. Yet in this particular area of regenerative medicine, the use of tissue through HTA and the use of embryos through HFEA are at the core of our work. Why are you not pushing for those to be brought to together in the HRA, so that we have this one-stop shop which is exactly what Professor Ali and others are looking for?

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

Sir John Tooke: If we hear evidence that those are tangible barriers to progress in this area, we can reassert that position. The establishment of the HRA has been a very significant development. We were very pleased last week to hear of the agreement that there would be piloting of a more unified approval system. The HRA has just started; it is assuming its roles and that was a very important first role. As an academy we will review the impact of the recommendations and the implementation requirements on a regular basis. If we see any impediments that need to be removed, we will state so very clearly.

Q70 Lord Patel: I should like to pick up on these barriers to translation. You gave the good example, Professor Ali, of gene therapy, where we were leaders but did not convert it. You mentioned GMP facilities. Who should fund more GMP facilities for that translation work to occur? If we do not, the same might be repeated in other centres.

Professor Robin Ali: I believe that it is necessary for there to be investment in GMP manufacturing in clinical academic centres for gene therapy and GMP facilities for regenerative medicine for producing cells for clinical trials. The reason why I believe in this so firmly is that I think these novel approaches and technologies are best developed in clinical academic centres. We have seen worldwide all the advances in gene therapy coming out of clinical academic centres, either here, in the US or in Europe, and not out of industry. Industry has invested billions of pounds in gene therapy without producing—with the very recent exception of Glybera, which has just been licensed—a major advance. The big breakthroughs have come from clinical academic centres using much smaller resources, but they have the breadth of expertise that is required. A combination of clinical expertise, basic science, and improved technology is all required to make progress. It is only at the later stages that industry is able to utilise that proof of concept and develop the pathway. That is true for gene therapy; it is going to be even more so for regenerative medicine, which is even more complex and will require a very sophisticated approach. It is difficult for me to imagine how small biotechs or even big pharma are going to be adaptable enough to develop this technology. Therefore, in order to support and give the freedom and flexibility to the clinical academic centres, we need the infrastructure to be able to develop GMP material for clinical trials without having to compromise and essentially do contract research for industry, which may be flawed in some ways, because there is a rush. Industry is required to push things through to clinical application before they are really ready, so they may not do the most sensible trials.

Q71 Lord Turnberg: I am slightly confused, because the previous panel speakers seemed to suggest that there were funding mechanisms for almost anything one wanted to do if you knew where to go. You are saying that there is certainly a gap at this further development stage before one can bring in industry rationally. I presume that you are talking to the MRC, NIHR, the Wellcome Trust and BHF. How do we square this circle?

Professor Robin Ali: I recognise that there are funding streams and there is interest and there is support from all these bodies. We have been supported by the Wellcome Trust, the MRC and NIHR. I would just suggest that the scale of the funding and what is available is perhaps not sufficient to meet the requirements in a visionary way and in a long-term capacity. Whilst we can talk to the bodies, and there is certainly support and interest, I would like to see increased support and increased levels of funding in this area.

Professor Graham Lord: I agree with what Professor Ali says around the complexity of this. That is why big pharma has not yet invested and why some institutions have also not necessarily invested. There is not a blueprint for how you move regenerative medicine into the clinic. It is not like, as Professor Tooke said, developing a small molecule as a treatment

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

where the pharma model is very well established, so you can take a blueprint off the shelf and say, “We’ll do that; it will require investment at these specific time points”.

Lord Turnberg: But other countries seem to be doing it.

Professor Graham Lord: I suggest that you need different funding sources to put this together. As Professor Ali said, you need a strategic vision of where this is going to go. Clearly, as we do not know how regenerative medicine is going to develop, there is a degree of risk in that. There is an issue of risk-taking within the UK compared to the US or maybe even Europe. A number of institutions have made that strategic commitment, so we have built GMP facilities for cell therapy through a combination of strategic investment, NIHR investment through the biomedical research centres, and MRC investment. You need to put together a number of different funders and you need a strategic vision, but you clearly need to be flexible to adapt as the science changes. That is one of the tensions here: it takes a long time to build this infrastructure. If the science changes and you are halfway through, you can be left with a bit of a white elephant. That has not happened yet. I think that there are a number of units around the UK that have GMP cell facilities—we are developing them ourselves and we have received very generous funding to do that. We need an institutional, long-term strategic vision that allows us to deliver regenerative medicine into the clinic when the time is right, subject to the appropriate regulation. The way that networks around the UK are starting to work and will need to work is that those facilities that are built by specific centres are accessible for other universities and hospitals. That is exactly how we intend to run our facilities. Because the funding models are challenging, you then link in with industry through investment like the TSB cell therapy catapult, which is embedded on the same floor at the moment but will move to the 12th floor of Guy’s tower. That is how you get linkages with industry to work together to develop these processes, because they are incredibly complex and no one knows yet what the appropriate funding model is to make a sustainable, viable market for these therapies, which will be required if they are going to become available on the NHS.

Q72 Lord Cunningham of Felling: Previous witnesses told us that one of the principal reasons why we were not making advances in translational work in clinical trials was that the science was not good enough yet—the research was good, but the understanding of the research meant that it was not ready to move into the translational phase. That is one of the reasons, I assume, why the biomedical research centres have been created, and obviously you are very enthusiastic about it, Professor Lord, because you are the director of one. On the other hand, Professor Ali has just told us that that is not the reason why his lines of research were not taken forward or developed. He said that it was lack of resources. Is part of the reason for our not making more advances in these areas of translation, regenerative research and clinical trials just lack of resources? You seemed to be saying, Professor Ali—I do not want to put words in your mouth—that we had thrown away a world-leading opportunity.

Professor Robin Ali: We are potentially not capitalising as we could. I do not want to suggest that the funding bodies and the BRCs are not interested; they are and we are supported. I just think that these programmes are very long term. The gene therapy programme that I have developed has taken 15 years to get to the stage of showing clinical benefit. There is a lot more that could be done. There is not possibly the realisation just how expensive and long term it is and how much resource is required to really take things through to the next step.

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

Lord Cunningham of Felling: But I am right in recording that you said that the French and the United States have done it?

Professor Robin Ali: They are putting a lot more resource into these areas and it is coming from different sources, whether government funding bodies or the charitable sector. The French have a charity called Genethon which has raised tens of millions of pounds to build GMP facilities. That is a big national charity with a long-term vision. That is not coming from the French Government, but from a French body that is really well positioned. There are many centres in the US with a combination of university facilities where they are able to raise large endowments to develop long-term infrastructure. I would not like to suggest that there is no support; there is support; it is just that the scale of the support is less than is required.

Q73 Lord Cunningham of Felling: Professor Lord, it may be a bit early to ask you this, but can you give us any examples which flow from the creation of biomedical research centres of where the translational regenerative research in clinical trials process has been dramatically or significantly improved?

Professor Graham Lord: There are a number of areas in terms of the time to starting a trial—I know that this is one of the major measures of the efficiency of a complex process. Clearly, there is the length of time to the finishing of a clinical trial, but, at the moment, the major metric is getting the first patient into a trial. Through the infrastructure that we have put in place, we have cut our time to first enrolment in the trial from 90 days to about 23 days. In terms of process, there has been a significant improvement around that and we are constantly monitoring this and trying to improve it all the time. That is the process and infrastructure that we have brought together. Through the biomedical research centres, we have been able to build these facilities. We have what we hope is going to be a robust pipeline of cell therapeutic and regenerative medicine projects coming through that infrastructure. But, as Professor Ali said, that has been based on 10 to 15 years or more of fundamental science that is now coming through. We saw an opportunity there and took a risk to build the facilities to translate that science. Some of the science is not ready; some of it is more mature. Regenerative medicine is a complex and broad area, so it is important that, when we talk about what is ready to be translated, that might be a small section of more differentiated cells or small molecules that regenerate endogenous stem cells or repair mechanisms where the science is more mature. The time at which you first take a new treatment into man is always going to be a nuanced judgment and a challenge. My final comment on this point would be about the proportionality that Professor Tooke discussed around regulation and where the risks are borne. Clearly, the most important aspect of this is patient safety. That is why embedding projects within NHS structures is absolutely fundamental. If you are doing a first-in man clinical trial, these risks have to be balanced against an uncertain outcome. My concern is that, if we now had to look at the ethics or the regulation around organ transplantation or bone marrow transplantation, they would never have happened. I guess that there is no definitive way to answer that.

Lord Cunningham of Felling: You said that it was essential that this be embedded in NHS structures, but they do not have NHS structures in France or the United States of America.

Professor Graham Lord: They do not; they do not have an NHS. I cannot speak to what the structures are like in France. Within the UK, I think that that is the way in which we make it sustainable and how we make it available, because the output, if we are successful, is a cost-effective treatment for patients for whom there is no current effective treatment.

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

The NHS is where that is delivered, so unless we do it being embedded within the NHS now, we will hit another barrier further down the road.

Sir John Tooke: A potential opportunity is to bring together effectively academia, the NHS and industrial partners and we are uniquely positioned to do that. It is highly dependent, of course, on an NHS culture that is supportive of research and we have seen some very positive structural moves in that regard in recent years. We know from the regulatory work that one of the biggest barriers is a concern at NHS Trust level about the risks associated with conduct of research and an unrealistic view of what the risks might be. So that needs continually to be watched. On resource, there is no doubt that we have a rich seam of fundamental science funding that is feeding our efforts in this regard. We now have superb experimental medicine funding through the BRC structures. At UCL as at King's, we are aligning that resource to help accelerate that passage through from discovery to something that can be applied. Yes, there are resources to support the later application, but that cannot be provided on a project-by-project basis. To set up core infrastructure for GMP requires a long, sustained commitment. All wise institutions are looking at how they use their resources strategically to effect that, but that is probably still the area that needs more attention.

Q74 Earl of Selborne: My question is to Professor Lord. I have great admiration for the leadership of the BRCs and understand completely that bringing together a small research group of international leaders from the NHS and universities is an excellent way to focus and achieve quick progress. As we have heard earlier today, it is also important to ensure that one has flexibility. There are new areas of science coming along which we have to feed in. To what extent are you able to balance these competing demands of having a tight-knit group which is focused but also of being receptive to other opportunities and innovations? It is possible to ride the two horses?

Professor Graham Lord: I guess that time will tell. I think that it is possible and has to be possible. That is the virtue of embedding world-class basic science within these structures. On the one hand, you can have a milestone-driven approach, so we have got to do A to go to B to go to C to go to D. Some of that is mapped out and some is not, so there needs to be flexibility in that process as well, because I am not sure that there is a well mapped out route that is optimal for every regenerative medicine solution and we are in the process of defining that with others around the world. At the same time, as new science comes along, you have to be aware of new opportunities. That is why having something that is embedded within the NHS but also within a university, where you have some of the best scientists in the world participating in these programmes or through networks feeding into them, is desirable. We absolutely have to stay flexible. How you do that with in-year budget spends is always a challenge and it takes quite a lot of our time to maintain flexibility while also trying to ensure that we invest the resources at the correct stage so that the programme is ongoing and does not then fail for lack of resource. I guess it is part of my job as someone running a biomedical research centre to make those judgments, obviously with expert advice at every point. I hope that we can do both.

Q75 Lord Patel: My interest is that we do not miss out, as we have done previously—for example, in monoclonal antibodies or in gene therapy—in regenerative medicine translation research, so that when the science is ready to be translated, we have all that is necessary in place to do the translation and we are not caught out by other countries such as France, the United States and maybe even Japan and others being better at identifying what would be required and putting it in place so that they jump the gun in translation and

Professor Graham Lord: If I gave the impression of being cosy, I apologise.

Lord Patel: No apologies required.

Professor Graham Lord: I think that sustainable funding with a strategic vision to build this infrastructure is absolutely critical. It is necessary but not sufficient. Unless you have the facilities, you cannot do the translation. How you ensure that we benefit maximally from that and how you protect your discovery or your process is a very challenging area that is to an extent outwith my expertise. When can you protect the intellectual property of your invention so that the commercial benefits as well as the health benefits stay within the UK? I think that part of that will be about how you understand the process of getting a molecule into the clinic. Again, I did not suggest that regenerative small molecules were more advanced scientifically; what I said was that process for getting those into the clinic was more established because it follows the more traditional pharma route of small molecules and phase 1, phase 2 and phase 3. So I am not necessarily sure that the science is more advanced than, for example, cell therapy. It is important that we identify what part of the value chain we can capture. I think that a degree of that will be whether regenerative medicine and cell therapy become a significant market. Again, we really do not know where, along that high-value manufacturing chain, we capture that expertise, which in some ways may be more valuable than protecting a chemical entity in terms of intellectual property. It is a challenging model, again. As well as the clinical trials model, the monetisation model for regenerative medicine is quite challenging. I think that we can capture a lot of that process and intellectual property. In many ways, that could help to retain that within the UK, because that know-how of developing a cell therapeutic is very hard to replicate; it is an enormous barrier to entry. An example from the commercial world is that Coca-Cola never patented its secret product and does not have issues with patent expiry.

Sir John Tooke: Just to build on that a little. We also need to look at how other academic resources can be brought to bear. For example, the whole area of regulatory science needs to be better developed. We need a more sophisticated view of regulation, particularly for these complex developments which often involve cells and scaffolds, for example. That discipline is in its relative infancy in the UK; the need is recognised in the US, but we need to get to grips with that agenda. The same will be true of trial methodologies. We need more sophisticated approaches to clinical trials, adaptive trial designs and so on that will enable to us to get the answers to questions faster and more efficiently.

Professor Robin Ali: I have two points, one in response to Lord Patel with regard to translation, particularly commercialisation of these novel programmes. The UK is quite different from the US and France in the culture for venture capital. We see a lot more interest and activity from venture capital for these technologies outside the UK. That really means that, in terms of the funding bodies, the UK has perhaps to be more visionary and to take more risk, because risk-taking and vision is happening outside the UK, coming from outside venture capital. There is also an issue around how the UK invests in technology, and it is not restricted to the clinical academic centres. There is a different culture here.

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

Q76 Lord O'Neill of Clackmannan: Both Professor Ali and Sir John have raised the question of regulation and the issue of clinical trials. We have had a lot of evidence where people have been making appeals for broad maps—whatever that means, but I think we know that they have in mind guidance notes or something like that. Catapult, in its evidence to us, said that, “too often researchers ... are forced to ... compromise trial designs that are smaller and cheaper but cannot generate clear efficacy data”. These are very serious charges, and obviously the clinical trials network and the clinical research network have some burden of responsibility there, but how do you feel the clinical trials could be improved, and who should be responsible for giving what seems to be a desire for a UK-wide lead? Sir John, you touched on it last.

Sir John Tooke: Thank you very much. Yes, I think that we need to move ever closer towards all trials being conducted by accredited clinical trials units which are academically led. We need to continue to re-emphasise the need for new methodological developments within clinical trial design so that we get clear-cut evidence of efficacy while avoiding the huge cost and scale of the more conventional design if that is possible. I suspect that that will be particularly true in this area where you are not talking about treating what may be tens of thousands of people; you are talking about relatively small numbers of people entering into such studies. Bolstering the academic engagement with clinical trials will be critical. That poses another infrastructure problem, which is that clinical trial methodologists are not necessarily the most highly valued in terms of their own research productivity. They are an essential part of the infrastructure but are difficult to recognise in any research assessment exercise. Universities that are heavily engaged in this are beginning to realise their value, but they are another infrastructure cost if one perceives them in that way.

Professor Robin Ali: I think, with regard to the clinical trial model here in the UK, we have a very good structure in general. The MHRA is a huge asset for the UK. I have always found it to be extremely helpful, very sensible and pragmatic. In comparison to European regulators and the FDA, I think that the MHRA is a national treasure. It is to be commended on how it approaches clinical trials regulation. On whether the model fits entirely with regenerative medicine, there is an issue around personalised therapies. Some therapy—for instance, an iPS approach—may involve generating medicinal products from a patient's own cells. If they have to be certified as GMP quality with the same rigour as a medicinal product that has been released for hundreds of thousands of patients, the costs are enormous. So I think that there is an issue around whether the manufacturing regulations can be adapted for personalised medicine, so that we can certify processes rather than cells themselves, especially if we take into account that the risk is to an individual, not to thousands of patients, and that these trials may involve just a handful of patients anyway. So it is increasing costs; it is increasing the burden. If I was going to suggest any adaptation, that is the one area that I would suggest that one can look at. The MHRA could be charged with looking at that with input from academics and industry. That would be specific to regenerative medicine and patient-specific cell transplants.

The Chairman: Lord Wade, did you wish to come in?

Lord Wade of Chorlton: It is on a slightly different point from this, but I wanted to wind up on some of the issues that Professor Ali and Sir John raised. Shall I do that right now?

The Chairman: Lord O'Neill wishes to follow up and then we will come to Lord Wade.

Q77 Lord O'Neill of Clackmannan: One is always tempted to draw an analogy with health and safety regulations and there is always the danger of throwing the baby out with the bathwater when you have patients there. You said that there is the MHRA; there is also

the Clinical Research Network. Are there too many people talking with different voices? One gets the impression from some of the evidence that we have had that frustration is felt about the lack of clear guidelines, if I can put it away. Perhaps we need to try a bit harder here. Would that be fair?

Sir John Tooke: That is a fair charge. The feedback that I get from academics on the ground is that they find this process difficult to navigate. They have their own responsibilities in terms of learning how the process works. I agree with Professor Ali's comments about the MHRA, which has become much more receptive in my experience and does a very good job, but researchers want easier access to the senior opinion within MHRA that can advise them about the co-development of the requirements for their study. I suspect that there is still limit in terms of what they are able to provide.

Q78 Lord Wade of Chorlton: We heard from Professor Ali about the role of venture capital. Sir John made exactly the same point, that, in actual fact, a lot of these things need not necessarily be dependent on big pharma to take forward, but that the role of smaller companies, funded from outside, could well also be an important part. Do you plan, if that is the way you think that it is going to go, engaging quickly and soon with the financial bodies? One of the biggest issues with raising money for technology is that the people you want the money from do not understand the technology. I have had no experience with the technologies that you are involved in, but I have had with other technologies and that is the first barrier to it. The first problem that you have got is not persuading them that you are going to make money out of it but showing how the technology is going to work so that they can fit it into their understanding of what a business is about. The other big issue is who is going to run the businesses. Scientists are not good at running businesses; you need leaders and businessmen to run businesses. You have got to attract them into that industry as well. I just wondered whether you, who are at the most important end of it, which is the development of these new contracts, are actually involved in any of those projects or whether you see a way of becoming involved, so that you can start to teach people now about the long-term benefits of what you are working with.

Professor Robin Ali: I think that, with hindsight, I would have liked to have engaged with industry earlier, thinking about a route to commercialisation and how we might take these technologies through to licensed products that could be commercialised, because that is the only way that we are going to get these novel therapies to patients. It is only if they are commercialised. We as clinical academic centres are not going to manufacture products and distribute them. So I think that we have been on a learning curve to understand what is involved in this process. There is a naivety within universities and clinical academic centres, and there may be a role for increasing that awareness and the potential for very early company structures. So, rather than the model that we tend to have in universities, we should develop IP and try to license it. Unfortunately, within a university context, it is quite difficult to see an exit strategy. Universities do not have the budget required for long-term maintenance of patents. With gene therapy and cell therapy, there are usually quite complex freedom-to-operate issues. We have to license many patents. There is often not a clear route through and it requires long-term development. That then potentially means that the patents have to be maintained for many years before there is an exit strategy. That is what universities really do not have a budget to do, so you need a commercial plan quite early on.

I think that if we saw more spin-out companies early on, that would help. We in clinical academic centres need to be more engaged at an earlier point in that process.

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

The Chairman: We have time for one more very brief question from Lord Willis, with very brief answers.

Q79 Lord Willis of Knaresborough: It is a brief question but it is fundamental. Professor Tooke, you have quite rightly highlighted, as have AMRC and Catapult in their submission, this business about the clinical trials. The NHS is not going to be a treasure, because it is going to be exactly the same as anywhere else. The US is finding the same problem, but it is getting through this clinical trial and efficacy much faster than we are. What advice are you going to give this Committee about a recommendation to government in terms of ensuring that we can forget the traditional pharma-clinical trials and how we go to a new one which enables us, when the science is right, quickly to go into phase-2 and phase-3 trials in order to be able to realise these advantages? I have heard nothing this morning which gives me any comfort in that direction.

The Chairman: Brief answers, please.

Sir John Tooke: I think that we have seen the time from approval of trial to recruitment improving. That needs to continue. It will continue with better harmonisation and better streamlining of our own processes. The only word of caution that I would add is that, in this field, the route to development of that final product, and the challenges of recruitment and application of what may be personalised therapies, mean that you cannot always apply the same yardsticks.

Professor Graham Lord: It is important that we work on the methodology that Sir John discussed, specifically adaptive trial design—so how we make bespoke trial design for regenerative medicine therapies, particularly cellular therapies—but also that we co-develop biomarkers and imaging technologies so that we can see where these cells are going and get surrogate markers of efficacy so that we can progress more rapidly with smaller numbers of patients through an adaptive trial design. We need to improve the efficiency of our process hand in hand with the scientific development of imaging and biomarkers.

Professor Robin Ali: The point that I wanted to raise is in relation to your question, Lord Willis. One of the reasons why we were so successful in the UK with our gene therapy trials is that we had an advisory board, GTAC—the Gene Therapy Advisory Committee—that acted as an ethics board but also provided support to the community. It had a lot of academics who were engaged in trials actually as part of the regulatory body, and they fed back into the academic community and gave advice. They were practitioners as well as being involved in regulation. That was one reason why we were so successful. I think that the plan is for that committee to go. I think that this needs looking at carefully because we are throwing something away that has real value. It also had a remit to look at regenerative medicine and complex cell therapies. This function has now been given to NRES, which I believe will not have the expertise because it will be a regulatory body. It will not have the academics who are engaged in the development of therapies involved in the regulation. I can understand why you might want, in order to streamline and to get fast decisions, to get away from troublesome academics who are really engaged at the cutting front, but there is a danger that you will not have appropriate regulation based on an understanding of the science. This could endanger the future, because it may allow trials that are in some way flawed to proceed.

Q80 Lord Willis of Knaresborough: So you would continue with this organisation?

Professor Robin Ali: I would continue with something similar to GTAC in structure; that is, with more involvement of leading academics.

Professor Robin Ali, University College London (UCL), Professor Graham Lord, King's College London, and Sir John Tooke, UCL – Oral evidence (QQ 64-80)

The Chairman: That runs us out of time. Thank you very much for your answers to our questions. You will receive a draft of the transcript in due course and you will have an opportunity to make corrections. If there is anything else that you wish to say to us in writing that will form part of our evidence base and be published, please feel free to do so. Thanks very much indeed.

Professor Robin Ali, UCL – Supplementary written evidence

Genethon (France)

1) Background history

Genethon was founded in France in 1990 by the Association Française contre les Myopathies (AFM) and the Centre d'Etude du Polymorphisme Humain (CEPH), using funds raised by an annual Telethon.

1990-1996: A genetics focused organisation

Between 1990 and 1996 the organization focused on the human genome (mapping and identifying genes).

In 1996, gene sequencing and genotyping activities were transferred to the French Government, so Genethon refocused its attention on therapeutic gene transfer.

1997-to date: A gene therapy focused organisation

Between 1997-2002 the mission of Genethon was to develop tools for delivering therapeutic genes in a therapeutic setting.

Between 2003-2007 Genethon set up a number of preclinical programs including developing GMP manufacturing for gene therapy vectors.

In 2005, its GMP-compliant vector production site was certified by the French Healthcare Products Safety Agency (AFSSAPS).

In 2006, Genethon launched its first gene therapy trial for gamma-sarcoglycanopathy,

In 2010, an international phase I/II gene therapy trial was launched for the immune deficiency disorder Wiskott-Aldrich syndrome, sponsored by Genethon

Several other gene therapy vectors/ trials are now in the pipeline.

2) Current Genethon gene therapy capability

In 2012: Genethon opened Bioprod, the world's largest gene therapy production plant.

This will offer unprecedented production capacity for clinical-grade gene therapy products for France (will also be open to other countries)

Bioprod Facilities

5,000 m² for bioproduction and gene therapy product monitoring

Bioprod Laboratories

Approximately 2,500 m² of Level 3 classified containment laboratories suitable for handling GMO and virus systems

4 production suites totalling 500 m²

2 aseptic filling suits with Class A isolators

120 m² of pilot laboratories for industrial scale implementation of optimized manufacturing processes

500 m² of GPP-compliant quality control laboratories

200-liter production system (bioreactor)

Bioprod Production Capacity

20 clinical batches a year at full capacity

Up 800 litres of bioreactor capacity for AAV product cultures (four 200-liter bioreactors)

Up to 100 litres of culture capacity for lentiviral vectors

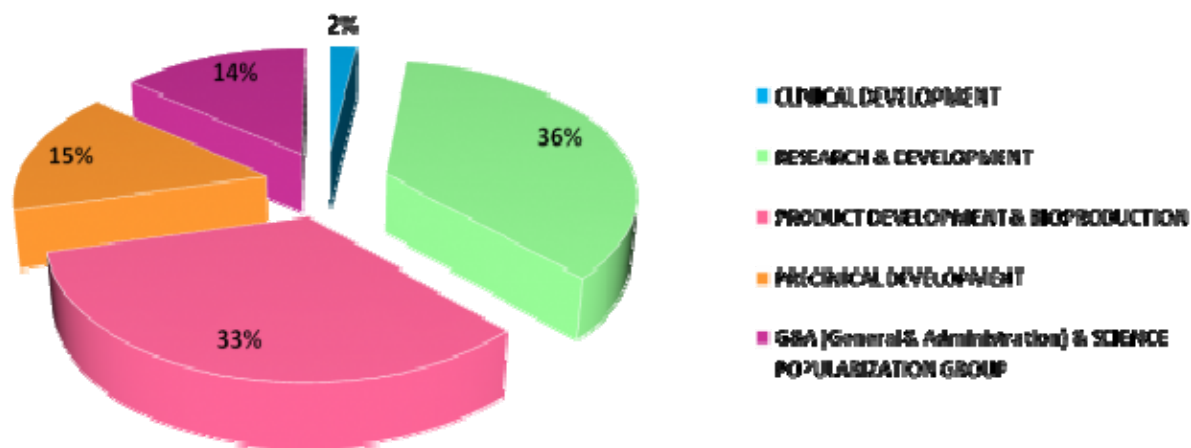
Bioprod build costs

The building of Genethon Bioprod, at a total cost of €28 million, was funded by:

The Association Française contre les Myopathies (AFM): €5 million; Ile-de-France Regional Council: €8 million; Essonne Departmental Council: €7 million; Genopole®: €8 million

3) Estimated Genethon expenditure on Gene Therapy

In 2011 Genethon had an income of c. €30 million, funded 90% by the Association Française contre les Myopathies through funds raised by its Telethon. If this figure were consistent over the last 5 years, it would suggest a total income of c. €120-150 million since 2008. A sense of the split of this investment comes from the following breakdown of spend by area in 2011.



So just in the last 5 years Genethon expenditure on GMP manufacturing alone is estimated to be c. €40 million (c. 1/3 of expenditure).

Annual running costs for the Genethon Bioprod is estimated at €5-8 million and will be financed by AFM using donations from the annual Telethon.

16 December 2012

Alliance for Advanced Therapies (AAT) – Written evidence

Beneficial Translational and Commercial EU Climate Needed

Advanced Therapies: Bringing New Therapies to Patients

Bringing New Therapies to Patients

1. The Advanced Therapies sector is developing new ways to treat debilitating conditions, diseases, and/or defects affecting many different patient populations. This relatively young field of science has the potential to deliver new, innovative therapies or even cures where more conventional approaches do not provide adequate solutions. As a result, ATMPs offer an important opportunity to make a significant impact on patients' lives.
2. Advanced Therapy Medicinal Products (ATMPs) are especially important as they can offer solutions for conditions that are more prevalent in the aging European population.
3. One can distinguish different types of advanced therapies and cell-based tools. For example, cell therapy and cell modulation therapy have been used to restore sight.
4. The European Medicines Agency (EMA) approved a gene therapy to treat a hereditary disease. Tissue engineering is being used for cartilage repair, wound management and healing. Medical devices and tools are also important for the advanced therapies sector, as they are used for diagnosis, in therapy, surgery and drug discovery.
5. Major companies as well as SMEs have many treatments in clinical development and leading research institutions worldwide are involved in advanced therapies research.
6. To date, ChondroSelect (TiGenix) is the only product that has been granted centralized marketing authorization in Europe. The gene therapy product Glybera (UniQure) may follow soon after a positive opinion from the CHMP earlier this year.
7. Several products are currently under evaluation at the European Medicines Agency. As of September 2012, a total of 7 marketing authorization applications have been submitted for approval, while 41 scientific advice procedures have been started. Currently, EMA has classified 63 products as an Advanced Therapy Medicinal Product.
8. Companies like Fibrocell, Organogenesis, Sanofi and Shire have products on the U.S. market now.
9. Approximately 325.000 patients have been treated with approved products in the U.S. In Europe, the number of patients is significantly lower at approximately 700.

Advanced Therapies Gaining Momentum in Europe

10. The U.S. has been pioneering the advanced therapies sector. However, the sector is gaining momentum in Europe, which is leveraging its strong science base towards new research & development activity in this field. Currently, there are over 80 companies working on ATMPs in Europe. Approximately half of these companies have products in clinical development. It is important to note that the interest from larger pharmaceutical companies and investors starts to grow.
11. Further growth and development of this important sector in Europe depends heavily on the regulatory and business climates, according to the participants of the Advanced Therapies Summit 2012. Especially important are a more predictable translational and commercial climate in Europe as a whole.

Beneficial Translational and Commercial Climate Needed at EU Level

12. The development of advanced therapies for patients requires large investments in time and money that cannot be done without legislation that offers a clear regulatory situation assuring fair and beneficial market conditions for new therapies.
13. The full development process for an innovative and potentially life-saving therapy can take 12 to 15 years, including preclinical and clinical safety and efficacy testing. The necessary financial investments often amount to a total of about € 1 billion.
14. Larger companies can make these large investments only when they can be reasonably certain that their investment will yield a return. Smaller companies will not attract enough investor money without such a certainty about future returns. Regulatory predictability, market size, market access, and reimbursement prospects are all critical factors affecting the level of certainty that an investment in this sector will generate a positive return.
15. It is especially important to note that the markets in many individual European Member States are too small to attract investor interest in funding the development and approval of a new advanced therapy product. Therefore, a beneficial translational and commercial climate is needed at the European level.
16. The Alliance for Advanced Therapies (AAT) believes that the following issues are especially important to stimulate advanced therapies innovation in Europe:
 - a. A harmonized and transparent implementation of the Hospital Exemption throughout the Member States; and
 - b. A proper implementation of the end of the transition period for non-registered ATMPs in the Member States.

Harmonized Implementation Hospital Exemption Crucial

17. The Alliance for Advanced Therapies (AAT) appreciates and supports the Hospital Exemption as a means to offer individual patients a treatment with a customized, innovative and safe product, particularly when a disease occurs so rarely that the regular development and validation of the required therapy is not feasible.
18. However, AAT would like to emphasize that the inconsistent implementation of the Hospital Exemption in the Member States and routine preparations of treatments under an exemption impede the development of new safe and effective treatments. Misuse of the Hospital Exemption limits the market size and the potential return on investment for future, centrally approved products. The use of the Hospital Exemption could therefore make it unaffordable to develop a centrally approved product. This means that certain advanced therapies would only remain available for a limited number of patients in a Member State. These local therapies would not be tested for safety and efficacy the same way centrally approved therapies are tested. Furthermore, these local therapies would not become available for all European patients. It is therefore crucial for the development of new advanced therapies that the European Regulation is correctly implemented in all of the Member States, so companies can count on a transparent and harmonized use of the Hospital Exemption in the Europe Union without unwanted and unfair competition, with the aim to benefit all eligible patients in Europe.
19. The Alliance believes that a harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients. It is in the best interest of patients to limit Hospital Exemptions to non-routine preparations of treatments based on article 28 of European Regulation 1394/2007 under all applicable safety and quality rules. Furthermore, Hospital Exemptions should no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal

Alliance for Advanced Therapies (AAT) – Written evidence

Product (ATMP) is available. At this moment, there is no European-wide legal certainty on this point.

19 September 2012

Alliance for Advanced Therapies

The Alliance for Advanced Therapies (AAT) promotes the interests of the advanced therapies sector in Europe.

AAT is a new type of alliance. The scope of the Alliance encompasses the whole innovation life cycle, from fundamental research to actual treatment. Therefore, AAT represents the research and innovation interests of companies, academic institutes, patient groups, regional organizations and other stakeholders within Europe.

The Alliance for Advanced Therapies provides a credible voice for the sector and offers members a valuable worldwide network within advanced therapies. AAT is the European chapter of the global Alliance for Advanced Therapies and Regenerative Medicine. This European Alliance works closely with the Alliance for Regenerative Medicine, the US chapter of the global Alliance.

AAT is a not-for-profit organization.

Alliance for Regenerative Medicine (ARM) – Written evidence

1. The Research Base

1.1 The UK is regarded as an international leader in the field of regenerative medicine and related areas of science and technology, with some notable breakthroughs having been achieved. Examples of significant research achievements include the first cloned animal, Dolly, in 1996; the application of bone marrow transplantation to treat sickle cell disease; exploring the potential application of retinal pigmented epithelial cells to treat macular degeneration, and; the recent example of synthetic scaffolds used in conjunction with stem cells to treat patients suffering from hip degeneration.

1.2 Strengths include the recent establishment of programs that are focusing on addressing key bottlenecks in the regenerative medicine sector. Relevant examples include the following: (1) Projects focused on promoting the field of cell therapy and providing infrastructure support to companies to run clinical trials or manufacture cell therapies (e.g. Cell Therapy Catapult Project); (2) Disease specific research centers (e.g. the London Project to Cure Blindness, at the University College of London, components of the Scottish Stem Cell Network focused on diabetes, cardiovascular disease, stroke, neurological and musculoskeletal disorders, North East of England Stem Cell Institute (NESCI)); (3) Programs that focus on cell therapy process development and scale up/manufacturing (e.g. Advanced Therapy Medicinal Products Manufacturing Community); (4) Clinical trial networks (CTNs) that are designed to facilitate the efficient implementation and conduct of studies in high need areas (e.g. ischemic stroke, cardiovascular disease).

1.3 Weaknesses include the following: (1) although London is a major international center for capital investment, there appears to be little institutional investment focused on regenerative medicine, cell therapy or other advanced therapies, consequently; (2) there are few regenerative medicine based companies in the U.K.; (3) there are no meaningful incentives in place to attract emerging/existing companies to establish an operational presence in the U.K.; (4) there are real and/or perceived bottlenecks that delay or adversely impact the speed and efficiency of clinical development, which increases overall costs and erodes value - although we note the recent solicitation by the MHRA requesting input on ways to provide patients faster access to medicines (the Early Access to Medicines Scheme), which, along with other initiatives could help address this issue; (5) there are perceived barriers regarding reimbursement, and similar to other countries, the efficiency of the process to obtain coverage and reimbursement should be improved, as this could stimulate further capital investment.

1.4 Lack of development capital clearly represents one of the biggest obstacles to development of regenerative medicine and cell based therapies. In general, funding for the field of regenerative medicine comes primarily from several sources: (1) government agencies; (2) philanthropic foundations; (3) venture capital, institutional investors, and the public markets; (4) established, profitable companies looking to enter a new area of opportunity. However, it is clear that a lack of funding has greatly impeded development, and has resulted in smaller, less informative clinical studies. In particular, we note that there does not appear to be any meaningful, well-coordinated national or international effort to leverage funding that might be obtained from various sources in order to achieve greater

focus and efficiency in driving preclinical and clinical translational research, as well as accelerate commercial development. We believe that such an initiative should be established as a public-private partnership. Further, we argue that the United Kingdom and the United States could (and should) work together to define and lead an international “Regenerative Medicine & Advanced Therapies Initiative”, analogous to the Human Genome Project, but with a direct focus on accelerating the development of new treatments for serious unmet medical needs.

2. Application of the Science

2.1 Perhaps the best way to assess whether the science is being translated into applications is to evaluate completed, ongoing, and formally planned clinical trial activity involving regenerative medicine therapies. A recent analysis conducted by ARM shows that there are over 240 registered clinical trials involving the use of cell therapy based approaches and other forms of regenerative medicine, including both autologous and allogeneic therapies. These trials cut across a wide range of clinical indications and disease areas. It is worth noting, however, the vast majority of clinical trial activity has occurred / is occurring outside the United Kingdom, with few representative studies having been conducted to date within the U.K., or involving U.K. sponsors or clinical institutions.

2.2 Since 2000, there has been a steady growth in the number of clinical trials involving both allogeneic and autologous cell therapies. However, many of these are relatively small studies, not designed to rigorously evaluate multiple dose levels (i.e. critically assess dose response), and many are open label, as opposed to robustly powered, double blind, placebo controlled studies. The design and limited size of these studies likely reflect a longstanding lack of funding for the area. Many of the sponsors of these studies are small, undercapitalized companies, which typically lack the financial resources to underwrite large, well powered clinical trials.

2.3 A recent analysis by ARM identified 20 cell therapy or donor derived tissue based products that are currently available commercially in the United States. However, it appears there are few regenerative medicine therapies that are approved for use and available within the U.K., either paid for through the NHS, or available privately. The limited examples we are aware of include several protein based regenerative medicine therapies (e.g. Epogen, Neupogen, and next generation versions) and at least one example of a cell based therapy based treatment (Chondroselect, an autologous cell therapy for cartilage regeneration in the knee). It seems, therefore, that the U.K. has historically been a slow adopter of cell based regenerative medicine products, but the reasons for this are unclear. Potential explanations include lack of institutional investment within the U.K., regulatory or financial constraints that impede or disincentivize clinical trials and subsequent commercialization activity within the U.K., and coverage and reimbursement practices that could create real or perceived barriers to commercialization, all of which act as barriers to private investment.

2.4 We believe the largest impact of regenerative medicine and advanced therapies will be felt in areas of significant clinical need, where traditional interventional approaches have either failed entirely, or have had limited impact, and where the cost and quality of life burden is very high. Specifically, within the next few years, and based on ongoing and planned clinical activity, we believe the greatest impact could be seen in the high need / high

cost burden areas that conventional approaches (e.g. pharmaceuticals, surgical intervention) have failed to adequately or fully address, including the following examples:

- ❖ **Cardiovascular disease** – There are multiple clinical trials focused on novel treatments for damage suffered by acute myocardial infarction (heart attack), congestive heart failure, and various forms of vascular disease, including intermittent claudication, peripheral vascular disease, peripheral arterial disease, and Critical Limb Ischemia (CLI). Together, these forms of cardiovascular disease represent a major burden on the NHS;
- ❖ **Hematology & Oncology support** – Provenge, a product treating prostate cancer received FDA approval in 2012. In addition, many clinical trials are focused on improving clinical outcomes in patients being treated for various types of hematological malignancies or other forms of cancer. This is not surprising, since the field of cell therapy was really born out of the pioneering work involving bone marrow transplantation, and subsequently hematopoietic stem cell or peripheral blood stem cell transplantation. In recent years this activity has broadened into chronic hematological conditions, and other areas;
- ❖ **Neurological disease and conditions** – Representative trials include treating damage from ischemic stroke (typically the leading cause of serious long term disability), Multiple Sclerosis, certain orphan neurological diseases, and damage from trauma (including traumatic brain injury (TBI), and spinal cord injury). Other active areas of research include cell therapy based approaches to treat Parkinson's Disease, Alzheimer's Disease, ALS, and other chronic progressive neurological conditions;
- ❖ **Inflammatory and immune conditions** – Examples include Rheumatoid Arthritis, Multiple Sclerosis, Inflammatory Bowel Disease, and a range of other conditions where acute and/or chronic inflammatory damage adversely affects patient health and well-being, and erodes quality of life;
- ❖ **Diabetes** – Diabetes and diabetes related complications represent a major cost driver for the NHS. Some recent reports suggesting the dramatic rise in diabetes related costs threaten to bankrupt the healthcare system in the coming years. Several regenerative medicine based approaches are focused on addressing the loss of islet cells and underlying drivers of the disease, including mitigation of the inflammatory process;
- ❖ **Orthopedic indications** – These are focused primarily on trauma related injury, as well as aging or inflammatory related bone, cartilage and soft tissue damage or degeneration. Affected areas of the body include the knee, hip, spine (e.g. intervertebral disc degeneration), and other areas;
- ❖ **Ophthalmological indications** – Relevant examples include the use of Retinal Pigmented Epithelial (RPE) cells to treat Macular Degeneration, which affects a significant number of the elderly, and poses a huge burden on quality of life, and individual productivity.

3. Barriers to translation

3.1 In general the clinical path is seen by patients, innovators, and investors as taking too long and being too expensive, with a low probability of success, partly as a result of entrenched regulatory hurdles. As a result, investors are not investing as much as we need. Regenerative Medicine is often viewed as an emerging and unproven area, with products being anticipated to be expensive relative to traditional pharmaceuticals and other biotechnology products; the perceived cost-risk-benefit profile may be having a

disproportionately negative impact on these types of opportunities which stifles development.

3.2 One way to address this could be to modify the clinical/regulatory framework so that therapies that have the potential to address specific areas of significant unmet medical need (which should be explicitly defined by the NHS) can be developed faster, and less expensively – perhaps with a corresponding requirement to conduct post-approval studies to validate safety and efficacy. Failure to adhere to this could result in subsequent loss of registration. The U.S. FDA instituted a similar policy several years ago -- known as "accelerated approval" -- to facilitate rapid approval of products for "serious or life threatening illnesses. This pathway was recently strengthened and enhanced through legislation. The FDA is currently developing its criteria for determining which indications meet the definition of "serious or life threatening".

3.3 The EU also provides for Conditional Marketing Authorisations and Exceptional Circumstances Authorisations in case of unmet medical needs, but the specific requirements under which they can be granted may not always be met by regenerative medicine products. These potential barriers should be considered.

3.4 Obtaining regulatory approval without obtaining adequate reimbursement in a timely and efficient manner is another big challenge, particularly for smaller companies. There is an opportunity to make modifications to the reimbursement process, and to facilitate earlier interactions between sponsors and the NHS / NICE, in order to increase the efficiency of the development process.

3.5 The establishment of national Clinical Trial Networks (CTN's) in specific disease areas is a powerful way to attract and incentivize translational activity in the U.K. CTN's can facilitate faster initiation and execution of clinical trials, reducing the overall cost and time of clinical development.

3.6 Another approach would be to encourage funding of "regulatory science"; the research necessary for regulatory agencies -- and commercial developers -- to better understand the scientific obstacles that block approval of products.

3.7 We recommend the NHS explicitly identify specific disease areas that qualify as "significant unmet medical needs", along with the creation of a framework designed to accelerate / catalyze development of regenerative medicine therapies targeting at treating those areas. Special emphasis should be given to those disease areas that represent a significant cost burden (e.g. chronic conditions that have a high cost of care, and significant quality of life impact). This framework should include modifications to the regulatory and reimbursement pathways that are designed to accelerate, streamline and increase the efficiency of development for safer, more effective, and cost effective therapies, and subsequent commercialization. In so doing, it could catalyze development of high risk / high impact technologies and approaches within the U.K., making it a true international leader in the field.

4. Barriers to commercialisation

4.1 In the UK, as elsewhere, an aging population provides a healthcare and societal challenge that affects patients, families, and society as a whole. As the population ages, rates of

chronic disease rise and the cost of our healthcare increases. Regenerative medicine, which targets many of chronic diseases of aging such as stroke, heart disease, and diabetes, holds enormous promise to reduce these burdens. Thus the value it can bring to society comes from improving medical outcomes in areas of significant clinical need, enhancing patient (and family) quality of life, and the potential to reduce overall long-term healthcare costs while also improving productivity.

4.2 For example, heart tissue damaged by atherosclerosis, chronic ischemia or a heart attack is weak and ineffective. Drugs can make the heart beat stronger and can reduce workload by controlling blood pressure, but even our best tools are frequently overwhelmed, and patient health declines quickly. Neither is a heart transplant the perfect solution, given the necessary immunosuppressive regimens required to prevent rejection, the high cost of complicated surgery and the limited supply of donor organs. However, regenerative medicine treatments that rescue and heal infarcted heart tissue could adequately address the multifactorial demands on a compromised cardiovascular system and prevent the decline in functional capacity resulting from the loss of heart tissue.

4.3 In another example, cell-based replacement skin products currently on the market treat diabetic foot ulcers, a complication of diabetes. Over 18 million patients suffer from diabetes in the U.S. alone, and each year nearly 140,000 of those patients will see a wound care specialist for a diabetic foot ulcer resulting from poor circulation. The consequences of not effectively managing the wound include chronic infections, laborious cleaning of the wound and in the worst cases, amputation. While there are drugs to fight infection, no drug available today will help the skin to grow back. Engineered skin products, Dermagraft and Apligraf, are the only therapies that actually accelerate healing, effectively closing the wound and preventing infection and other dire consequences, and studies have shown that these types of products are not just clinically effective, they are also cost effective.

4.4 The prevailing evidence suggests that efforts to date have not resulted in significant investment in the area within the U.K., as evidenced by the small number of companies and limited number of clinical trials being conducted.

4.5 One approach to translate technology from academia into commercial entities would be for the U.K. to promote the formation and launch of a large number of new companies focused on the development of *de novo* technologies in the field of regenerative medicine, but given that there are already a significant number of operating companies, and many are undercapitalized, this might not represent the most effective strategy. An alternative strategy might be to attract existing/emerging regenerative medicine companies to expand their operations into the U.K. through the use of financial incentives.

4.6 Several approaches to this should be considered. One market driven approach that has been debated in the US to attract existing/emerging regenerative medicine companies to the U.K. would be to allow international companies to monetize accumulated “trading losses”/NOL’s in the U.K. For example, small companies could “sell” their trading losses to U.K. companies or investment funds (i.e. that are based in the U.K. and pay taxes in the U.K.), but only if the international company agrees to establish operations in the U.K. and invests all of the investment in the U.K. For investment funds, there could be a further requirement that their ability to utilize the purchased trading losses requires a commensurate investment into the newly created U.K. entity (i.e. the entity that receives

and invests the funds from the monetized trading loss/NOL), providing further leverage, and creating an even greater magnet.

4.7 As with pharmaceuticals and other biotechnology products, intellectual property is **critical** to promoting the development of regenerative medicine therapies. Given the cost of development, and length of development time, without IP protection, institutional investor would avoid investing the amount of capital necessary to develop these types of therapies. In addition, the protection of intellectual property through a prolonged period of data protection is also very valuable to protect 'know-how' associated with these products.

4.8 In general there are four types of models: (1) service models (e.g. processing of cells); (2) device based approaches (e.g. the use of devices that facilitate the rapid and efficient processing of cells), (3) allogeneic based approaches (e.g. cells derived from a healthy donor, subsequently expanded and characterized to treat many patients); (4) tissue engineering based approaches. Each model has unique challenges and opportunities.

4.9 The biggest barriers to investors are evidence of clinical validation, preclinical validation, scalability of the technology (e.g. manufacturing), economic parameters (e.g. COGS and other financial practicalities of the technology), perceived risk and cost of clinical development, and perceived risks associated with coverage and reimbursement. Overcoming these barriers was discussed above.

5. International comparisons

5.1 In the US, laws were recently enacted that will speed the approval of safe and effective therapies -- including regenerative medicine therapies to market. As noted above, the US has enhanced its program of accelerated approval – as a way to expedite development of therapies to treat serious or life threatening illnesses. In addition, the US FDA will be developing a new and more precise risk-benefit paradigm within which it will make approval decisions. This should add predictability to the regulatory review process. Finally, US law now requires that FDA develop a process to allow rapid review and approval of products for "breakthrough therapies" for unmet medical needs.

5.2 In addition, the California Institute for Regenerative Medicine (CIRM) has instituted programs to support development and commercialization of regenerative medicine therapies. This includes "disease team" grants -- funds for multi-disciplinary research groups specifically designed to support activities that lead to filing of an Investigational New Drug application.

5.3 In general, there is not yet good international harmonization regarding standards that govern the development of regenerative medicines and advanced therapies, however we note that there is effort being focused on this area, such as with the creation of the ATMP framework. However, U.S. companies conducting clinical trials in Europe are frequently frustrated by the lack of regulatory consistency among countries in the EU, including the UK, and the inefficiency of having to conduct separate meetings with each regional regulatory authority. This can add substantially to the time and cost of establishing clinical trials in Europe in multiple countries.

5.4 Certain countries lack the regulatory infrastructure or institutional capabilities to regulate or provide proper oversight regarding the clinical use or commercial exploitation

of potential new therapies, including the use of stem cell and regenerative medicine therapies. Unfortunately, this has resulted in the emergence of unregulated commercial activity for cell therapy based treatments, which ARM strongly believes represents a danger to patients, and a threat to innovation. There are multiple instances of business offering commercial “stem cell therapies”, and charging patients a significant amount of money for “treatments” that have never been clinically validated, and are poorly characterized and unproven. This represents a real threat to patients, both economically and medically, and represents a violation of their right to informed consent. To address this risk, governments and stakeholders should develop an education campaign for patients and provide information explaining the greater safety and efficacy of approved treatments, as well as providing information about clinical trials currently underway for illnesses for which there is no approved treatment.

19 September 2012

Professor Peter Andrews, University of Sheffield, the Intellectual Property Office and Lawford Davies Denoon – Oral evidence (QQ 196-213)

Professor Peter Andrews, University of Sheffield, the Intellectual Property Office and Lawford Davies Denoon – Oral evidence (QQ 196-213)

[Transcript to be found under Intellectual Property Office](#)

Anscombe Bioethics Centre – Written evidence

Key Points

- Both research and translation of research are matters of ethics and the public good and not only matters of commercial advantage.
- It is important to get the views of the public on the translation of technology and not only the views of those with professional scientific or commercial interests.
- Because of the danger of hype, sometimes as a result of political pressures, it is important to test against recognised metrics the claims of scientists and technologists both as to the current ranking of the research and as to the potential for translation.
- Ethical questions are both important in themselves and important in assessing the commercial obstacles to translation of technologies nationally and internationally, as is evident from the Brüstle case.
- **We recommend that the Committee encourage governments and other funders to consider the ethical concerns associated with regenerative technologies before funding or promoting them. It is to the advantage both of society and of science and commerce if technologies are promoted that are ethically accepted both in this country and in the rest of Europe.**

I The Anscombe Bioethics Centre

- I.1 The Anscombe Bioethics Centre in Oxford is the oldest national bioethics centre in the United Kingdom, established in 1977 by the Roman Catholic Archbishops of England and Wales. It was previously known as The Linacre Centre for Healthcare Ethics and was situated in London before moving to Oxford. The Centre engages with the moral questions arising in clinical practice and biomedical research. It brings to bear on those questions principles of natural law, virtue ethics, and the teaching of the Catholic Church, and seeks to develop the implications of that teaching for emerging fields of practice. The Centre engages in scholarly dialogue with academics and practitioners of other traditions. It contributes to public policy debates as well as to debates and consultations within the Church.
- I.2 The Centre welcomes the opportunity to respond to the House of Lords Select Committee on Science and Technology Consultation on Regenerative Medicine, recognizing that this Consultation covers important ethical issues of wide concern. Our response does not rely on premises held by Catholics only: on the contrary, the arguments presented are potentially acceptable to those of other faiths, and of no faith.
- I.3 Given the concerns and expertise of the Centre this response covers matters of ethics that impact on research and on the translation of research to commercial applications. It does not directly address the scientific or commercial merit of such research.

2 Public engagement

- 2.1 The translation and commercialisation of stem cell research and regenerative biotechnologies are not only matters of scientific and commercial interest but are of public interest. They involve or imply ethical questions which are of interest to the public as a whole. However, the 2008 Survey of Public Attitudes to Science, commissioned by Research Councils UK, found that only 21% of the public agree that ‘the public is sufficiently involved in decisions about science and technology’.¹
- 2.2 The Code of Ethics adopted by the Royal Academy of Engineering includes the aspiration to ‘be aware of the issues that engineering and technology raise for society, and listen to the aspirations and concerns of others’.² This is closely parallel to the Universal Ethical Code for Scientists, which urges scientists to ‘Seek to discuss the issues that science raises for society. Listen to the aspirations and concerns of others’.³ These statements mirror the wish of the public (manifested in the Survey of Public Attitudes) for greater communication and consultation.
- 2.3 It is thus contrary both to the wishes of the public and to the aspirations of the scientific community, as expressed in such official Codes, to devise policy on scientific research and translation of biotechnology without simultaneous and sufficient engagement with the public and consideration of ethical issues.
- 2.4 Another finding of the 2008 Survey of Public Attitudes to Science was that the public are wary of too close a link between business and science and are less trustful of scientists to the extent that they are reliant on particular funding. For example, 60% held that ‘scientists are too dependent on business and industry for funding’, while 72% thought that ‘the independence of scientists is often put at risk by the interests of their funders’.⁴

3 Critical evaluation of scientific and commercial claims

- 3.1 A study by Timothy Caulfield published in *Trends in Biotechnology* provides evidence to justify this caution. Having investigated various cases of media hype over biotechnology he concludes that this is not simply a result of inaccurate reporting by scientific journalists, but that the exaggerations are often created by the scientific community itself. He suggests that the ‘hyping of research’ may result from the increasingly commercial nature of the research environment. He therefore recommends that ‘given the growing evidence of the impact of commercial forces on... the reporting of research results, governments should consider the development of a system that enables the independent assessment’.⁵
- 3.2 It is hoped that the House of Lords Committee will be more rigorous in examination of evidence than the House of Commons Select Committee on Science and Technology. In a Report on a related issue, that committee referred to ‘UK’s leading

¹ Public Attitudes to Science 2008 A Report Prepared for Research Councils UK and the Department for Innovation, Universities and Skills by People, Science & Policy Ltd/TNS, p. 24.

² Royal Academy of Engineering Statement of Ethical Principles

http://www.raeng.org.uk/societygov/engineeringethics/pdf/Statement_of_Ethical_Principles.pdf

³ Universal Ethical Code for Scientists

http://www.dius.gov.uk/science/science_and_society/public_engagement/ethical_code

⁴ Public Attitudes to Science 2008 A Report Prepared for Research Councils UK and the Department for Innovation, Universities and Skills by People, Science & Policy Ltd/TNS, p. 30.

⁵ Caulfield, T. ‘Biotechnology and the popular press: hype and the selling of science’ in *TRENDS in Biotechnology* Vol.22 No.7 July 2004.

position in stem cell research’⁶ and to an alleged ‘competitive advantage UK scientists have in stem cell research’.⁷ These comments echoed remarks made in the BioIndustry submission⁸ and by Professor Colin Blakemore.⁹ However, in no case was evidence provided for the UK’s alleged world leading position. In contrast, in a report commissioned by the North East England Stem-Cell Institute (NESCI) to measure world ranking, US institutions are apparently portrayed as having a commanding lead in the sector with very few UK centres able to compete.¹⁰

- 3.3 Similarly, claims in evidence for the ‘world leading’ position of particular research projects, or of the United Kingdom as a whole, in relation to a certain sector, should not be encouraged, such as in the call for evidence by the Committee, nor accepted without evidence. Indeed, the position of the UK in any field might best be assessed by establishing metrics and other objective measures for such assessment, perhaps with assistance from independent professional advisors. If such measures were published then this might discourage extravagant claims and facilitate informed debate.

4 Ethics as both essential and useful

- 4.1 The Anscombe Bioethics Centre, and other similar Centres, exist because of the importance in itself of maintaining ethical standards in research and in the application of research in medicine and technology. There are, of course, arguments among Centres, scholars, and traditions of thought in relation to what actions are ethical or unethical. Nevertheless, there is agreement that ethical values or principles are essential to the proper evaluation of research and technology. Unethical research should not be conducted and should not be facilitated by funders or regulators.
- 4.2 It is also the case that, even apart from the importance of the inherent integrity of scientific research, there are good commercial reasons to be aware of ethical issues. Ethical concerns do and should inform regulatory and legal decisions both nationally and internationally. They can also affect the public acceptance of technology. This was illustrated very well by the Brüstle decision of the European Court of Justice in 2011 in which technologies that relied on the destruction of human embryos were not given patent protection.¹¹ That was because of an ethical judgment, common in many countries and expressed in the European Parliament, that human embryos should not be destroyed for financial gain, and that human tissues should not be traded for financial gain.
- 4.3 The Brüstle decision was both reasonable and predictable,¹² but unfortunately this perspective was not well represented in the media. In retrospect the warnings of doom and dire consequences as a result of the decision can be seen as themselves irresponsible and as endangering investment in a wide range of technologies. Had more attention been paid earlier in the process to the importance of the ethical acceptability of the technology then funders and biotechnologists would have been

⁶ House of Commons Science and Technology Committee Report: Fifth report of Session 2006-07, Government proposals for the regulation of hybrid and chimera embryos, paragraph 104.

⁷ HCSTC Report, paragraph 105.

⁸ HCSTC Report, Ev 108.

⁹ HCSTC Report, Oral evidence Q 251.

¹⁰ Corbyn, Z. ‘UK’s reputation as world leader in stem-cell research challenged’ Times Higher Education 22 January 2009. <http://www.timeshighereducation.co.uk/story.asp?storycode=405090>

¹¹ Jones, D.A., Agius, E., Altisent, R., et al., ‘Letter: More at stake in stem-cell patents’ Nature (30 June 2011) 474: 579.

¹² Abbot, A. ‘The Cell Division’ Nature (15 December 2011) 480: 312.

more careful to distinguish some highly contentious technologies from other technologies which are both commercially promising and ethically acceptable.

- 4.4 We recommend that the Committee encourage governments and other funders to consider the ethical concerns associated with some regenerative technologies before funding or promoting them. It is to the advantage both of society and of science and commerce if technologies are promoted that are ethically accepted both in this country and in the rest of Europe.**

20 September 2012

Anthony Nolan – Written evidence

Anthony Nolan manages and develops the UK's biggest and most successful register of potential bone marrow donors and banks umbilical cord blood, also for use in stem cell transplants to treat blood cancers and disorders. Haematopoietic stem cell transplantation is the most developed area of regenerative medicine, with applications reaching over 14,000 in the period between 2004-2009 alone.¹³

Anthony Nolan's register of bone marrow donors was the first such register to exist, with other countries following suit. The organisation also carries out research into the matching process, with the aim of improving patient outcomes. Furthermore, the UK hosts the human leukocyte antigen (HLA; or tissue type) nomenclature database; an international resource to which all newly discovered tissue types are added.

This means that our knowledge of the genes from which a person's HLA type is determined, is vast. I have provided examples below of how this knowledge can be applied in practice. These examples are an indication that routine HLA typing could provide patient specific information now that we hope to gain from whole genome sequencing in the future.

Research and application

Our Histocompatibility and Immunogenetics labs predominantly HLA type every person who joins our register, as well as some blood cancer patients, under contract with hospitals who do not have their own labs. This is the essential process behind ascertaining whether patient and donor match.

The labs additionally offer HLA typing to hospitals treating patients with ankylosing spondylitis, because the patient's tissue type necessitates treatment modification for some patients. Furthermore, the labs offer tissue typing to hospitals treating patients with HIV. This is because a particular drug given to patients with HIV can be three times more toxic if that patient has a particular gene in their tissue type. We test for the presence of this gene so that clinicians can modify the treatment accordingly.

These examples demonstrate stratified medicine in practice, brought about through an understanding of the processes behind regenerative medicine. For these reasons, Anthony Nolan agrees that the UK is a world leader in regenerative medicine. However, there are weaknesses that result in barriers to the realisation of the promise of regenerative medicine.

For example, Anthony Nolan banks blood collected from umbilical cords, which would otherwise be discarded. Those that are not banked for clinical use in stem cell transplants are available for use in research. The UK is limited in the number of umbilical cords it can collect, due to funding. Anthony Nolan and NHS Blood and Transplant manage eleven collection centres between them. The two organisations have, for the last two years, been funded by the Department of Health to run expanded cord blood collection in centres around the UK. However, without further funding to open more, or increase collection hours for those currently operating, there is a limit to the number of cord units that can be collected.

¹³ British Society of Blood and Marrow Transplantation

A similar predicament with Anthony Nolan's adult register presents the same problem. Stem cells transplants can only be carried out between well matched donors and patients. A lack of donors, together with a limited cord blood provision, limits the number of transplants carried out. Many patients die waiting for a matching donor, while others die as a result of the transplant itself. We can only ameliorate this particular field of regenerative medicine by carrying out more transplants, which requires greater availability of young, healthy donors.

Barriers to commercialisation

In our field, research involves understanding the genetics of tissue types better so that we can find the very best match for a patient in need of a bone marrow donor. This helps to save lives and save the NHS money, but it's informing clinical behaviour, rather than creating a drug or device.

Developing practice and behaviour has a capacity to improve health and deliver public spending efficiencies in clinical settings, public health and in social care. However, the lack of intellectual property that can be derived from such research hampers private investment. The consequences of such research will save lives and deliver spending efficiencies so should be considered just as important as cancer drugs.

A further barrier in our field is the cost associated with banking umbilical cord blood. We have made large investments with matched public funding, but until the UK's own inventory of banked cord blood is bigger, clinicians who want to transplant stem cells from cord blood into their patient are forced to opt for more costly cords overseas. Commissioners and hospital budgets may present a barrier at this stage, preventing further practice of this fledgling field of medicine.

International comparisons

Countries that do have stem cell registers and cord blood banks employ a number of policies and cultural tools to support the operation of stem cell transplantation. Two such examples are particularly striking.

In Germany, the number of people on bone marrow registers exceeds a few million, compared to the few hundred thousand registered in the UK. This can be partly attributed to public and charitable funding, but also to a distinct culture, where public duty may be more embedded.

In Spain, the blood from umbilical cords is collected almost as a matter of course, by the Spanish equivalent of NHS Blood and Transplant. Any cords banked privately are available to patients via the public system as and when needed, with the state refunding the parents' original investment. Spain's register of adult donors is comparatively small, with their need for transplants largely met by their cord blood provision.

21 September 2012

Apax Partners, Cenkos Security and Imperial Innovations – Oral evidence (QQ 170-195)

[Transcript to be found under Cenkos Security](#)

Applied regenerative science group, UCL (Royal Free, UCLH, GOSH campuses) – Written evidence

Authors: Martin Birchall, Adrian Thrasher, Mark Lowdell, Paolo DeCoppi

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

- A. There have been a number of seminal discoveries and first-in-human studies in the UK, including those from our own institution. The UK ranks very highly (possibly top three in world) for basic stem cell science. However, our resources and their distribution are weaker than those of our main ‘competitors’.

Where does the UK have strengths and weaknesses in the field?

A. Strengths are in basic, translational and clinical arenas. We are very strong in basic/discovery stem cell science, gene therapy and some aspects of materials science; we have performed first-in-man studies of gene therapy (e.g. Thrasher, Ali), fetal stem cell therapy (Reneuron), autologous stem cell therapies (limbal stem cell trials at UCL and Newcastle) and cellularised, tissue-engineered ATMPs (Birchall, Lowdell, Seifalian) for example. Clinically, the most obvious strengths are the comprehensive support from the NIHR trials network and the NHS itself which give unparalleled access, at least in theory, to up to 60M patients (6m in UCLP AHSN alone) in an environment of world-standard governance (from publication and regulation points of view). The latter should make us highly attractive to industry and overseas investigators alike, but other issues mean this remains poorly exploited.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

A. MRC budget is around 10M pa for RegenMed, whilst CIRM in California put in around \$200M and AFIRM another 0.5billion (and these are only two of the US funding bodies supporting this work). UK support is trivial compared to US, Germany, Japan, Korea and China. Wellcome streams are now very difficult indeed to access, and NIHR only support clinical (or the latest preclinical) science, making the jump across the ‘valley of death’ very difficult for UK investigators. The UK RegenMed industry is embryonic to say the least and is not in a position to help. TSB support has therefore been equally difficult to allocate and the wisdom of its spending has been called into question. UK Universities are highly variable in the degree to which they have been prepared to buy into the future of RegenMed (e.g. Edinburgh invested substantially, London Universities hardly at all).

Application of the science

Is the science being translated into applications?

Applied regenerative science group, UCL (Royal Free, UCLH, GOSH campuses) – Written evidence

A. Very slowly, but this is to be expected, given the timespan of developments such as gene therapy for example. The UK has two licensed products, whilst South Korea license about two per annum presently and already has 18 licensed regenerative medicines.

What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally?

A. Regenerative skin replacement products are in clinical use based on extracellular matrix. Cellularised sheets are in trials for skin ulcers and burns, and in early trials for mucosal replacement in urethral stricture and corneal disease. There are a number of examples of therapies in phase I/II and first-in-human studies presently, but these could not be described as ‘treatments’ in the more general sense at this stage of gestation.

Which treatments are available on the NHS or through private healthcare?

A. Some of the skin regeneration products are available commercially. Autologous chondrocyte therapy is available as a licensed medicine from at least on private healthcare provider although not yet available on the NHS.

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

A. The key questions and those to which there are no definite answers. The potential exists for regenerative medicine to form a major part of healthcare delivery in the longterm. It is unlikely this will be the case as quickly as 5 years, but we may see the beginnings at ten years. This is because the raft of late preclinical and early clinical treatments being studied presently will, even with a fair wind and adequate funding, take ten years to go through phase I/II and then III clinical trials before being assessed by NICE and similar for general dissemination through the NHS.

The authors believe that RegenMed will fulfil this promise, but for the UK to benefit financially in the 5-10 year zone, we have to (a) increase the direct funding available to HEI investigators (MRC and NIHR, not TSB since 90% of clinical trials in this field are currently still in academia and not in the nascent biopharma industry) and (b) make the regulatory and trials organisational framework of the UK one that overseas (and home) investigators and companies see as a place they can perform their studies at speed and reasonable cost with a higher degree of regulatory certainty to allow investment. This specific problem is an EU issue in fact since lack of regulatory harmonisation is leading to such insecurity within the field that commercial funding is very poorly available. As an example, Chondrocelect is the only licensed cellular regenerative medicine in the EU but some member states are allowing hospitals to manufacture an unlicensed “biosimilar” in order to avoid the cost of the licensed alternative. Investors are citing this as sufficient regulatory uncertainty to refuse to invest in commercial trials. One of us (ML) is funded by the Commission to assess this lack of harmonisation and is reporting back in early October.

Barriers to translation

Applied regenerative science group, UCL (Royal Free, UCLH, GOSH campuses) – Written evidence

- Are the actions outlined in the Government's *Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Strategy Board's *Strategy for UK Regenerative Medicine* sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

What difficulties are encountered when conducting clinical trials and how could these be overcome?

A. The regulatory pathways are still, whilst somewhat better than the US, labyrinthine and off-putting for overseas investigators, whilst demoralising for home investigators. The clinical trials pathway has evolved to lead to a licensed product with a marketing authorisation. Many RegenMed products will never achieve this status (e.g recellularised trachea, gene/cell therapies for rare inherited diseases) and yet are valuable treatments with considerable clinical and economic impact (many of these could be developed as orphan products). Furthermore, cell-based regenerative medicines are regulated as drugs, not devices or tissue, which applies a regulatory framework into which they fit very badly. The MHRA understands this and is supportive but only very experienced centres such as UCL which has taken such a diverse range of therapies to trial, are well placed to develop new therapies. We would propose that the MRC is supported to collaborate with the Catapult TIC to provide a "one stop shop" of expertise (not funds) for academics to take new therapies to trial. It would remain the role of the investigator to seek funding. This might appear to be the aim of the current round of MRC/TSB Centres of Excellence but that has not been the outcome of that funding call. An exercise in market research and then marketing of the fantastic networks and patient populations we have in NHS/NIHR should be undertaken for presentation to industry and HEI's internationally. We need to open the doors for business.

What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

The gap between late preclinical and clinical trials remains large and very expensive. The MRC's total budget for RegenMed could realistically support only five projects per annum, possibly fewer. This is grossly inadequate if we are to capitalise on the basic and translational science strengths we so demonstrably hold here.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

A. We are not at this point presently in RegenMed, so this question is, to an extent, theoretical.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy?

A. Most of the first phase treatments (gATMP therapies which are cell/tissue/gene/tissue-engineered combination products, 5-10 years) are for orphan disorders. Income for these will come from medical tourism as well as IP from associated devices and protocols. Typical

Applied regenerative science group, UCL (Royal Free, UCLH, GOSH campuses) – Written evidence

ATMP profit per patient treated might be £50,000, with a potential pool of 200 patients per annum for each of ten products totalling £100M p.a. For 'mass market' products, such as those for joint, skin and eye disorders, margins will be much smaller, but patients would number in the tens of thousands per annum, totalling several £billion potentially. However, for reasons above, full realisation of these incomes is likely to take longer than ten years. Thus, in the meantime, there is a need for the economy to benefit from the attraction of RegenMed clinical trials with an early gain in income resulting.

What is its value to society?

A. Economic benefit would bring social benefit. One-off, effective treatments for conditions normally requiring sustained longterm healthcare investment (e.g. organ transplantation, arthritis, diabetes, metabolic and haematological disease) would provide further economic and social gains, and return more patients to society and to work. Treating conditions where there is currently no treatment (e.g. some eye and blood disorders) saves lives and returns patients to work and society. A recent Austrian trial of a novel and simple RegenMed therapy for diabetic ulcers demonstrated how patients with persistent, long term chronic disease could be cured with massively improved morbidity and annual savings in sterile dressings alone of £30,000 per annum, per patient. Similarly, we have shown that curative bone marrow gene therapy for one inherited immunodeficiency saves 200-300 thousand pounds per year per patient which otherwise is spent on enzyme replacement therapy.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

- A. This is a fundamental misunderstanding of the issues. For companies to develop, there need to be products sufficiently developed to take forward towards market. Presently, 95% of even clinical work internationally is in the academic sector. Without substantial increased support to translational science in universities, there will simply be no industry. 'You can't pump what you don't have'; this issue has called into question from some quarters the wisdom and timeliness of the substantial investment in the 'catapult centre'.

These comments apply to the home-grown sector. In order to attract the growing overseas commercial sector, the changes above to regulation, and focus/facilitation and marketing of the NIHR/NHS engine needs to be urgently addressed.

What role does patenting play in the commercial development of regenerative treatments?

A. This depends on the product. Technology and materials based treatments have considerable potential, whilst those based on cells have much less.

What business models are most appropriate to support the development of regenerative treatments?

- A. This is an area which also needs investment. The models will vary with the product. A cheaper, off the shelf, ECM skin product might be marketed like a device or a

drug. Gene therapy has special considerations. Complex ATMP's such as cellularised scaffolds may need to look to licensing/shareware and medical tourism as income streams. Other models also need exploration.

Certainly we need to think beyond conventional pharmaceutical drug development and drug delivery. It is already apparent that many RegenMed products will need some aspect of their manufacture near to the patient. At present there is a single UK trial of a regenerative medicinal product derived from an embryonic stem cell. This is an “off-the-shelf” allogeneic product yet still needs thawing from cryopreservation and dosing within a 4 hour travelling distance of the patient. If the current clinical trials in the UK and the US continue to be successful this is an ideal candidate for commercialisation but only if an infrastructure of hospital-based “cellular pharmacies” are in place across the UK such as the three highly specialised, MHRA licensed facilities we have across UCL to deliver these products close to the patients. Alternatively the UK should centre its RegenMed investment around those centres of excellence in translational RegenMed therapy to work in partnership with the developing biopharma industry. This was the original plan of the Cell Therapy Technology Innovation Centre, one which was shelved in favour of the TSB Catapult.

What are the barriers to securing finance to develop such treatments?

- A. The UK investment is small presently, indeed tiny compared to our main competitors. There is practically no industry (home grown at least) that is capable of supporting early phase studies, let alone phase 3 trials. Both need addressing as above.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

- A. It will be some time before this is a current question. Present pricing structures are inadequate for conventional treatments (e.g. the real costs of delivering outpatient endoscopy and some surgical procedures in our practices), so are most unlikely to meet the needs of a complex future including regenerative products. Now might be timely to initiate work in this area, but other areas are more urgent.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

- A. There are insufficient, fully staffed and licensed, accredited facilities capable of delivering GMP products in sufficient numbers for phase 2 trials, let alone phase 3. The lack of sufficiently qualified and experienced staff is probably more critical than the lack of physical space, though both are an issue.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

- A. Improved application of existing regulation, increase funding to HEI's, expand GMP facilities in critical centres (many already exist but they are not where the research / patients are in many cases. Many are within the NHSBT network which is ill suited to early phase trial work where flexibility of process is needed while products develop. NHSBT will have a significant role to play in this field when products are fully developed and need routine production processes which are well controlled and reproducible), train more staff in all parts of this field.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

- A. Where they are more stringent, e.g. some aspects of the FDA, they should benefit UK; where they are more facilitatory, e.g. South Korea and non-EU Europe, they are attracting the sorts of trials that we would like here.

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

- A. No.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

- A. Good question. There should be a website/phone line and information campaign such that people considering overseas access to treatments can obtain expert, balanced UK opinion on the known safety and outcomes of the treatments they are considering in these centres. Some may be fine (e.g. retinal stem cells in California), and others not (e.g. unregulated clinics in Russia and Mexico). The recent re-emergence of the discredited therapy of subdural injection of bone marrow derived stem cells for treatment of a variety of neurological diseases in the Lebanon (with cell processing being conducted under HTA licence in Uxbridge, UK) is a case in point. The clinic originally operated in Germany but, after a series of well publicised deaths, was shut down. Distressingly, it has now re-opened in the Lebanon and attracts patients for whom no conventional treatment exists.

20 September 2012

Arthritis Research – Written evidence

1. Arthritis Research UK welcomes the opportunity to respond to the House of Lords Committee on Science and Technology Inquiry on Regenerative Medicine.¹⁴ Through the examples in this submission we provide a brief overview of our charity's involvement in this area, and views of some of the researchers we support. We would be pleased to expand on the points below, and to provide further information to the Committee as oral evidence.
2. Arthritis is the UK's fourth largest medical research charity. Our vision is 'a future free from arthritis'. Our remit includes arthritis and musculoskeletal conditions, which are disorders of the joints, bones and muscles – including back pain – along with rarer systemic autoimmune diseases such as lupus. Together, these conditions affect around ten million people across the UK and account for the fourth largest NHS programme budget spend of £5 billion in England.¹⁵ Arthritis is the biggest cause of pain and disability in the UK and each year 20% of the general population consult with their GP about a musculoskeletal condition.¹⁶ As a charity we fund research, provide information to patients and educational resources for healthcare professionals.
3. Our research strategy includes the goal that by 2020, working with our partners, we will 'Be at the forefront of international efforts to harness the potential of stem cells'. More specifically, the charity will encourage 'a well developed programme of research in the UK with the necessary expertise, investment and infrastructure to carry out internationally competitive research aimed at using the body's own cells to replace worn out joints in disorders such as osteoarthritis'.¹⁷
4. Osteoarthritis is the most common type of arthritis, affecting 8 million people nationwide. There are, for example, over 5.5 million people in the UK with painful knee osteoarthritis, and as age and obesity are risk factors for knee osteoarthritis the prevalence of this condition is predicted to increase. Whilst healthy joints move painlessly due to an even layer of smooth cartilage coating the ends of bones, in osteoarthritis cartilage becomes thinned and pitted, and can wear away completely, causing severe pain and disability.¹⁸

Regenerative medicine in musculoskeletal conditions

5. 'Regenerative medicine' refers to the use of methods to replace or regenerate human cells, tissues or organs to restore or establish normal function – including cell therapies, tissue engineering, gene therapy and biomedical engineering techniques.¹⁹

¹⁴ House of Lords Committee on Science and Technology (July 2012) Inquiry on Regenerative Medicine: Call for evidence

¹⁵ Department of Health (December 2011). England level programme budgeting data 2010-11.

¹⁶ Arthritis Research UK National Primary Care Centre, Keele University (October 2009). Musculoskeletal Matters.

¹⁷ Arthritis Research UK (December 2010). Working in partnership towards a future free from arthritis, Our research strategy 2010-2015.

¹⁸ For information about osteoarthritis see <http://www.arthritisresearchuk.org/arthritis-information/conditions/osteoarthritis.aspx>

¹⁹ House of Lords Select Committee on Science and Technology (July 2012) Inquiry on Regenerative Medicine: Call for evidence

6. In the musculoskeletal field, there are a number of disorders which are the result of trauma and degeneration where engineering replacement tissues has the potential for substantial benefit. In addition to osteoarthritis, there are unsolved problems including sports injuries to tendons, ligaments and cartilage, as well as fractures with delayed healing. Unlike other areas of medicine, tissue engineering requires that the new tissues have the same mechanical (structural) characteristics properties as well as the functional properties of the original tissue.
7. Approaches to restore damaged musculoskeletal tissues are dependent on the development of effective solutions involving tissue 'scaffolds', biological factors and cellular strategies. This brings unique scientific and regulatory challenges to regenerative medicine in musculoskeletal conditions. Whilst some new therapies in development are based on differentiated stem cells, it is also important to recognise that other cell types may also be used.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

8. The use of regenerative medicine for musculoskeletal conditions is an area in which the UK has considerable expertise, and there are examples in this field in which the UK has established an international lead. For example, the identification and characterisation of a population of cartilage progenitor cells in human articular cartilage was achieved in the UK.²⁰ As far as we are aware, the Arthritis Research UK Tissue Engineering Centre is one of the first initiatives in the world dedicated to the development of regenerative medicine approaches, including adult stem cell engineering, for disorders such as large joint osteoarthritis. It has the ultimate goal of developing interventions which can be delivered widely and affordably within the NHS and can either reduce or postpone the need for surgery such as joint replacement.²¹

Where does the UK have strengths and weaknesses in the field?

9. Progress in regenerative medicine requires multidisciplinary expertise, including the involvement of basic scientists, engineers and clinicians. Such cross-disciplinary working, and the ability to involve teams in both hospital and academic settings, can be a UK strength. The Arthritis Research UK Tissue Engineering Centre is a multi-site centre of excellence which brings together experts including cell biologists, material engineers and orthopaedic surgeons, working collaboratively to deliver clear research themes.
10. Academic clinicians play a key role in the translation of scientific discovery through delivery to the patient via the clinic. It is important to ensure that the UK develops and supports sufficient academic clinicians in this field to enable translation of research and subsequent implementation within the health service.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

²⁰ Williams et al. (2010) Identification and Clonal Characterisation of a Progenitor Cell Sub-Population in Normal Human Articular Cartilage. PLoS ONE 5(10): e13246. doi:10.1371/journal.pone.0013246

²¹ <http://www.arthritisresearchuk.org/research/our-centres-of-excellence/tissue-engineering-centre.aspx>

11. In the UK there is a strong involvement of academia, charities and the NHS in the field of regenerative medicine, with a range of funders supporting key national facilities.²² As a charity, Arthritis Research UK funds a range of pre-clinical and clinical research in regenerative medicine. The following sections provide examples of the research we support.

12. *Arthritis Research UK Tissue Engineering Centre*

Launched in October 2011, the Arthritis Research UK Tissue Engineering Centre is led by Newcastle University and is based at four sites across the UK: Newcastle University, the University of Aberdeen, Keele University/the Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, and the University of York. It brings together leading clinicians, engineers and biologists from research and clinical groups. The Centre aims to regenerate bone and cartilage by using patients' own stem cells to repair the joint damage caused by osteoarthritis. It is funded by a core grant of £2.5 million over five years from Arthritis Research UK with a further £3.4 million pledged by the four participating universities.²³ This is also an example of the role that funding from an independent charity can play in supporting cross-institutional collaboration.

13. *Clinical Trials*

Arthritis Research UK supports work including:

- REACT: Arthritis Research UK has funded clinical research to review and follow a cohort of patients treated for cartilage defects with autologous chondrocyte implantation (implantation of the patient's own cartilage cells) with a follow-up of up to 15 years. There is much to learn from this cohort, including for example, the factors which predict the 80% of patients who benefit from such approaches, and factors which associate with those who do not report improvement.²⁴
- ASCOT: This future prospective randomised trial will compare chondrocyte and mesenchymal stem cell treatment for early osteoarthritis of the knee. A third group in the trial will be treated using both cell types, as there is evidence that the combination may be better than either cell type alone.

14. *Project Grants and Fellowships*

Arthritis Research UK supports a number of Project Grants and Strategic Fellowships which use regenerative medicine approaches to address a range of different research questions, for example:

- Research to address important questions which will help in the development of a stem cell therapy for the treatment of intervertebral disc degeneration, one of the major causes of low back pain.^{25,26}
- Research to determine how stem cells regenerate cartilage in osteoarthritis.²⁷

²² Examples include the Tissue Engineering and Regenerative Medicine Centre (TERM) at Imperial College London, and the Wellcome Trust-Medical Research Cambridge Stem Cell Institute.

²³ <http://www.arthritisresearchuk.org/research/our-centres-of-excellence/tissue-engineering-centre.aspx>

²⁴ <http://www.arthritisresearchuk.org/news/press-releases/2010/july/new-cell-therapy-treatment-for-osteoarthritis-to-be-trialled-in-uk-first.aspx>

²⁵ <http://www.arthritisresearchuk.org/news/press-releases/2009/july/scientists-edge-closer-to-exciting-new-back-pain-treatment-using-stem-cells.aspx>

²⁶ <http://www.arthritisresearchuk.org/research/grant-tracker-items/2012/development-of-a-stem-cell-therapy-for-treatment-of-intervertebral-disc-degeneration.aspx>

²⁷ <http://www.arthritisresearchuk.org/news/press-releases/2010/may/scientists-in-new-stem-cell-research-that-could-prevent-osteoarthritis.aspx>

- Research to explore whether embryonic stem cells can generate the cells needed to repair joint cartilage.²⁸

Application of the science

What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally?

15. The majority of applications in musculoskeletal health have been for cartilage repair, with some work focusing on bone regeneration. Research to restore cartilage has also led to progress in other fields. For example, Arthritis Research UK Professor of Rheumatology and Tissue Engineering at the University of Bristol, Professor Anthony Hollander, developed techniques to form human cartilage from a patient's own stem cells. This technology contributed to an international collaboration to grow the first trachea (wind-pipe) for transplant from a patient's own cells.²⁹

What potential does regenerative medicine hold to treat disease in the next 5-10 years?

16. As in many biomedical research fields, it is important to recognise that the timescales between initial research discoveries and the delivery and take up of health interventions are often long (up to decades), variable and difficult to predict.
17. However, in the next 5-10 years one of the aims of research funded by Arthritis Research UK is to develop the capability to treat the joint damage caused by osteoarthritis at an earlier stage. If successful, it is hoped that these techniques slow down the progression of the disease and therefore delay the requirement for joint replacement. Such approaches are needed because, although joint replacements are often highly successful, joint replacements can, despite variations in design, fail over the lifetime of the younger active patient. Techniques that can delay the first joint replacement may prevent joint revision in later life – which can be costly and carry significant risks.
18. The future work of the Arthritis Research UK Centre for Sports and Exercise Injuries will also encourage the development of cellular therapies for a range of musculoskeletal conditions.³⁰ For example, rupture of the cruciate ligament surrounding the knee is a common sporting injury which can lead to osteoarthritis. Current therapy to treat cruciate ligament damage relies on a surgical approach. However, we anticipate the development of innovative and more effective approaches which may involve cellular, or combined cellular and surgical, techniques. Future collaboration between Arthritis Research UK's centres of excellence will facilitate this work.

Barriers to translation

[Are actions sufficient] ... to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation?

²⁸ <http://www.arthritisresearchuk.org/news/press-releases/2009/july/scientists-use-stem-cells-to-treat-osteoarthritis.aspx>

²⁹ Macchiarini et al (2008) Lancet. 13;372(9655):2023-30.

³⁰ <http://www.arthritisresearchuk.org/news/press-releases/2011/july/national-centre-for-sports-injuries.aspx>

19. The cost and complexity of clinical trials governance in regenerative medicine is significant, and due to the evolving nature of the process can be difficult to predict in terms of time and money. There is a need for effective partnerships between the NHS and research groups for clinical trial delivery. On-going challenges include:
- The complexity of the regulatory environment for therapeutic products which involve both cellular material and non-biological components (scaffolds).
 - A lack of flexibility in regulation, particularly for pilot studies.
 - Complexity of licensing for cell therapy products.
 - Cost of license applications and inspections is great and difficult to predict accurately.
 - A lack of Qualified Persons with cellular therapy expertise to assist the process of approval by the Medicine and Healthcare products Regulatory Agency (MHRA), and on-going governance of cell production. Training in quality control of cell production could usefully include cell biologists as well as pharmacists. A current European Union Framework Programme 7 project 'Academic GMP' aims to address some of these points.³¹
 - European regulation of advanced therapy medicinal products (ATMPs). Current EU legislation hinders development of novel cellular therapies due to the need for expensive good manufacturing practice (GMP) compliant processes which are inflexible and based on drug therapies.
20. Additional barriers to translation include:
- Difficulty in securing agreement for the allocation of the 'excess treatment costs' component of research costs associated with clinical trials.
 - Although risk can be minimised, the risks of application of new treatment may not be known until a trial takes place. Researchers are personally responsible for the accuracy of data collection and analysis and may not have extensive resources to ensure this accuracy. Fear of litigation can therefore act as a barrier to translation

Barriers to commercialisation

What business models are most appropriate to support the development of regenerative treatments?

21. Models of working which support collaboration between academic groups are important, and charity funding can be an important mechanism in bringing groups together in this way. Many cellular therapies are developed and pioneered in academia. It is important that investment from the pharmaceutical industry complements charity, NHS and Government support - closer integration of the sector, bringing a two-way model between academic and the industry sector would be beneficial. Additional means of supporting the sector include:
- Pharmaceutical company investment into earlier stages of research.
 - Initiatives to bring together infrastructure and academia in a 'critical mass'.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

³¹ <http://www.academic-gmp.eu/>

22. In relation to regenerative medicine approaches in musculoskeletal health, there is strong support for the advancement of techniques involving cell therapy related operations in countries including Belgium and the Netherlands. There may be opportunity to learn from the work in these countries.

Contact details

23. We are very grateful to the following for their contributions to this response:
- Professor Andrew McCaskie, Professor of Orthopaedic Surgery, Newcastle University
 - Dr Sally Roberts, Spinal Studies & ISTM, Keele University
 - Professor Anne Dickinson, Professor of Orthopaedic Surgery, Keele University
 - Professor James Richardson, Professor of Orthopaedic Surgery, Keele University

21 September 2012

Association of British Neurologists (ABN) – Written evidence

The Association of British Neurologists welcomes this invitation from the House of Lords Select Committee on Science and Technology to submit a response to the Committee's inquiry into regenerative medicine.

The Association of British Neurologists (ABN) is the professional voice of neurologists in the UK with over 1300 members. With almost 10% of these members living and working overseas, the ABN is also a body of international standing in the field of neurology. A registered charity, our objectives are encapsulated in our mission statement: *'to promote the delivery of the best care for people with neurological conditions, by providing and supporting excellent research and education and championing equitable and excellent standards of care.'*

As the Select Committee's guidance advises, we will restrict our comments to the points listed in the *Call for Evidence*.

We are happy to accept the Committee's helpful definition of "regenerative medicine" : -

'the term "regenerative medicine" is used to refer to any methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function. This includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, as well as the more traditional therapies of pharmaceuticals, biologics and devices. The inquiry will also extend to cell therapies that have applications in other areas of medicine, for example, the use of cell therapies to control immune responses to conditions such as paediatric steroid resistant GvHD I, or the use of stem cells for drug screening.'

The Association of British Neurologists does not consider itself competent to comment on the state of regenerative medicine across the whole spectrum of clinical disease; rather, our expertise lies within the specialist area of disorders of the nervous system. We will broadly therefore confine our comments to **Regenerative Neurology**.

Within this area, however, we would wish to emphasise two key points.

The first is that neurological diseases have a major impact in society, and are amongst the most difficult and challenging disorders to treat in medicine. Damage to the nervous system, whether occurring through such diverse process as progressive neurodegeneration as in **Parkinson's disease, multiple sclerosis, motor neurone disease, or Alzheimer's** (to name just a few), trauma (**head and spinal cord injury**), or disorders of the circulation (**stroke**), share two core features: they commonly cause major individual and societal morbidity and, currently, they are completely incurable. **Regenerative medicine is widely seen as having the potential to bring about a sea change in the medical treatment of all these disorders, with dramatically positive implications for society and for healthcare.**

The second key point is that, at present, the UK would by any serious authority be ranked extremely highly in the international scientific field of regenerative neurology; we are currently at the forefront of translational medicine in this sphere. Pioneering reparative or regenerative neurological clinical trials – in some instances, the first in the world – in Parkinson's disease, multiple sclerosis and stroke have all been completed (or are currently underway) in the UK, in the main designed, conducted and published by British academic neurologists working out of regional neuroscience centres in England, Scotland and Wales. The UK is also and to no lesser an extent generally agreed to have played (and continue to

play) a leading role in the laboratory-based pre-clinical science underpinning these early phase clinical trials. We should stress that this pre-eminent position is held not just in the area of stem cells but in gene therapy (perhaps particularly relating to mitochondrial disease), growth factor treatment (in Parkinson's disease, for example), and in other aspects of restorative medicine.

This combination – common diseases which are incurable and which have a major societal impact, and the UK's world-leading position in regenerative neurology – offers, we submit, hugely important opportunities : it is crucially important that the position is maintained and enhanced. We suggest the UK government can play a major role in promoting British regenerative neurology, in facilitating strategic and targeted investment, and in helping to remove the principal barriers to this vital translational research.

Application of the science

The UK leads the world in translating laboratory-based regenerative *neuroscience* into patient-based regenerative *neurology*. Whilst it may be invidious to pick out examples, the Committee clearly requires firm evidence: some illustrations of internationally leading translational research achievements in regenerative neurology in the UK might include an ongoing clinical trial in acute stroke in Glasgow³²; the first regulated trials of reparative stem cell therapy in multiple sclerosis in Bristol and also in Edinburgh, London and Cambridge³³; European leadership from Cambridge in the development of stem cell therapies for Parkinson's disease³⁴, at Oxford, Cardiff and London in the preclinical research underpinning such therapies, and in clinically testing growth factor therapies for Parkinson's disease in Bristol³⁵; world class research into gene therapy for mitochondrial disease in Newcastle³⁶. Many other examples might be added. This list, incomplete as it is, also might help answer the committee's questions concerning the likely time frame clinical benefit: in regenerative neurology, translation to early phase clinical trials has already commenced, holding out a realistic prospect of clinically meaningful benefit within a 5-10 year time frame.

Barriers to continued translation

There are three sets of barriers to clinical translation: the UK and EU regulatory systems, finances, and plant.

Regulation is a difficult topic. Plainly it is vital that vulnerable patients are protected; that desperate individuals with incurable neurological diseases are not exploited; and that the potential risks associated with injecting or implanting certain types of stem cell (or bioactive molecule) – which include tumour formation, infection (itself including prion infection causing diseases such as Creutzfeldt-Jakob) and rejection, are as far as is possible, eradicated. But the current regulatory framework for even more conventional (pharmacological) clinical trials in the UK is widely recognised as being excessively burdensome and inhibitory, representing a serious disincentive to clinically orientated research – while that for innovative cell therapy trials is even more daunting. To take some illustrations: a study by Warwick Business School reported that, over the last decade, UK

³² <http://clinicaltrials.gov/ct2/show/NCT01151124>

³³ www.nature.com/clpt/journal/vaop/ncurrent/abs/clpt201044a.html;

[http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422\(11\)70305-2/fulltext](http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422(11)70305-2/fulltext)

³⁴ <http://www.transeuro.org.uk/>

³⁵ <http://www.nature.com/nm/journal/v9/n5/full/nm850.html>

³⁶ <http://www.wellcome.ac.uk/News/Media-office/Press-releases/2012/WTVM054145.htm>

clinicians conducting trials found the average time to prepare, submit and receive an outcome for a regulatory application is now 114 days³⁷. The Association of Medical Research Charities has reported that between 2000 and 2006 the proportion of the world's clinical trials conducted in the UK fell from 6% to 2%, in part because of more attractive regulation and incentives elsewhere³⁸. A better, faster, and more streamlined regulatory framework, perhaps specifically designed for regenerative trials aiming to treat otherwise incurable neurological conditions, that remains capable of fully protecting patients yet does not positively inhibit sound clinical studies, is urgently required.

Funding for translational regenerative neurology studies currently stems from the UK Research Councils, from the medical charities, and partly also from industry. The EU is also a significant provider. The recognised excellence in the UK within this specialist area of clinical science has guaranteed reasonable levels of funding from all these sources thus far, but the trend in more conventional clinical trials for the UK to lose out to overseas centres – largely because of regulatory difficulties – will surely similarly soon impact on commercial regenerative medicine studies. It is also the case that opportunities for patenting and commercial profit derived from many types of cell therapy (particularly including autologous cells) can be extremely limited, and the non-commercial funding bodies must be sensitive to this and respond accordingly if future patient benefits are to be realised.

Finally, the delivery of almost all forms of cell therapy requires dedicated **plant** that is not widely available currently in the UK. Facilities for cell harvesting, preparation and delivery are needed and, naturally, units with sterile, pathogen-free environments are not inexpensive.

As a further point, however, it should be noted that the maintenance and extension of the UK leadership in regenerative neurology not only offers serious potential benefits for UK patients and society, together with the reputational advantages of scientific excellence in the area (and the many important indirect subsidiary benefits this brings – inward investment, scientific expertise migrating to the UK, etc). There has also, very recently, been some publicly aired consideration of the potential commercial and other benefits of a proposed overseas 'marketing' by the NHS of some specialist areas of excellence in clinical care. Regenerative cellular and molecular therapy for neurological disease represents an enormously exciting area where such a strategy could prove powerfully successful. Paradoxically, the silver lining of the notorious regulatory framework in the UK is that it offers significant attractions to both doctors and patients outside the UK who struggle to identify safe and well-regulated suppliers from the rapidly increasing number of highly dubious for-profit 'stem cell clinics' currently advertising their untested products at exorbitant prices from questionable facilities in central America, the Far East and Russia. They will have substantially greater confidence in cell and other regenerative neurology treatments delivered with a UK badge.

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³⁷ http://www2.warwick.ac.uk/fac/soc/wbs/research/ikon/research/clinicaltrials/managing_clinical_research_in_the_uk_-_summary_of_findings_-_swan_robertson_evans_-_ikon_group_dec2009.pdf

³⁸ <http://www.acmedsci.ac.uk/index.php?pid=99&puid=172>

Association of the British Pharmaceutical Industry (ABPI) – Written evidence

1. The ABPI welcomes the opportunity to respond to the House of Lords inquiry into Regenerative Medicine. Regenerative Medicine (RM) is a very broad field as indicated in the Call for Evidence and, in line with this definition, also includes stem cell biology, *in vitro* screening, protein and cellular therapeutics. This brief submission highlights some of the many issues that industry faces in translating RM into patient benefit.

2. The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of bioscience in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

3. The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

4. Some of the key challenges in developing innovative new medicines include:

- The costs and risks of bringing new medicines to the market are increasingly high;
- Recognising, valuing and rewarding innovation appropriately are critical to industry's ability to sustain long term investment in R&D that will deliver new medicines in the future;
- As the pharmaceutical industry continues to evolve there is an increasing need for partnerships between industry, academia, healthcare providers, regulators, and medical charities if we are to deliver innovative medicines to patients and improve health outcomes.

Key recommendations:

- **Government must ensure that there continues to be a strong ethical and governance framework of evidence-based permissive policies that support this rapidly evolving area of research.**
- **Sustained support for a unified UK strategy in developing RM products, for example, through continuity of funding beyond the initial five years for national platforms such as the cross -Research Council RM Platform and the Technology Strategy Board (TSB) Cell Therapy Catapult.**
- **RM may require new and different aspects of value to be taken into account during their evaluation by Health Technology Appraisal (HTA) bodies and payers, and therefore different models may be required to assess value. Early dialogue between stakeholders including government, regulators, HTA bodies, academia and industry should be established to progress these discussions and work to develop an evaluation framework suitable for RM products in focussed disease areas.**

The research base

5. Regenerative Medicine (RM) is a discipline that has the potential to offer treatments in areas of unmet medical need, including conditions such as diabetes, Parkinson's disease, stroke, spinal cord injury and heart disease and thus promises to have a significant role in improving patient care in the future. The UK is a leading force in this area and the underpinning research base is strong as is the robust ethics and governance framework. The UK is therefore well placed to capitalise on this strength and translate ideas from the research base into clinical outcomes and economic benefit. There are, however, a number of key challenges that must be overcome if we are to succeed in delivering positive health outcomes for patients.

6. Through public funding the UK has established a number of excellent research networks, research centres and associated infrastructure that have promoted research into RM and which help secure a strong foundation in RM. These include the cross-Research Council RM Platform launched earlier this year - a national programme in RM funded by MRC, BBSRC, EPSRC (£25m over five years).³⁹ Research centres of excellence that include two MRC funded centres – the Cambridge MRC Centre for stem cell biology and RM⁴⁰ and the Edinburgh centre for RM.⁴¹ Enabling infrastructure includes the UK Stem Cell Bank,⁴² and the £50m Technology Strategy Board Cell Therapy Catapult Centre.⁴³ The national research network, the UK National Stem Cell Network (UKNSCN) that coordinated the various regional networks (eg the Scottish Stem Cell Network (SSCN), London Regenerative Medicine Network (LRMN)) – will close and be incorporated into the RM Platform. The positive research environment has leveraged pharmaceutical industry participation. Stem Cells for Safer Medicines – a public-private partnership of five government departments and three pharmaceutical companies⁴⁴ is one such example.

7. Basic biomedical research remains essential to aid our understanding of cell differentiation and ageing, disease and regenerative mechanisms, cellular reprogramming and the extra cellular environment. Advances in bioengineering, bioinformatics, predictive modelling and systems biology will also continue to be important. As the field is broad the industry would welcome the opportunity to engage in shaping the strategic direction of focussed programme(s) of research in key disease and/or therapy areas.

8. In addition, as in all emerging areas of science, it is vitally important that patients clearly understand the risks and benefits of cell based therapies. Activity by initiatives such as Sciencewise⁴⁵ and organisations such as the International Society for Stem Cell Research⁴⁶ are valuable in facilitating public engagement with the issues, and the latter in helping and supporting patients in making informed decisions.

9. Of the therapeutic areas of potential application it remains important that funding be prioritised for fundamental and translational research into understanding areas of major unmet medical need including diabetes, cardiovascular disease, stroke, dementia and respiratory disease.

³⁹ <http://www.mrc.ac.uk/Fundingopportunities/Calls/UKRMP/MRC008535>

⁴⁰ <http://www.mrc.ac.uk/Ourresearch/Unitscentresinstitutes/UnitCentreDetails/MRC002080>

⁴¹ <http://www.crm.ed.ac.uk/>

⁴² <http://www.ukstemcellbank.org.uk/>

⁴³ <http://catapult.innovateuk.org/cell-therapy>

⁴⁴ <http://www.sc4sm.org/>

⁴⁵ <http://www.sciencewise-erc.org.uk>

⁴⁶ <http://www.isscr.org>

Disease Areas

I0. A number of disease areas merit in depth attention due to unmet medical need, lack of current chemical or biological therapy or are areas in which the basic science is promising potential treatment.

I1. Diabetic retinopathy is now the most common cause of vision impairment among those of working age in Western society. The majority of patients with type I diabetes will develop retinopathy and about 20-30% will become blind.

I2. Cardiac regeneration - Currently the US has very strong academic based research and is leading in cell based therapies as well as in the discovery of therapeutic molecules to enhance endogenous regenerative capacity of the heart. The UK is continuing to strengthen its research efforts in cardiac regeneration. In order to further strengthen cardiac regeneration research and R&D leading to new innovative medicines it will be important to develop and validate clinical biomarkers for regeneration; predictive models for clinical efficacy as well as patient safety.

I3. Pancreatic regeneration - Islet transplantation represents proof of concept for cell based diabetes therapies but supply issues mean this is not realistic for most patients.

Recommendations to sustain scientific excellence

- The UK must continue to ensure that there is a strong framework of permissive policies that support this rapidly evolving area of research.
- Continuity of funding for the cross Research Council RM Platform beyond five years to demonstrate support for the unified UK strategy in developing RM products
- Establish research infrastructure for clusters of academic clinical centres focused around or adjacent to the appropriate NIHR Biomedical Research Centres
- Consider establishing additional Innovation Knowledge Centres (in addition to the current one in Medical Technology) to assist the academic centres to become more competitive, business oriented, multidisciplinary and aligned with the translational needs of the RM sector
- Establish an, international programme of cross-sector knowledge exchange composed of, for example, professorial travelling scholarships, secondments and sabbaticals.

Application of the science

I4. RM encompasses a variety of potential therapeutic options including stimulation of repair mechanisms, cell transplantation, cell engineering and use of acellular products. However, the range of different products (for example autologous as well as allogeneic products) poses different safety as well as unique manufacturing barriers.

I5. RM also draws on resource and expertise from other areas of science, particularly the physical sciences and engineering in order to be delivered and utilised. New diagnostic and imaging techniques, tissue and cellular scaffolds, matrices and manufacturing technologies will all be essential.

I6. Stem cells have potential utility in *in vitro* efficacy testing and safety screening for new drugs. A number of different sources of stem cells (e.g. embryonic, induced pluripotent, adult stem cells) are being investigated for utility in drug safety and efficacy assays. Use in

safety assessment is the focus of several industry-academic consortia including, for example, the private-public funded partnership Stem Cells for Safer Medicines (SC4SM) and an EU Innovative Medicines Initiative project. At present no cell line exists that can fully mimic human hepatocytes and relying on fresh human tissue is a challenge. Consequently there is a need for production of viable hepatocytes. SC4SM are seeking to differentiate stem cells into hepatocyte-like cells on a sufficiently large scale to be used in drug safety and efficacy screening. The impact of which would be to reduce the costs and length of time currently experienced in early stage drug screening. Others have focused on cardiomyocytes (heart cells) and pancreatic cells for drug screening.

Barriers to translation

17. Challenges and opportunities exist across the discovery, translational science and clinical development and health delivery continuum. While clinical development of small molecules and biological products are reasonably well characterised and understood, development of regenerative cell therapies requires a different product development approach. There is therefore a pressing need for connectivity between communities engaged in early stage product development, clinical delivery and evaluation, and manufacturing, as well as with regulatory agencies to explore and understand the complex nature of the clinical development requirements for cell therapies. Shaping a clinical development road map / UK framework for different therapy options to ensure optimal trial design, product safety and efficacy would be helpful. Clinical trial design for evaluating regenerative cell therapies pose particular challenges and requires focused attention and development. For example, selection of the clinical indication, appropriate patient population and long-term follow up will require careful consideration and definition. Despite creation of the UK Stem Cell Tool Kit, uncertainty remains in both academia and industry on the appropriate regulatory path, particularly where RM extends beyond stem cells. For example, the inherent individuality and uniqueness of products in some areas of RM may require a case-by-case approach in the identification of risk and related mitigation. Considerations of appropriate patient number and requirement for placebo-controlled trials may need to be re-examined for RM products across all phases of clinical development.

- **Recommendation:** Regulators to hold joint workshops, for academia and industry, on the regulatory framework for Advanced Therapy Medicinal Products (ATMP) to aid a clear understanding of principles
- **Recommendation:** Research funders and regulators to establish a clinical development road map, facilitated by initial knowledge exchange between experienced developers, based on proposed best practice to gain marketing approval
- **Recommendation:** Regulators to engage with industrial experts in the drafting of future regulatory guidelines in RM, including dialogue on the one-size-fits-all limitations/relevancy in RM
- **Recommendation:** Regulators in Europe to strive to improve the process of Marketing Authorisation Application for small and medium enterprises (SMEs)

18. Despite significant public investment in RM, key areas of funding gaps remain both in key translational stages, as well as key disease areas. The field is now sufficiently mature to warrant a greater share of funding in early stage and Proof of Concept (POC) clinical studies. This is critical to moving translation forward given the significant gap in funding of POC clinical studies which are necessary to gain further investment and business development by large companies.

19. As the sector has been dominated by many academic and small biotech organisations, there is a lack of critical mass in generating quality evidence of efficacy from clinical POC trials across disease indications due to resource restrictions and lack of funds. To redress this resource imbalance, the activities of the TSB Cell Therapy Catapult should be complemented by a stronger clinical focus on regenerative cell therapies.

20. Clinical research funding should be targeted into disease areas and indications that are optimally suited from a clinical development, health payer reimbursement and commercial viability perspective. We believe that success demonstrated by illustration with a few examples is critical for promoting industry-wide engagement and inclusion of RM approaches. Dialogue with industry consultation including input on feasibility for manufacturing, scalability, transportation and delivery solutions in consideration of commercial viability will be needed.

21. The use of living cells and/or components present significant additional challenges of Chemistry Manufacturing Control, transport and delivery of therapies. For example, cell based therapies that are not personalised have manufacturing challenges concerning the standardization of cell characterisation and performance, whereas personalized cell therapies have demonstrable weaknesses in lack of consistency and functional integrity. Developing a robust supply chain infrastructure for both types of therapy is a priority.

- **Recommendation** : Early dialogue with industry on manufacturing, scalability, transportation and delivery solutions and consideration of “commercial viability” as criteria for translational and applied funding
- **Recommendation**: Establish a separate Research Council/TSB funding stream solely for larger scale POC studies in regenerative cell therapies
- **Recommendation**: Public sector clinical research funding should be focused for maximum impact, to disease areas and indications best suited for clinical development and commercial viability.

22. We recognised that it is challenging to define a regulatory framework without a clear understanding of the types of therapy that will fully emerge RM. However, it is important to ensure that the dialogue continues, as the science and technology develop, and that clear guidance is available as the pipeline of therapies evolves. We anticipate that some pertinent issues will be explored in a Ministerial Industry Strategy Group (MISG) New Technologies Forum in late October⁴⁷ on which we will participate.

Barriers to adoption and commercialisation

23. Manufacture of cell-based medicines will require the use of techniques and technologies that are different to the current established processes for chemical- and biological- based medicines. The UK is well placed as a location for high value or advanced manufacturing because of the strong science and skills base. However, to be successful there needs to be greater collaboration between industry, NHS and academia on RM. Recent announcements of fiscal incentives such as the Patent Box, proposed simplification of R&D tax credits and phased lowering of corporation tax to keep up with global competition will likewise be applicable and beneficial for RM. Additionally for RM, the funding of risk sharing partnerships should be expanded to attract industry and grow a critical mass in the UK.

⁴⁷ <http://www.mhra.gov.uk/Howweregulate/Medicines/MISGNewTechnologiesAdvisoryPanel/Forums/index.htm>

- **Recommendation:** Adoption, by funding bodies, of risk sharing partnerships with industry, e.g. as modelled by Cancer Research UK's Clinical Development Partnership initiative.

24. The value of such innovative medicines must be recognised, innovative treatments that benefit patients must be used by the NHS and appropriately rewarded if companies are to be encouraged to invest upfront in the development of high-risk RM products – given that for chemical- and biological-based medicines, the cost of upfront investment by developers is £1 billion per new medicine.⁴⁸ Further, the potential market(s) is likely to be niche and small, this coupled with the requirement to demonstrate cost effectiveness and positive health technology assessment outcomes will be important decision making factors.

- **Recommendation:** Joint government, HTA, academic and industry identification of indications of high unmet need to justify cell-based therapy, and framework and criteria for marketing authorisation, for example agreement on “significant improved outcomes” definitions for subsequent application during regulatory and reimbursement reviews.
- **Recommendation:** RM may require new and different aspects of value to be taken into account during their evaluation by HTA bodies and payers and different economic models may be required. Early dialogue between stakeholders including government, regulators, HTA bodies and industry should be established to progress these discussions.
- **Recommendation:** Consultation by the National Commissioning Board with the pathfinder Commissioning Groups and with Specialist Commissioning to raise awareness of RM developments and create a set of guidelines for RM developers to optimise prospects for adoption of new treatments
- **Recommendation:** Government/HTA bodies to publish requirements for evaluating RM products early on to allow companies time to design studies with the required end-points, both clinical and economic.

25. Many biopharmaceutical companies are engaged in discovery-stage stem cell projects and some companies are actively investigating tissue regeneration. Most projects are related to safety screening or are focussed on the potential to use small and large molecules to modulate endogenous stem cell fate. Within the cell therapy area investment opportunities are seen as high-risk due to the lack of specific data requirements from regulators, the recent uncertainty in Europe around intellectual property (IP) and the patent landscape, and the associated risk in achieving successful short-term return on investments by SMEs to justify continued cash flow by their investors. These collectively impact on investor sentiment.

26. In order to prepare for these novel therapies it will be important to ensure that a robust health economics framework is developed in parallel. Without this pharmaceutical companies will find it challenging to determine the return on the significant R&D investment.

- **Recommendation** – Stakeholders to work to develop a health economics framework suitable for RM products in focused disease areas.

International comparisons

⁴⁸ Paul S.M. et al. How to improve R&D Productivity: the Pharmaceutical Industry's grand challenge. Nature Reviews Drug Discovery 6, 203-214 (2010)

27. Investment in RM is occurring in a number of countries around the globe. For the UK to stay ahead it will be important to ensure a well networked community, including academia, industry, regulators and manufacturers working together in pursuit of common objectives.

28. The UK legislative framework has helped to build and maintain public support for this field enabling ethical exploration of a broad range of potential regenerative medicine interventions. This is to be commended.

29. It is essential that the current interest and momentum in RM is maintained and enhanced with appropriate level of academic funding and thoughtful consideration of funding gaps. The US state of California has been visionary in its recognition that RM may generate significant cost savings in the future to healthcare systems because of its potentially curative nature and has put considerable funds in this area with the establishment of The California Institute for Regenerative Medicine (CIRM) and a \$3 billion commitment. However, there is also the need for specialist funds available to SMEs and mid-size pharmaceutical companies in the context of a risk-reward framework. In this regard, the CIRM's Strategic Partnerships Awards initiative is a good example. Other countries with strong competitive positions in RM include: South Korea and Israel, while countries like China continue to emerge as potential leaders in Regenerative Medicine.

- **Recommendation:** Implementation by research funders of matching funding schemes for Industry, focussed on enabling POC clinical trials

30. In terms of inventiveness as measured by number of patents, the UK is a world leader in the bioscience sector. However, when comparing expected level of performance in RM patent generation compared to bioscience as a whole, the UK falls below Israel (top of league), Australia, Canada and the US.

31. Israel is punching above its weight in RM with a number of home grown companies and several products in Phase III of development. Government support is highlighted by Israel's Ministry of Health operating a committee for registering cell-based therapeutics.

32. We hope this response is helpful to the Committee in its inquiry into Regenerative Medicine and we would be delighted to give evidence.

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Association of medical Research Charities (AMRC) – Written evidence

1. Key points:

- Medical research charities are an integral part of the UK's medical research sector and are major investors in regenerative medicine.
- Regenerative medicine is generally at the basic stage of research but some charities are funding clinical trials of stem cell therapies. It is important that public investment in a broad science base continues to underpin future innovation.
- Charities invest at all stages of the therapy development pathway and can direct funding to areas that lack investment from other sources. Charities often partner with industry to de-risk their investment into new unproven areas of research such as regenerative medicine.
- Regenerative medicine poses unique challenges to regulation, which must be designed to allow a proportionate and flexible approach as novel therapies are developed.
- The public stands to benefit hugely from regenerative medicine but must be able to have confidence in regulation and should be at the heart of its development. With their link to patients and supporters, charities can facilitate this.
- UK patients are at risk from unproven therapies being offered abroad. Charities are a trusted source of information for patients seeking information and advice.
- For the UK's advantages in regenerative medicine to deliver, the Government must continue to invest in people and research as well as develop a regulatory and commercial environment that promotes research and innovation.

2. The Association of Medical Research Charities (AMRC) is a membership organisation of the leading medical and health research charities in the UK. AMRC has 125 member charities that together invested over £1 billion into UK research in 2011/12, equating to approximately one third of all public expenditure on medical and health research. Our members are focused on benefiting patients and many have strong patient groups allied to them, they are the voice of these patients and of the 11 million members of the public who expressly choose to support medical research through donations every month.⁴⁹
3. We welcome this timely focus on regenerative medicine as a promising field of research for future therapies. AMRC contributed evidence to the BIS/DH report, *Taking stock of regenerative medicine*, which acknowledged that “charities constitute an integral part of the UK's medical research sector and have invested strongly in regenerative

⁴⁹ Charities Aid Foundation/NCVO report (2011) *UK Giving 2011* http://www.ncvo-vol.org.uk/sites/default/files/clickable_UK_Giving_2011.pdf [accessed 2 August 2012]

medicine”⁵⁰, and also the subsequent strategy, launched by the research councils (MRC, EPSRC, BBSRC and ESRC) and the Technology Strategy Board (TSB), to guide UK investment in the field for the next five years.⁵¹ Both documents provide a sound summary of the state of regenerative medicine in the UK today and make recommendations that should be taken forward.

4. We echo the conclusions of these two documents: that the UK should pursue a strategy to support the full spectrum of emerging regenerative technologies, develop the commercial environment to support their development and future-proof regulation so it is not to become a barrier to advances in regenerative medicine. We also agree that the research is generally at an early stage and so fundamental research investment is essential alongside strategies to encourage translation. A joined up approach “from bench to bedside” is required to deliver new therapies to patients as soon as possible. Like the research councils and TSB⁵², charities are addressing the distinct needs of the different stages of the therapy development pathway and should be considered key partners in developing and delivering the UK strategy.

How does the UK rank internationally in regenerative medicine? What are the UK’s strengths and weaknesses in the field? Who are the major funders?

5. Like all fields of science, regenerative medicine is an international endeavour, with most researchers working in collaboration both with UK-based partners and those overseas. A relatively liberal approach to stem cell research and strong science base make the UK an attractive place to conduct research into regenerative medicine.
6. From 2005-2009, 29 AMRC members invested a combined total of almost £38 million into regenerative medicine. In the years 2005-2008 investment was on average £6 million per year, but it significantly increased in 2009 to £13 million.⁵³
7. Within the AMRC membership, the charities investing greatest in regenerative medicine are those dedicated to diseases for which it holds the greatest potential for new treatments. For example, the nature of early stage multiple sclerosis – that it is caused by a defective immune system potentially amenable to bone marrow-derived stem cell treatments – means that significant advances have been made in the attempt to develop treatments using regenerative medicine. The MS Society is exceptionally active in the field as a result. The UK is a leader in stem cell research in MS and a majority of stem cell trials are either led by or involve a UK-based researcher. Other countries that are playing a major role in stem cell research for MS include Italy, Canada and Australia, although the US is catching up.

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| 8. CASE STUDY: The MS Society is currently co-funding with the UK Stem Cell Foundation an early stage clinical trial of a regenerative therapy. It is funding the UK arm |
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⁵⁰ BIS/DH (2011) *Taking stock of regenerative medicine* <http://www.bis.gov.uk/assets/biscore/innovation/docs/t/11-1056-taking-stock-of-regenerative-medicine.pdf> [accessed 2 August 2012]

⁵¹ BBSRC, EPSRC, ESRC, MRC, Technology Strategy Board (2011), *A Strategy for UK Regenerative Medicine*, <http://www.mrc.ac.uk/Newspublications/News/MRC008536> [accessed 2 August 2012]

⁵² *Ibid.*

⁵³ AMRC member research grant database. Search terms “stem cell” OR “tissue engineering” OR “transplant” OR “regeneration” were used to extract relevant grants and manually checked for false positives. These figures do not include capital grants or infrastructure projects.

of an international phase 2 trial of patient-derived mesenchymal stem cells (MSCs) with the aim of limiting damage to, and stimulating the repair of, myelin. The charity is also funding a phase 1b/2a clinical trial of a drug with the potential to stimulate endogenous brain precursor cells to repair myelin damage caused by MS. The charity is also investing in basic research in regenerative medicine.

9. **CASE STUDY:** The British Heart Foundation's latest fundraising campaign for research, Mending Broken Hearts, focuses on raising £50 million to fund research into regenerative medicine. Their ambition is to be "pioneers in regenerative medicine". £1 million raised in this appeal was invested in the Scottish Centre for Regenerative Medicine (SCRM), which opened in May 2012 and will carry out cutting edge stem cell research for a number of conditions and be home to world-leading experts. BHF aim to establish one or two further centres for cardiovascular regenerative medicine in Autumn 2013 and are seeking outline bids for awards to support them. A total of £6 million will be available for this initiative, to be invested to complement funding provided by the research councils, for a four-year funding period.

10. **CASE STUDY:** Regenerative medicine is also showing huge potential in the field of ophthalmology. Fight for Sight, the UK's largest charity funding medical research into sight loss and eye disease, is currently funding 11 projects, totalling nearly £2.8 million, in this area. The charity does not have funding rounds that are specifically targeted at regenerative medicine but as it is an active area of research at universities and hospitals throughout the UK it receives, as part of its annual grants round, numerous world class applications investigating regenerative medicine for the treatment of many eye diseases.

11. Basic research in other fields can also contribute to the development of regenerative medicine. The Wellcome Trust and Cancer Research UK are major investors in basic research investigating stem cell biology and developmental biology. This develops and maintains expertise and resources in the UK, creating a fertile environment from which advances in regenerative medicine can grow. Funding from BBSRC and MRC also has the same effect by strengthening the science base. This is a case for continuing funding for basic research.

Is the science being translated into practical applications? What treatments are available on the NHS and privately? What is the potential for regenerative medicine in the next 5-10 years?

12. The field of regenerative medicine is generally at an early stage and the majority of charity funding is for basic research, however, significant progress is being made in translating discoveries into treatments (see also paragraph 8).
13. Charities fund research at all stages of the therapy development pathway, with many targeting funding to stages that are not attracting investment from other public or private sources. A number of our members also have close industry ties and actively seek to establish collaborations or agreements with companies to commercialise promising technologies.

14. **CASE STUDY:** A current research project funded by Restore, the burn and wound research charity, is attempting to improve readily available commercial skin substitutes,

such as Integra®, by promoting growth of blood vessels to aid integration of the artificial product with the patient's own skin. This commercial application stems from fundamental research, also funded by Restore, which determined the conditions necessary to form new blood vessels in the laboratory from endothelial progenitor cells taken from new burns patients.

15. **CASE STUDY:** Professor Anthony Hollander, Arthritis Research UK Professor of Rheumatology and Tissue Engineering at the University of Bristol, developed techniques to form human cartilage from a patient's own stem cells. The technology contributed to an international collaboration to grow from a patient's own cells, the first trachea for transplant. Claudia Castillo received the world's first lab-grown trachea transplant at the Hospital Clínic of Barcelona in 2008. There have been numerous successful transplants since, including the first for a child, performed at Great Ormond Street Hospital.

16. **CASE STUDY:** Regenerative medicine for the restoration of vision is at a notably advanced stage. The first embryonic stem cell treatment for age-related macular degeneration (AMD) and the related condition Stargardt's Disease, has already started trials in the UK. The therapy was developed by Advanced Cell Therapy, a US company that got regulatory approval to conduct the trial at London's Moorfields Eye Hospital. The company is also running concurrent trials at several sites in the US.

What regulatory barriers and challenges to innovation are there in this interdisciplinary field? How can these be overcome?

17. Clinical trials of cell therapies pose unique challenges to classic drug trial designs. They have a high level of uncertainty as there are particular difficulties in predicting potency for cells which, unlike drugs, have the potential to multiply. Furthermore, they tend to be stratified – focused on particular forms of a disease – meaning they affect a small population, making it difficult to recruit the numbers of participants required for traditional trials. (see also paragraph 29)
18. More adaptive licensing approaches are being developed which may offer solutions to some of these problems and prevent regulation from becoming a barrier to medical advances.⁵⁴ To move to a more adaptive system will require a strategic change to how we regulate; future regulation must be developed with an eye to the need to be flexible and able to evolve to suit innovative technologies. The novel and untested aspects of regenerative medicine, and in particular stem cell therapies, understandably rouse public interest and in some cases concern. The public must be able to feel confident in the regulation and application of groundbreaking research and treatments. Adaptive licensing takes a more flexible and proportionate approach to risk, patients must be involved in discussions to define the right point on the risk-benefit spectrum for novel therapies.

19. **CASE STUDY:** A recent citizens' jury convened by the University of Glamorgan and Genetic Alliance UK, found that patients were adept at understanding the higher risks

⁵⁴ Clinical Pharmacology & Therapeutics (2012); 91 3, 426–437. doi:10.1038/clpt.2011.345
<http://www.nature.com/clpt/journal/v91/n3/full/clpt2011345a.html> [accessed 2 August 2012]

associated with therapies for rare or serious conditions and want the chance to take those risks in pursuit of care or cure.⁵⁵

20. We welcome the government's plan to establish a group of experts drawn from government, regulators, the NHS, industry, and the academic and third sector communities to discuss healthcare regulation issues including the development of new initiatives and innovations.⁵⁶ We urge this group to be ambitious in its proposals.
21. We also welcome the establishment of the Health Research Authority (HRA) as part of a reform and streamlining of the regulatory system. If successfully implemented, this will benefit a great deal of health-related research, including regenerative medicine. Overly-complex approval systems, often involving multiple committees that meet at uncoordinated intervals, currently lead to delays in research getting underway. We are pleased that the HRA appears to be taking a proactive approach to streamlining the regulatory process and we look forward to seeing how these positive changes affect medical research.
22. Regenerative technologies share many of the same barriers to commercialisation as other interventions, these include most notably the "valley of death", whereby researchers and small and medium sized enterprises find it difficult to obtain investment for the development of products that are not yet proven to be effective. The novel and sometimes controversial nature (in the case of embryonic stem cells) of regenerative therapies adds to the perception of risk among investors, as does ambiguity in patent law for inventions involving stem cells.

What is the current and potential value of the sector to the UK economy?

23. Regenerative medicine will help patients and their families who suffer from a range of debilitating and fatal diseases. This will have huge implications for the health and wellbeing of the UK population.
24. **CASE STUDY:** In recently-published research it was reported that human stem cells can partially restore hearing to deaf gerbils.⁵⁷ This research, partly funded by Action on Hearing Loss, is an early stage in understanding how we might use regenerative medicine to restore human hearing. Such a treatment would be of huge value to UK health and wealth. Hearing loss affects one in six of the population, and tinnitus one in ten. The prevalence of these chronic conditions increases with age – half of all people over 60 have a hearing loss. With an ageing population, the number of people affected by hearing loss and tinnitus is set to soar. Both hearing loss and tinnitus can have profound effects on quality of life. By 2030, hearing loss will be ranked the ninth most disabling condition globally, just two ranks below chronic obstructive pulmonary disease. Both hearing loss and tinnitus can result in feelings of isolation and depression, reduced physical and psychological wellbeing, and social withdrawal.⁵⁸

⁵⁵ <http://www.geneticalliance.org.uk/docs/citizens-jury-report.pdf> [accessed 14 September 2012]

⁵⁶ Department for Business, Innovation and Skills (2011), *Strategy for UK Life Sciences*, <http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-1429-strategy-for-uk-life-sciences> [accessed 2 August 2012]

⁵⁷ <http://www.nature.com/news/human-embryonic-stem-cells-restore-gerbil-hearing-1.11402> [accessed 14 August 2012]

⁵⁸ Action on Hearing Loss (2011) *TRIH: Advancing medicines to protect and restore hearing and silence tinnitus* <http://www.actiononhearingloss.org.uk/your-hearing/biomedical-research/trih.aspx> [accessed 19 September 2012]

Is the Government doing enough to attract investment in companies working in this area? What business models are most appropriate to support development in this area?

25. Medical research charities are an asset to the UK research and development environment. With flexible funding models, charities are able to target money to where it is needed to correct market failure, often supporting promising early stage research before the technology is proven and when financial risks for industry may be higher.

26. **CASE STUDY:** In 2007, the UK spent £1.34 on research into hearing loss for every person affected. This compares to £14.21 for sight loss, £21.31 for diabetes, and £49.71 for cardiovascular research.⁵⁹ Charitable funding for hearing loss research is therefore meeting an area of high unmet need. The Action on Hearing Loss Translational Research Initiative for Hearing (TRIH) supports research with a strong commercial potential that is likely to attract follow-on funding at the conclusion of the grant and is open to academic institutions or small/medium enterprises (SMEs).⁶⁰ Demonstrating the unique qualities of the charity sector, it offers funding and partnership opportunities to allow industry to enter hearing research in a low-risk way, provides a research hub to coordinate and link up research efforts, and engages patient support for, and participation in, clinical trials for hearing loss and tinnitus globally. Cell-based therapies to restore hearing are defined within the scope of TRIH and feature in the research strategy of Action on Hearing Loss.⁶¹

What can the UK learn from international competitors about supporting the development and commercialisation of regenerative medicine?

27. The number and diversity of medical research charities in the UK is unique internationally and provides a distinct advantage. AMRC members' priorities are to develop new treatments for patients and so are able and willing partners in the research and development of regenerative medicine.
28. Charities act as hubs for research, bringing together researchers, clinicians and patients to identify areas of unmet need and agree strategic goals. Even for charities focussed on the UK research sector, conferences and meetings will often have an international attendance. These events offer learning and best practice sharing opportunities, not just for research but also in treatment and regulation.

29. **CASE STUDY:** In 2009, the MS Society hosted an international conference in London, bringing together MS researchers, people affected by MS and funding bodies from around the world to agree a consensus on how stem cell-based clinical trials for MS treatments should be conducted.

30. **CASE STUDY:** Fight for Sight, in partnership with other organisations in the eye sector, is involved in a Sight Loss and Vision Priority Setting Partnership overseen by

⁵⁹ Action on Hearing Loss (2010) TRIH: Hearing matters <http://www.actiononhearingloss.org.uk/supporting-you/policy-research-and-influencing/research/hearing-matters.aspx> [accessed 19 September 2012]

⁶⁰ <http://www.actiononhearingloss.org.uk/your-hearing/biomedical-research/trih/about-trih.aspx> [accessed 15 August 2012]

⁶¹ <http://www.actiononhearingloss.org.uk/~media/Documents/Biomedical%20research/Biomedical%20Research%20Strategy%2020112013.ashx> [accessed 15 August 2012]

the James Lind Alliance. The project aims to use the views and experiences of patients, carers and healthcare professionals to determine priorities for research. This helps research deliver products that are of true value to patients and address unmet needs in medicine, the hallmarks of innovation.

31. Charities should be key partners when formulating policies related to regenerative medicine, such as funding strategies and regulatory regimes.

What risks do UK citizens face when travelling to other countries for regenerative treatments?

32. With their strong patient links, charities have direct experience of the hopes of patients and also their concerns. Many AMRC members receive inquiries from the public about the possibility of travelling abroad for regenerative medicine therapies and are a valuable source of reliable information. Such inquiries tend to increase following media coverage of medical breakthroughs and potential new treatments.

33. **CASE STUDY:** The MS Society has produced information for MS patients about stem cell therapies in response to enquiries that they have received.⁶² In it, the MS Society “strongly discourage people with MS from approaching ‘stem cell clinics’ that are offering ‘stem cell therapies’ outside of an official clinical trial.”

34. **CASE STUDY:** Fight for Sight is aware of patients – mainly children – with optic nerve atrophy from birth who have gone to China for stem cell therapy. The charity has successfully discouraged others that were seeking similar therapies in both China and Germany. The German clinic, called the X-Cell clinic, has since closed but has reportedly re-opened in Lebanon.⁶³

35. **CASE STUDY:** With the launch of their high-profile Mending Broken Hearts Campaign, which focussed on regenerative medicine, the British Heart Foundation received an increase in enquiries from individuals who were aware of certain stem cell-based regenerative lung therapies available abroad but not in the UK. Questions were generally based around the safety and costs of such treatments and why these options are not available in the UK.

36. We believe regenerative medicine has the potential to make a substantial and beneficial impact in a range of disease areas. Medical research charities, with their focus on specific diseases and close links to patient populations, are major stakeholders in the UK’s regenerative medicine strategy. They have expertise across the board, from pioneering research in the laboratory to the needs and concerns of patients, and make a valuable contribution to the research base as well as driving treatments through the development pathway. But charities can only continue to do this in partnership with Government, which plays a vital role in funding education and training, investing in basic and applied research and infrastructure, and prioritises the development of a regulatory environment that promotes innovation.

⁶² <http://www.mssociety.org.uk/sites/default/files/Stem%20cell%20therapies%20in%20MS%20booklet%20-%20Feb%202010.pdf> [accessed 30 August 2012]

⁶³ <http://www.telegraph.co.uk/active/9367208/Founder-of-XCell-stem-cell-clinic-accused-of-stealing-to-fund-lavish-lifestyle.html> [accessed 15 September 2012]

20 September 2012

Azellon Cell Therapeutics – Written evidence

Author: Professor Anthony P Hollander, Arthritis Research UK Professor of Rheumatology and Tissue Engineering, Head of The School of Cellular and Molecular Medicine, University of Bristol and Chief Scientific Officer of Azellon Limited. This submission is written on behalf of Azellon.

Background

Azellon Limited is a spin-out Company from the University of Bristol. It is a virtual company outsourcing manufacture and the management and conduct of clinical trials. The Company is funded to conduct an MHRA approved Phase I/IIa clinical trial during 2012/13. Patient recruitment is underway and the first patient will undergo bone marrow biopsy and subsequent implantation of our product at the end of September 2012. Azellon feels that it can provide useful input to the on-going review of Regenerative Medicine because of its unique position at the interface between an active University research group, commercialisation partners and clinical providers. Our comments in response to questions raised in the call for evidence paper will be limited to those areas where we have expert knowledge and will reflect our direct experience. We believe that the company's role in translating scientific discovery into commercial and clinical reality could provide a useful template for future projects.

The Research Base

The UK has a strong research base that is, however, lacking expertise in some areas of translation such as knowledge of regulatory process and project management for product development. A particular concern is that Universities have a limited capacity to support patents through to National stage because of the costs of developing a patent in each individual country. Research groups are therefore forced to form spin-out companies at too early a stage (i.e. before the technology itself is well developed) in order to bring in a source of funding for the patent development costs. The alternative is to file patents in a very limited number of territories, which may then hamper subsequent access to international markets.

Application of the Science

Azellon is developing a patented, platform technology using mesenchymal stem cells (MSC's) to repair damaged tissue and the Company's initial focus is on the repair of avascular (white) zone cartilage tears of the knee meniscus, a growing market with significant unmet need. This will be a unique, first-line treatment using the patient's own adult stem cells in-seeded into a biological scaffold. There are very few examples of regenerative medicine products that have been invented as part of a University programme and been taken through the commercial development route and into clinical trial. Azellon's experience in progressing along this challenging pathway may provide a useful illustration for other early stage companies as new technology emerge from Universities across the UK.

Barriers to Translation

Clinical governance: Few regenerative medicine based products have been successful in reaching the clinical trial stage after commercial development and so expertise in handling these products by contract research organisations is limited. Centralising information on

trials via the Comprehensive Clinical Research Network (CCRN) will help to share knowledge and lessons learned.

Cell manufacture: Azellon are working with North Bristol NHS Trust for the conduct of the Phase I/IIa trial and the product is being manufactured at NHS Blood and Transplant (NHSBT) Centre in Speke, Liverpool. It would be preferable for the manufacture of this autologous product to be closer to the patient group. It is therefore likely, as the number of cell products expands, that NHSBT will need to further develop its capacity to provide a cell production service at different locations. Our experience is that provision of cell production in the private sector is limited, expensive to access and inflexible with respect to timing of access to facilities. There is a significant opportunity for NHSBT to fill this gap using a semi-commercial approach but with flexibility and a cost model that is more attractive for early-stage cell therapy companies.

Regulation: Regulatory concerns are often described by others as potential barriers. Azellon's experience of Ethical Committees has been very positive. Review and approval times have been reasonable. Equally, MHRA have provided responses within expected time frames. However willingness to invest is hampered by a perceived barrier, of extended timescales and high development costs to achieve product registration.

Barriers to Commercialisation

Reimbursement: Attracting investors into spinouts such as Azellon is particularly challenging because of the uncertain pathway to reimbursement and an inability to tell potential investors when there will be a product to sell and generate income. Spinouts or start-up companies in the cell therapy area need to be able to sell a product based on very early clinical safety/efficacy data whilst still amassing Phase IIb data. At present the absence of any clear path to reimbursement makes it difficult to attract investment even if the product does receive regulatory approval. These products may require a much more complex health-economic model to demonstrate that their long-term benefits offset against a very high initial unit treatment cost.

Cost of cell production: Azellon's autologous product will require significant onward investment for the optimisation of the formulation potentially to an allogeneic therapy and a scaled-up GMP manufacturing capability on at least two sites. Such GMP facilities need to have a business case that is not impossibly expensive or inflexible in terms of timing. As discussed above, this may be better provided by NHSBT than through the private sector.

NHS readiness: Clinicians and NHS technology adopters require training in order that they become more familiar with cell therapy opportunities. Additionally clinicians/users require detailed specific training in the procedures for storing, handling and administering cell therapies, in particular tissue engineering products, because these procedures are often critically important in successful use of these products. NHS/NICE also need to understand a completely different cost model for cell therapy versus acute/chronic traditional treatment regimes.

Regulation: We are not aware of any formal attempts to harmonise regulatory/technical data requirements between the EU and the US. Such harmonisation would be of significant value for companies developing products intended for a global market. The fact that some countries in the Asian region currently regulate some regenerative medicine/tissue

engineering products as medical devices, which are covered by a completely different framework, also makes harmonisation of requirements extremely complicated.

Cell therapy tourism: The UK is well placed to manage the balance between hype and hope. There is a very real possibility that carefully developed cell therapy products will benefit patients in the longer term and this possibility is discussed in the UK media in a balanced way (the Science Media Centre is particularly helpful in maintaining that balance). However the lure of some patients to quick fix cures in far away countries despite the lack of evidence of efficacy or safety is a challenge for the sector. If there are failures of therapy or serious side effects in any one case, this may send a negative signal that will hold back development of the field. Such adverse publicity would also inhibit investors who are already nervous about this challenging commercial area. Whilst such serious outcomes have been avoided to date, we need to be ready to deal with the situation should it arise. Therefore some thought should be given to a) ensuring greater awareness amongst the public of the difference between paying for an unproven therapy abroad and entering a regulated clinical trial in the UK and b) being ready to deal quickly and effectively with adverse news stories from failed stem cell tourism to ensure it does not tarnish the well controlled UK sector.

[Transcript for Professor Anthony Hollander to be found under Intercytex Ltd](#)

20 September 2012

Professor Roger Barker, University of Cambridge, Professor Michael Schneider, Imperial College London and Professor Peng Tee Khaw, UCL Institute of Ophthalmology – Oral evidence (QQ 21-41)

Professor Roger Barker, University of Cambridge, Professor Michael Schneider, Imperial College London and Professor Peng Tee Khaw, UCL Institute of Ophthalmology – Oral evidence (QQ 21-41)

[Transcript to be found under Professor Peng Tee Khaw, UCL Institute of Ophthalmology](#)

[Written evidence to be found under Parkinson's UK](#)

BioIndustry Association (BIA) – Written evidence

About the BIA

1. Established in 1989, the BioIndustry Association (BIA) exists to encourage and promote a financially sound and thriving bioscience sector within the UK economy and concentrates its efforts on emerging enterprise and the related interests of companies with whom such enterprises trade. The BIA represents innovative healthcare-focused bioscience companies, including over ninety per cent of biotech medicines currently in clinical development in the UK. BIA members are at the forefront of innovative scientific developments targeting areas of unmet medical need and this innovation will lead to better outcomes for patients, to the development of the knowledge economy, and economic growth.

2. The BIA has engaged with its members in formulating this response to gain their views of the regenerative medicine sector.

The BIA response

3. The BIA welcomes the House of Lords Science and Technology Committee's inquiry into regenerative medicine. We believe that this is a key sector within life sciences and has significant potential to impact on the nation's health and wealth. However, to achieve its full potential government support and regulatory frameworks need to be optimal.

4. This inquiry into regenerative medicine should also be considered in the wider life sciences policy environment. For example, the sector has warmly welcomed the Strategy for UK Life Sciences, announced by the Prime Minister in December 2011, and is already extensively engaged in implementation of the actions. The accompanying Innovation, Health and Wealth report and its focus on the uptake and diffusion of innovation is also welcome.

Question 1. The research base

5. There is a mixed outlook in relation to the UK regenerative medicine field. In basic research the UK continues to excel, however with regards to translation and commercialisation of regenerative medicine the UK arguably lags behind our competitors.

6. Strengths -

- UK remains a world-leader in developmental biology, cell and stem cell basic research
- Large academic capacity, multiple academic centres of stem cell research excellence
- Research Council support - >£100 million invested in academic stem cell research
- Charity Support - including significant level of financial support from Wellcome Trust, British Heart Foundation, UK Stem Cell Foundation, Dystrophic Epidermolysis Bullosa Research Association (DeBRA)
- High level of co-ordination between all the stakeholder groups - formal and informal
- UK has a complementary mix of cell therapy companies plus the essential service, tools and technology companies
- Strong political support and positive public perception

7. Weaknesses -

- We remain behind Singapore, South Korea, Israel, and the US amongst others in translational research and developing products in the clinic
- Commercial research and development (R&D) activity is low and lacks critical mass to be internationally competitive
- It remains very difficult to find funding for R&D, despite the obvious commitment from the Technology Strategy Board (TSB)
- The regulatory environment is overly complex and repetitive as outlined in the Academy of Medical Sciences (AMS) report and this affects cell therapy as it does other medical products
- UK investments tend to be considerably smaller than in the US and leave companies underfunded and vulnerable to economic cycles

Question 2. Application of the science

Current position -

8. Regenerative medicine cell-based therapies are already in routine clinical practice. For example, today there are seven US Food and Drug Administration (FDA) approved cell-based therapies and one European Medicines Agency (EMA) approved product.⁶⁴ These therapies comprise five tissue-engineered skin, two cartilage cell therapies and a prostate cancer vaccine.

9. In the period between 1998 and 2010, over a third of a million patients have been treated with these products, resulting in both lives saved and improved quality of life for patients. The overwhelming majority of treatments have taken place in the US and not a single patient has received one of these therapies in the UK. This raises the very significant question of why? It is possible that the companies have not applied for marketing authorisation within the EU, this again would raise the question why? The answer is not clear, Apligraf was by far the most widely used regenerative medicine between 1998-2010 in terms of number of patients treated.⁶⁵ In 2001 a centralised marketing authorisation application was made to the EMA for Apligraf, however due to business reasons the application was withdrawn, it is unclear whether a further application has been made.

Potential future position -

10. One method to predict the future potential of regenerative medicine is to review potential therapies and their specific stage in the clinical trials process. Over the last 10 years, 2,500+ trials involving cell-based therapies (haematological and non haematological) have commenced with the majority either currently enrolling patients or still gathering clinical data. Nearly 10% of these trials are in Phase III and if successful are therefore only a few years away from commercialisation. Unfortunately the vast majority of all the cell-based clinical trials are outside of the UK. While it is difficult to put precise figures on where trials take place, 72% of trials between February 2000 and June 2010 were registered with the FDA.⁶⁶ The UK is missing out on the benefit of hosting these trials. These include - inward

⁶⁴ Mason C. & Manzotti E. Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010. *Regen. Med.* 2010, 5(3), 307-313. In addition to the therapies listed in this paper Provenge a cell-based prostate cancer vaccine has also received FDA approval (while not classically defined under the heading of Regenerative medicine, it is cell based)

⁶⁵ *Ibid.*

⁶⁶ Culme-Seymour E.J., Davie L.N., Brindley D.A., Edwards-Parton S. & Mason C. (2012). A decade of cell therapy clinical trials (2000–2010). *Regenerative Medicine*, July 2012, Vol. 7(4), 455-462.

investment, gaining core experience, MHRA⁶⁷ regulatory approval, potential for early market adoption and thus availability to NHS patient.

Near term (<5 years) -

11. Due to the time frame, likely clinical impact in <5 years must either be currently regulatory approved or at the late (Phase II or III) clinical trials stage including:

- Cardiovascular: Vascular shunts for dialysis patients (Cytograft, USA); Peripheral vascular disease (Aastrom, US and Pluristem, Israel); Vascular patches (Tissue Regenix, UK); Cardiac disease – heart attack/heart failure (Multiple trials globally)
- Neurological disorders: Stroke (ReNeuron, UK); Chronic spinal cord injury (StemCells, USA); Amyotrophic lateral sclerosis (Neuralstem, USA)
- Musculoskeletal degeneration and trauma: Accelerated fracture healing; Cartilage regeneration (Genzyme, USA and TiGenix, Belgium); Meniscal tissue (Azellon, UK)
- Age Related Macular Degeneration and Stargardt Macular Degeneration (ACT, USA)
- Skin (Intercytex Ltd, UK)

Longer term (<15 years) -

12. Phase I trials of Human Embryonic Stem Cell based therapies are only just being approved in small numbers, and the first commercial products are probably 10-15 years from marketing approval. We would expect to see a number of therapies entering Phase III clinical trial as well as a few therapies applying for/gaining marketing authorisation including a number from the list above. Additional indications include:

- Diabetes Type I (inability to produce insulin c.f. Type 2 diabetes associated with obesity)
- Central nervous system (CNS) diseases (inc. Parkinson's disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis)
- Neurological disorders, including dry age-related macular degeneration, (Neucentis, UK and Advanced Cell technology, US)
- Tissue-engineered blood vessels for coronary artery bypass grafting and peripheral vascular disease (Cytograft, USA)

13. In addition, it is possible that in 10 years, scientists will have gained a much deeper understanding of how to stimulate the body's own repair process, perhaps moving towards/in early clinical trials of small molecules and biologics either singularly or in combinations.

14. Successful products including erythropoietin (EPO) and bone morphogenetic proteins (BMP) are already available that stimulate blood and bone formation, and there is considerable work being carried out around the world in bone formation. In addition, substantial effort is being put into research around the world in academic laboratories and in UK companies (Epistem, UK) to fund similar regenerative factors for other tissues.

Question 3. Barriers to translation

15. One of the main barriers to translation is access to the levels of funding required to get the product to market. Access to finance remains a large barrier for the wider biotech sector and is felt even more acutely in regenerative medicine given the higher risk profile.

⁶⁷ Medicines and Healthcare products Regulatory Agency

To overcome this issue either funding must increase or the cost of translating a technology must be reduced, by reducing the regulatory burden without compromising the need to provide safe and efficacious products.

16. Venture capital funding for regenerative medicine companies is incredibly difficult to come by, and public listings are rarely seen in the sector. The TSB grants are well received, and the Biomedical Catalyst is seen as a good addition to the funding landscape. However the size of the budget that the TSB controls and the need to provide matching funds may limit its impact. Furthermore the requirement that academic collaborators are funded in full for their work in projects for which TSB is providing 50% or 75% of project costs, necessarily means that the company leading the project receives significantly less than the “headline” percentage grant support.

17. The Cell Therapy Catapult has also been well received although it will take time for its impact to be realised and there is some concern that it could become a “state funded competitor” to small and medium sized enterprises (SMEs) already in the sector.

18. Government can ease the access to finance issues that regenerative medicine companies face by reducing the red tape, balance the risks and remove repetitive regulations as described in the AMS. It is critical that the industry can demonstrate to investors and stakeholders that returns can be realised with a successful product. Regenerative medicine therapies are not the same as traditional medicines with respect to their cost of goods or their clinical and social outcomes e.g. returning patients and their carers back to employment, and they have the potential to replace lifelong chronic treatments with acute cures.

19. In addition the government could also act as a direct enabler of finance, as opposed to a provider by introducing Citizens Innovation Funds (CIFs)⁶⁸ a UK version of the French - Fonds Communs de Placements dans l’Innovation (FCPI). CIFs are a tax advantaged investment scheme that would allow mid-net wealth individuals to invest in highly innovative UK companies. We believe that CIFs could release £300 million per year of investment into innovative UK companies, and there is no reason why funds focussed on supporting regenerative medicines could not be launched.

20. Alongside access to finance there are a number of additional technical barriers to translation -

- Shortage of appropriate animal models and in particular large animal models of degenerative diseases
- Outcome measures and surrogate markers/end points for clinical trials
- Lack of availability of funding for animal work especially large animal studies for safety/toxicity. These studies are essential to de-risk potential therapies to a point where SMEs can get investment in order to proceed to Phase I. University researchers are also not rewarded for pursuing this type of work as it is unlikely to lead to publication in high quality peer-reviewed journals

21. Clearly it would be wrong to claim that barriers to translation are purely issues of finance and regulation, fundamental shortcomings in currently available science also contribute.

⁶⁸ <http://www.bioindustry.org/document-library/citizens-innovation-funds-report/>

Question 4. Barriers to commercialisation

Current and potential future value of the sector to the UK economy -

22. Today, 80% of healthcare costs go towards treating chronic diseases, such as arthritis, diabetes and heart failure, which in the future could potentially be treated using regenerative medicine and cell therapies.

23. There has been much media hype of some of the more dramatic regenerative medicine therapies and the sector is sometimes seen as all hype and no results but that is not the case, particularly in the US. It is estimated in 2009 in excess of 100 million patients in the US could have been treated with cell-based therapies.⁶⁹ The main targets are heart disease, diabetes, neurodegenerative diseases, musculoskeletal disorders, spinal cord injury, stroke, autoimmune diseases and major trauma. The current worldwide sales of regenerative medicines already make it a multi-billion pound industry. The cell therapy industry alone (as compared to regenerative medicine which includes small and large molecules, devices and cells) had global sales of £250 million in 2008, and is predicted to grow to £1.6 billion by 2012 and £3.1 billion in 2014,⁷⁰ with even greater growth expected to follow.

24. It is important to note that there are also significant cell therapies in development that provide treatment although not classically defined under the heading of Regenerative medicine.⁷¹ These include Provenge (Dendreon), a cell-based prostate cancer vaccine with reimbursement in the USA set at £57,000 and expected through Medicare alone to generate sales of £1 billion per annum by 2014.⁷² The overall market predictions above are considered conservative given the existing clinical demand and the volume of cell therapy clinical trials that are currently underway.⁷³

Current state of commercial regenerative medicine sector -

25. A number of the major barriers to translation also hold true for commercialisation and these have already been covered in the response to question three. In summary, these barriers include access to finance, lack of clear regulatory process and uncertainty over reimbursement levels and who will pay for these therapies.

26. With specific regard to commercialisation:

- The proposed early access scheme has the potential to make a difference in the field of regenerative medicines, although these are only proposals at the current stage and it is unclear if the policy will be implemented and, if so, what the eligibility criteria, scope and level of reimbursement for products in this scheme will be available.
- While a small number of regenerative medicine companies have tried to reduce their need for investment capital by providing commercial tools and services, this approach is not seen as a truly viable business model in the long term.
- It is widely felt that the “none-routine” definition of the advanced-therapy medicinal products (ATMP) hospital exemption scheme is being abused throughout the EU, and is discouraging innovative firms from developing new therapies as they believe that there is not a level playing field. TiGenix who have received EMA marketing

⁶⁹ Evers P: Advances in the Stem Cell Industry. Global Business Insights (2009)

⁷⁰ *Ibid.*

⁷¹ Mason C. and Manzotti E. Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010. Regen. Med. 2010, 5(3), 307-313

⁷² Businessweek: www.businessweek.com/news/2010-11-17/dendreon-s-provenge-extends-survival-u-s-panel-says.html

⁷³ Evers P: Advances in the Stem Cell Industry. Global Business Insights (2009)

authorisation for ChondoCelect have found that the hospital exemption scheme is effectively blocking their access to the market.

- Intellectual property arrangements and Government grants currently favour academic partners in collaborative research and development, at the expense of the industrial partner(s) who need to provide matching funds. This prevents collaborative projects from being initiated as the industrial partner can end up in effect sponsoring the academic partner or it can substantially reduce the commercial outputs of the projects.
- As stated earlier the US market for regenerative medicines is considerably more developed than in the UK. Consequently providing support to UK companies in accessing the US market would boost investor confidence and drive investment.

Question 5. International comparisons

Regulatory bodies -

27. It is important to emphasise that overall the UK cell therapy and regenerative medicine industry perceives the MHRA to be highly professional and competent in its activities. It is also worth noting that ATMPs are regulated centrally by the EMA and the MHRA is only responsible for authorising clinical trials within the UK. The UK is represented at both the EMA's Committee for Advanced Therapies (CAT) and its Committee for Medicinal Products for Human Use (CHMP), and has been closely involved in ATMP scientific advice and as Rapporteur for marketing authorisation applications for ATMPs.

28. It is also worth highlighting that the EMA offers reduced fees in relation to ATMPs, with a 90% fee reduction for scientific advice for SMEs and 65% for others. SMEs and hospitals can also apply for a 50% reduction in the marketing authorisation fee providing that they can prove that there is a particular public health interest in the Community in the ATMP.

29. In the case of human embryonic stem cell research, the UK (unlike other countries) obliges all new embryonic stem cell lines to be deposited at the UK Stem Cell Bank which then makes them available to researchers. There is currently no mechanism for the long-term exclusive use of a cell line by a company developing a cell therapy and no ability for the company to control how the deposited cells are used or what data will be generated. This is an obstacle to commercial investment.

Funding -

30. There are numerous international examples of alternative funding models which have raised significant levels of finance from the general public for the funding of innovative sectors. Schemes such as the Californian Proposition 71 which raised a \$3 billion bond for stem cell research and the French FCPI scheme (as discussed in question 3) which has raised over €6 billion for innovative companies are novel funding mechanisms that the UK regenerative medicine sector could potentially benefit from.

31. The other side of the coin, is the attempt by some MEPs to remove European funding for embryonic stem cell research from Horizon 2020, while the amounts are small it sets a bad precedent in regards to public funding to embryonic stem cell research and will reduce investor confidence.

20 September 2012

British Heart Foundation (BHF) – Written evidence

Summary

- There are significant opportunities to develop cardiovascular regenerative medicine in the UK, which could benefit people with heart failure and other cardiovascular disorders
- Currently more than 750,000 live with heart failure in the UK, but an ageing population will mean even higher numbers in the future
- The UK has a number of strengths within cardiovascular regenerative medicine, including the expertise within the research base, variety of funding sources, the progressive regulatory environment for stem cell research, and public support for regenerative medicine
- Addressing knowledge gaps that require further basic scientific research and preclinical testing, in addition to gaps in the critical mass of interdisciplinary science within the cardiovascular field, is needed to make substantial advances in cardiovascular regenerative medicine
- Addressing continuing problems within the NHS related to bureaucracy, incentivisation of clinical research, and the effective adoption of innovative therapies, is necessary to ensure future regenerative medicine therapies reach patients
- The BHF's investment of £50 million over the next five years will provide the resources to create new centres with the critical mass of interdisciplinary science needed to make real advances in cardiovascular regenerative medicine

1. Background

1.1 The British Heart Foundation (BHF) is the nation's heart charity. From new discoveries about how the heart develops in the womb, to developing the treatments that could mend broken hearts in the future, we are the single biggest independent funder of cardiovascular research in the UK – funding around £100 million each year.

1.2 Our research portfolio extends from fundamental laboratory-based molecular, biological and genetic studies to large scale clinical trials of novel and existing preventive and therapeutic interventions.

1.3 Regenerative medicine is reaching an exciting stage within cardiovascular research, which is reflected in the BHF's priorities for research in the future. We welcome the Committee's interest in this area of research and our responses to the questions posed by the inquiry draw on our expertise in the cardiovascular aspect of this field.

1.4 For some people who survive a heart attack, the damage to their heart muscle can lead to debilitating heart failure, for which there is no cure. There are more than 750,000 people in the UK with heart failure, which is one of the commonest reasons for emergency medical admissions (about 5 per cent), readmissions and hospital bed-days occupancy.⁷⁴ An ageing population, coupled with the fact that more people now survive heart attacks, mean even

⁷⁴ NHS Information Centre. *National Heart Failure Audit 2010: Report for the audit period between April 2009 and March 2010*; 2010. Available at: http://www.ic.nhs.uk/webfiles/publications/002_Audits/NHS_IC_National_Heart_Failure_Audit_2010_04-01-11.pdf

higher numbers are expected in future. If our goal of regenerating the heart is achieved, it should substantially improve the lives of heart failure patients – reducing the need for specialist care and resulting in fewer hospital admissions. Cardiovascular disease cost the health care system in the UK around £14.4 billion in 2006.⁷⁵ Providing services to patients with heart failure in England costs the NHS an estimated £625 million per year.⁷⁶ Regenerative medicine therapies could therefore result in significant savings for the NHS.

1.5 This is an essential time for investment in cardiovascular regenerative medicine. At present, damage to the human heart leads to irreversible loss of cardiac myocytes, and our treatments for the failing heart can only mitigate the effects of this damage. We cannot yet replace these damaged cells with fully functional cells capable of restoring the function of the heart. However, we can see other instances within nature where this process can occur. Unlike humans, zebrafish can for example fully regenerate their hearts after significant damage. There have been recent rapid advances in stem cell biology that have shown that human embryonic or induced pluripotent stem cells can be converted in vitro into cardiac myocytes, though the molecular signals are not yet fully understood. Clinical studies in patients have shown that delivery of autologous cells derived from bone marrow into a damaged heart is safe, but that the beneficial effects are small and almost certainly not related to differentiation of new myocytes from stem cells.

1.6 The BHF believes that now is the right time to invigorate research in this field to enhance our understanding of stem cell differentiation into cardiac and vascular cells. We can then translate this understanding into effective ways to mend a broken heart or damaged peripheral blood vessels.

2. The research base

• How does the UK rank internationally in the scientific field of regenerative medicine?

2.1 The UK is currently in a very strong position in the field of regenerative medicine, with a highly active history over the last four decades. The UK has been a leader in stem cell research, with discoveries including the first isolation and characterisation of embryonic stem cells in mice by Sir Martin Evans. Since 2000, a number of developments have advanced the stem cell research environment to help to develop this world-leading position.

2.2 In 2002 the UK Stem Cell Bank was created, the world's first such repository, to hold high quality stem cell lines from adult, foetal and embryonic tissues.⁷⁷ Jointly funded by the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), the first cell lines were deposited in 2004.

2.3 Both the UK Government's 2011 Taking Stock of Regenerative Medicine in the United Kingdom⁷⁸ and the Research Councils' recent UK Strategy for Regenerative Medicine report that the UK is one of the leaders of research into regenerative medicine internationally. This is equally true within the cardiovascular field.

⁷⁵ British Heart Foundation Health Promotion Research Group. *Coronary Heart Disease Statistics 2010 edition*; 2010.

⁷⁶ *Ibid.*

⁷⁷ www.ukstemcellbank.org.uk

⁷⁸ Department of Business, Innovation and Skills. *Taking Stock of Regenerative Medicine in the United Kingdom*; 2011. Available at: <http://www.bis.gov.uk/assets/biscore/innovation/docs/t/11-1056-taking-stock-of-regenerative-medicine>

2.4 The UK's position at the forefront of this research has been assisted by a supportive regulatory climate and favourable public opinion.⁷⁹ The strengths of the UK system present opportunities to lead the application of basic research to clinical benefits and attract talent and investment from abroad in stem cell research.⁸⁰ It is therefore important that the UK is taking full advantage of the favourable environment for stem cell research.

2.5 Within cardiovascular research, a number of world-leading researchers in the UK are at the forefront of regenerative medicine. The BHF currently funds a number of leaders in this field, including:

- Professor Michael Schneider, BHF Professor of Regenerative Cardiology at Imperial College London
- Professor Paul Riley, BHF Professor of Regenerative Medicine at the University of Oxford
- Dr Anastasis Stephanou at University College London, and
- Professor Roger Pedersen, Professor of Regenerative Medicine at University of Cambridge.

2.6 Professor Michael Schneider and his research team at Imperial are exploring ways to repair the damage to heart muscle caused by heart attacks. They want to know what changes in the heart muscle cells drive them to die, and find out if stem cell therapies are able to repair the damage. His work is aimed at investigating the biological intricacies of healthy and diseased heart muscle cells, to find out which molecular components are switched on or off when they are damaged. Professor Schneider's team were among the first scientists to show that several genes involved in 'apoptosis' - a process where unwanted cells are programmed to destroy themselves – may also prevent heart muscle cells from degenerating.

2.7 In addition, Professor Schneider is also working on adult cardiac stem cells – studying the pathways involved in cardiomyocyte differentiation during development using a combination of these cells and embryonic stem cells. This work aims to gain a better understanding of how this differentiation occurs during development and apply the results to help restore cardiac muscle number and function following injury in the adult heart.

2.8 Professor Paul Riley and his team have demonstrated in mice that certain adult heart cells can be stimulated chemically to repair heart damage.⁸¹ The chemical, a protein called thymosin β 4 ($\tau\beta$ 4), helps specialist cells surrounding the heart move to the damaged area of the heart and turn into new heart muscle, helping the heart pump efficiently once more. Professor Riley's team targeted stem-like cells called progenitor cells in the epicardium, the outer layer of the heart. In the embryo, these epicardium-derived

⁷⁹ Medical Research Council, Biotechnology and Biological Sciences Research Council, Sciencewise. *Stem Cell Dialogue*; 2008. Available at: <http://www.bbsrc.ac.uk/society/dialogue/activities/stem-cell-dialogue.aspx>

⁸⁰ Medical Research Council. *Stem cell science in the UK – key facts about research, regulation and funders*; 2008.

⁸¹ Smart N, Bollini S, Dubé KN, Vieira JM, Zhou B, Davidson S, Yellon D, Riegler J, Price AN, Lythgoe MF, Pu WT, Riley PR. De novo cardiomyocytes from within the activated adult heart after injury. *Nature* 2011, 474(7353):640-644. Available at: <http://ukpmc.ac.uk/abstract/MED/21654746>

progenitor cells (EPDCs) are able to transform into a number of specialist cells including heart muscle. Scientists thought this ability was lost in adults but BHF-funded researchers have shown that it can be reawakened.

2.9 They restored the EPDCs' embryonic potential by treating the healthy hearts of adult mice with T β 4. This appeared to 'prime' the heart for repair. When damage to the heart occurred, a booster dose of T β 4 was given, and this sparked the EPDCs to transform into new heart muscle and integrate with existing healthy muscle. Crucially, muscle is not formed if the EPDCs have not been pre-treated with T β 4. Professor Riley and his team are now pursuing research into the genes that dictate how these special cells can turn into new heart tissue.

2.10 **Dr Anastasis Stephanou** is trying to develop a new way to grow sheets of working heart muscle. He believes that in future, these sheets of muscle could be inserted to replace areas of the heart damaged after a heart attack. Currently there is no reliable technology to manufacture heart muscle of good enough quality to replace damaged tissue. Creating heart muscle is a huge challenge. Each individual cell must line up perfectly with its neighbours and needs its own supply of oxygen to give it the energy it needs, provided through a network of tiny blood vessels. And for heart muscle to work properly, beating cells and blood vessels need to sit within a network of proteins made by another type of cell, called a fibroblast.

2.11 Dr Stephanou has harnessed the potential of a type of technology called 'electrospraying', more usually found in a physics laboratory. Electrospraying uses microscopic 'hoses' and electrical currents to build three-dimensional structures. Dr Stephanou has already used an electrospraying machine to combine beating heart cells, blood vessel cells and fibroblasts into a layer that can beat for several hours. His latest BHF grant aims to improve this technique, aiming to build structures in which cells communicate with each other and pass on electrical current like normal heart muscle. If successful, this project could help lead to new tissue engineering techniques to replace damaged heart tissue.

2.12 **Professor Roger Pedersen** is another world-leading stem cell researcher who has been attracted from the US to conduct his work in the UK, having previously studied at Stanford, Yale and Johns Hopkins before coming to the University of Cambridge. Professor Pedersen has been provided with a special joint project grant from the BHF and the MRC. This is one of 3 such grants in the UK (the others are to Professor Schneider and to Professor Cay Kielty in Manchester) designed to pump-prime the development of research centres for stem cell experts working on heart and blood vessel regeneration.

2.13 One part of this research programme aims to help generate stem cells with a particular genetic error, already known to cause a rare but fatal type of high blood pressure called pulmonary arterial hypertension (affecting the arteries that supply the lungs). With this population of cells, scientists hope to understand how the genetic mutations cause the disease, which could help to develop drugs which might help restore the natural function of the gene in blood vessels.

- **Where does the UK have strengths and weaknesses in the field?**

2.14 The main strengths the UK holds in cardiovascular regenerative medicine centre around five key areas:

- expertise within the research base
- variety of funding sources
- the progressive regulatory environment for stem cell research
- public support for regenerative medicine, and
- the NHS as a host of clinical trials.

2.15 As highlighted above, we have clear expertise in the UK focused on regenerative medicine in cardiovascular research that is internationally recognised. These experts in the field are backed up by the facilities provided within the UK. In the case of Professor Schneider, the world-class facilities available at Imperial College combined with the funding provided by the BHF enabled the UK to attract a world-leading scientist in regenerative medicine to leave Baylor College of Medicine in Houston, Texas in 2007 – a success for both the BHF and the UK research base. This appointment also helped to secure a further £2.2 million investment from the European Union.

2.16 Resources dedicated to this field of research are also being increasingly provided. For example, the new Scottish Centre for Regenerative Medicine at the University of Edinburgh has purpose-built facilities for developing new regenerative therapies. The BHF's contribution of £1 million is helping to ensure this will be a centre for cardiovascular research in regenerative medicine in the future.

2.17 As explored further below, the UK has a number of different funders of cardiovascular research into regenerative medicine. This includes not only the BHF, but also the Research Councils, the European Union, and other charities and funding organisations such as the UK Stem Cell Foundation. These combine to provide a variety of different funding opportunities for scientists in this field.

2.18 The Committee's report in 2002 on stem cell research recognised that embryonic stem cell research is necessary to maximise the potential of stem cells.⁸² It is the UK's progressive environment permitting research of this type that has helped make it a world-leader. This was highlighted most recently during the passage of the Human Fertilisation and Embryology Act in 2008 that included provisions for the creation of human admixed embryos – embryos containing human and animal material. As there are a limited number of human embryos available for research, this could provide an alternative source for stem cells more in the future. Organisations such as the Human Fertilisation and Embryology Authority (HFEA) were important during the passage of this legislation in providing expertise that helped to alleviate public concerns. With the Department of Health currently consulting on plans to potentially transfer the responsibilities of the HFEA to other organisations, it is essential that this does not come at the cost of the expertise provided by the HFEA on developing issues such as these in research.

2.19 In 2008, public opinion on stem cell research was explored through the Stem Cell Dialogue, set by the Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC), and Sciencewise. This highlighted that there was

⁸² House of Lords Select Committee on Science and Technology. *Report on Stem Cell Research*; 2002. Available at: <http://www.publications.parliament.uk/pa/ld/ldestem.htm>

widespread conditional public support for stem cell research and therapies in the UK.⁸³ The BHF funds research involving both embryonic and adult stem cells, with funding in these areas likely to increase substantially in future years – producing information leaflets explaining why both approaches are necessary to help allay any concerns from supporters that we receive. It is our hope and expectation that we will ultimately learn how to induce adult cells, either from the bone marrow, skin or possibly from the heart itself, to repair the damage caused by a heart attack. But, to do this, we need to understand the molecular signals that determine why a cell becomes a heart cell in the first place, and the way to do that is to study embryonic cells.

2.20 In addition, the facilities provided by the NHS present a key strength for regenerative medicine in the UK. The NHS has also demonstrated itself to be well-placed to host clinical trials for cardiovascular regenerative medicine, as evidenced by those that are already taking place at the University of Bristol, led by Professor Gianni Angelini, BHF Professor of Cardiac Surgery. Professor Angelini's team is conducting a trial involving patients that have recently had a heart attack, who are being injected directly into the heart with a particular type of stem cell, called CD133 cells, which are derived from bone marrow cells taken from their own hip bone. The facilities provided by the NHS help enable ground-breaking work of this kind to take place in the UK.

2.21 However, there are also several areas at present that present a challenge to regenerative medicine in cardiovascular research:

- knowledge gaps that require further basic scientific research and preclinical testing, and
- gaps in the critical mass of interdisciplinary science within the cardiovascular field that are needed to make substantial advances.

2.22 At present, it is still too soon to say which areas of cardiovascular regenerative medicine will provide the best chances for effective translation into therapies. This could involve the delivery of stem cells into the heart, delivering defined molecules to encourage resident stem cells to repair the damage, or tissue engineering to create grafts. All three of these topics require further basic scientific research and preclinical testing before they become suitable for clinical delivery.

2.23 Furthermore, to further develop cardiovascular regenerative medicine we need to improve our understanding of how to identify potential stem cells within resident populations of cells both within and outside the bone marrow. We must also ensure that we have a much more refined approach to tracking the movement of stem cells to target organs, and monitoring their residence within target organs and measuring their contribution to cardiac performance.

- **Who are the major funders of research in the field of regenerative medicine? What funding is available?**

2.24 The BHF is the major funder of cardiovascular research in the field of regenerative medicine, currently funding approximately £38 million in the UK. In February 2011, we

⁸³ Medical Research Council, Biotechnology and Biological Sciences Research Council, Sciencewise. Stem Cell Dialogue; 2008. Available at: <http://www.bbsrc.ac.uk/society/dialogue/activities/stem-cell-dialogue.aspx>

launched an appeal to fund a new programme of research into regenerative medicine, Mending Broken Hearts.⁸⁴ This is expected to be a 15-20 year research programme, aiming to commence early clinical trials within five years and full clinical trials in about 10 years. We aim to invest £50 million into this programme over and above our normal research spend, and will raise this over the next five years.

2.25 Our Mending Broken Hearts programme will provide increased funding for the scientists with the best ideas in cardiovascular regenerative medicine. We will provide the resources to create new centres with the critical mass of interdisciplinary science needed to make real advances in cardiovascular regenerative medicine. For example, as noted above, the BHF has committed £1 million in partnership with the MRC (who are funding £1.5 million) to fund three centre development grants to strengthen the infrastructure for cardiovascular research involving stem cells. In addition, we plan to establish one or two Centres for Cardiovascular Regenerative Medicine in autumn 2013 and have received outline bids for the awards that will fund these. This funding will be awarded in the context of, and in addition to, £20 million of funding that will come from UK tax-payers via the UK Regenerative Medicine Platform, which is being led by the MRC.

2.26 An additional source of funding for many of the teams the BHF funds within regenerative medicine is the European Union, through Framework Programme 7 (FP7). The European Parliament is currently deciding which areas to fund within the replacement to FP7, Horizon 2020, which will fund research and innovation between 2014 and 2020. We are concerned that some Members of the European Parliament are attempting to amend the provisions of Horizon 2020 preventing any funds being granted to projects using embryonic stem cells. We believe that any scaling back of this investment would send out a dangerous message that could seriously damage this area of research in Europe, to the detriment of patients in the future – and call on the Government to champion this within the EU.

3. Application of the science

- **Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?**

3.1 We do not believe that this area of research is fully ready for translation at this stage, and feel that more basic science must be done before we arrive at a stage where translation is realistic. The UK is currently running several trials using stem cells from bone marrow cells, but these are tending to show small benefits on existing heart cells, rather than myocyte regeneration.

- **What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?**

3.2 Within cardiovascular regenerative medicine, we believe that the therapeutic areas where clinical impact is most likely in the medium to long term is ischaemic myocardial damage (where blockages in the coronary arteries have reduced blood flow to the heart)

⁸⁴ www.bhf.org.uk/findthecure

and tissue ischaemia (where blockage in peripheral arteries for example leads to poor circulation in the legs). We anticipate that though these are unlikely to develop beyond early phase clinical studies within the next five years, proven therapies for both areas will be developed within the next 15 years.

4. Barriers to translation

- **Are the actions outlined in the Government's *Strategy for UK Life Sciences*, their report, *Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Board's *Strategy for UK Regenerative Medicine* sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?**

4.1 We are encouraged that the Government has recognised that there are significant regulatory barriers and challenges to innovation in the UK, which are not limited to regenerative medicine but are affecting medical research broadly. While for cardiovascular research, regenerative medicine is not yet at the stage where substantial translational research can take place, we welcome changes that could help to ensure speedy translation when the science reaches this stage.

4.2 Within the *Strategy for UK Life Sciences*, we particularly welcomed the Government's commitment to amend the NHS Constitution to change patients' default position to enable the use of patient data for medical research unless they opt out, in addition to being approached about research studies for which they may be eligible. This will help researchers to recruit patients into clinical trials.

4.3 Both *Taking Stock of Regenerative Medicine in the UK* and the *Strategy for UK Regenerative Medicine* provide useful responses to the field's needs and opportunities, recognising the current strengths of the UK in addition to the areas requiring focus to progress the science towards clinical therapies. There are a number of additional areas that we believe the Government should focus on in order to improve the environment for clinical trials in general in the UK.

4.4 The BHF strongly supports the Academy of Medical Sciences' report on research and governance, which has identified the main obstacles to effective translation. The complexity of the regulatory pathway, delays and duplication for permissions from NHS Trusts, and the problems within the culture of the NHS to facilitate research were all areas that we highlighted in our response to the Academy's call for evidence. The creation of the Health Research Authority is the first step towards helping to simplify the regulatory pathway, facilitate research and ensure that governance does not impede progress. We believe the Government should ensure the full implementation of the Academy's recommendations as soon as possible.

4.5 We have long highlighted the EU Clinical Trials Directive as a barrier to clinical research in the UK, and its replacement with a new Clinical Trials Regulation is currently being considered in Brussels. It is vital that this new legislation helps rather than hinders clinical research in the UK.

4.6 With regards to the NHS, a key barrier to date has often been that research is not seen as a core function by many within NHS Trusts. A much more research-oriented mentality is needed, particularly among health service managers, to ensure that R&D departments promote and facilitate research. The Health and Social Care Act 2012 placed duties on all the main commissioners and providers to promote research – it is vital that this supportive attitude towards research is now embedded into practice on the ground.

4.7 The NHS has also traditionally been very slow to adopt new technologies. This is partly due to an inherent cultural conservatism, but is often also a result of a lack of funds to adopt the new technologies on a broad scale. Without a ring fenced budget aimed at adopting new technologies into NHS practice, we believe that it will be difficult within the current financial climate for any new technology to be introduced, unless it can be shown to reduce costs from the outset. New technologies often begin by costing extra, but as clinical experience helps to refine these technologies, they can save money for the NHS over the long term.

5. International comparisons

- **What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?**

5.1 We are aware of concerns within the regenerative medicine community in the UK and other EU Member States with regards to the ruling by the European Court of Justice in 2011 on patents for therapies resulting from human embryonic stem cells. By the Court's interpretation of the EU Biotechnology Directive, these patents are not allowed within in the EU – whereas for many of the UK's competitors this is possible. While we believe regenerative medicine treatments for conditions such as heart failure are more likely to use cells other than those derived from embryonic stem cells, this potential disadvantage around commercialisation could impact the UK's overall attractiveness in this area of research.

- **Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?**

5.2 The BHF is aware that a small number of private clinics abroad claim to offer effective stem cell therapies.⁸⁵ These operate without rigorous regulation, and offer untested therapies that have not undergone the thorough animal testing or phased clinical trials that are required for licensed therapies elsewhere.

5.3 In 2008, the International Society for Stem Cell Research (ISSCR) released professional Guidelines for the Clinical Translation of Stem Cells that call for rigorous standards in the development of stem cell treatments, including stringent evaluation and oversight from national agencies. Earlier this year, China's Ministry of Health announced a halt to all unapproved stem cell therapies, in addition to their intentions to tighten regulation and oversight.⁸⁶ Greater regulation is needed internationally in this area to protect the public from misleading medical advice and ensure that other nations are meeting the UK's high standards for safety.

⁸⁵ Coghlan A. New Scientist. Death revives warnings about rogue stem cell clinics; June 2010. Available at: <http://www.newscientist.com/article/dn19056-death-revives-warnings-about-rogue-stem-cell-clinics.html>

⁸⁶ http://www.isscr.org/ISSCR_Applauds_Start_of_China_s_Year_Long_Campaign_to_Halt_Unauthorized_Stem_Cell_Treatments.htm

- **What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?**

5.4 The UK National Stem Cell Network has described these treatments as at best ineffective, positively dangerous, and potentially fatal.⁸⁷ These experimental treatments, which have not been properly tested and approved for human use, often involve a type of stem cell being injected into a diseased area of the body. Without knowing the consequences, this places a significant risk to the patient. There have been examples in the past where tumour lesions developed in patients following unlicensed treatments involving injected stem cells, which have led to fatality.⁸⁸

5.5 The ISSCR has created a website that provides the public with information evaluating the claims made by clinics on stem cell therapies.⁸⁹ We support the efforts of the ISSCR and others to shine a light on these clinics to help ensure that patients are made fully aware of the risks involved. We have so far received only a small number of enquiries from the public with regards to any 'regenerative treatments' available abroad.

5.6 Within the UK, patients are aided by organisations such as the National Institute for Health and Clinical Excellence to help protect them from non-evidence based practices in the NHS.

20 September 2012

⁸⁷ www.uknscn.org/downloads/stem_cell_tourism.pdf

⁸⁸ Nagy A. Quaggin SE. Stem Cell Therapy for the Kidney: A Cautionary Tale. J Am Soc Nephrol 21: 1070–1072, 2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20558540>

⁸⁹ www.closerlookatstemcells.org

British Heart Foundation (BHF) – Written evidence

British Heart Foundation (BHF), Government–Department of Health (DH), Medical Research Council (MRC) and Wellcome Trust – Oral evidence (QQ 42-63)

Transcript to be found under Government–Department of Health

British Heart Foundation (BHF), Government–Department of Health (DH), Medical Research Council (MRC) and Wellcome Trust – Oral evidence (QQ 42-63)

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[Transcript to be found under Government–Department of Health](#)

British Society for Blood and Marrow Transplantation (BSBMT), the British Society for Haematology (BSH) and the Royal College of Pathologists (RCPath) – Written evidence

We are writing on behalf of the British Society for Blood and Marrow Transplantation (BSBMT), the British Society for Haematology (BSH) and the Royal College of Pathologists (RCPath). We would agree with the select committee that the UK is a world leader in the field of regenerative medicine and haematopoietic stem cell transplantation.

Haematologists are at the forefront of stem cell research and have also pioneered the delivery of haematopoietic stem cell transplants. Such transplants currently represent the most well developed example of human stem cell use in the restoration of defective organ or cellular function.

The UK has a long history of innovation in the field of stem cell transplantation for haematopoietic and immune system disorders. Haematologists collect, store and use stem cells to enable the regeneration of a normal bone marrow and a normal immune system in patients who have marrow or immune system dysfunction. Such disorders can result from either congenital or acquired diseases or as a result of curative chemotherapy given for malignancy.

There has been a dramatic increase in haematopoietic stem cell transplantation activity over the last 5-10 years. In the 5 year period from 2004-2009, 14,366 haematopoietic transplants were performed; 1,748 paediatric transplant and 12,618 adult transplant procedures. In 2010, 3,032 stem cell transplants including 1,231 autologous transplants (using the patient's own cells) and 1,801 allogeneic transplants (using cells from a volunteer donor) were undertaken in the UK. The UK Haematology community aims to transplant all patients who require the procedure, to safely deliver the treatment and to improve the outcomes of transplantation. The UK is at the forefront of achieving the highest possible standards for stem cell transplantation and has an excellent quality management track record.

Stem cell transplantation in Europe and in the UK has always been carefully regulated; both activity and outcomes are carefully monitored through the EBMT and the BSBMT. The EBMT, together with their US counterparts, have also put in place a set of standards to maximise the quality and safety monitoring of transplant units worldwide (FACT-JACIE). The UK has been quick to adopt JACIE accreditation with the vast majority of allograft centres meeting JACIE requirements well ahead of other leading nations.

The BSBMT collects data on patient demographics, transplant type and transplant outcome for every transplant performed in the UK. The society then produces a comprehensive annual report along with an accompanying peer review. The BSBMT is at the vanguard of data management worldwide and the annual report is widely held to be the best report produced by a national transplant association. The most recent report, which was published in August 2012, is enclosed (enclosure 1).

The research portfolio and output of the UK haematology community is internationally recognised as first class. There is published evidence of key translational research documenting the UK contribution to our understanding of HLA matching and also graft

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versus host disease. In parallel with these scientific research achievements, UK stem cell transplant centres have successfully published clinical research, which has influenced transplant practice globally. This has often been facilitated through the BSBMT clinical trials committee (CTC).

The BSBMT CTC is an active part of the organisation. The group meets three times a year and performs high quality outcome-based studies addressing specific study questions and hypotheses. The BSBMT office staff (data managers and a part-time statistician) perform these studies in addition to their other roles, as outlined above, of collecting and curating clinical outcomes for every transplant performed within the UK. The chair and secretary of the CTC are volunteers from the transplant community and all principle investigators and study participants contribute in a voluntary manner. Despite restrictions, outcome studies are regularly produced and published in peer-review journals. These have a major impact on transplant practice both in the UK and internationally.

Given the nature of the CTC, which has no separate funding or infrastructure for prospective clinical trials, the output tends to address predominantly retrospective outcome studies. The CTC provides a forum for discussion of prospective study questions and for dissemination of protocols and results. The CTC would be perfectly placed, as it lies under the auspices of an active and interested transplant society, to be more actively involved in the running and governance of clinical trials in this area, if sufficient funding and infrastructure could be obtained. To date, this has been exceptionally challenging.

Infrastructure problems extend beyond the CTC to the transplant centres, where data manager and research nurse posts are frequently insufficiently funded, and the R&D process is arduous and frequently unregulated (in terms of turn around times). In a recent analysis of one of our prospective UK clinical trials (investigating aspects of cord blood transplantation) we showed that even after the trial was open centrally, it took a mean time of 300 days to get R&D approval within individual NHS Trusts.

This compares unfavourably to Clinical Trial Networks both on the continent and in the USA, where central funding is usually available and the clinical trial governance structures are less complex and time consuming. The number of regulatory bodies with clinical trial oversight in the UK is in itself a challenge which stifles innovative research.

In answer to the specific requests of the Committee:

The UK ranks very highly in the field of haematopoietic stem cell transplantation. There are a large number of high quality transplant units all of which comply with the highest possible international quality standards.

The field of haematopoietic stem cell transplantation enjoys an outstanding level of collaboration between transplant centres, the NHSBT, Anthony Nolan as well as cancer charities and representative organisations such as the BSH and the RCPath.

Research funding in this field has been poor and has largely relied on the generous support of charities such as Cancer Research UK (CRUK), Anthony Nolan and the Leukaemia and Lymphoma Research Fund (LLR). These charities raise funds from public donations and only disburse funds to projects that have undergone stringent peer review. There has been

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some funding from Wellcome and the MRC but there is very little direct government funding of haematopoietic stem cell transplant research. The absence of research investment has hampered the research and trial activities of the UK transplant community. Indeed current NHS pressures are having an impact on transplant research. We certainly trail our European and US colleagues in terms of research funding.

There has been a huge growth in the number of haematopoietic transplants performed over the last 5-10 years as we have developed safer methods of transplanting older patients (these patients were often denied transplants before 2000 because of the high toxicity of more traditional transplant procedures). The UK has been at the forefront of developing these reduced-intensity procedures. The UK is also developing the science for investigating alternative sources for stem cells (to allow all patients access to the potential benefits of stem cell transplantation) including cord blood and haplo-identical donors, although funding of these procedures has at times been difficult to obtain. In particular the development of cord blood transplantation has been hampered by a lack of investment and this has meant the UK trails other leading nations. These alternative donor sources are vital to address the transplant needs of ethnic minority groups where more traditional donors are often not available. There is likely to be further growth of haematopoietic transplant activity in the next 5-10 years.

The transplant teams are also committed to monitoring the outcomes of stem cell transplantation and produce high quality data as seen in the BSBMT report. This enables not only the opportunity to ensure the UK is at the forefront of best clinical practice but also provides reassurance that the NHS investment in stem cell transplantation represents value-for-money. However, the funding of this important registry has been tenuous and difficult and is run on a financial 'shoestring.' Indeed there is no identified funding for this registry beyond March 2013.

We are happy to provide more information for the committee and to support the work of the committee in this important field. We believe the UK is right at the very forefront of haematopoietic stem cell research and the application of human haematopoietic stem cell transplantation. The UK has a tremendous haematopoietic stem cell transplant resource and we believe we are in an excellent position to help the committee with their aims.

Authors:

Professor Graham Jackson – President of the BSBMT

Professor Gordon Cook – President Elect of the BSBMT

Dr Bronwen Shaw - Chair Clinical Trials Committee BSBMT

Mrs Keiren Kirkland - Head of BSBMT Data Registry

on behalf of the BSBMT, BSH and RCPath

20 September 2012

British Society for Haematology (BSH), the Royal College of Pathologists (RCPATH) and the British Society for Blood and Marrow Transplantation (BSBMT) – Written evidence

British Society for Haematology (BSH), the Royal College of Pathologists (RCPATH) and the British Society for Blood and Marrow Transplantation (BSBMT) – Written evidence

[Submission to be found under British Society for Blood and Marrow Transplantation \(BSBMT\)](#)

British Society for Oral & Dental Research – Written evidence

How does the UK rank internationally in the scientific field of regenerative medicine?

Many of the Dental Schools in the UK are contributing to research programmes in regenerative medicine. UK Dental Institutes have achieved international recognition, as highlighted in the RAE 2008 and other research metrics. There are major units within King's College London, the Universities of Cardiff and Sheffield with active groups engaged in stem cell biology, tissue engineering and reparative dentistry.

In the field of e.g. dental regeneration, King's College London Dental Institute is still the ONLY group to achieve whole tooth generation using cultured adult cells. As a typical example of the challenges facing UK regenerative medicine, this has not been translated to the clinic, due to funding agency expectations that a clinically applicable product be delivered within a three-year grant timeline.

The UK dental research groups have excellent basic science, which is relatively well funded, but there is poor funding to achieve translation. The US, Japan, Singapore and China are our direct competitors with significant long-term funding pipelines, perhaps with more straightforward routes to clinical application. In Japan there are labs with very long term support from industry and in the US CIRM and the NIH has invested millions. China has facilities and infrastructure but, so far, lacks expertise

Where does the UK have strengths and weaknesses in the field?

STRENGTHS:

- Stem cells – pluripotency, lineage differentiation, tissue replacement, immunomodulation, organ development
- Stem cell bio-processing
- Biomaterials (acellular/cellular) – strong links between Bioscience/clinical science departments and engineering departments
- Cell imaging – conventional imaging and a drive to develop novel, non-destructive imaging for long term *in situ* tracking
- Strong links between the HEIs and the NHS (e.g. academic health science centres) and a robust but bureaucratic and slow ethical review system to drive the development of clinical trials

WEAKNESSES:

- A clear understanding of what the 'niche' is in order to exploit this as part of a regenerative medicine approach
- There is a tendency toward development of *in vitro/ex vivo* approaches (i.e. growing organs in the lab) rather than understanding the fundamental principles to drive *in situ* repair/regeneration, which would be clinically most useful: commercial buy-in to this is lacking.
- Limited coordinated cross-country infrastructure/funding
- Limited clinical translation

Who are the major funders of research in the field of regenerative medicine?
What funding is available to support this research?

MRC, EPSRC, BBSRC, Wellcome – through a number of cross/inter-disciplinary initiatives. TSB has some funding for translation but nowhere near enough to translate a significant number of potential products/therapies. European Union FP5 & 7 funding can be significant. Smaller funding from NC3Rs, charities e.g. Furlong, Orthopaedic Research UK (although not directly targeting regenerative medicine most of the time). There is limited investment from industry in the current financial climate and few, if any, Government incentives for industry investment.

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

Limited number of actual translations in the UK:

There are a number of therapies that are in the clinic or clinical trials. Quick overview below:

- Limbal stem cells for corneal regeneration: e.g. Moorfields Eye Hospital
- Chondrocytes (not stem cells but a cell therapy) - numerous hospitals e.g. Oswestry, Institute of Orthopaedics, RNOH
- Mesenchymal stem cells :
Many hospitals use bone marrow aspirates that are concentrated to increase density of MSCs for bone repair
- Heart failure – Kings College – human trial
- Cartilage – Bristol University
- Many trials by REMEDI, Galway, Republic of Ireland
- Neural stem cells : Phase I stroke therapy RENEURON (spin off from Kings).
Currently in Phase II clinical trials: regular updates on their website
<http://www.reneuron.com/>

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

Probably limited numbers due to remaining issues with scale up and the need to develop autologous rather than allogeneic therapies. BRC's and e.g. the TSB Catapult Initiative may lead to increased delivery.

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: *Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

These strategies are certainly a step in the right direction, coordinating the activities of the major research councils and the TSB and targeting different elements of the developmental/translational pathway. Support of the underpinning cross-disciplinary research is crucial and must be sustained if UK PLC is to have anything to translate in the future. Links with external bodies are also crucial. Overall, the budget is small unless industry can be tied in. The development of regional (physical) centres bringing the best expertise together could seed faster development (if infrastructure and funding are

provided). This would have to be de-coupled from the *Research Excellence Framework* to get HEI buy in.

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

Estimations for stem cell therapy world-wide are approx. \$64Billion by 2015 – through direct disease therapy, cell storage and the industry providing support for these programmes. The value for society is huge as whilst the average life span is increasing the number of disease-free/healthy years is not. Regenerative medicine is key to relieving human suffering and restoring quality of life to individuals.

Society's expectations have increased with regard to disease treatment and healthcare. As a result, development of novel technologies are necessary to respond to healthcare needs- this is a major global goal. Patients expect improved therapeutic treatments of disease, advanced detection and therapies. Stem cell therapy has the potential to be cost- effective in the long term.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high-risk area? If not what more should Government do?

The TSB funding is allowing some findings to translate through to market but these are limited, There is no long term (15-20 year) funding pathway to allow translation from basic findings through to delivery to patient. Projects stall most often after the basic, underpinning research is undertaken and the Research Councils fail then to renew funding (although programmes like the MRC translational stem cell programme are attempting to change this). There is limited industry 'buy in' until near to the end of the pathway (a programme of co-funding from an early point in the pathway could be useful provided all those involved (individuals, HEIs, industry) share in the commercial development to support further research and development of future ideas). Whilst much effort is undertaken to drive inter-disciplinary research this is still limited and often challenging. Key also is adequate GMP facilities across the UK to enable on-site preparation of cells for patient therapy (there is no coordinated activity in this area – GMP 'centres of excellence' maybe?). Taking this one step further, regional Regenerative Medicine Centres should be developed (infrastructure and long term funding coming from investment from Government and buy in from relevant HEIs – and may be industry) with direct links to the NHS to drive 'bench to bedside' therapies. Whilst individual HEIs are attempting this on a smaller scale, few lack the realist budget to make significant advancements.

What role does patenting play in the commercial development of regenerative treatments?

Absolutely crucial as industry is vital in the development of regenerative medicine therapies and they generally won't pursue research that isn't IP protected. However, HEIs are just getting to grips with IP development and hence spin out/licencing activities are still in their infancy.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

Infection/major health issues, lack of governance, bogus (un-proven) therapies, over pricing.

(Response derived from information primarily supplied from King's College London and the University of Cardiff).

20 September 2012

Professor Robert A Brown, University College London – Written evidence

The UK is undoubtedly a world leader, in general, in Regen med., probably being positioned between 1 and 3 in most of the central strands and sub-activities, in terms of originality and applications.

The ‘applications’ are best considered under two headings:

Therapeutic (implants, cell therapies etc) and Models (3D tissue equivalents for research, pharma/tox testing, diagnosis – animal sparing etc).

The needs, technological demands and opportunities are in fact quite distinct, though UK is (for pretty obvious reasons) world leading in the model applications. Equally obviously, the therapeutics is primarily focused on translation to clinical practice and patients whilst the models have a more immediate impact translation to industry.

The direct value of the ‘model sector’ to UK industry is potentially huge as it BOTH promises to provide new opportunities and high selection rates for ailing pharma and chemical, as well as the cosmetics industries, and to generate **new** specialist industries for making and supply of the plethora of 3D, non-animal (tissue equivalent) test systems that will be needed (eg. see TAP-Biosciences Ltd, Royston).

However, it is far less widely appreciated that the approaches and base technologies for these two sectors will almost certainly differ significantly (ref 1: chapters 2 & 6). Specifically, ‘growing’ tissues, albeit ‘in the patient’ or ‘in bioreactors’ is sometimes a viable approach where patient’s own cells are to be used for therapeutic implants. However, such approaches (at present) are very slow and produce one off structures, well adapted to the patient surgical practice but very expensive and far too variable for use as test-bed systems.

Here we have another useful bifurcation of processes in TERM involving:

Growing/culturing tissues on temporary scaffolds (which disappear) –need here is for SPECIAL CELLS and new control processes and bio-factors.

Fabricating tissue directly (without immediate cell involvement, though ideally around the required cells). This can involve tissue layer fabrication and engineering, bio/cell-printing or some electro-spinning. In this, cells are passive components to come to play later. The key is to be able to make and assemble NATURAL, protein materials with 3D micro-structure, rapidly.

One final classification which is very useful in practical TERM is the distinction between ‘types of tissue target’. It is largely true that the problems and technologies involved at all stages are very different for producing:

CELL-Rich tissues (eg. liver, heart, Lung, Kidney), and

MATRIX-Rich tissues (skin, blood vessels, bone, cartilage, eye, ligament-tendon)

Potential for Utility.

There is clearly a huge variety of possible approaches to the use of advanced bio-technologies and cell-based approaches for both therapeutic and modelling applications. However, it is equally true that many of these POSSIBLE combinations will either be inherently inappropriate for certain classes of application, or will not even be likely to produce what is implied by the term ‘regeneration’ (ie. restoration of ORIGINAL tissue structure and function, prior to damage]. Many current approaches are ‘engineered/assisted tissue repair’, labelled (?) *regeneration* for a range of reasons. It can be unhelpful to include these, or it might be better to avoid such wide use of the term regeneration (which is a very rare achievement in biomedicine).

The example provided of- ‘GROWING’ a new TRACHEA is a good example of this. Although it is a remarkable piece of innovation and surgically very exciting, it is not such a good example of regen med. Firstly, this is a matrix-rich tissue where the bulk matrix is not regenerated and certainly not GROWN (in fact they are either a non-degradable polymer support –ie a prosthetic- or a cadaveric de-cellularised matrix scaffold). The key part is that the patient’s own cells are seeded over these supports to form a protective, hopefully functioning cell layer. These are exciting approaches to bio-engineered repair, similar to new approaches to improve (metal and plastic) joint or bone prosthetic implants by incorporation of cell layers and depots. However, we should be clear that these cannot (are unlikely to) lead to the high target of new tissue regeneration any time soon and so we should be careful with their positioning.

Because this is a relatively new subject with a continuing, rapid influx of new talent and new approaches (or vocabulary), from different fields it is easy for there to seem to be a diffuse cloud of ‘great potential’. In fact a little rational separation and route-planning can be EXTREMELY useful in critically understanding where things are coming from (and likely to go). I have recently attempted just such a general work (in the form of an entry textbook), from which it is possible to find a more detailed account of this reviewer’s analysis.

- I. Extreme Tissue Engineering: concepts and Strategies for Tissue Fabrication. Brown RA. 2012. Wiley-Blackwell; Oxford.

20 September 2012

Bupa – Written evidence

Introduction

Bupa's purpose is to help people lead longer, healthier, happier lives.

Bupa is the UK's leading healthcare group. We provide personal and company health insurance, run care homes for older and disabled people, provide workplace health services, health assessments, health coaching and home healthcare.

- Bupa Health and Wellbeing is the UK's largest health insurer serving close to three million people.
- We have 51 Bupa centres which offer a range of services and treatments, such as health assessments, weight management advice and sports injury treatment.
- Bupa Cromwell Hospital provides patients with access to 400 of the country's top consultants. The 128-bed purpose-built facility covers 50 medical areas focusing on oncology, paediatrics, orthopaedics and cardiac services.
- Bupa cares for over 18,000 older people in the UK in over 300 homes. Over 70% of our UK care home residents receive state funding.
- We work with more than 200 NHS hospitals and 50 PCTs providing healthcare at home to over 15,000 people.

With no shareholders, we invest our profits to provide more and better healthcare. We are committed to making quality, patient-centred, affordable healthcare more accessible in the areas of wellness, chronic disease management and ageing.

For more information, visit www.bupa.com.

Application of the science

1.0 Which treatments are available through private healthcare?

1.1 This is a difficult question to answer because of the very wide sweep of the definition of regenerative medicine being used for this inquiry. It could be argued that everything that is done with curative intent, rather than with palliative intent, should be included as it seeks to restore or establish normal function.

1.2 Answering in the spirit rather than the letter of the question, Bupa's UK private medical insurance routinely funds:

- Bone marrow transplantation as part of the treatment of haematological malignancies
- ChondroSelect (currently the only Advanced Therapy Medicinal Product) for knee lesions
- MACI (a trade mark) for knee lesions
- InductOs for acute tibial fractures
- Bone morphogenetic protein (BMP7) for delayed union of traumatic fracture
- Regranex for full thickness, neuropathic diabetic ulcers

Bupa – Written evidence

- any biologic mesh for sacrocolpopexy for vaginal vault prolapse repair (according to NICE IPG 283)
- platelet rich plasma for tennis elbow (according to NICE IPG 279)

1.3 We can and often do make discretionary payments to support Bupa members participating in formal medical research. In this context, we have been/are funding:

- Autologous peripheral blood progenitor cells & hyaluronic acid for knee cartilage lesions NCT01076673
- Carticel for knee cartilage lesions (NCT00158613)
- Cytovir to prevent/control CMV reactivation after bone marrow transplantation NCT01220895 and NCT01077908
- Strattice for incisional hernias (where there is infection) NCT01083472

1.4 The Bupa Cromwell Hospital in London does not offer facial injections of platelet rich plasma ("Vampire Facelifts") as it is unclear what result clients should expect from this cosmetic procedure.

Barriers to translation

2.0 What barriers are encountered when seeking approval for the use of such treatments through private healthcare?

2.1 Bupa strives to ensure that its members are only treated using evidence based methods and products. We have developed in-house a group of algorithms to facilitate the rapid clinical health technology appraisal of tests, and of medicines, interventional procedures [see Warren V. J Health Serv Res Policy 2007;12:142-6], and cell based therapies. The cell-based therapies algorithm was developed as part of the Department of Business, Innovation and Skills' Technology Strategy Board's Commercialising Stem Cells project (2010-12). A paper on its development and use has been submitted to the journal 'Regenerative Medicine'.

2.2 We expect to see high quality clinical research output on safety and efficacy which shows that one or more specific patient groups derive sustained benefit (improvement in life expectancy and/or in relevant quality of life) from the use of the test or treatment under consideration. We also have a duty to members claiming for other pathologies, and to non-claiming members, so favour care which has a cost proportionate to the benefit delivered.

2.3 Bupa Health and Wellbeing, the Bupa UK private medical insurance business, considers regenerative medicine to be a completely new class of treatment and will define it as such in policies from January 2013.

2.4 Bupa Health and Wellbeing forecast that regenerative medicine will increase the cost of medical insurance by an additional 10% by 2020. This is additional to the current rate of medical inflation for private insurance running at 9.9% per year.

International comparisons

3.0 What risks do UK citizens face when travelling to other countries for regenerative treatments?

3.1 Bupa perceives a need for public education on regenerative medicine and its potential to improve health, because regenerative medicines may be over-hyped, especially to vulnerable patients. For example during 2011, a request for funding was received from an ex-pat member of our International scheme requesting funding for treatment with mesenchymal stem cells for brachial plexus injury, to be delivered by lumbar puncture. We requested that the German team offering this treatment in Egypt confirm our understanding that they were not conducting formal medical research to evaluate this regenerative medicine and that there were not relevant peer reviewed clinical papers in the literature. Their reply did not address these issues and so we concluded that we had been correct in our assessment that there was no evidence base.

Conclusion

4.0 Regenerative medicine is an exciting advance, but treatments must be based on clear evidence and patient expectations on outcomes managed and agreed in advance of any procedures.

11 September 2012

Bupa Health and Wellbeing UK, National Institute for Health and Clinical Excellence (NICE) and TiGenix NV – Oral evidence (QQ 214-243)

Bupa Health and Wellbeing UK, National Institute for Health and Clinical Excellence (NICE) and TiGenix NV – Oral evidence (QQ 214-243)

[Transcript to be found under National Institute for Health and Clinical Excellence \(NICE\)](#)

California Institute for Regenerative Medicine (CIRM) – Written evidence

We thank you for the opportunity to contribute to the House of Lords Regenerative Medicine call for evidence. CIRM is a leading international funding organization with the mission to support the development of regenerative medicine therapies. As an organization, we believe regenerative therapies will play an integral role in the advancement of clinically- and cost-effective health care delivery.

The unique value of regenerative medicine lies in its capacity to reverse the course of disease and injury, by providing economically beneficial -- “hitting a six” -- therapies. From the standpoint on national health policy, this potential deserves sustained investment in research and development. Approximately half of the total burden of disease in developed nations – impact of a health problem in an area measured by financial cost, mortality, morbidity, or other indicators – can be attributed to five underlying disease conditions: cardiovascular disease, cancer, diabetes, HIV/AIDS and acute injuries (see attachment 1).⁹⁰ Evidence to date suggests regenerative medicine (as defined by the Committee on Science and Technology) holds promise for preventing, treating and/or reversing each of these conditions. The CIRM [Disease Team research portfolio](#) provides further evidence of this potential.

Recent breakthroughs reinforce our belief that regenerative medicine represents a platform for the development of clinically- and cost- effective health care delivery. Consider the recent example of the synthetic windpipe, or trachea, made from minuscule plastic fibers and covered in stem cells. The synthetic windpipe has been successfully used in patients with otherwise inoperable cancers. Trachea transplants have simultaneously eliminated cancerous tissue and improved function (e.g. ability to talk) in patients.

A second example involves heart disease, a chronic condition with the highest per capita and national costs for services. Societal costs multiply because of ongoing reductions in work and productivity as well as reduced quality of life. Clinical studies are underway to use stem cells to reverse damage resulting from heart attack.⁹¹ Individuals with severe damage experience diminished physical capacity and reduced quality of life. A regenerative therapy would be highly cost-effective because repairing tissues enables greater productivity and quality of life. Applications for new stem cell-based therapies are also being developed for cancer, HIV/AIDS, neurological disorders, acute injuries among other diseases.⁹²

CIRM views the UK as an essential partner and collaborator in fulfilling this promise. As described below, UK teams in collaboration with CIRM partners are playing a leading role in the development of regenerative therapies. This role has been greatly enhanced by Parliamentary policy (such as sustained support for MRC programs), and future decisions should reinforce the UK’s historically competitive position in this emerging field of science and medicine.

⁹⁰ Michaud K. [The Burden of Disease and Injury in the United States 1996](#). Health Affairs, 4, no. 11 2006.

⁹¹ See <http://www.cirm.ca.gov/Grant/human-embryonic-stem-cell-derived-cardiomyocytes-patients-with-end-stage-heart-failure-0>

⁹² see http://www.cirm.ca.gov/Our_Funding/Progress_Toward_Therapies/stem-cell-therapies-discovery

The Research Base:

A CIRM review of publication frequency in stem cell science and regenerative medicine demonstrated the UK ranks among the top tier of nations, and brings a range of research capacities to the regenerative medicine space. For the purpose of this call for evidence, here we highlight specific example where basic and clinical researcher involving UK teams have impacted CIRM programs.

Basic Research:

Basic scientific research and infrastructure forms the foundation for progress in regenerative medicine. The UK has shown longstanding leadership in critical aspects of basic research in stem cells and regenerative medicine. For instance, John Gurdon pioneered methods to “reprogram” cells to an embryonic state using nuclear transfer. Martin Evans isolated the first mouse embryonic stem cells. More recently, Austin Smith house become a leader in the field of mouse and human embryonic stem cell research, identifying key proteins that control stem cell behaviour. Fiona Watt is renown for her work on understanding how “adult” stem cells are organized and maintained in skin and other tissues, and the role they can play in cancer.

In terms of infrastructure, the UK Stem Cell Bank represents an important international resource to support basic research in regenerative medicine. The UKSCB continues to be one of the top sources of stem cell lines for basic and clinical research. Besides being a leading distribution centre for cell resources, the bank has been extraordinarily generous in providing technical expertise to CIRM and other international collaborators. This expertise has informed the development of cell banks in California and with UKSCB participation in expert peer review, it has influenced CIRM funding decisions.

The Sanger Institute is a leader in genomics, and they are now, in parallel with CIRM, turning their attention to building large bio-banks of “personalized” stem cells, which can be used to study the genomic contribution to diseases, and to provide a resource for basic research on disease causation, and for drug discovery. We look forward to ongoing collaborations with the Sanger team to inform the development of CIRM-funded genomics and bio-banking initiatives.

Clinical Studies:

The UK MRC is CIRM’s second largest collaborative funding partner. CIRM’s Grants Working Group, comprised of leading researchers in the field of regenerative medicine, has evaluated collaborative proposals involving UK and California research centers. Two MRC funded teams are among a select group of researchers with meritorious proposals for clinical studies. These clinical studies are aimed at the development of cancer therapies and treatments for blindness (age-related macular degeneration).

In addition, to bringing world-class expertise in these disease areas, the MRC effectively leveraged its own research funds through this UK/California collaborative mechanism. The MRC committed \$8.3 million, which was combined with a CIRM commitment of \$35 million to support clinical studies. Thus, from a public policy perspective, it is important to recognize how commitments in the UK have a multiplier effect when they are committed in collaborative research ventures.

Application of Science:

As evidenced by the combined \$43.3 million in clinical studies, the UK is at the forefront of translational applications. CIRM considers the effort involving the University College London's team in macular degeneration to be one of the most promising therapeutic opportunities in the next 5-10 years. Macular degeneration is the leading cause of blindness, so reversing the course of disease would represent an extraordinarily cost to benefit ratio. Further, because the eye is not readily susceptible to adverse immune reactions and injected cells can be monitored, there is a very favorable clinical safety profile.

Regulatory Policy:

It is also important to acknowledge the UK's leadership in policy development, oversight and public engagement. The UK has done more than any nation to inform policy development at CIRM. For example, HEFA's leadership in the area of consent for embryo donation and evaluation of public support for human embryonic stem cell research provides the evidence base to support effective public policy. The governance scheme of the UKSCB provides assurance that distributed materials conform to the highest international standards for research ethics. This leadership role is so substantial that in 2005 CIRM recognized HEFA licensing and UKSCB oversight requirements as substantially equivalent to the institute's policies (the only recognition provided to an outside jurisdiction at the time). This recognition enabled expedited flow of research materials from HEFA licensed laboratories and the UKSCB to California researchers.

Barriers to Translation:

For many chronic diseases, where regenerative therapies are being developed, a major challenge is to adequately demonstrate that a new therapy is an advancement over the existing standard of care. For fatal disease such as ALS and Huntington's disease, where there is no effective standard of care, trials may be initiated more easily. In contrast, there is an established standard of care for most major chronic conditions including cardiovascular disease, cancer, diabetes, HIV/AIDS and acute injuries. The identification of patient cohorts must be more selective and involve balancing disease severity with range of risk benefit criteria. The aforementioned macular degeneration study is one where risk benefit criteria favor clinical innervation.

At this time, our experience with cell-based therapies across a broader disease portfolio is limited, so the challenge is developing the evidentiary base to inform decision-making including regulatory determinations and the assessment of risks and benefits. The UK is rich in clinical capacities capable of advancing knowledge. National health records and registries enable effective selection and follow up of patient cohorts. Well-developed systems for ethics review and public consultation support effective balancing of scientific and social considerations. A mature regulatory infrastructure informs safe and effective cell processing and product manufacturing. The existence of world-class treatment centers enables the effective delivery therapies and ongoing patient monitoring. To overcome existing barriers, policymakers should ensure that expertise is devoted to cell based therapies and biological products existing within the entire system.

Barriers to Commercialization:

UK representatives are involved in a number of organizations related to the commercial advancement of regenerative therapies. Organizations such as the BIA Cell Therapy & Regenerative Medicine Industry Group, International Society for Regenerative Medicine and the Alliance for Regenerative Medicine are working to address barriers to commercialization. UK representation is integral to these organizations, and we are confident they will serve to facilitate commercial opportunities.

There are specific issues where initiatives emanating from the committee on Science and Technology may serve to advance the field. The recent ruling of the Court of Justice of the European Union in *Brustle v Greenpeace* has highlighted the potential for legal and policy decision to impact commercial development in the life-sciences. CIRM recently indicated its desire to formally collaborate with Professor Aurora Plomer, Director of the Sheffield Institute of Biotechnology, Law and Ethics. We believe it is important to evaluate the impact of this ruling on national research programs and evaluate where new initiatives are advisable, in light of this ruling, to support commercial development.

On a related issue, there have been indications that there is opposition to including embryonic stem cell research in the Horizon 2020 research program. CIRM was created to provide regenerative medicine researchers with the opportunity to pursue all promising avenues of scientific inquiry. [As we have documented](#) with previous research, efforts to segment funding opportunities in this manner will undermine medical innovation, deter human capital and increase the cost of research programs. Again, we believe the committee should consider policies to avoid such conditions in the UK.

Attachments:

Attachment I: CIRM Therapy Development Pipeline: Selected awards focusing on bringing new therapies to clinical application for 38 diseases (not published here, but can be found at <http://www.cirm.ca.gov/therapies-discovery>).

21 September 2011

Cambridge National Institute for Health Research (NIHR) and Scottish National Blood Transfusion Service (SNBTS) – Written evidence

1. Response to call for evidence:

1.1 *A strategy to maximise the utility of induced pluripotent stem cells (iPSC) for regenerative medicine in the UK population and worldwide.* Craig J. Taylor, Sarah Peacock, Afzal N. Chaudhry, Philip A. Dyer, Eleanor M. Bolton, J. Andrew Bradley. An expert group of scientists and clinicians working in the field of tissue transplantation at the Cambridge NIHR and the Scottish National Blood Transfusion Service.

2. Background:

2.1 The therapeutic application of human stem cell technology in regenerative medicine, with the replacement of diseased and damaged tissue with healthy tissue has the potential to benefit tens of thousands of UK citizens with a range of neurodegenerative, autoimmune and cardiovascular diseases. The question arises how best to realise the full potential of stem cell therapy and offer affordable and durable treatment on such a large scale.

2.2 At the present time, there are no functional tissues, derived in a laboratory setting from human stem cells that can be used to replace and repair diseased and damaged tissues such as insulin-producing pancreatic beta cells, myocardial cells, neurological tissues, or renal tissues. Certain stem cell therapies are currently used in clinical practice: CD34+ blood stem cells are effective for replacing a patient's white blood cells (including cells of the immune system) but there is a need for close HLA (tissue type) matching between the stem cell donor and the patient to avoid rejection of the stem cells, and to avoid graft versus host disease, when the donor stem cells recognise the patient as 'foreign', and attempt to destroy patient cells. Similarly, partially differentiated or multipotent stem cells such as mesenchymal stem cells (MSC, often obtained from the umbilical cord or from adipose tissue) are used in clinical trials in an attempt to integrate them into the patient's remaining healthy tissue and to encourage the patient's own tissue stem cells to regenerate, but it remains unclear how efficacious these cells are, and whether or not HLA-mismatched MSC persist in the patient or are rejected. The ability to create clinically useful insulin-producing cells, or sheets of myocardial tissue, or neurological tissue for example, from stem cells remain major research goals to be realised possibly within the next decade. However, once these tissues are created, the likelihood that they will be recognised as foreign, and be rejected by the patient's immune system remains relatively unexplored.

2.3 This response to the Select Committee on Regenerative Medicine draws on the expertise of transplant clinicians and scientists to consider the practicalities and physiological implications of regenerative medicine. We address two areas of the **Call for Evidence**: under **Application of the science**, we discuss the possibility of rejection of stem cell-derived tissues and how to avoid it; under **Barriers to translation**, we identify the ethical considerations of our approach to avoiding tissue rejection.

3. Application of the science:

3.1 This response addresses the potential that stem cell-derived tissues for regenerative medicine may be rejected by the patient's immune system. It explores strategies for providing known, HLA-typed stem cells for research into directed differentiation (to create specific functional tissues) and into drug discovery (for treating inherited diseases) and,

eventually, for regenerative medicine to avoid rejection of the stem cell-derived tissues and minimise the requirement for treatment with immunosuppressive drugs. We propose that the UK Stem Cell Bank at Potters Bar, or similar, could be populated *at the present time* with as few as 150 lines of induced pluripotent stem cells that bear the optimal combination of HLA types selected to provide the best possible HLA match for the greatest proportion (93%) of the UK population. This approach is directly applicable to the establishment of similar stem cell banks in other countries worldwide, such as Japan where the government is already considering a proposal by the stem cell pioneer, Shinya Yamanaka, to establish a bank of the type that we propose.⁹³ We argue that our approach to creating such a stem cell bank is practicable and achievable; indeed, more practicable than that proposed by Yamanaka.

3.2 The case for an HLA-typed Stem Cell Bank

3.2.1 In clinical practice, stem cell derived tissue created from the intended recipient offers the possibility of personalised stem cell therapy in which the patient's immune system will accept the tissue transplant, or graft, as 'self' and graft rejection would not occur. In theory, 'self' stem cells are readily obtained by reprogramming adult cells such as skin fibroblasts to produce induced pluripotent stem cells (iPSC) as described by Yamanaka et al.⁹⁴ In practice, this is problematic due to the low success rate and consequently, high cost of obtaining iPSC from adult tissue. Individualised iPSC therapy is expensive and may only benefit wealthy individuals able to pay for their treatment.

3.2.2 An alternative approach is to establish a public stem cell bank that contains a range of clinical grade stem cell lines derived from iPSC, capable of large scale expansion *in vitro* and able to treat a potentially unlimited number of patients. In the case, however, of iPSC-derived tissue transplanted into an unrelated recipient, there is potential for the tissue to be recognised as 'foreign' by the recipient immune system and undergo subsequent allograft rejection.^{95,96}

3.2.3 Experience from clinical cord blood stem cell and solid organ transplantation has shown that matching of donor and recipient HLA types, together with effective immunosuppressive therapy is able to minimise the problem of allograft rejection and improve transplant outcome. We propose the establishment of national and international induced pluripotent stem cell banks comprising cell lines expressing a range of HLA types that are selected to represent different geographical populations and ethnic groups worldwide and provide HLA matched stem cells for the majority of potential recipients.^{97,98}

3.3 Identifying and banking iPSC obtained from volunteer donors with the required HLA types that match the UK population.

⁹³ Cyranoski D. Stem-cell pioneer banks on future therapies. *Nature* 2012; 488: 139.

⁹⁴ Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131: 861-72.

⁹⁵ Bradley JA, Bolton EM, Pedersen RA. Stem cell medicine encounters the immune system. *Nat Rev Immunol* 2002; 2:859-71.

⁹⁶ Fairchild PJ. The challenge of immunogenicity in the quest for induced pluripotency. *Nature Reviews Immunology* 2010; 10: 868-75.

⁹⁷ Taylor CJ, Bolton EM, Pocock S, Sharples LD, Pedersen RA, Bradley JA. Banking on human embryonic stem cells: estimating the number of donor cell lines needed for HLA matching. *Lancet* 2005; 366:2019-25.

⁹⁸ Taylor CJ, Bolton EM, Bradley JA. Immunological considerations for embryonic and induced pluripotent stem cell banking. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2011; 366: 2312-2322.

3.3.1 We provide a practical solution for populating a therapeutic iPSC bank with a relatively small number of lines that will enable HLA matched tissue transplantation for the majority of the UK population.⁹⁹ The UK has a significant advantage in this respect in that we are the only country to have already calculated the optimal combinations of HLA types that provide the minimum number of volunteer iPSC donors that would match the HLA types of all 10,000 individuals considered as a representative cross-section of the UK population. We have also shown that individuals with these selected HLA types are already known to volunteer haematopoietic stem cell donor registries (such as the British Bone Marrow Donor Registry and Anthony Nolan Bone Marrow Donor Registry) that could form a readily available source of volunteer iPSC donors.

3.3.2 The 10 most common donor HLA types that are known to be available among UK volunteer stem cell donors would provide an HLA match for 53% of UK recipients and the 50 highest ranked (most common, available) donor HLA types would provide HLA matched tissue for 79% of UK recipients. Increasing the size of a UK iPSC bank to include the 150 highest ranked donors would match 93% of the UK population, with reduced requirement for immunosuppression.

4. Barriers to translation:

4.1 Volunteers listed on UK national haematopoietic stem cell (HSC) donor registries have only consented to provide HSCs for a single recipient in need of a transplant and have not been asked to consent for donation of tissue from which an iPSC cell bank could be created that had the future potential to help many thousands of recipients. The ethics of seeking consent from the donor registry to approach such individuals and request their consent for tissue for an iPSC bank would need to be addressed. To pursue this approach would necessitate extensive consultation and agreement from national volunteer HSC donor registries. The ethics of seeking consent from individuals with the required HLA types for donation of tissue (e.g., blood or skin biopsy) from which iPSCs could be derived requires careful consideration. However, such volunteers have already expressed their willingness to donate HSCs harvested from blood or bone marrow to treat a single anonymous individual. In the case of iPSC therapy, the opportunity for selected volunteers to help a potentially unlimited number of patients might be an attractive and achievable proposition. We encourage UK policy makers to use this approach to identify and select the optimal HLA-typed volunteer donors to match a potential UK iPSC recipient population.

Authors:

Dr. Craig J. Taylor PhD, FRCPath

Consultant Clinical Scientist, Director of Histocompatibility & Immunogenetics, Tissue Typing Laboratory, Cambridge University Hospitals NHS Foundation Trust.

Dr. Eleanor M. Bolton PhD

University of Cambridge, Cambridge University Hospitals NHS Foundation Trust.

Mrs. Sarah Peacock, BSc (Hons), MSc, dipRCPath

Principal Clinical Scientist, Tissue Typing Laboratory, Cambridge University Hospitals NHS Foundation Trust.

⁹⁹ Taylor CJ, Peacock S, Chaudhry AN, Bradley JA, Bolton EM. Generating an iPSC bank for HLA-matched tissue transplantation based on known donor and recipient HLA types. *Cell Stem Cell* 2012; 11: 147-152.

Cambridge National Institute for Health Research (NIHR) and Scottish National Blood Transfusion Service (SNBTS) – Written evidence

*Dr Afzal Chaudhry BSc (Hons), MA(Med Ed), PhD, FHEA, FRCP, FAcadMed
Consultant Nephrologist and Clinical Lead for IT, Cambridge University Hospitals NHS Foundation Trust.*

*Professor Philip A. Dyer, OBE, PhD, FRCPath
Consultant Clinical Scientist, Director of Histocompatibility & Immunogenetics, Scottish National Blood Transfusion Service, Professor in Transplantation Science.*

*Professor J. Andrew Bradley, MBChB, PhD, FRCS, FMedSci
Professor of Surgery, University of Cambridge, Cambridge University Hospitals NHS Foundation Trust.*

20 September 2012

CASMI (Oxford-UCL Centre for the Advancement Sustainable Medical Innovation) – Written evidence

CASMI has been invited to submit evidence on ‘Adaptive Licensing’ (AL) and its potential applications in cell therapy. We will outline the AL concept, what we see as the current state of regulation in cell therapy, the key differences between drugs and cells as therapeutic agents and conclude with some suggestions about how AL might apply in this newly emerging field.

This evidence relates specifically to the cell therapy component of regenerative medicine. Many of its observations, however, apply also to gene therapy and other advanced therapies.

‘Adaptive Licensing’

The realisation that drug development and regulatory approval have become too rigid and cumbersome is now quite general, although that does not mean there is a global consensus about how to move forward. In Europe the European Medicines Agency has indicated their willingness to pilot an approach to enable earlier access to a medicine on a conditional approval basis, with further data on efficacy and safety collected following such an approval.¹⁰⁰ This can mean access to patients without (or before) the conduct of a formal ‘Phase 3’ trial, a trial that typically adds around 3 years in delay and often tens of millions of pounds in cost.

This ‘AL’ route does not appear to require any new legislation and, with support from CASMI, the UK government and the MHRA are seeking to have the UK participate in this pilot evaluation.

However, AL is just one key element of what CASMI terms as the adaptive approach to the whole innovation process.¹⁰¹ This broader concept would bring together the key stakeholders (sponsor, regulatory authority, HTA agency and patient representatives) to design a medicine-specific development pathway that takes account of disease severity, acceptable benefit/risk considerations, and the need to collect ‘value’ information to support the ultimate pricing. For most such applications, careful patient selection (e.g. via stratifying biomarkers) will be necessary to ensure that the medicine is focused on the group of patients likely to have the highest benefit/risk ratio.

Status of Cell Therapy regulation and key differences from conventional medicines

CASMI recently completed a review of the status of regulation in the CT field and concluded that regulatory authorities were showing appropriate flexibility in their early treatment of cell therapies. It must be borne in mind, however, that most therapies are still at the clinical trial stage: no cell therapy has yet received full marketing approval in Europe from the Committee for Advanced Therapies (three approvals have been granted elsewhere).

¹⁰⁰ Eichler, H. G. et al. Adaptive Licensing: taking the next step in the evolution of drug licensing. *Clin Pharmacol Ther.* 91(3), 426-37 (March 2012).

¹⁰¹ Barker R. A flexible blueprint for the future of drug development. *Lancet.* 375, 357-59 (2010).

Our review highlighted a key UK deficiency: the number of regulatory professionals that understand the field. This means that sponsors often struggle to access the advice they need in a timely manner. We recommended that a national resource be created, perhaps by the Cell Therapy Catapult, to act as a hub for such expertise, connecting companies and other researchers with relevant experts.

As is probably self-evident, the nature of cell therapies will require a much more adaptive approach than has been customary for pharmaceuticals. Cell therapies can be derived from mature cells, either autologous or allogeneic, or from embryonic or adult stem cells; they can also be applied locally or systemically. While some early applications have been in areas of high unmet need, such as spinal cord repair or Parkinson's Disease, trials are also underway in more common conditions, such as joint osteoarthritis. Therefore not only will there be a wide variety of potential safety issues (from effectively zero therapy-related issues for most autologous transplants, to the risk of tumourogenicity for some stem cell applications), the acceptable balance of benefit with such risks will also vary widely.

Clinical trials will also typically be done on a small number of subjects, because of either the rarity of the condition or the cost of trials, making conclusions from such formal trials less conclusive. Despite smaller numbers, Phase 1 and 2 trials in cell therapy seem to be taking longer than for medicines. (Phase 1 however is typically in patients rather than healthy volunteers, so they do yield some efficacy data.) If patient access is not to be too delayed, an adaptive licensing approach would seem worthwhile investigating for cell therapies from the outset.

In fact, we believe that the full adaptive approach, with therapy-specific development plans agreed across stakeholders (as defined above) will be particularly appropriate for cell therapy. Not only will patients seek early access to revolutionary therapies, and formal trials will have their limitations, but health systems will need to define upfront the 'value' information required to support the relatively high prices - and costs of treatment administration - that cell therapies will typically involve. Some of this data may emerge from trials, but real world data collected after conditional approval will give a more accurate picture of the economics, and will enable the sponsor to either support or modify their price.

Further complications lie ahead. We will see combination products, such as cells combined with physical scaffolds for musculoskeletal applications. Will these be licensed as separate entities or will the combination need to satisfy regulators? Constructive early dialogue between sponsor and regulator will be critical.

12 February 2013

Cell Therapy Catapult Centre (CT Catapult) – Written evidence

Executive Summary

1. The Cell Therapy Catapult Centre (“CT Catapult”) was established in May 2012 as one of seven Catapults being created by The Technology Strategy Board under £200m of core funding from Government.¹⁰² The CT Catapult is specifically established to exploit the strong UK capability in cellular therapy basic science and to provide further resources and expertise to support industry and progress therapies to the point where there is sufficient evidence of efficacy, safety, manufacturability, cost effectiveness and market potential, to accelerate the creation of a large (>£10bn) industry generating both health and wealth for the UK. Our three primary recommendations to this inquiry are:
2. The UK has a strict but permissive regulatory regime which has given advantages to the UK, however; regulatory review of a cell therapy may currently involve up to four separate bodies (MHRA, HFEA, HTA and the GTAC function of NRES). The MHRA has a prime role in the field; however, overlapping functions have been introduced as the field has emerged. This multi-agency process can cause delay and cost, which can be a burden to SMEs in particular. Navigating this process can be challenging for potential inward investors to the UK. It is current Government policy to streamline this situation and to reduce the regulatory burden in a more efficient system. The CT Catapult is strongly supportive of this process and believes that this streamlining is critical to the growth of UK industry and encouraging inward investment.
3. The NHS has a significant role to play both in clinical trials of cell therapies and in their subsequent adoption. In both aspects it is well recognised that the NHS is currently too slow. The report on innovation and adoption in the NHS, launched by Sir David Nicholson in December 2012,¹⁰³ recognises this clearly and makes specific strong proposals to allow early initiation of trials of novel therapies and technologies and for their subsequent rapid adoption, if successful, across the whole of the NHS. Achieving these targets is again critical, both to the CT Catapult’s success and more broadly in making the UK the global location of choice for these therapies. We strongly support this initiative, therefore, and encourage NHS and DH to continue to drive it forward as fast as is practical, particularly for cell therapy development.
4. Better “translation” of medical research is much discussed but has variable interpretation. For many academics, translation means taking early research through to small first-in-man studies and consequent publication of papers. This is sometimes referred to as reaching technology readiness level (TRL) 6.¹⁰⁴ This is very distinct from the subsequent large scale translation (or TRL 7-9) activities by which an interesting science outcome is then transformed into a safe, effective, and affordable therapy that can be widely available and commercially viable. The CT Catapult operates in TRL4-7 de-risking therapies and overcoming barriers that enable investment in TRL 8-9 through conventional finance and industry. We believe that the significance of these later

¹⁰² BIS press release: Government announces £200m Investment for Technology and Innovation Centres. October 2010.

¹⁰³ Nicholson report: Innovation Health and Wealth: accelerating adoption and diffusion in the NHS. December 2011.

¹⁰⁴ A strategy for UK Regenerative Medicine. Research Councils and TSB. March 2012.

development stages in achieving long-term success must be better recognised both by all stakeholders and in future policy setting for RM.

Introduction

5. The Cell Therapy Catapult Centre (“CT Catapult”) was established in May 2012 as one of seven Catapults being created by The Technology Strategy Board under £200m of core funding from Government.¹⁰⁵ The Catapult programme of national technology and innovation centres was initiated from the Hauser Review¹⁰⁶ of March 2010 to create new, substantial industries that grow and remain, long-term, in the UK. They offer a new approach to bridging the investment “valley of death”,^{107,108} by providing funding and support mechanisms to progress promising science through to a point where “investable propositions” exist, which are then capable of attracting conventional commercial finance. The key criterion for success is that a successful Catapult-supported programme will result in a significant proportion of the “value stack” arising being generated and retained in the UK, for example by continuing, local manufacture of the resulting product and global sales.
6. The CT Catapult is specifically established to exploit the strong UK capability in cellular therapy basic science and to provide the further resources and expertise to progress from this research base, to support industry to develop technology and to take specific selected therapies to the point where there is sufficient evidence of efficacy, safety, manufacturability, cost effectiveness and market potential, such that the risk is then at a level that further investment by conventional market finance is feasible. The Regenerative Medicine industry in the UK and elsewhere is a nascent, emerging one with limited experience, skills and case precedent to date. This is both the challenge and the opportunity for the UK to take a lead and establish a world class capability in development and exploitation. The CT Catapult is currently being established in London at Guy’s Hospital, with a plan to grow to around 100 people with related laboratory development facilities and business expertise, such that promising therapies can be managed and progressed effectively, typically through to successful conclusion of Phase 2 clinical studies. In addition the CT Catapult will assist industry by providing integrated support to address business, technical, regulatory, and supply chain barriers. The CT Catapult will be financed by a long-term core grant of £10m pa from the Technology Strategy Board, with plans for up to a further £20m pa from other grant programmes and commercial contracts.
7. The primary requirement of the CT Catapult is to demonstrate, through successful projects and industry assistance that the UK as a system has the capability to effectively progress cell therapies from basic science through translation and on to their full exploitation and adoption. Aside from many scientific and technical challenges, this also requires the effective engagement and coordination of other key UK stakeholders, in particular the NHS and the regulatory bodies. Real demonstration to the world of this national system capability will, we believe, be the primary stimulus to building a substantial long term industrial base in the UK.

¹⁰⁵ BIS press release: Government announces £200m Investment for Technology and Innovation Centres. October 2010.

¹⁰⁶ Hauser report: The Current and Future Role of Technology and Innovation Centres in the UK. March 2010.

¹⁰⁷ Hauser report: The Current and Future Role of Technology and Innovation Centres in the UK. March 2010.

¹⁰⁸ Sir David Cooksey report: UK Health Research, 2006.

Barriers to translation

Regulatory Environment

8. The regulatory environment is one of the key challenges encountered for the clinical development of cell therapies. This is a fast evolving field and an approach is needed that takes into account the stage of development and a case-by-case assessment of the individual risks of each therapy. In the UK, relevant regulations in the development of cell therapies include the Tissues and Cells Directive, Clinical Trials Directive, Human Fertilisation and Embryology Act, Medicinal Product and Advanced Therapy Medicinal Product legislation.^{109,110,111,112} Development of a cell therapy may currently involve four separate bodies (MHRA, HFEA, HTA and GTAC function of NRES) overseeing parts of the regulations. For GTAC, HFEA and to some extent, HTA, their role in this regulatory process for cell therapies is an adaption from their primary purpose, introduced to fill gaps as the field started to emerge. Whilst these functions have successfully maintained public confidence in this emerging technology and allowed the initial development of the field, this complex landscape has led to some ambiguity for sponsors about the exact approval requirements for their respective therapies in a process that is lengthy, complex and uncertain with areas of overlap between the remit of the various bodies. This is translating into a competitive disadvantage for the UK, slowing the progression of therapies from the UK Research base and facing potential inward investors with complexity.
9. We support the Government's stated policy to streamline this situation through the formation of the Health Research Authority^{113,114,115} and consolidation to reduce the regulatory burden into a more efficient and coherent system to work alongside the MHRA. We would encourage the rapid conclusion of that process. In particular, a clear delineation between the remit of the MHRA and HRA (GTAC) in the scientific review of clinical trial applications is welcomed. Generating a clearer and faster (e.g. 30 days) total review process for cell therapy clinical trials will decrease time and cost to firms whilst increasing clarity and giving the UK a competitive edge. Providing the expertise and infrastructure to efficiently navigate and help optimise the regulatory process will be a goal of the CT Catapult.

Clinical trial set-up and conduct

10. Previous reports into UK Regenerative Medicine^{116,117} highlighted the role the NHS could play in the conduct of clinical trials in this field. The CT Catapult aims to increase the number of cell therapy clinical trials being conducted in the UK, through Catapult led pilot programs and collaborative and contract research that can be attracted to the UK. Focus in the following areas is important:

¹⁰⁹ Medicines for Human Use (Clinical Trials) Regulation, 2004.

¹¹⁰ Reg. EC 1394/2007 on Advanced Therapy Medicinal Products.

¹¹¹ European Union Tissues and Cells Directive 2004/23/EC implemented into law as the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

¹¹² Human Fertilisation and Embryology Act 1990.

¹¹³ Liberating the NHS: Report of the arm's length body review, July 2010.

¹¹⁴ Public Bodies Reform Proposals for Change, October 2010 and December 2011.

¹¹⁵ Consultation on proposals to transfer functions from the Human Fertilisation and Embryology Authority and Human Tissue Authority; HRA; June 2012.

¹¹⁶ A strategy for UK Regenerative Medicine. Research Councils and TSB. March 2012.

¹¹⁷ Taking stock of Regenerative Medicine in the UK: BIS. July 2011.

a. Trial start-up:

11. The time to start-up trials is recognised as a major obstacle to conducting clinical research in the UK and one of the key factors that has driven down the overall number of clinical trials conducted in the UK. It is a major objective of the Nicholson Review¹¹⁸ to improve the performance of the NHS in this area. The NHS R&D approval process is complex, has historically operated to very slow and uncertain timelines and with a lack of oversight and accountability at the site level. Recent initiatives by the NIHR and NOCRI are specifically aimed to address these issues through the implementation of clinical trial networks, outline costing templates and the model Industry Collaborative Research Agreement. The CT Catapult fully supports continued focus on progress in this area, and if the 2013 Nicholson benchmark of 70-days from receipt of a valid protocol to recruitment of the first trial participant can be achieved or exceeded for cell therapy trials, this will significantly increase the UK competitiveness.

b. Trial recruitment:

12. Decreasing the time to start-up clinical trials is important, but equally so is the performance of sites to meet recruitment targets during study conduct. Common challenges in this area include allocation of time, sufficient trial experience, infrastructure, and motivation. The NIHR has invested in Biomedical Research Units which are focussed on translational clinical research in priority areas of high disease burden and clinical need and this may prove to be a good match to clinical studies for regenerative medicine therapies. Cell therapy trials bring particular challenges and opportunities for patient recruitment. Establishing clinical ‘champions’ who can advocate for such studies with their peers within the NHS will be important. Cell therapies often represent a ‘personalised’ medicine approach and hence better use could be made of the NHS electronic health records system that holds potential to help identify potential trial participants in a way that is not possible in most other countries. The initiative to improve access for patients to clinical trial information could also be impactful to harness patient enthusiasm and motivation for regenerative therapies.

c. Manufacturing and supply infrastructure:

13. Sponsors with early products face difficulty meeting requirements for a full GMP process based on the standards achievable for traditional small molecules and an approach better tailored to the therapy and stage of development is advocated. Requirements in areas such as batch potency, release and comparability testing, in particular, should bear in mind that the product is a living cell, ‘batch’ sizes for cell based therapies can be very small (e.g. individual patient dose batch for an autologous therapy), and the testing requirements can become unfeasibly time and material consuming as well as prohibitively expensive. In terms of infrastructure, whilst there has been an investment in the UK in GMP facilities, there is still a shortage of suitably trained and experienced staff to produce therapies. Supply of therapies to clinical sites is challenging based on the often very short shelf-life of the product. In order to help address this challenge, there is considerable opportunity, as recommended by

¹¹⁸ Nicholson report: Innovation Health and Wealth: accelerating adoption and diffusion in the NHS. December 2011.

Nicholson, to leverage the expertise of the UK National Blood Transfusion Services where there is experience of handling and delivering cells and tissue products.^{119,120}

Reaching Large Scale Translation

14. Design of clinical trials and financing for adequately controlled and sized clinical studies is also challenging, particularly for the translation to many patients in Phase 2/3 trials (defined as TRL7-8 in ref 4) and preparation for adoption and commercialisation (TRL9). The potential of the cell therapy field to provide therapies for diseases that are poorly served by traditional therapies is significant, but more therapies need to progress to clear demonstration of efficacy. This requires both expertise and adequate funding as too often researchers and SMEs are forced to adopt compromise trial designs that are smaller and cheaper but cannot generate clear efficacy data. The additional knock-on of the scarcity of investment is the inability to strategically execute on manufacturing improvements, which results in sub-optimal process development leading to therapies that appear prohibitively expensive. Further financial initiatives to maintain and grow the UK manufacturing base and attract new therapies to be developed in the UK are needed. New infrastructure such as the CT Catapult will provide an acceleration of promising projects through Phase 2 clinical development through access to funding and concentration of expertise. The CT Catapult will place contracts with Contract manufacturers to produce clinical trial material from well worked out processes and thereby technology transfer expertise that will assist the growth of the industry. This will provide further proof of concept and substrate for successful commercialisation.

Barriers to Commercialisation

Access to finance and business models

15. Regenerative Medicine has to be seen as an emerging industry with considerable long term potential but, by implication, one where many of the key technical and commercial aspects have yet to be resolved and demonstrated. There is currently systemic market failure, i.e. both structural and financial. There are weak financial markets, the existing industry base is small and under-resourced, both in the UK and more generally, and until there is solid evidence of routine translation from basic science through to commercially successful application (and there is essentially none at the moment in UK or elsewhere) then it is unlikely that conventional venture or industrial investors will make many major commitments to this space. It is probable that the conventional “biotech start-up” business creation model will have limited relevance in the development of the RM industry (as discussed in the Taking Stock of Regenerative Medicine report¹²¹).
16. The particular challenges to commercialisation, compared to current small molecule (pharma) and large molecule (biotechnology) approaches for cell based therapies are:
- They are much more difficult to research, develop and test because of the wider and novel range of technical skills required, combined with the current lack of precedents, experience and case history

¹¹⁹ Taking stock of Regenerative Medicine in the UK: BIS. July 2011.

¹²⁰ Nicholson report: Innovation Health and Wealth: accelerating adoption and diffusion in the NHS. December 2011.

¹²¹ Taking stock of Regenerative Medicine in the UK: BIS. July 2011.

- They are likely to be substantially more difficult to manufacture and supply to a competitive price, requiring novel process technologies and multi skilled personnel.
17. These are both major challenges but, if addressed well, also become very significant opportunities to develop and retain a substantial, competitive, and world-class industry for the UK, provided it can marshal its combined resources effectively and address these challenges in a timely and committed fashion. The underlying issues that relate to growing this new industry relate less to Government support for existing industry (in which there are currently relatively few companies) and more to demonstrating that the UK, as an integrated development and exploitation system, can take regenerative therapies through from basic research all the way to routine adoption and use. Only when that has been shown on a number of occasions will conventional investment have the confidence to enter the arena in the UK. Relative to Hauser, a number of “investable propositions” first have to be created through mechanisms such as the CT Catapult and complementary resources in the NHS, the regulators and the science base.
18. The basis of the CT Catapult business model is that for an early emerging industry it will seek to take promising science by selected projects through to successful conclusion of a Phase 2 clinical study in order for conventional investment to be feasible at that point. The model presumes that this can be achieved primarily from grants and support from both government and other bodies such as charities. Initial analysis suggests that typically two clinical studies per year could be initiated by the CT Catapult using this mechanism, and potentially more with increased funding.
19. The global pharmaceutical industry is currently valued at some \$800bn with the US and Europe each valued at approximately \$300bn. There is rapid growth in emerging markets and in developed markets the industry faces both a patent cliff and rising demand through age related demographics. The future value of the global regenerative medicine industry is difficult to estimate, however, analysis of the US market by a number of bodies suggests that by 2020 the cost of provision of chronic healthcare there, presuming only by conventional therapy and support, could exceed \$750bn. This figure is clearly unsustainable such that novel technologies must be found, particularly ones that offer “cures” rather than continuing chronic or palliative support. Aside from commercial considerations, the benefit to UK society of success in this arena is significant in terms of healthcare affordability, resolution of many of the otherwise unmet medical needs and the positive impact on support costs and quality of life for an ageing population. Individual cellular therapies have the potential to span everything from orphan indications to conventional “blockbuster” therapies. Individual markets where cell therapies could have significant impacts include major disease such as diabetes where the current cost of diabetes in the UK alone is £10bn (Source Diabetes UK). The global cell therapy industry was estimated to have an annual turnover of \$1bn in 2011 and is estimated to grow to \$5bn by 2014 (Mason Regen Med 5(3) 2010, Mason Regen med 6(3) 2011). Recent \$1bn acquisitions by Shire Pharmaceuticals and Teva Pharmaceuticals are indicators of growing corporate interest in Cell Therapies. The CT Catapult will drive the formation of SMEs to seed the growth of the UK industry. At the same time the CT Catapult will foster the adoption of cell therapy by major pharmaceutical companies; as a key part of their portfolios and driver of growth. CT

Catapult is targeting the development of an industry worth in excess of \$10bn for the UK, over the next 10 years

Cost effectiveness assessments and adoption into the NHS

20. For cell therapies, the requirement for a large and often long term data package at application for an initial marketing authorisation and the burden of manufacturing site / cell bank comparability is a significant hurdle. Flexibility already exists around data packages for orphan /rare diseases and there are possible routes for cell based therapies through hospital exemptions and specials licenses (and an accelerated approval path in the US) but a pragmatic, streamlined mainstream approach in this area would provide a commercially viable path to patients for ground breaking therapies.
21. In general regenerative cell based therapies are likely to be more expensive than conventional drugs. However, these therapies may well be one-off cures as opposed to continuing through-life treatments. It is not clear that NHS purchasing constraints reflect that balance appropriately. Some evidence suggests that a RM based “cure” may only be affordable under current guidance if its cost is no more than the equivalent cost of two years chronic therapy. This clearly makes little sense for effective and economic treatment of otherwise life-long conditions. Establishment of benchmarks for the overall costs to the economy of long term care (spanning several budget holders) would enable the comparative costs of regenerative medicine products to be placed into context.
22. There is limited experience to date with the successful translation of cell based therapies through approval and then cost-effectiveness assessment and into adoption by the NHS. The first cell based therapy to be approved under the new EU framework was Tigenix’s ChondroCelect® in 2009. Navigating the reimbursement system in the EU with 27 countries with 23 different languages is a very complex procedure. NICE has not yet reported completion of assessment of this product but initial indications are that regenerative medicine products will need to follow a lengthy 2 stage sequential process consisting of the intervention procedures pathway to examine safety and efficacy, followed by health technology appraisal to examine cost-effectiveness. A faster, parallel process with more predictable outcome would be advantageous for patients and the industry. Interestingly, BUPA has rapidly adopted the ChondroCelect therapy into its portfolio through the clinical decision algorithm. Innovative cost and risk sharing approaches have been adopted recently for high cost products outside the regenerative medicine space such as Lucentis and Sutent, although introduction of such approaches or those where the burden of ensuring long term patient compliance with activities such as rehabilitation schedules is shifted onto the sponsor, may not be viable for therapies developed by SMEs with limited resources. There may need to be involvement from government to facilitate early adoption (through underwritten or staged payment schemes) whilst the industry becomes established.
23. Following on from approval and reimbursement decisions, the challenge ahead for commercial success for cell based therapies is adoption into the NHS, leading to wide scale use in the relevant patient population. The need for faster adoption of innovative therapies is the subject of the Nicholson report.¹²² Adoption into the NHS could be facilitated by the establishment of a single specialist national commissioning structure for regenerative medicine products.

¹²² Nicholson report: Innovation Health and Wealth: accelerating adoption and diffusion in the NHS. December 2011.

International comparisons

Translation of therapies

24. The US has a much larger number of SMEs in the regenerative medicine sector than the UK and other European countries. Reasons for this include the greater access to debt finance, the scale of private philanthropic investment, and the fluidity of leading academics between academia and industry with it being normal for leading academics to have company involvement. In contrast the UK has good systems to foster collaboration between industry and academics, but less fluidity. Greater access to finance would greatly assist SMEs in the UK, albeit that is unlikely to improve in the near future. The US is currently establishing the NIH Centre for Regenerative Medicine to accelerate clinical translation and also already has the state funded California Institute of Regenerative Medicine. The funding and mission of the CT Catapult provides the UK with a centre to accelerate the clinical translation of therapies.
25. Within Europe, Germany has historically had a particularly strong cell therapy sector, including research, commercial therapies and service provision (reagents, automation technology, contract manufacturing). Germany was an early adopter in the cell therapy space, particularly in autologous cell therapy. The German government makes very significant investments in supporting the continued growth of the regenerative medicine sector in Germany, including grants to researchers, funding of translational centres, support for research conducted in SMEs (including spin-outs from academic centres) and funding for clinical research programs. Other countries in Europe, notably Belgium, Netherlands, France and Sweden, are also receiving significant government support for research, and increasingly translational and clinical based activities as well as growth of regenerative medicine manufacturing/reagent services.
26. Looking out to Asia, there is a significant emergence of a cell therapy sector. Examples include accelerating Research and clinical translation in iPS cells in Japan, where the RIKEN Centre plans to start a clinical trial of RPE derived from iPS cells for macular degeneration next year (2013), in commercialisation in South Korea where the regulatory authority has adopted fast track for cell therapies licensing 3 therapies in 6 months and in a GMP manufacturing sector in Singapore where the business environment is attracting export of manufacturing activities by CMOs). The UK can expect increasing competition from Asia and the environment in the UK will need to be favourable for UK companies to keep expertise and investment in the UK and to win inward competitive investment for development and manufacturing contracts.

Regulations

27. Development of cell therapies in the UK is covered by the clinical trials directive (CTD) and ATMP regulation (1394/2007); which sets out the clinical and regulatory path for product approval. Since Dec 2009, the committee for advanced therapies (CAT), which includes UK representation, has been the EMA's group focussed on advanced therapies and providing scientific advice and review of ATMP applications. To supplement the EMA guidelines on human cell based medicinal products, CAT has published several reflection documents, including classification of ATMPs, development of stem cell-based medicinal products, and tissue engineered products.

28. Development of therapies derived from human embryonic stem cells is controversial in the EU. Horizon 2020 will provide EU funding for research and innovation over the next six years but MEPs from some countries are advocating exclusion of hESC derived projects from this scope. It is important that the UK government strongly supports the statements made by organisations including the Wellcome Trust, Association of [Medical Research](#) Charities, British Heart Foundation, European Genetic Alliances' Network, Medical Research Council, and Parkinson's UK to enable the development of these potential therapies for patients.
29. As regulations and guidance have been emerging for cell based therapies, there has been an effort to build-in harmonisation, particularly between the FDA and EMA. This is an emerging area and not surprisingly, there are areas that require further harmonisation. Examples include the requirement for non-clinical models (homologous vs. non-homologous, duration and type of long term safety data) and quality requirements (control of starting materials, acceptability of cell lines derived in the UK due to historical concern over BSE/TSE risk, need for full GMP, sterility tests, environmental monitoring in GMP suites and QP release).
30. Additionally, there are areas where national authorities within the EU take different approaches, such as the frequency of use of hospital exemptions and certification required at import for clinical trials.
31. Further harmonisation between countries in the EU and between the EU and the US would facilitate the efficient development of cell based regenerative therapies, reducing cost and time. Industry bodies in this area, such as AAT and ARM can help highlight and advocate for change in these areas. However regulatory harmonisation in even conventional therapy areas remains mostly aspirational and substantive harmonisation progress in RM is unlikely to happen in any foreseeable timescale.
32. Unfortunately, very permissive, or unenforced regulatory and legal frameworks in some countries have led to the growth of un-regulated stem cell clinics. This involves the administration of un-licensed, unproven and un-controlled therapies often to very vulnerable patients and there are estimated to be over 700 such clinics operating in mostly developing countries including Costa Rica, Argentina, China, India and Russia. Such clinics represent a risk to patients and to the future of cell based medicine. Supporting the growth of the regenerative medicine industry in the UK towards development and adoption of licensed, safe, and effective therapies will better meet the needs of these patients.

20 September 2012

Cell Therapy Catapult Centre, TAP Biosystems and EPSRC Centre for Innovative Manufacturing in Regenerative Medicine – Oral evidence (QQ 267-282)

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[Transcript to be found under EPSRC Centre for Innovative Manufacturing in Regenerative Medicine](#)

**Cell Therapy Catapult Centre and Technology Strategy Board (TSB)
– Oral evidence (QQ 283-294)**

Evidence Session No. 12

Heard in Public

Questions 283 - 294

TUESDAY 18 DECEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Keith Thompson, Chief Executive Officer, Cell Therapy Catapult Centre; and **Dr Zahid Latif**, Head of Healthcare, Technology Strategy Board.

Q283 The Chairman: I would like to welcome our second witness panel. In a moment, I will invite you to introduce yourselves for the record and make any brief opening statements that you may wish to make, but do please keep them brief. I shall start with Dr Zahid Latif from the Technology Strategy Board.

Dr Latif: Good morning. My name is Zahid Latif. I am head of healthcare for the Technology Strategy Board and the lead on its regenerative medicine programme there.

Keith Thompson: Hello again. I am Keith Thompson, CEO of the Cell Therapy Catapult.

The Chairman: Thank you very much. I would like to kick off with a general question. We will no doubt follow up with some details on it as we move forward.

Dr Latif, can you tell us about the support that you are giving overall to regenerative medicine to encourage the translation of research into the clinic and to develop it for commercial benefit to the UK and, within that, how you as a funder see the role of the Cell Therapy Catapult Centre?

Dr Latif: For this, we need to undertake a slight history lesson of the Technology Strategy Board. When we started in 2007, we embarked on an activity to try and focus on particular

areas, and regenerative medicine and cell therapy was one of those areas that our governing board felt was really a ripe opportunity for investment. We were able to make a commitment of around £18 million of funding into that area, and we were able to get additional core funding from the research councils at that time, to create a regenerative medicine programme of about £20 million to support companies to get to the clinic.

There were also other elements in there, because we recognised that for the companies to get to the clinic they needed underpinning tools and technologies. Then you get into the challenges of how you enable those companies to have the right tools to get to the clinic faster, but also to start unpacking issues around value systems and business models. For the companies that are developing these therapies, what is their business offering going to be? Is regenerative medicine or cell therapy a product, or is it a service?

With that programme, we started to embark on this journey with the UK sector, in building a load of linkages both with academia and industry. We made our final round of commitments to funding that programme last year, and we are seeing funding for four companies taking their products into the clinic.

The Chairman: Would you just say what the four companies are?

Dr Latif: The four companies, if you take regenerative medicine in its broadest sense, are TAP Biosystems, with David Newble, and Cell Medica and Neotherix, and then there is Orthox, which were awarded four grants to help them get into the clinic.

The Chairman: What are the therapies that they are now trying out in phase 1 and phase 2?

Dr Latif: The TAP project is for corneal stem cells, for blindness or damage to the lens. The Cell Medica product is for T cell immunotherapy for people who have undergone bone marrow transplantation, where they may be immunocompromised. It is to prevent some form of infection. The Orthox product was a cartilage repair, but it was a biomaterial rather than a cell therapy in that case. The Neotherix was a wound-healing product, but again that was a biomaterial. We took the view that regenerative medicine at that point was any approach that would lead to regeneration of cells, tissues or organs. It was not specifically cell therapy.

The Chairman: Are all four of these now in phase 1 or phase 2 clinical trials?

Dr Latif: They are embarking on that now.

The Chairman: Have they received regulatory approval for clinical trials?

Dr Latif: Again, if we go back to the history of the programme, one of the challenges that the industry requested that we try to address was how they get people's products towards or into clinical studies. I raised the question back to them, "How many of you are ready today to get into the clinic now?" They sort of um-ed and ah-ed and came back with the view that some of them were maybe a year or two years away, because they needed to get some of that regulatory approval work done or some of that pre-clinical work done. The programme has been working with projects in order to get them closer into the clinic.

Some of the projects that we have funded, including the Intercytex project on epidermolysis bullosa, went through a small clinical study. The TAP and the Cell Medica products again have gone into a small clinical study as well, some of the others are slightly further behind.

The Chairman: Has all the funding gone to these companies rather than to academics in universities?

Dr Latif: Not all the funding. The way that we operate with our collaborative R&D funding is that a proportion of the funding will go to the companies and a proportion will go to the academics if there is collaboration in there. We were particularly keen to try to ensure that the companies were able to get a sizeable chunk of the money to help them address some of their challenges, but the partnerships that they built with the academic groups were there to work with the academic partners to address some of their pre-clinical or clinical challenges, so I would not necessarily say that money had to go entirely to the companies. Some of the money went to the academics because they were working on that industrial-led project.

The Chairman: Could you tell us very briefly from your perspective what you think the role of the Cell Therapy Catapult Centre is?

Dr Latif: We recognised that funding alone was not the issue in this particular space if you wanted to get things to move faster. There was a recognition that we needed to build a capability that the companies could collectively work with and use that would allow them to get where they needed to be faster.

The Chairman: Can you unpackage that? What do you mean by a capability that they could use?

Dr Latif: People talk about infrastructure and they immediately think about a big building with shiny kit. What we needed to think about was that there is a need for that sort of infrastructure, but it is the expertise headed alongside that that companies can tap into, utilise and work with in order to help them get to where they need to be.

Shiny bits of kit and big buildings are one thing, but having an organisation that learns and can recycle that learning is really beneficial to a lot of the small companies that may have to learn all these things by themselves. That learning is not recycled or used if they have succeeded or failed. Having a shared capability that companies could tap into is really valuable, because that capability would bring experience of successes but also of failures.

The Chairman: It is a repository of knowledge and advice.

Dr Latif: Yes, as much as it is about the piece of infrastructure. It takes the two in order to make it work.

Q284 The Chairman: Keith Thompson, do you see yourself as a repository of knowledge and advice? Is that the main role of Catapult?

Keith Thompson: Partly. You have to start by asking yourself what the issues are that are holding the UK back from capitalising on the investment in the science base. I see and the industry advisory group sees three principal problems.

One is a business problem. Are these products capable of being manufactured to a price point? Are they capable of being reimbursed by health systems? What are the health economics of it? We intend to build a repository of expertise from health economists and business analysts, with investment-friendly understanding.

The second one is the manufacturing and supply issue, which we have talked about a lot already. Typically, what happens with a promising therapy that comes out of the research sector, or some of the SMEs that are often undercapitalised, is that the processes are

essentially laboratory, hand-cranked processes. When they come out to be manufactured, frankly, the processes are not up to it. What we are putting together is a physical infrastructure and skilled teams that have done it in the bio-industry that are working with hands-on people themselves, to work on cracking the process development problem. Our capabilities will allow us to go across manipulated cells, somatic cells, 2D and 3D scaffolds, ES and iPS cells, and working again with the downstream bits like freezing cells and delivering them.

These are real tangible things that aid reproducibility and reliability and get at the cost of goods so that people know that they can manufacture these things. Big pharma will not pick up a process that it does not think it can manufacture or control or develop the regulatory package. That is a real gap in the system right now. It is a big investment.

For the last bit, and this again comes back to knowledge repository and recycling, we will be having substantial clinical operations and regulatory departments, where we have hired people from industry who have done it before and can do it again, and act as the bridge that many of these small companies simply cannot afford. I was very pleased that we were able to hire the former executive director of clinical research from Pfizer in cell therapy to act as the leader of this group. So it is both knowledge and repository and physical capabilities.

In some respects, we deliberately have not duplicated GMP manufacturing space, because we know that there is enough out there. What they are lacking is bang-on, souped-up processes that they can put into the space. Our strategy is to develop really good processes and transplant them—to technology transfer them into the space. We then get the products that we and industry want, but also they learn what the very best processes are so that they can suck in more business from home and abroad.

The Chairman: Is there adequate funding to do all of this? It is a question that Lord Cunningham touched on earlier. Is your £50 million over five years going to deliver?

Keith Thompson: We put to the TSB a case for the core funding of £70 million, because it will take time to build up this other revenue.

The Chairman: Will £70 million be enough? Would that be your dream ticket?

Keith Thompson: If I had £100 million, I could spend that, no problem, but £70 million is a substantial amount of money and it will fund a good number of feasibility studies. It will fund 11 or 12 pre-clinical projects, and we will be able to get one or two projects into phases 1 or 2 each year.

The Chairman: What is your estimate of what it costs to take an idea out of the research laboratory and get it into phase 1 or phase 2 clinical trials? What would be a typical number?

Keith Thompson: A typical number is £2 million to £3 million.

The Chairman: Over how many years?

Keith Thompson: Over two to three years.

The Chairman: That is £2 million to £3 million over two to three years.

Q285 Earl of Selborne: Clearly, generating the sort of funds that you are looking for over the next five years is a major issue, given the size of the industry and given the

reluctance of big pharma. Some people put hope in new, innovative funding streams like citizens' innovation funds. Is that pie in the sky, or does it have any prospects?

Keith Thompson: Certainly, the BIA is really pushing that and it is a relatively new initiative, which we welcome. Another funding stream that we think has quite a lot of mileage is from the charitable sector. We believe that there are some parts of the charitable sector, like Cancer Research UK, that are very well funded with their own facilities. There are other bits that have the funding but no facilities or expertise. We certainly want to reach out to charitable funding and to work with them on advancing their projects, but advancing them in a highly disciplined biopharmaceutical approach rather than an academic-driven approach, because that is what is needed.

Earl of Selborne: Is there anything that this Committee could do to help structure that sort of funding? Are there any recommendations that we could make?

Keith Thompson: I am rather struck by the German approach of matched funding from other sources for clinical trials, because that is when it gets expensive.

Dr Latif: I want to reiterate that, as well as the investment into the Catapult Centres, the Technology Strategy Board will be continuing its funding for its business-led R&D projects. Our budget is for around £30 million over this year. As well as the Catapult Centre providing that critical mass, and the funding that it receives to provide that capability, what we are also doing is providing funding through the regenerative medicine programme of £30 million, but also there are other areas such as biomedical catalysts as well.

The reflections are that Government funding for business-led projects is better now than it ever has been, but it can never be too much because we are not short of good ideas. The challenge is how to focus that money in an effective way to get the outcomes that we are seeing with regard to the evidence to drive further investment into the area.

Q286 Lord Cunningham of Felling: Mr Thompson, forgive me if missed this in your submission, but are you in the process of preparing a series of recommendations to the Government or the Technology Strategy Board about what extra funding is going to be required over the next three, four or five years? Is that a piece of work in progress, or have you not got there?

Keith Thompson: We have completed a five-year strategic plan, fully costed and fully funded, which has triggered that £70 million, and it forecasts where the other revenues would come from. We have not done anything over and above that because that is the Catapult strategic plan, which is due to go to the Treasury for sign-off.

A related comment to that is that, in our interactions with the community, we have been surprised by the level of interest from some of the venture capitalist funds that exist out there. We thought that it would take longer to get that interest and that they would have to see more demonstration of products coming through that they could invest in. We have been talking to several funds, and what they are really keen on is the idea that there is this repository of knowledge and expertise that they can go to that is independent of their original investment, so that you can, if you like, join it up. I am hopeful that pure financial investors will become interested earlier in the cycle than I had originally planned for.

Lord Cunningham of Felling: As things stand, you are looking at £70 million over the next five years—if you get it.

Keith Thompson: Yes. In the fifth year of our plan, I have budgeted for £20 million of income, so the total is—I can give you the exact number if I can dig it out. It is a bigger number.

The Chairman: You can send it to us.

Q287 Baroness Perry of Southwark: Mr Thompson, earlier on you said that you wanted the UK to be a leading centre, and we in this Committee certainly endorse that. As so many trials now move into the possibility of commercialisation around the world, and in other centres as well, it is going to become a very globally competitive race.

Keith Thompson: Yes.

Baroness Perry of Southwark: How do you plan to make sure that the opportunities, the jobs and the investment stay substantially a UK operation and that we do not have foreign companies moving in and pinching our best ideas, our best technologies and our best young people?

Keith Thompson: I lived through the monoclonal antibody world, and my first company still exists in Scotland. It still employs about 100 people and it turns over about £35 million. That is principally because it is a licensed manufacturing facility. They do not move.

One of the elements is to try to attract manufacturing and bits of the manufacturing chain that are hard to move. That is why we keep coming back to this manufacturing bit. Cell therapy is hard; it is not an easy space. Getting more companies that are capable of getting a critical mass of expertise and an interwoven web of dependency in the supply chain is important. There are companies that provide assays, and there are companies that provide specialist clinical services and manufacturing in addition to a strong research base. Companies gravitate to places that know how to do it. It will be harder to just lift these industries and move them.

Q288 Lord Patel: Very briefly, if the intention is to identify research that is at the point of going to phases 1 and 2 of clinical trial and then to identify the appropriate clinicians who might be involved in it, and at the same time to get industry interested at that stage and liberate its own funding, is it a model that you think Catapult will have to create, or is there learning to be had from such models that exist in other parts of the world? Everybody in the world is chasing this regenerative medicine.

Keith Thompson: We have certainly looked at other countries and tried to work out what they have done well and what they have done badly, and I would not want to criticise other countries.

The learning points for me are in a few places. For instance, CIRM has had £3 billion; it is a huge amount of money. They have invested an awful lot, but they have not got a great deal of translational traction for that amount of money. That has been changing recently. I met Alan Trounson yesterday, who was interested in the business model that we have. In particular, the focus on the kind of manufacturing development and clinical trials is key.

The space that I have tried to make sure that we stay in is this translational space, because some of the centres have allowed themselves to be sucked back into basic research. As far as I am concerned, that is a job for the research councils. My job is to try to pick their stuff up, put my shoulder behind it and shove it over the finish line. Although it is interesting to go back into basic research, I want to avoid it wherever possible.

Q289 Lord Willis of Knaresborough: First, in terms of the charity sector, I chair the AMRC, and we are setting up an industry board to advise us for the very first time. We would be interested to hear from you; if you contact us, we will send you an official invitation. That is important in order to get those near-to-market therapies through.

I have two questions. The first is on the actual size of the cake. On your website, you state that, currently, there is a \$1 billion business in terms of stem cell therapies worldwide. What proportion of that does the UK have? You state that, by 2014, it is going to be \$5 billion. Has the TSB set a strategy target to say how much of that \$5 billion we want in the UK? It would be useful to say how you are going to get from where you are now to where you want to be. It would help this Committee in terms of saying what we need to recommend to the Government in order for you to get that. At the moment, I have no idea as to where you are aiming for, other than, “We want a bit more.” That is not really good enough for us, although I do not mean that in an unpleasant sense.

Keith Thompson: No; I understand.

Lord Willis of Knaresborough: Although I do tend to be unpleasant.

My second question is this. I think that you are riding an impossible horse, unless you tell me differently, in that the horse is in one sense being pointed toward research excellence and turning that into economic capital, but, also, the TSB is putting its Catapults in various centres around the regions of the UK in order to satisfy a regional regeneration target. Was the Catapult placed in London on the basis of commerciality and excellence, or was it put there because London had to have something in the south of the capital?

Keith Thompson: I shall answer a bit, and I shall probably ask Zahid to answer a little as well.

In terms of the size of the cake, those estimates of £1 billion or £5 billion were published, I think in a Chris Mason paper, which I think appeared to be a well-researched piece. Off the top of my head, I cannot tell you how much is in the UK; perhaps you can.

Dr Latif: It will not necessarily be in the therapy area, but it is probably going to be almost certainly in the underpinning tools and technologies, so that it will be in a lot of the supply chain.

Lord Willis of Knaresborough: It is none, then; it is nothing.

Dr Latif: I would have to go back to the original data and have a look at it. I cannot comment.

The Chairman: Could you possibly send us a note giving an answer as best you can to Lord Willis’s question?

Keith Thompson: Yes. The second bit is where we are shooting for. You can market research and you can analyse and forecast as much as you like on what might happen, but I have simply approached it from this point of view.

The global pharma industry is worth about £800 billion, give or take. Biologicals are worth about £100 billion of that, but it has taken about 30 years to get to that point. Monoclonal antibodies, a British invention, made here and researched here, with all the underpinning technologies, are worth about £45 billion and growing at 5% per annum. It is a really strong sector, but relatively little of that value stack remains in the UK.

If we look out another 10 or 15 years, I need to have some assurance that we are on the road to something that looks like a £10 billion industry. That sounds like a big number. However, it takes maybe a couple of major therapies to come out the other end, supported by perhaps two or three orphans and then the supply chain that goes around that. It soon adds up. Our target is ambitious. It is to get that and not try to win the pots and pans of the supply chain of the industry.

Lord Willis of Knaresborough: I still do not have a clue as to what your target is.

Keith Thompson: It is £10 billion.

Lord Willis of Knaresborough: In 15 years?

Keith Thompson: Yes.

Lord Willis of Knaresborough: How much of the £5 billion for 2014 do we aim to get?

Keith Thompson: For 2014? I do not think that I have metricated that near-term.

Lord Willis of Knaresborough: My issue here with you is that money is clearly in very short supply. No matter how we dress it up, it is in incredibly short supply, yet we are spreading it over a whole series of different potential therapies in the hope that one of them might come up somewhere. I do not get this at all. Perhaps it is because I am stupid.

Lord Winston: I agree absolutely with what Lord Willis is saying.

Keith Thompson: In 2014, we will have opened our labs. In terms of the industry's development, to the best of my knowledge, there will not be a major British product that will have got out at the other end. However, the supply chain grows. I think that it is now in the order of hundreds of millions, and we can certainly forecast that and come back to you with a number.

Q290 Lord Patel: Will you very briefly say what your labs will be doing?

Keith Thompson: The laboratories will be engaged principally in developing the processes, working on the cost of goods, getting them fit to go into GMP manufacture and working on the analytical techniques.

Lord Patel: Why will Catapult be doing this?

Keith Thompson: There is a real gap there. There is a process development gap. It is one of the things that is holding the industry back. It is not allowing the industry to get away from these clean rooms and not giving confidence to the regulators.

Lord Patel: What will be the cost of these labs?

Keith Thompson: I think that we have budgeted about £5 million for them.

Lord Patel: Over what time?

Keith Thompson: That will go in place over the next 12 months.

Lord Patel: That is £5 million over 12 months, but your budget is only £10 million. How much is your budget?

Keith Thompson: I believe that our budget next year is £12 million.

Lord Patel: So £5 million of that will go into labs.

Keith Thompson: That is right.

Lord Patel: Into infrastructure?

Keith Thompson: It will go into capital, yes.

Q291 Lord Willis of Knaresborough: The second part of my question was why London?

Dr Latif: I might be able to address that. We went through a process in 2011 in order to look for people to bid to run the Catapult. We received three bids. They all had their particular strengths, but in all cases the assessment panel felt that there were significant weaknesses and significant gaps.

We worked through this with our exec management team and the governing board of the Technology Strategy Board, and they took the view that we needed to build these things differently. Rather than putting them out for competitive tender, which was essentially a devisive process, we needed to look at how Catapults were established and to do it differently. We worked with the assessment panel, which became our advisory board eventually, to articulate what were the five criteria that would be needed to establish the centre. Based on those criteria, we would make decisions around where the Catapult would be located.

The five criteria were basically along these lines. The first was global accessibility—a globally accessible hub. The second was access to the financial community, because the industrial partners felt that it was really important to make sure that the investment community were aware of the potential Cell Therapy Catapult and the Catapult could engage with them closely. The third one was access to clinical trials patients, but at scale, and that got us into the position of needing to be close to the teaching hospitals and close to research clinicians. The fourth one was industry access, essentially being where a chunk of the businesses were. The fifth criterion was access to academic expertise as well.

When you look at the UK, that gets us down to London. Then, with a property consultant, we undertook a search for premises, based around the outline business plan that we had for 10,000 sq ft of location in and around the London area. We had a shortlist of three locations, and the Guy's facility was on that shortlist. It ticked a lot of the boxes that we had with the criteria.

Lord Cunningham of Felling: You said originally that you had three applications. Was the current choice one of those three?

Dr Latif: No, it was not.

Lord Cunningham of Felling: That is quite interesting. They did not apply and yet they ended up getting it.

Dr Latif: The critical thing here is that the decision to position it in Guy's Tower was a property decision.

Lord Cunningham of Felling: A cynic might say that you wrote the requirements so that there was only one outcome.

Dr Latif: When we got to London, we had to look around, and the property consultant went out and asked everybody who had the available space. This was strictly a property transaction; it was not necessarily to segment people out. The critical thing is that we need to build linkages to the academic bases, and we need to build linkages to the hospitals and industry. By stopping the process where we were and creating a level playing field, we were trying to make sure that the Catapult was accessible and not siloed into one particular institution.

Q292 Lord Broers: What efforts have been made to ensure that the Catapult and other TSB activities in this space learn from the experience of international examples? It is quite clear that very much more money is being spent overseas than we are spending ourselves. What are we doing to try to learn from what they will be learning after spending all their money?

Dr Latif: I shall answer this first, because the Technology Strategy Board has been through the regenerative medicine programme building a lot of linkages internationally. We went out to visit CIRM two years ago. This summer I was also out in Toronto with the Canadian Centre for Regenerative Medicine. The critical thing is that, yes, in the Californian case people have a vastly bigger pot of money to disburse.

The Canadians, funnily enough, are funded at a lower scale than the Catapult, but you must realise that it is not necessarily just the power of the amount of money that goes in; it is what you can leverage with it. Particularly, as was reflected back to me by the Canadian centre, their closeness to the hospitals and all the research infrastructure means that they can tap into that and leverage off the existing investments that have been made in other areas. That is a critical lesson to be learned with regard to how you take the amount of money that you have and make the most of it, based around all the other investments being made in the UK.

Lord Broers: Can we benefit from their clinical trials? To what extent can we take theirs as validation of what we might want to do?

Dr Latif: There are probably two elements to this. There is the regulatory element of how you get to clinical trials, and then there is clinical trial design. On the regulatory front we have the regulatory system that we have, and we have to try to work within that and to influence it in a way that would help accelerate the route to getting these clinical studies off the ground. The clinical infrastructure is an important component of that.

With regard to clinical trials design, it is really difficult in this space because there are a lot of people who have tried but failed to demonstrate that their clinical studies have worked. It is about recycling that knowledge in order to help to get to an optimal way of designing a clinical study for a particular therapy, because one size does not fit all in this particular case.

Keith Thompson: I shall talk about the clinical trial bit first, if I may.

The Chairman: Keep it fairly brief, please.

Keith Thompson: Sure. Basically, the average number of patients in a trial in phases 1 and 2 is less than 20, so these are small trials. You always like to do some more than that, but what you are trying to get is to prove that it is worth investing in the next size trial. As a for instance, we have analysed internationally the trials that are currently being carried out. There is a trial called Cardio3 in congestive heart failure that has 240 patients as a single arm. Aastrom has 594 patients in critical limb ischaemia. The number for the Mesoblast and

Teva congestive heart failure trial is not known yet, but I was told by somebody from Mesoblast that it would be similar to the Cardio3—about 240. Osiris has 240 in graft-versus- host disease and 270 in Crohn's disease.

Looking at what has become acceptable internationally is a key part of the overall Catapult strategy in order to advise on trial size and design, because you have to be able to prove the clinical hypothesis—either prove that it does not work or that it does work. These are precisely the sort of things that we would want to do.

In relation to international activity, I have already talked about that, but a key difference between us and Toronto is that they do not do clinical trials. They mainly work on the process development and enabling the technology side. A key difference between us and CIRM is that the latter is, essentially, a funding organisation that works with trials. They have mainly people doing this, but they have invested in facilities and they have also invested in basic research. So we are looking at this to try to optimise where we sit in the translational space.

Q293 The Chairman: One of the things that I picked up from our visit to CIRM was not just the scale of funding. When we asked them what it cost to take research out of the laboratory and put it into phase 1 or phase 2 clinical trials, as I recollect it, their typical funding was more in the order of \$20 million over four years. You gave a figure of £2 million over two to three years, so we are faster, more efficient and cheaper than them. That was an interesting comparison.

I was also struck by the way that CIRM sets very clear milestones, so that the people undertaking the translation have a milestone-driven project and, at any stage if they are not meeting the milestones, the funding is withdrawn. Do you think that your shorter, cheaper model should be milestone-driven as well?

Keith Thompson: Absolutely. It is fully our intention to run stage-gated processes or milestones. We will not keep half-dead projects alive. We cannot afford to.

The Chairman: For clarification, why is it so much cheaper and quicker here?

Keith Thompson: To a certain extent, clinical trials in the US can be more expensive because they are all on a commercial model. To a certain extent, we can leverage some NHS infrastructure by doing that.

Q294 Earl of Selborne: Pursuing the issue of international comparison, Mr Thompson, you have talked a lot about monoclonal antibodies, something that was invented in this country or an innovation of this country. However, as you said, now that it is expanding, we have not got much of the action any more compared to what we had at the beginning. Are there lessons here for the Catapult and for TSB for the growth of regenerative medicine? How are we going to ensure that we keep our share of it? Are there lessons to be learned from monoclonal antibodies?

Keith Thompson: I absolutely think that there are lessons. At one point I worked for a US company that undertook strategic reviews of where they were going to invest in its manufacturing facilities, and they looked at all the environment around staff, tax and all the things that can influence a decision.

What I would say is that, for the first time in a long time in the UK, the fiscal environment is better than it has been for a long time. Corporation tax is better than it has been, and the R&D tax credits are in place. Lastly, and probably most importantly, the availability of the

Patent Box will allow significant advantages for those technologies that have been developed and exploited here. That is one way of keeping it that did not exist when things were being exported.

The last one comes back to the sheer know-how and ecosystems that allow these difficult things to be manufactured here. Importantly, if we get the manufacturing bridgeheads for the EU into the UK, then that should be a lasting protection, but not a guaranteed protection, against exporting the jobs. There is an inevitability of a significant proportion of these businesses being acquired at some point by large healthcare, and it is the issue of what remains when that happens.

The Chairman: What about patenting issues? Are you helping small companies or academics with patenting?

Keith Thompson: We certainly intend to set up an ability to understand freedom to operate and understand what patent portfolios and families might look like.

The Chairman: Will you provide funding to help with that?

Keith Thompson: We would certainly provide, as part of feasibility studies, reviews of the patent landscapes to the companies or academic partners that were interested in that space. It is a very complex environment, so we will intend to operate there.

The Chairman: Thank you very much indeed for your evidence in this session. You will receive in due course a copy of the transcript, and you are welcome to make minor corrections to it. There are one or two items that you have offered to follow up in writing to us, and we very much look forward to receiving those. Thank you very much indeed.

Cenkos Security, Imperial Innovations and Apax Partners – Oral evidence (QQ 170-195)

Evidence Session No. 7

Heard in Public

Questions 170 - 195

TUESDAY 20 NOVEMBER 2012

Members present

Lord Krebs (The Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Baroness Perry of Southwark
Lord Rees of Ludlow
The Earl of Selborne
Baroness Sharp of Guildford
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Dr Navid Malik, Head of Life Sciences Research, Cenkos Security, **Dr Nigel Pitchford**, Managing Director of Healthcare, Imperial Innovations, and **Dr Steven Dyson**, Partner, Healthcare team, Apax Partners, gave evidence.

Q170 The Chairman: I should like to welcome the second panel of three witnesses and in a moment invite you to introduce yourselves for the record and make any brief statements that you wish to at that time. I remind everyone that the proceedings are being webcast. Without further ado, I invite the panel to introduce themselves, starting with Dr Dyson.

Dr Steven Dyson: I am Steven Dyson, a partner and co-head of healthcare at Apax Partners. I am also a non-executive director of KCI and LifeCell—two US companies which sell regenerative medicine products.

Dr Nigel Pitchford: Good morning, I am Dr Nigel Pitchford. I head the healthcare team at Imperial Innovations. Within our portfolio we also have a business called Cell Medica, which is involved in cell therapy.

Dr Navid Malik: Good morning. My name is Navid Malik. I am the head of life sciences at Cenkos Securities, which is a stockbroker. I am also on the board of a regenerative medicine company called Northwest Biotherapeutics, which is based in the US. We are broker to two regenerative medicine companies, ReNeuron plc and Scancell plc.

Q171 The Chairman: Thank you. I should like to kick off by asking you about different business models for the commercialisation of regenerative medicine research—what kinds of funding are available and what business models are appropriate. Perhaps I can start with Dr Dyson.

Dr Steven Dyson: Ultimately, to be commercially successful, regenerative research needs to lead to an actual medical product which is going to address a clinical need at an affordable price. We look at this in two different categories within regenerative medicine research. At the simpler end, these will be products which in some way encourage the body's own regenerative capabilities. This could be a medical device or a pharmaceutical device. The regulatory pathway in general is relatively simple and clear. In those situations and circumstances, the classic technology transfer business model followed by angel, venture or large company R&D budget funding is appropriate. For more complex regenerative research—stem cells, gene therapy—our view is that a different model is needed to move the research further along the development pathway as it takes longer and there is more uncertainty. It really needs to be funded by alternative sources to get the product further along the development pathway before the involvement of classic commercial funding.

Q172 The Chairman: What would be the alternative sources?

Dr Steven Dyson: It could be charitable funding or government support. However, as regards the point where research or technology transfer ends on these more complicated products, it is typically 10-plus years before you get to a commercialisable product. That is too long and too high risk to constitute an attractive return to enable typical pharmaceutical med-tech or venture capital R&D funding to pick it up at that stage.

Dr Nigel Pitchford: I echo Steven's points about the viability of some of the very early-stage nascent technologies that we are looking at, particularly those that have very long lead times to commercialisation. From a fund manager's perspective, these technologies are incredibly difficult to fund within a venture capital context because of time and capital requirements. Typically, we look at them within the context of the universities with which we associate—Imperial, UCL, Cambridge and Oxford—being exciting places of research but where that research is quite often complemented by government funding, including TSB biocatalyst funding, reducing the need for early venture capital rounds which has been put in place to advance those technologies further down the path to finding commercial funding themselves. We will probably address later the issue of the length of time between venture capital or other forms of commercial money taking an interest in those types of business and getting a commercial return. Trying to deliver a commercial return around those investments is part of our business; that is what we aim to do. If the timelines involved are very long, it makes it incredibly difficult for us to work round that. Some of the funding is provided by Government or charities, or increasingly by evergreen type funds. Our situation is slightly different from that of a normal VC fund in as much as we are an evergreen fund. That allows us to take a slightly more relaxed view about time and capital constraints than would a classic VC, but we still have to look at opportunities in the context of being able to make a return from them.

Dr Navid Malik: Having conducted a lot of equity research on regenerative medicine companies since 2005 and floated a number of these companies in the public markets internationally—both UK organisations and US businesses floating in London—I believe that the funding environment has changed dramatically. Currently, fund managers in the big pension funds and insurance funds are looking for businesses within biotechnology which have revenues and profits because they have a wealth of potential options to invest in

businesses in other sectors along those lines. For biotechnology companies, and more specifically regenerative medicine companies, the business model as I see it today from the experience I have in raising money for these companies is that effectively these companies need to get to a stage where they can carry themselves into late stage clinical development on an appropriate risk/rewards basis. However, institutions are reluctant to fund early stage development programmes in the clinic through equity venture capital as the risks are deemed too high. Therefore, the business model should be about derisking these investments to enable more sophisticated investors to pick up the baton and move forward with them, not abandon them at an early stage so we do not even get the chance to get into this very exciting industry.

Q173 The Chairman: Thank you. Perhaps I could focus this point on Dr Pitchford. We have heard a suggestion from other witnesses that universities may be encouraged to form spin-out companies in this area at too early a stage. Do you think that point is justified?

Dr Nigel Pitchford: I think it is horses for courses, to be honest. You cannot be overly generic about that. Within the Imperial College/Imperial Innovations context, we tend to encourage projects that are coming through Imperial College to be funded at an early stage by government money or money that is associated with non-diluted grants. We encourage that development but with us looking over the shoulder of those involved and helping to form some of the proposals that go alongside the grant proposals in order to take them to a certain stage.¹²³ However, I guess that that operates within a context of Imperial Innovations having a reasonable amount of money and being used to dealing with that technology transfer with Imperial College. Other universities may be encouraged to look at external sources of funding at an earlier stage.

Q174 The Chairman: Perhaps all three of you could respond to a couple of points that have been made to us about SMEs. One is the suggestion that SMEs might outsource some of the developmental stages to bigger companies and thereby reduce the financial risk which might be associated with developing a capability in house. Do you think that that is a sensible proposition? The other suggestion is that when SMEs are newly formed, they might wish to secure additional revenue streams by contracting out their services. Perhaps Dr Dyson would like to kick off.

Dr Steven Dyson: I think they are very good ideas. The challenge of the first one, contracting out the development, is that of ensuring that the SME does not lose its intellectual property or know-how. In the regenerative medicine area, the protection is really around know-how—how you make the cells and repair the tissue—and is less about specific patents. There is a concern that, if I as a company ask another company or even another body to help me scale up or manufacture my product, all my know-how will leave my company. That is quite different from the small molecule world where once you have the IP on the compound, it is very strong.

The second one is in some ways fundamentally critical. If you are a small company and it is going to take you 10 years to get your main product approved, you need to think of ways of finding alternative sources. An example of that is the company we now own, LifeCell. It was founded back in 1986 as a spin-out from Houston University as a way of freeze-drying tissue without damaging it. It seems strange now, but it managed to do an IPO in 1992 with no products, which is reflective of a very different climate. In 1993 it launched its first product, which is a regenerative human-based tissue product, and it was still losing money in 2001.

¹²³ Advance them to a more fundable point.

How did it finance itself between 1993 and 2001? Some of it was the money it raised in the IPO, but then you are dependent on the public markets. It also sold its cryo-freezing technology to industrial applications outside of healthcare across the world. That was really how it kept itself going.

Dr Nigel Pitchford: Again, I would agree with Steven. The difficulty for many young companies in this space is trying to strike a balance between the funding they can realise from external sources, the funds they can generate from their own sources of revenue, which may be providing contract services to other people, and the loss of their own intellectual property. As Steven rightly says, particularly in this area the concept of intellectual property is actually a broader concept than we are classically used to around pharmaceuticals. The concept of working with cells and tissue requires an awful lot of skill, know-how and knowledge. That is what is effectively being encapsulated within the context of a company. It is the skill, knowledge and know-how that we as investors are looking to invest in because they are going to drive the future of the business. Hard-core intellectual property around the composition of matter, which is what we are more accustomed to in the therapeutics environment, is much harder to achieve here. We have to strike a balance between what can be brought in to help support a company: by out-licensing contract revenues, or funding directly and giving away your crown jewels.

Dr Navid Malik: The core competencies of a business relate to its programmes on which it has raised money because grant funding has been received, or there is an investment thesis around the core programme that needs to be defended. I can see the arguments for outsourcing development for non-core programmes where you can collaborate within a university environment, other SMEs or major healthcare companies in order to develop the parallel track opportunity. But for a core programme you have to remember that this is a knowledge-based industry with high barriers to entry because you are working with living cell products. Therefore in derisking these developments, you need to keep control of that programme. Additional revenue streams can be drawn on in relation to the contract services-type model, but they will never bring in the kind of funding you need to obviate the need to raise capital to run a clinical trial.

Q175 Lord Wade of Chorlton: What you describe is the traditional fund-raising way where a struggling fellow has an idea, he starts up a little business and then when he makes some money, somebody comes along and invests something in him. That has been the picture of UK development for a long time. Capital stands well clear until it is certain of being able to go in and take over a business that is going to be successful from day one. Yet one of the difficulties they have when going in with the money is not just the fact that the technology may not be right, but there may be little management, knowledge of marketing, sales and all those other activities that turn something into a business. What we have been discussing—Lord Willis referred to this earlier—is that this is an industry which could evolve like the microprocessing industry in the past. We had a number of little companies that tried to struggle with manufacturing, but we ended up with one company, Intel in America. Investment was prepared to fund Intel. At some stage this industry could be the same. Suddenly there could be a requirement for funding for one major cell manufacturing unit, if you like, which makes the technology available to all the people who are going to use it for different purposes. That is what is emerging. At what stage does the financial industry say, “We will take charge of this. We will raise a major fund that we will now invest in this important development that will dominate not just the UK but the world in terms of this particular technology”. The person who does that is going to make a fortune. If not, we are going to end up a fabricated little business struggling away, just as we did in the

microprocessing industry. One or two companies have done well because they specialised, but most have disappeared. What do you think is going to happen? When are you guys going to grab the nettle and say, “Let’s raise a major fund from the pension funds. Let’s have a £500 million fund and make a go of this”? When is that going to happen and who is going to take the lead?

Dr Nigel Pitchford: Lord Wade, I think that that would be a difficult proposition, certainly in the current environment. To my mind, comparisons with other industries like semi-conductors and chips are quite difficult to make in this context because semi-conductors and chips are very scalable. You can manufacture them in high volume and sell them around the world. The sort of therapies that we are talking about in regenerative medicine are more bespoke. They tend to be tailored towards the individual. That is part of the conundrum. The other part of the conundrum is that it is not clear, when you have gone to the effort and invested the money in making products, exactly what requirements are going to be placed on you in a clinical context in order to get regulatory approval. It is also not clear what the reimbursement regime will be around your products as you go forwards. That makes it difficult to make a compelling business case at the moment at the commercialisation phase for these products. You can do so more obviously for a product that you can easily scale up. However, I accept the challenge. At Imperial Innovations we invest very early into projects coming straight from academic labs within the university. We are one of the people who do accept the challenge of trying to build early-stage companies and make that happen, but for the sector as a whole, regenerative medicine is a slightly different beast. The pharmaceutical companies need to get together with the broader healthcare environment and agree on how to solve some of the issues around regulatory approval, reimbursement risk, process control et cetera. If they can be solved and people get interested in the products that come out as a result, the industry will start to blossom. When the industry starts to blossom, money will flow to it.

Dr Navid Malik: I just wanted to say that I agree with Nigel. There are challenges with respect to a number of these areas. However, in order for us to understand this, we should take some note of what is happening in other countries. If you look at the US, there are state funds of billions of dollars, such as those in California in regenerative medicine, which in the early years were being used to fund an educational programme around what stem cells and regenerative medicine entailed. They have suddenly woken up to the fact that they need to provide funding for translational medicine and clinical trials. So they are now funding multiple companies. StemCells Inc, for example, has raised \$40 million from this organisation to run clinical trials. All that is occurring at a very acute and important stage in the US. However, in Europe there are two things going on that are extremely important to take note of if we are to see this as a future growth driver for healthcare in the UK. First, in France, near Paris, a major manufacturing cluster has been launched which is solely dedicated to regenerative medicine, where \$143 million has been invested.¹²⁴ This information has recently been published, and five companies have already established themselves around that. There is going to be a cluster around that manufacturing consortium that is totally dedicated to this space. In Germany, they are providing matched clinical trial funding for matched phase one and phase two clinical trials. One of the companies on which I am on the board, North West, had US\$5.5 million of matched funding provided to it to carry out a phase one trial in immune therapy and cancer, using cell therapy products. There are challenges, but we have to take note of what is going on internationally, because we are at risk of seeing other territories take on regenerative

¹²⁴ Note from witness: \$39 million of public funds and \$104 million from the consortium members.

medicine in a more potent way, and there is no secret source to this. This is really about learning a lesson from internal resources and what is happening internationally within the scientific community.

Dr Steven Dyson: The only thing I would add is that if you look at the other parts of the medical industry, whether it is the pharmaceutical industry or the medical technology industry, the great returns have not accrued to the contract manufacturers. They have recruited the holders of the intellectual property. The margins on contract manufacturers for the pharmaceutical industry are 8% or 10%, and therefore being the huge manufacturer for all regenerative medicine products may not be the most attractive place to be. It is a necessary criteria to help lots of small companies with innovative ideas get their products to market and help them to scale up, but history has said in terms of returns that it may be that unlike in other industries, such as the semi-conductor industry, you would rather be the pharmaceutical company or the patent owner than you would be the contract manufacturer.

Q176 Lord Cunningham of Felling: What is happening in other countries with a view to stimulating industrial commercial development? The cell therapy catapult in the UK has a budget of £50 million over five years. Is that sufficient to make a quantitative and qualitative difference to what is happening here?

Dr Navid Malik: In my view if you look at the funding requirements for clinical trials, it is a very positive start and it certainly sends the right signal to draw in investors such as the pension funds and insurance funds, which would need to take up those programmes and fund them at a later stage, including corporate partners. However, when you think about the presence that regenerative medicine can command as an industry, there are very few industries that, like us, are at the dawn of something that could generate manufacturing revenues, logistic revenues and clinical revenues in an industry which is aligned with both a financial dividend, as in equity returns for investors, and a social dividend, because we are looking to find significant breakthroughs for these diseases. My experience has shown that we need to put a lot more investment into these companies, because otherwise there could be situation similar to that of one company that I IPOd i.e. floated onto the market in London. It was bought by a US peer group company for a fraction of what it was worth, and that company has gone on and commercialised revenues from that business. That is my greatest fear—that we will get to the inflection point and we will lose the momentum because of lack of funding. I think that equity investors will fund this space, but they need a lead. They need someone to take the baton alongside them. These investors are not sophisticated in some respects; they are generalist investors and need someone to validate what they are trying to do.

Lord Cunningham of Felling: So is that a yes or a no?

Dr Navid Malik: It is a start. Yes, it is great that this amount of money is available, but we could have multiples of the return in coming years as products reach the market—and many are lining up—but we need to put more money in. It is a start, but we need a consortium effort to bring more capital into the sector, because the returns are going to be much better with a well funded industry.

Q177 Baroness Perry of Southwark: My question is about the reasons for reluctance on the part of investors to step up to the plate in quite the way we might wish them to. Perhaps I may press you a little further on what kind of things might make a difference in this country? We have heard you say that there are models in other countries where

investors are putting in their money. Would it take one really good example of a successful regenerative therapy? We could say, “Gosh. We have cured some terrible disease through a piece of research”. Would that make a difference? Would investors begin to step up and say that this is going to pay? Or is it just the problem of seeing how reimbursement would be possible, particularly within our NHS structure where there is a lot of regulatory mess in the way of delivery?

Dr Steven Dyson: If you look at the barriers to investment, there is not just one. You have the clinical trial pathway, which is not completely clear because these are new products. You have the regulatory challenge of getting your product approved, and it is still very unclear as to exactly what is required. It varies by country; there is no harmony across different geographies and, in some ways quite rightly, the regulators are working out what is needed as they go along. The more products they see, the more they will refine and define the rules. We have already talked about the challenge of scale in manufacturing. One of the big challenges is, if you do not know how much it is going to cost you in the end to make your product, you do not know your cost of goods and you therefore do not know how much you are going to have to charge the end customer, whether it is the NHS or a similar body abroad. You do not know whether the product has a realistic price tag. Finally, you have the challenge of reimbursement. If you could address each of those issues, you could make the UK a very attractive place, not just for what we are focusing on now, venture funding, but for US companies to develop their products in the UK. Europe has a big advantage over the US in regulatory terms. At the company where I sit on the board, we can get our products approved in Europe much more quickly than we can in the US. In fact, the FDA is in some ways behind Europe in terms of approval; so there is a benefit there. Having said that, most hospitals in the US have a code. If you have a product, they will let you have reimbursement pretty easily for a few years to get the product tried out. If you try to do that in the NHS, it is a battle, hospital by hospital, and it can feel like there are lots of barriers. The UK has a huge opportunity because the NHS is a single body. No other country has such a similar overarching body. You could, if you really wanted to encourage a new product, set up a fund which says, “If you have developed a regenerative medicine product in the UK and brought people here early, we will for two or three years give you automatic reimbursement to get your product rapidly adopted into the NHS. If, after that time, you have not proved that it is worth having, then, fine, the funding stops”. However, if you could do that, combined with a fast-track regulatory approval and perhaps some of the ideas around getting the manufacturing expertise into the UK, you will find companies such as ours in the US saying, “The place that we should go to develop our products is the UK, because we can get on the market quickly, collect the data and then take the product to other countries at a later date”.

Q178 Baroness Perry of Southwark: I thought that NICE was the model for making that happen. NICE is supposed to be a central body that says to all NHS trusts, “Go ahead and use this product”.

Dr Steven Dyson: I think NICE is, but—

Q179 Baroness Perry of Southwark: Why does it not work then?

Dr Steven Dyson: There are a couple of things. Some products are too small for NICE to review. It will assess the maximum potential of a product. If every patient who could possibly use it in the UK will result in a cost of £20 million, it is not worth doing a review, so the matter will be assessed at a local level. NICE does not review every product. As regards medical technology, NICE is very focused on pharmaceuticals, particularly big new

products which could have a major impact on the NHS. Our company in the US has the biggest regenerative medicine product globally—we have over \$400 million of revenue—and it is now in the UK. It has not gone before NICE but is being used on a hospital-by-hospital basis. It is still being used in small amounts but you have to make a case for every single hospital. In other European countries each doctor has to assess each case, decide whether it is an exception and put in a special form which says, “This patient is an exception. Please fund the product”. Perhaps you could take away some of those barriers, but my point is that it is not a matter of any individual barrier but rather of the full package. You have to look right from the beginning to getting the product paid for and on the market. You need the whole suite of measures, with someone saying, “Come to the UK, we want to help you through from an idea to getting it used”. If not, I think you will find companies like ours much more inclined to do all their development work in the US.

Q180 Baroness Perry of Southwark: That is very helpful.

Dr Nigel Pitchford: I echo that sentiment and repeat what I said earlier. In part, we can try to compete at the technology level but, frankly, we have world-class research groups. There are world-class research groups in America and elsewhere across Europe and, increasingly, in the Far East, so we can try to compete on that level but the odds are that it will be difficult to do so. If you are looking at where we can bring a national advantage to trying to kick start an industry, it could well lie in the areas that Steven has just outlined. It could well lie in the use of clinical facilities in the NHS, getting rapid regulatory approval, having a streamlined process for reimbursement and our taking a lead around that reimbursement and regulatory approval being applicable across all the EU. Similarly, a lot of medical devices companies are currently relocating from the US to the UK or to Europe because they see a regulatory route which includes getting only a CE mark as being highly preferable to going through the FDA. We are starting to see a relocation of people here because the environment encourages them to go down that track to get commercial revenues. That is ultimately what it is all about. If we can improve the visibility and viability of driving commercial revenue for some of the industry’s products, we stand a very good chance of being able to create an industry here where, at technological, academic and other levels, we are going to be on a level playing field with other people. We have the ability to create an unlevel playing field in particular areas but we need to drive that agenda.

Dr Navid Malik: I agree with Nigel and Steven. The UK has the infrastructure within NRES (National Research Ethics Service). It has put together the effective single application. You can do a clinical trial across multiple hospitals and sites, so that important part of the equation has been established: high-quality clinical trials can be done in the UK today in regenerative medicine. In terms of NICE and reimbursement, certainly as regards the healthcare and pharma companies I talk to, regulatory challenges are less of a concern. Their major concern is reimbursement. This comes back to the manufacturing argument: can you make the product at an economical level which makes it worth while pursuing? However, we should not lose sight of the clinical data from large phase 3 trials, or perhaps proof of concept trials at an earlier stage in phase 2. As those clinical data come through, the regulators and reimbursement authorities will have a learning curve that will enable them to understand what they need to do in order to meet these technologies halfway, and, likewise, NICE for the bigger indications—bigger diseases—where regenerative medicine can play an important role. In orthopaedics, for example, we already have approvals in this space. Then the reimbursement challenges will fall a little bit lower. However, it is very important that we have the right level of clinical data to show clinicians, reimbursement authorities,

regulators and investors that this is exactly the space where we need the platform and where we need to deliver the new medicines in the future.

Q181 Lord Willis of Knaresborough: I thank you all for those answers. It was good to get such a positive way forward because I am a reggae fan and this inquiry reminds me of Johnny Holt's wonderful song "There Are More Questions Than Answers" in that it seems to be going round and round. I come to intellectual property, which we mentioned earlier. Can I start with you, Dr Malik? In terms of getting investment outside the state, or, I suppose, even within the state, and particularly within academia, how important is IP to this space?

Dr Navid Malik: On a generic level, patents in such a property are very important for all investors. However, I cite the example of Shire Pharmaceuticals, which bought Advanced BioHealing last year. The latter company produced a product called dermagraft, which was once investigated by Smith & Nephew. It is a living cell product which is used for diabetic foot ulcers, so it is a proper regenerative medicine product with real manufacturing challenges which have been overcome and a regulatory pathway and reimbursement. I think that the patent for that product expires in a year or so. When the deal was done, everyone questioned why Shire would do such a thing. However, I argued that, yes, we need patents and we need protected methods of manufacturing which you do not disclose publicly—they are better than a patent in effect—but we also should remember that these are living cell products. Therefore, I think this is going to be a mixture of protected markets through market exclusivity or orphan drug status, which you typically get in the US and Europe for smaller niche indications, but more importantly, because these are living cell products, there is no generic route. You can copy an aspirin molecule and create a copy for an antibody but you cannot copy a living cell product. So, yes, patents are important but we should not be fixated just on IP. As Nigel and Steven have said, this is more about the secret know-how of the business. A living cell product gives us much more interesting barriers to entry which in the very short and medium term I do not think will be overcome by competition, and therefore investors should warm to that.

Dr Nigel Pitchford: We would consider know-how, particularly processing and manufacturing know-how, as being intellectual property within the context of a company. If it is held, is well researched, and is highly reproducible, we would consider that to be intellectual property, not within the classic sense of having a patent, but within the sense of it being a valuable asset that the company owns and can gain leverage on. We view know-how in that context. The important point there is that that still has to be protectable, so you still have to have protection mechanisms in place.

Q182 Lord Willis of Knaresborough: I was going to ask you that question. How do we do that?

Dr Nigel Pitchford: When considering a company that is based around know-how, these are trade secrets and you have to be able to protect yourself against people leaving and being able to set up somewhere else and reproducing the same effect externally. There are legal ways of doing that: for instance, by imposing restrictions on their activities. This is quite difficult to achieve. However these manufacturing processes are also quite complicated. The reason why there are trade secrets and know-how around them is because they are quite long complicated processes, and deal with living cells, which are not particularly easy to standardise. People have different expertise at different parts of the value chain and at different parts of the processing and manufacturing chain so it is quite difficult, unless you

have a whole team walk out, for them to be able to reproduce these things in a different environment.

Q183 Lord Willis of Knaresborough: So the lack of IP, Dr Dyson, should not be a barrier to your investors?

Dr Steven Dyson: We bought a company last year—LifeCell—that was founded in 1992. It basically makes either human or porcine tissue that is used for surgical procedures. The key is to wash it enough—I simplify—to remove all the cells that would cause an immune response, but not so much that your own cells cannot grow into it so that it becomes part of you. It is a very fine balance, and a very secret set of steps. Very few people in the company know all the steps and all the solutions, and how long you do each step for. We were comfortable that this did not have IP; it was know-how. Companies have come in to try to come up with something similar. We would say that their products are different. People can debate whether they are better or worse, but they are clearly different. From our point of view, getting IP is not critical. Freedom to operate is more of a challenge. When we look at the acquisition of small companies, we have to consider whether a highly complicated set of other patents that have been issued or are in the process of being issued in lots of different geographies could impact the company's ability to be allowed to develop its product. In some ways this is a much harder problem. It is very expensive to work out what all these different patents are. Some overlap with others. A lot of them have not been tested in court, so you do not know whether they would stand up. So you have to make difficult judgments. You could do all this work and develop a product and at the very end someone else could claim that you had infringed their patent. For small companies, the costs and challenges of working out freedom to operate are bigger than getting protection for their own products.

Q184 Lord Willis of Knaresborough: So getting that legal support would be useful, if we made that recommendation? A small company cannot do that.

Dr Steven Dyson: It is very expensive. You have to look in lots of places, and some products have not gone through the whole process. Then it is a judgment about whether the patent will be issued and, if it were litigated, whether your product would be judged to have infringed the patent. It is complicated and expensive.

Q185 Lord Willis of Knaresborough: Can I come back to you, Dr Malik, for one final point? You mentioned that in the company that you floated there was an issue of a patent running out. Clearly, patents are important where they are appropriate. Would it help in this space for the length of patents to be longer?

Dr Navid Malik: That is a very good point. One of the issues that Shire had—if you could call it an issue—was that a living cell product did not fall under data exclusivity clauses in Europe, so the company could not take advantage of them. For example, it launched products in the rare disease space and has a big franchise for treating children with attention deficit and hyperactivity disorder, a condition of the central nervous system. It takes advantage of market exclusivity. The clinical trial data that it generates in getting to the market is protected legally for a period of time: three, five or potentially 10 years. Shire is launching a drug next year in the CNS region that has no patent. It could get a 10-year protected market, but no such path exists for regenerative medicine, as far as I am aware. It could be a good way of helping companies that risk investing, helping payers and helping reimbursement authorities to see those products come through if a protected market existed, as it does with small molecules and antibodies.

Q186 Lord Willis of Knaresborough: Chair, it would be really useful if we could have a note on that for the record.

Q187 The Chairman: Would you mind sending it to us?

Dr Navid Malik: Yes, I can send you a note on that, definitely.

Q188 Lord Patel: This is a very brief question, to which I would like a brief answer. Following your comments, let us take the example of embryonic stem cell therapy that is going to trial next year for age-related macular degeneration. From what you say, I gather that if those clinical trials are seen to be going well, because it is a living cell there is no patent involved, so the only thing that could be protected is the manufacturing aspect, for which we have no facilities.

Dr Navid Malik: The companies that are doing these trials in their early stages, such as Advanced Cell Technology in the US and StemCells Inc, do have patents, but the manufacturing barriers are still high because they are using proprietary cells; they have a proprietary route in manufacturing these cells and finishing the final product. As these companies get into bigger clinical trials, there will be a natural barrier to the entry of competition because it will be very difficult to copy these products. So I do not think that there is an undue risk there, because in effect there is no industry today where you can see a generic copy of a living cell product. No one has even come close to producing such a thing. We are at a very early stage in the process. These companies will probably play out by filing new IP or creating new ways of manufacturing: for example, automation. At the moment many living cell products are produced by a manual process. Companies will probably go down the route where they provide automation, so they can close the system and will not need big, clean rooms to make the products. You will be able to manufacture them cheaply. This comes back to how much they cost to make, and also efficiency. That will add further barriers to entry to the industry to allow the companies to commercialise their products successfully.

Q189 Lord Patel: Let me use another example, because you are so knowledgeable about this: that of red cells.

Dr Navid Malik: Red blood cells? You can get blood transfusions, bone marrow transplants et cetera. It is a very well trodden path for the industry. It is also a personalised medicine. You take cells from a matched donor to provide a therapy to the patient who needs it. Decades of experience have shown how to do that efficiently. However, for products that are not taken from a patient but are produced as an off-the-shelf product, the knowledge and the learning curve are just not there. Even if someone perfects a way of copying the cells, it is so far out that the industry will be blossoming by then; it will be large and very successful. I do not think that we should focus on that. It is not a concern today as far as I can tell.

Q190 The Chairman: Perhaps I could come back to a question about patenting, and whether the European Court ruling on the patenting of embryonic stem cells has had, or is likely to have, an impact on investment in this area.

Dr Navid Malik: I have floated both embryonic and adult stem cell companies. It is a little like the argument that was made when the human genome was sequenced that you could not own a gene. However, there are many successful products that work against genes and against mutations. In effect, it is not about whether you can patent an embryonic stem cell.

It is about the “productisation” of cells and how you deal with treating embryonic stem cells as a product. Not having a patent on an embryonic stem cell is not a barrier to entry, just as it is not a barrier to entry that someone does not own a particular gene in our body. You cannot patent genes that exist naturally in human beings anyway. So that issue has already been in the gene therapy space and it has not caused a major issue. In the adult stem cell space we tend to have patent-protected products in the main anyway, which are allowed.

Q191 The Chairman: So is the short answer no, it does not necessarily provide a barrier to investment?

Dr Navid Malik: No, it does not.

Q192 The Chairman: Do the other two panellists agree?

Dr Nigel Pitchford: I would tend to agree, yes. Ultimately the value proposition here for any investor and for anybody seeking to create a company in this area is about being able to successfully create a product and get it into the market and into a space where people are willing to pay for it. The challenges come later in the process rather than earlier. As we discussed, some of the issues around intellectual property—specifically patents—could prove to be a bit of a red herring. The challenges are around how we gear the industry towards making a product successfully commercialisable.

Q193 The Chairman: Dr Dyson, do you agree?

Dr Steven Dyson: I agree. Ultimately, you have to convince your investors, whoever they are, that you will have a protected product and therefore make it a commercial success. Patents are only one example. The benefit of patents is that they are very simple to explain to people. “I have my product and it is patented” is a very simple story. If you do not have that message—and pharmaceuticals tend to have that message—you have to start explaining that you have secret know-how or a secret delivery method but you cannot say what it is. You can explain it to people, but it makes the story more complicated. For example, with public market investors who have lots of other things they could invest in, experience shows that the more complicated the story, the harder it is. They ask: “Do you have a patent or not?” We say, “It doesn’t matter”. They say: “Well, we’ll find one that does, because it’s easy”.

Q194 Lord Wade of Chorlton: Perhaps I may ask a further question of Dr Malik. You kindly referred to my question about activities taking place in France and Germany. Where did the money come from to invest in those activities?

Dr Navid Malik: The money came from the States in the main. In Germany it was purely local government that funded the trial and others like it. In France it was a mixture of public and private financing.

Q195 Lord Wade of Chorlton: But did the Government or private financing take the initiative?

Dr Navid Malik: The Government took the initiative; it was not taken by private investors.

The Chairman: I should like to draw the session to a close and thank our three witnesses for their helpful evidence. You will receive a transcript of the session, which you will be able to correct. If there are any points that you were not able to make that you would like to add in the form of a written statement, we would be very pleased to receive it. Dr Malik,

you agreed to send us a short written summary of your response to Lord Willis. Thank you all very much for coming.

Consulting on Advanced Biologicals (CAB) Ltd, LGC and Genetic Alliance UK – Oral evidence (QQ 330-342)

Consulting on Advanced Biologicals (CAB) Ltd, LGC and Genetic Alliance UK – Oral evidence (QQ 330-342)

[Transcript to be found under Genetic Alliance UK](#)

Consulting on Advanced Biologicals (CAB) Ltd – Supplementary written evidence

I. Introduction

This evidence is divided into opening thoughts, additional comments related to the proposed questions for discussion provided prior to the oral evidence session, and other additional evidence.

Opening thoughts

I have a rare combination of experience having worked in biotech including a cell therapy company and for the MHRA (primarily undertaking EMA assessment) and now provide specialised consultancy services for a range of developers from academic through to large Pharma. Although I now focus on regenerative medicine (primarily ATMP's), I have also worked on many types of biological products. This experience has led me to determine that the difference between working with established traditional biotech/pharma and SME's developing ATMP's is the level of experience and understanding of regulation. Established biopharma do not require an explanation of why certain data are needed. By contrast, new SME's typically require an explanation. It is precisely this lack of understanding as to why certain types of data are necessary, that is a symptom of a deeper lack of understanding of how the inter-dependent parts fit together. There is a tendency for such organisations to learn in an incremental fashion, which means they only understand what is needed to get to the next stage and therefore often have no idea about issues that will come later, some of which needed to be considered early on.

It is also a common held belief within the cell therapy (those making cell-based medicinal products) industry that it is harder for them than for traditional biotech (e.g. recombinant proteins) where the regulatory route is more established. Firstly I would clarify that to me regulatory route means legal basis, and aside from exemptions there is only one route, a full market authorisation through the EMA. The process is the same for other biologics and small molecules (although there are for them options for abridged procedures). What developers really mean by regulatory route is the data requirements; how do they get the data, how many studies do that have to do and what are they? In a recent publication I concluded that this issue lies with the basic science since regulation is science-led¹²⁵. I would add to this conclusion (thankfully voiced by others in their evidence) that there is a need to invest in regulatory science, not just the policy end of regulation, but the hard science. In my view investing in enabling regulatory science is a better use of public money (e.g. by the Catapult) than spending it on clinical trials, since if the probability of success of cell therapy products is anyway similar to other medicines, only 13-32% of products entering the clinic are eventually licensed, with biologics being towards the upper end (DiMasi et al¹²⁶). While biotech products have a greater chance of success, we can only speculate as to whether cell therapy will be better or worse at this point. If we combine this

¹²⁵ <http://rsif.royalsocietypublishing.org/content/early/2010/09/14/rsif.2010.0442.focus.full%20>

¹²⁶ <http://www.nature.com/clpt/journal/v87/n3/abs/clpt2009295a.html>

observation with that of the EMA^{127,128}, then success rates may be lower in the short-term because the developers on average are less experienced.

For these reasons I am unconvinced that tax payers money should be used to fund clinical trials unless there is claw-back from those that are successful; the likelihood of failure and the amount of money involved is too high. This is why the model for developing medicines relies on commercial support, that way the successes pay for the failures. Another personal fear is that the general lack of acute toxicity means that perhaps less will be filtered out at phase I, and for SME's in particular the fast-to-phase III approach forced on them by lack of investment may mean fewer fail in phase II-type studies, and consequently a greater proportion will fail in phase III. This is undesirable because phase III studies are larger and more expensive, the objective should be to fail poor products quickly, efficiently and cost effectively, and not drag them through to the end before reaching this conclusion. I have no data to support this personal concern, and I suspect insufficient data is available for the time being to make a comparison, since so few have reached marketing authorisation (MA).

Returning to regulatory science, a quick web-search identified a small number of university courses in the USA, but none in the UK. If we are to support regenerative medicine and more broadly the development of more complex biological medicines and other novel science, then I think acknowledging the need for regulatory science as a discipline would be an enabler. Some EU agencies undertake some research, some of which may well be regulatory science, but the MHRA does not to my knowledge. The FDA do this and recently published a paper on characterisation of MSC's. The upcoming merger of the NIBSC with the MHRA could be an opportunity to do wet-science in this area, and of course for cell therapy we have the Catapult, but I think a separate centre for regulatory science that isn't too focussed on specific product categories would be more broadly valuable to the UK. There is also important work on-going at the LGC. I would envisage a small University department undertaking research and running a post-graduate course, PhD studentships etc. The UK has a reputation for pharmaceuticals, we have the EMA here in London and the UK is very active and we undertake a lot of EMA work, our CHMP member is the vice Chair, and many others have key positions on EMA committees; yet we do not apparently invest in regulatory science. This does seem short-sighted. I also comment elsewhere that there is a shortage of regulatory professionals, yet getting into regulation is a catch 22, industry demand experience so until you have some it is near impossible to get a regulatory position. Many like myself fall into regulatory by accident, but there isn't a clear career path into regulatory; a course of this nature may provide a path.

II. Evidence related to possible questions from the Select Committee

I. Some witnesses have told us that the regulatory process for regenerative medicine in the UK is too complex, with too many regulators involved. What is your assessment?

Due to the paucity of experience with other medicinal products I often get the impression cell therapy developers think it is cheaper and simpler to develop a recombinant protein. I would say this is unlikely to be true based on the data they actually generate. For instance

¹²⁷ Regnstrom J, Koenig F, Aronsson B, et al. (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency; EJP 66:39-48 (copy can be found here: http://peer.ccsd.cnrs.fr/docs/00/53/79/93/PDF/PEER_stage2_10.1007%252Fs00228-009-0756-y.pdf)

¹²⁸ http://ec.europa.eu/research/health/pdf/event02/constantinos-ziogas-02_en.pdf

I'm told manufacturing costs are high for cell products, yet they are manufactured at small scale using simple equipment and many disposables. In contrast traditionally recombinant protein are often made in large stainless steel bioreactors and purified through numerous downstream columns etc. For market authorisation they need to make a number of commercial scale batches of product, this can be thousands of litres. What is really meant is the unit cost of a dose is higher, as are the cost of goods per patient treated, but the initial investment I suspect is considerably lower (however I don't have any data to support this). It is true that the tools needed to characterise biotech products are better established, but it is not straightforward, and compared to overall product complexity (living cell versus single protein) most cell therapies are much less well characterised. In my view they are also less well characterised in relation to the tools available, with developers often applying rather few methods. Compared to development of biotech products I think regulatory agencies are accepting minimal data for clinical trials at least, my worry is whether it is understood how much more is needed at marketing authorisation application (MAA). This is a two edged sword, if regulators are too light on clinical trials inexperienced developers will fail at MAA because of the tendency for them and their investors to misinterpret a clinical trial approval as proof their development is on-track. Unfortunately this is a long way from true; the focus (quite rightly) of clinical trial assessment is safety of the study subjects, not sufficiency of current development for market authorisation. This is very commonly reflected at marketing authorisation¹²⁹, where for example deeper assessment of changes to manufacturing can identify insufficiencies in the data generated to confirm manufacturing changes between in particular phase II and III did not alter the product.

The committee may be interested in some evidence to support my assertion that inexperienced companies are less likely to be successful, even though it seems logical enough.

- (a) Section 1.5.1 of the EMA report on Performance of the Agency's scientific procedures: Survey 2009 for medicinal products for human use¹³⁰.
- (b) Related publication by CHMP members¹²⁷

Returning more specifically to the question, having worked from different sides of the regulatory system I believe it is fair, and importantly I struggle to see how it could be less onerous without dropping standards. Many of those that complain about the regulatory burden seem to me to perceive what they are doing as less complicated than it is. For instance, if they were developing a new car they would not have any doubt they needed a large multidisciplinary team, a large amount of money and would need to focus heavily on safety. Developing a cell therapy is probably scientifically more complex, and certainly has greater uncertainties since the underlying science is less mature. In an interview for BBC radio 4's 'In Business' programme in June 2005¹³¹, the then CEO of GSK, Jean-Pierre Garnier, likened developing a new pharmaceutical to putting a man on the moon, I've offered a more conservative analogy.

I believe many of these objections will recede as developers become more familiar with the system and better understand the scientifically solid reasons behind the regulatory expectations. I certainly feel I've observed this with my clients, those who are better

¹²⁹ <http://www.nature.com/nrd/journal/v7/n11/full/nrd2728.html>

¹³⁰ http://www.emea.europa.eu/docs/en_GB/document_library/Other/2010/03/WC500078395.pdf

¹³¹ http://www.bbc.co.uk/radio4/news/inbusiness/inbusiness_20050623.shtml

informed are less inclined to question the need for certain data, they come to understand why and that it is necessary.

However, clearly there are difficulties with the EU regulatory system, many of which are related to the fact that the system is based on harmonisation of regulatory expectations and procedures between 30 member states of the EU/EEA, rather than a federally centralised system like the FDA. The EMA works well and reduces the regulatory burden for developers wanting to market across the EU; they need only a single license. In contrast clinical trials are a national responsibility, with developers needing to seek approval in each country they are undertaking clinical trials; be that an EU member state or a third country like the US. It is somewhat unfair to compare the US to the EU in this respect, but since the final MAA is granted by the EU Commission it can seem puzzling that clinical trials need to be approved nationally. Thankfully the current proposals to amend the clinical trials directive are trying to address this by setting up a mutual recognition-type process, standardising document requirements and creating a single submission regardless of how many member states are involved. These are all extremely promising proposals and should go a long way to simplify clinical trials approvals for multinational EU trials.

When it comes to variability of regulatory expectations and guidance, I hear two conflicting views on a regular basis:

a. There are endless rules

This isn't in my view fair, relatively speaking (to complexity) there are relatively few absolute rules, medicines are primarily regulated through scientific principles, you are asked to demonstrate your product is safe and efficacious (risk/benefit is acceptable) and of a consistent suitable quality. How you achieve this is to a large extent up to you – but it must be scientifically sound. The available guidelines, in particular those harmonised through ICH¹³², convey those principles and these are common to ICH regions (US, EU and Japan along with many other jurisdictions who are not official signatories). Some guidelines are tailored to small molecules, some biotech, relatively few to ATMP's but few of the available guidelines are product-specific because the differences between products are significant enough that a product-specific guidelines would be too specific. Indication-specific guidelines are more common since they relate to best clinical practice in evaluating treatments for specific conditions.

b. There is no specific guidance

As indicated above, guidelines cannot easily be specific to a product or even product category because too many factors influence decisions, e.g. the indication, the approach to manufacturing, presentation of the product etc. It is rare to have absolute requirements since there are nearly always situations where the requirement could not be applied, or another approach might be better. For some well-established and widely used medicines that are no longer covered by IP, because many manufacturers make generic versions there is more extensive guidance available. But it must be appreciated detailed product-specific

¹³² International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to agree common technical standards.

guidance cannot be written for most products, and where there is no option for generics or biosimilar (as with ATMP's), would be pointless to write.

It's important to remember the science is moving quickly: regulation is always playing catch-up. However, the system itself is extremely flexible BECAUSE there are few hard rules, but this puts the onus on the developer to determine the data requirements. To emphasise this further the EMA from the start has indicated they are prepared to consider a risk-based approach to development.

Those developers who complain that there should be more specific requirements simply haven't considered the consequences, this would stifle innovation if it was possible, which it isn't because to write specific guidance the regulators would have to know what needs to be done (which is not possible when its new) and then if the developer wanted to take different approach they would be blocked. Regulators are not developers, their role is scientific evaluation of the evidence – a kind if peer review, albeit with teeth.

My personal view is that the complexity of developing any medicinal product is understandably daunting, and without experience of developing medicines can seem impossibly complicated. So when experience is limited (most cell therapy developers) this makes it very difficult to make good decisions, and importantly understand the possible ramifications of those decisions. Some developers are not only inexperienced, but simply don't know what they don't know. The mismatch is that there are plenty of regulatory professional with biological experience, and a good number of people who have good cell therapy experience very few with both. Experienced regulatory professional are expensive and in relatively short supply (if the number of calls I get from head hunters is anything to go by). Either cell therapy developers need more money to hire appropriate people, or need more money to supplement this with experienced consultants.

It would be a good use of government funding to support/subsidise good quality training for SME's in regulation of medicines and devices. Currently most SME's simply cannot afford the sort of training they need and I suspect rely (also from personal experience of working in an SME) primarily on attendance of conferences and workshops and learning from others. CAB Ltd attends many key meetings each year and while we do our best to give presentations on key topics, a 20-30 minute talk cannot substitute from more in-depth training. Even a full day workshop on a topic like 'Characterisation' can only touch on key issues. What is needed are courses that cover these topics in depth at a price that will allow all key staff within a company to attend relevant modules. This training should of course go beyond regulation, but also include reimbursement, patents etc. The obvious vehicle for this would be the Catapult, but I should commend the ATMP Manufacturing Community (AMC, <http://www.atmpmanufacture.org>) for attempting to tackle this problem within the UK community.

On the other hand, at a recent AMC meeting I surveyed the audience as to whether they had read all the key guidelines, the response was disappointingly few, and some admitted to not having read any of them. This was an academic/SME audience, most of which were involved in manufacturing of ATMP's.

Some Indicative Metrics on Guidance

>50 European Pharmacopoeia chapters and monographs relevant to ATMP's, ignoring raw materials monographs (<http://advbiols.com/documents/PhEur.swf>).

Table 1: Indicative numbers of guidelines available that have at least some relevance to the development of cell-based medicinal products (excludes gene therapy).

Summary of Guidelines			
Discipline	EMA	FDA	ICH
Quality	14	37	17
Multi-disciplinary	6	3	1
Clinical	15	9	20
Non-clinical	5	9	TBD
Miscl.		3	
GTP's	TBD	18	
GMP	TBD	10	
Totals	40	89	38
Grand Total Identified to date	167		

The table above was prepared in 2010 and are not accurate final numbers; furthermore additional guidelines have been release since this was prepared. The clinical guidelines identified excluded indication-specific guidelines. Most of these guidelines are not however specific for ATMP's and part of the problem is that developers may not otherwise realise they are at least indirectly relevant and convey regulatory principles.

In the defence of the EMA, they have written a significant number of guidelines in a short space of time for an emerging field which accounts for only 4-5% of the scientific advice requests, and <2% of MAA's submitted (average 90-100 MAA's submitted to EMA each year, around half of which are new active substances)¹³³.

Thanks to the support of the TSB, CAB Ltd has developed a series of web-tools to help cell therapy developers find relevant guidelines (ICH, EMA and FDA), see <http://www.advbiols.com/Resources.php>. The same information is also available within PAS 83¹³⁴ and PAS 93¹³⁵, documents published by BSI thanks to support from BIS.

Regulatory Burden

Many complain about the burden of regulation, this is of course inevitable if you regulate something as complex as the development of medicines; you can't regulate without the information and this puts the onus on developers to prepare it. Is there scope to reduce this? Perhaps, but these are likely to be minor refinements. The bulk of clinical work in regenerative medicine in the UK (and much of the EU) is unusually academic, and the issue there is that they embark on these clinical studies without understanding the resources that

¹³³ Based on data available from the EMA website.

¹³⁴ <http://shop.bsigroup.com/en/forms/PASs/PAS-83/>

¹³⁵ <http://shop.bsigroup.com/en/forms/PASs/PAS-93/>

will be needed. Most SME's eventually have one or two people fairly much dedicated to regulatory because it is an essential discipline for medicines development. The NHS or academic centre(s) could invest in some sort of centralised regulatory support team. It may even be that the new Catapult could provide this service.

There certainly needs to be more realism among academics and their funders. Over the last few years I have been approached by a number of academic groups around the EU asking to quote for regulatory support for their projects. I know my rates are not as high as a typical biotech consultant, yet in most cases I have had feedback that they felt could not request that much money from the grant funder (including EU Framework grants). It's also harder for me to give advice when there isn't a clear objective beyond the proposed clinical trial, sometimes I'm told they do not envisage a market authorisation, the indication is too rare. This naturally leaves me asking why they are doing the clinical trial at all? The best way to make a product available to the wider public is to obtain a market authorisation; otherwise you have to rely on named-patient exemptions such as Specials and Hospital Exemption. These exemptions limit access, they don't have evidence for efficacy (save anecdotal evidence from small numbers of patients) let alone cost-effectiveness for reimbursement; so will never meet their potential, or worse, may not actually be effective and hence a waste of scarce resources.

There needs to be a better understanding that there are conditional and exceptional circumstances for MAA which can allow approval with more limited data. To take the recent approval of Glybera as an example, the total number of patients treated for this orphan indication (lipoprotein lipase deficiency) was only **27** – enough for an exceptional circumstances approval by the EMA¹³⁶. This product is now potentially available in 30 countries of the EU/EEA, amounting to around 500 million people, subject to reimbursement agreements by healthcare providers. I'm regularly told by developers their indication is too small to warrant an MAA, in most cases the disease is far more common than lipoprotein lipase deficiency, which has a prevalence of around 0.02 in 10,000 (equivalent to 1,013 individuals in the EU). Any of those who have said the indication they are studying is not big enough would be undertaking an initial trial in maybe 10-15 patients, so would be half-way there at the end if the situation were similar – though of course many factors affect how many patients are needed for approval.

However, while I emphasise the best outcome for patients are controlled clinical trials and market authorisation, it isn't necessarily the best outcome for the market authorisation holder to be a hospital or university – this would be a paradigm-shift. However, companies such as Shire have demonstrated that orphan medicines can be profitable, and they are looking to cell therapy with their recent acquisition of Dermagraft (human fibroblast-derived dermal substitute).

The EMA offer significant fee reductions to developers of orphan products, especially SME's. However, few member states offer national incentives¹³⁷ to developers. The UK could consider whether additional incentives at a national level are possible; they could for instance mirror the EMA's fee reductions for MHRA scientific advice, inspections and perhaps clinical trial application fees. It may also be worth considering whether fee reductions could be offered for Human Tissue Authority licensing also.

¹³⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/07/WC500130153.pdf

¹³⁷ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

As requested during the oral evidence I have attempted to collate some information on costs, these are presented elsewhere in this document.

Can we simplify the UK regulatory structure?

EU Tissues and cells (EUTCD).

The UK has two authorities responsible for aspects of the European tissues and cells directive (EUTCD; Directive 2004/23/EC), the HFEA for gametes and HTA for somatic cells, although these authorities have other responsibilities too. Since the competent authority for medicinal products is the MHRA, this means that if you are for instance deriving human embryonic stem cells for clinical applications you will need to liaise with all three of these authorities. In contrast, many point out in the USA the FDA covers all these activities related to the use of human cells for clinical use.

To bench-mark the UK against other EU member states I have prepared the figure below by asking how many different competent authorities does each member state have to cover blood, tissues and cells, reproduction (gametes), organ transplantation, medicines and medical devices. For the 25 member states for which I had data, this means there are 50 different competent authorities a developer might need to contact; the average is 2 per member state. Interestingly 10 of the 25 (40%) member states have all these activities under a single authority; it might be interesting to poll stakeholders in those countries to enquire whether they find the system less complicated. This may not be the full picture, since GMP inspections and tissue establishment inspections are sometimes covered by regional authorities, e.g. Germany and Spain, meaning in some cases there are additional agencies involved. Not captured here is the fact that Germany has two competent authorities for medicines, PEI cover ATMP's and other more complex biological, and BfArM cover the rest.

During my oral evidence session I was asked if I could confirm whether this information is still correct since it was based on a 2007 survey. Unfortunately I was unable to do this systematically within a reasonable timeframe with the resources available to me; however I do not believe the picture has changed significantly. Comparing some more recent lists of competent authorities didn't identify any obvious changes, other than re-branding of some agencies (e.g. the French authority Afssaps is now called ANSM).

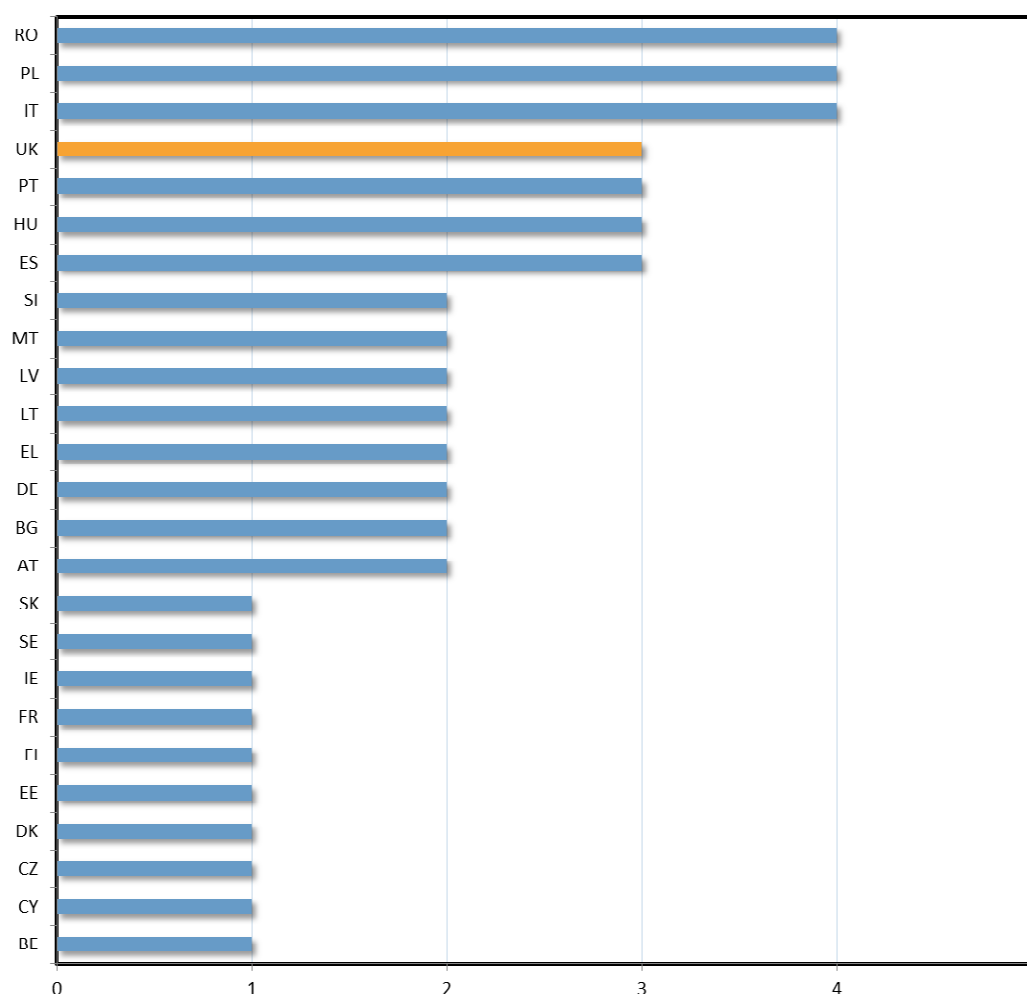


Figure 1: Number of competent authorities covering medicines, medical devices, organ transplantation, tissues and cells, reproduction and blood by EU member state.

While a one-stop shop might seem attractive, splitting responsibilities between agencies is not necessarily less efficient than having a single authority, since divisions within authorities can be as detached as if they were different organisations – some have expressed this view for the FDA, they are not always well joined up. However, one immediate possibility that might offer efficiencies is combining facilities inspections such that a single inspection covers tissue establishments (HTA responsibility) and medicinal manufacturing (MHRA responsibility). I believe this is already happening to some degree, although there may be room for further consolidation.

Personally I don't think the current HFEA, HTA and MHRA being separate is a major problem, more significant is the lack of harmonisation in implementation of the European Tissues and Cells Directive across the EU. It would be worth investigating further the approach to implementation and identifying the most efficient approach and working with member states to agree a more common approach. In 2008 the EU Commission published a summary of a Questionnaire on the transposition and implementation of the European Tissues and Cells regulatory framework¹³⁸; I have attempted to digest some of the

¹³⁸ http://ec.europa.eu/health/blood_tissues_organ/docs/tissues_responses_2008_en.pdf

responses. Since member states vary so much in population size I have normalised by population.

Of 25 member states for which there is data, the average number of tissue establishments per million of population is 6.1 (range 0=EE to ~19=DK) the UK actually has only around 4-5 per million. These numbers are very approximate since Germany for example claims over 1,000 (2008 population 82.6 million), rather than a specific accurate number. What it shows is the UK has relatively few Tissue Establishments relative to our population. This needs to be investigated a little more to understand why. The probably reason why Germany has so many and cannot easily give accurate figures is that facilities licensing is handled regionally, so many more competent authorities than the UK. It is also important to acknowledge these data are also rather old now, and come from a period when member states may not have completely implemented the directive.

Given that the UK appears to have more activity than most other member states in this field, it may even suggest we are quite lean with facilities licensing. However, these data are a little difficult to interpret, so we cannot rely on the detail, but broadly I think the optimistic interpretation of this is that the UK defines a tissue establishment in a similar way to most other member states. By this I mean they probably have the balance right as to what constitutes a tissue establishment, e.g. is it the NHS trust, the hospital, the building or the department that needs the license? But it would be worth investigating this further to ensure the system doesn't over burden those attempting to deliver cell therapy.

As indicated elsewhere, it might also be worth benchmarking the UK with respect to the cost of licensing since I have had some indications the UK is expensive, compared to Germany at least.

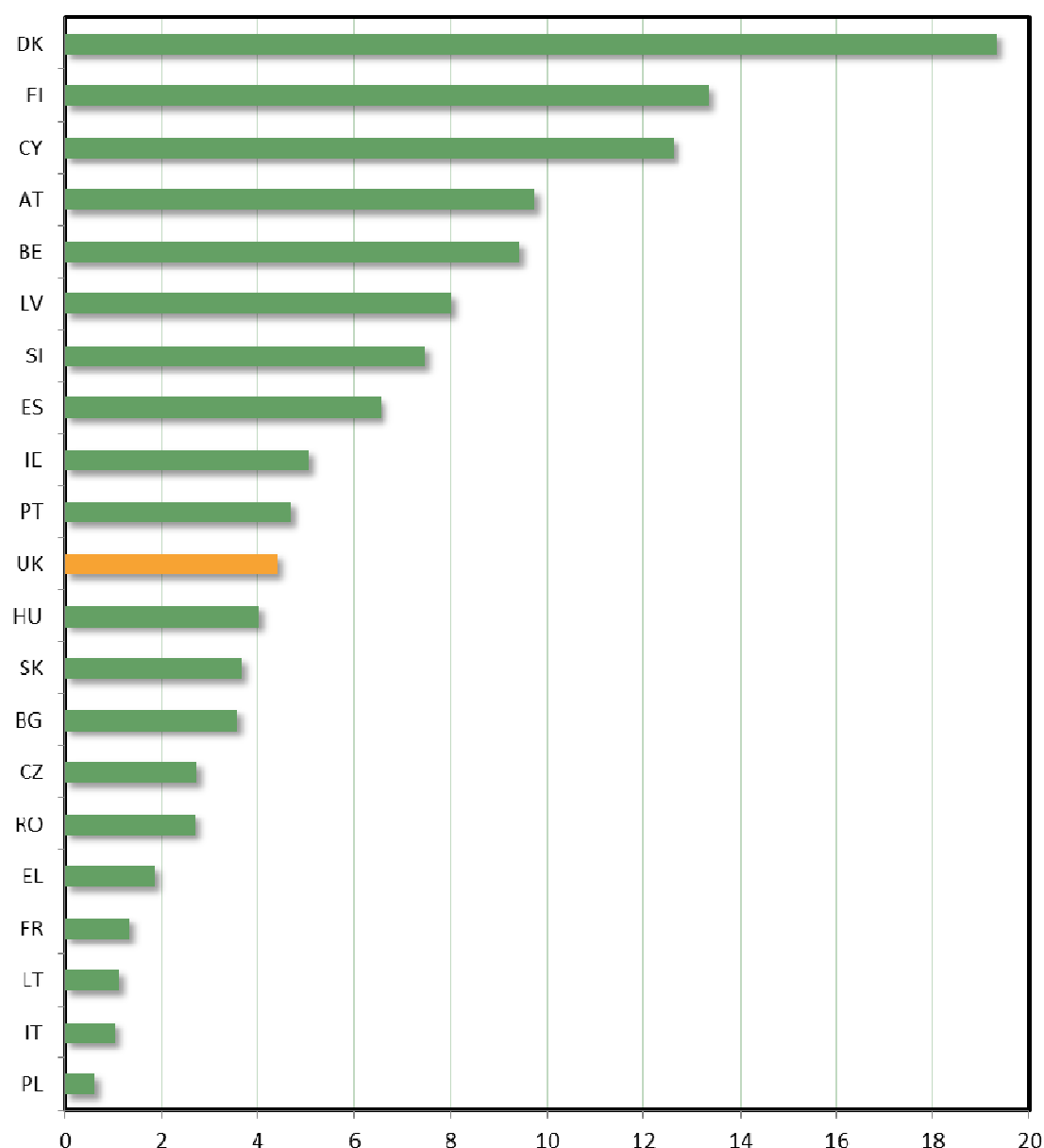


Figure 2: Number of tissue establishments per million population for EU member states.

This issue of tissue establishments will disproportionately impact autologous products since the patient needs to donate the material for manufacture, the more centres that offer the treatment the more licenses that are required, even during clinical trials. Once on the market the developer will be faced with the need for tissue establishment licenses at all clinical centres in all countries where the product is made available. This will be a drain on their resources, and adds to the overall costs to what are already expensive products per dose (although in most cases only a single or small number of doses will be necessary, compared to say monoclonal antibodies which may require regular dosing over months or years). Again to attract cell therapy developers the UK needs to be competitive both with respect to regulatory procedure and to licensing costs. This should be investigated further.

Medicines and clinical trials Directives.

I also see very little opportunity to make changes here, the key issue of the complexity of multi-national clinical trials approval is being addressed by the EU Commission, hopefully those proposals will be adopted and improve the situation.

The MHRA in my view is already doing a good job to balance the need to protect public health and foster innovation. I comment a little further below.

A number of others have commented on things like adaptive designs which show promise to streamline clinical development. This is not an area for which I have expertise, but it is worth noting that the few attempts to use adaptive designs to date have been problematic. The idea is old enough that if this was a magic solution I have no doubt it would already be widely used by large bio/pharma since they are also keen to keep costs down, and they have the resources to make this work if it's possible. Importantly there are no legal/regulatory barriers to stop companies using adaptive designs, it just the risk of failure and the added complexity that have limited application to date. Certainly an area that would benefit from some further work.

Possible supplementary questions:

- *Are UK regulators willing to engage with and provide advice to researchers and companies considering applying for regulatory approval?*

Absolutely, the MHRA are very good as are the EMA and many of the other EU agencies. When you consider what a small proportion of their work ATMP's represent (2-5%), the EMA has invested disproportionate resources in forming a new committee, and activities such as the interested parties meetings. Also recent metrics from the innovation task force (ITF) suggests around half of the informal briefing meetings over the last few years have been to discuss ATMP's. These meetings are free and mostly intended for early stage discussions on scientific and regulatory issues. The MHRA along with a few other agencies now have a special 'office' for innovation with the objective of supporting new technologies.

- *Can you offer specific examples of regulators offering contradictory advice?*

Nothing immediately springs to mind, though no doubt I have seen at the very least minor discrepancies. What is more common are differences of opinion between assessors, EU agencies and between the EU and FDA. Within the EU this can be dealt with by seeking advice from the EMA, since it is a consensus view of all member states. For clinical trials this can be more problematic, especially since EMA scientific advice takes a long time to complete. It may be that future changes in clinical trials process will help, if member states can discuss their differences and agree a way forward. I am not sure however if this will happen, but the UK should perhaps push for the system to do this, so long as it doesn't result in significant delays for the sponsor.

One of the obstacles in getting to the bottom of such claims is that the developer is unlikely to be able to reveal enough information into the public domain for such 'complaints' to be independently evaluated. From my own experience, sometimes developers misunderstand regulators, and no doubt vice versa. There is an issue of slightly different language, and sometimes a language barrier (non-native English speakers) between developers and regulators. Having been on both sides I understand why regulators phrase things as they do, but to the uninitiated it can be misunderstood. In particular, the regulators do not like to

give a definitive ‘no’ or ‘yes’ when giving advice, because they understand there may be another way that is acceptable that they didn’t think of. Also any scientific advice they give is necessarily based on the information provided by the developer, which cannot realistically include everything. It’s also not their job to direct product development, only review it, and they obviously cannot offer solutions even though they may know how others have solved the problem for reasons of confidentiality. Furthermore, they have no knowledge of the business issues that inform a developers decisions etc. Consequently the best they can do is point the developer in a different direction if they feel they appear to be off-track. It is vital that developers understand these limitations prior to taking advice to get the best from it.

- *How well are regulators communicating regulatory requirements and the support and advice services available? For example, how effective have tools like the Stem Cell Toolkit been in providing guidance? What more could be done to provide clarity on regulatory requirements?*

I can’t comment on how useful the stem cell tool kit is, but I think this should have been an ATMP tool-kit, since there are many non-stem cell ATMP’s being developed. A few EU regulators do the conference circuit and speak regularly, and some even help organise sessions and workshops. The ISCT have a strong focus on regulatory, but while the FDA reach out to them to attend, they have to reach out to EU regulators, and it is often fairly hard to get their attendance, especially when outside the EU (but then that is true mostly of the FDA). The MHRA’s policy on speakers is a barrier here, even for not-for-profit conferences the speaker has to really want to attend and push the case internally (personal experience from my time at the MHRA). Where the conference is for-profit, the MHRA charge a fee of around £1,500 in addition to expenses; not many conference organisers in the regened sector are happy to pay this. In my experience the MHRA did not appreciate or acknowledge the value to their own staff of attendance at such events, it is important for assessors to keep up with the evolving science, conferences are one way to do this.

The problem in my view is not the availability of information, but knowing where to find it; this comes back to the need for more regulatory professionals within academia and SME’s. All Agency websites I’ve looked at are difficult to navigate, but the EMA’s site is not as bad as the FDA site, the guidelines are well organised once you find the right section. I have myself attempted to tackle this issue by putting web-tools on my website and through the update to PAS 83¹³⁹ (BSI, free download) but making sure people know where to look remains a problem – this is back to education. The Catapult could create and maintain a web-resource that puts more links etc into one place, although this will likely miss gene therapy and developers of other types of product. Again the sheer complexity of developing such products means there are different resources in different places all of which are valuable to developers – let alone the need to consider regulatory regimes beyond Europe.

2. A number of submissions of evidence to the committee raised the costs of gaining regulatory approval and compliance, which can be particularly prohibitive to SMEs and start-up companies in the field. What action can be taken to address this issue?

¹³⁹ <http://shop.bsigroup.com/en/forms/PASs/PAS-83/>

During my oral evidence I mentioned that a client had commented to me that their tissue establishment license in Germany had been very much cheaper than in the UK (to collect biopsies for an autologous investigational product). I cannot find those numbers, but believe it was something like 10 fold different. The Committee asked me if I could provide some example numbers, I have attempted to do this, these are divided by activity below.

Tissue Establishment Licensing

Unfortunately this proved rather too difficult with the time and resources available to me. Licensing of tissue establishments can include fees for the application, annual maintenance (often based on facility size), and inspection fees (usually per inspector per day or per hour, plus their expenses). However, roughly speaking a new application to the HTA would cost between £5,800 and £10,050, depending on the type, size etc of tissue establishment. In stark contrast, if you apply for a tissue establishment licence in France, this is FREE. The only other authority I started to investigate was the Irish Medicines Board (who also cover tissue establishments) and their **annual fees** ranged from €1,000 for establishments with <5 staff, to a maximum (large complex establishment) to €16, 669 (~£13,835).

Clinical Trials Applications (and amendments)

I was able to find information for all 27 member states, although since fees are adjusted each year these may be up to a year out of date.

The average fee range (low to high and converted to GB£) for a clinical trial authorisation (CTA) covering phase I-III is £701 - £1,877 (range £0 - £7,885). The lower end will be skewed because at least 11/27¹⁴⁰ (40%) of agencies waive the fee for non-commercial applicants. In contrast the upper end will also be slightly skewed since at least 4/27 agencies apply higher fees for ATMP's. At least one agency (Italy) offers a lower fee for ATMP's. The MHRA charge from £2,255 - £4,244 for a CTA, notably the lower end of their fee structure is above the upper end of the average for the EU27 (see [Figure 3](#)).

While the UK ranks as the fourth most expensive in [Figure 3](#), both IT and SE offer fee waivers. Consequently the UK and Germany can be considered the most expensive agencies.

Many clinical trial approvals also need to be amended during the trial for various reasons. Data from 21 EU authorities were collected; again the cost of an amendment can vary depending on the stage or complexity. The low and high averages for 21 agencies are £110 - £242 (range £0 - £1,245); the MHRA charge between £0 and £795.

The MHRA also charge an annual service fee of £345 per CTA, similar fees for other agencies were not investigated.

While fee reductions or waivers could be offered for clinical trials approval, it's important to understand that the cost of preparing regulatory documentation far exceeds the relatively small cost of agency review. But this is simply part of the cost of development and cannot be avoided if you regulate.

¹⁴⁰ I was not able to confirm whether all agencies offer fee reductions for non-commercial trials, consequently this figure may be higher. Notably the UK does not.

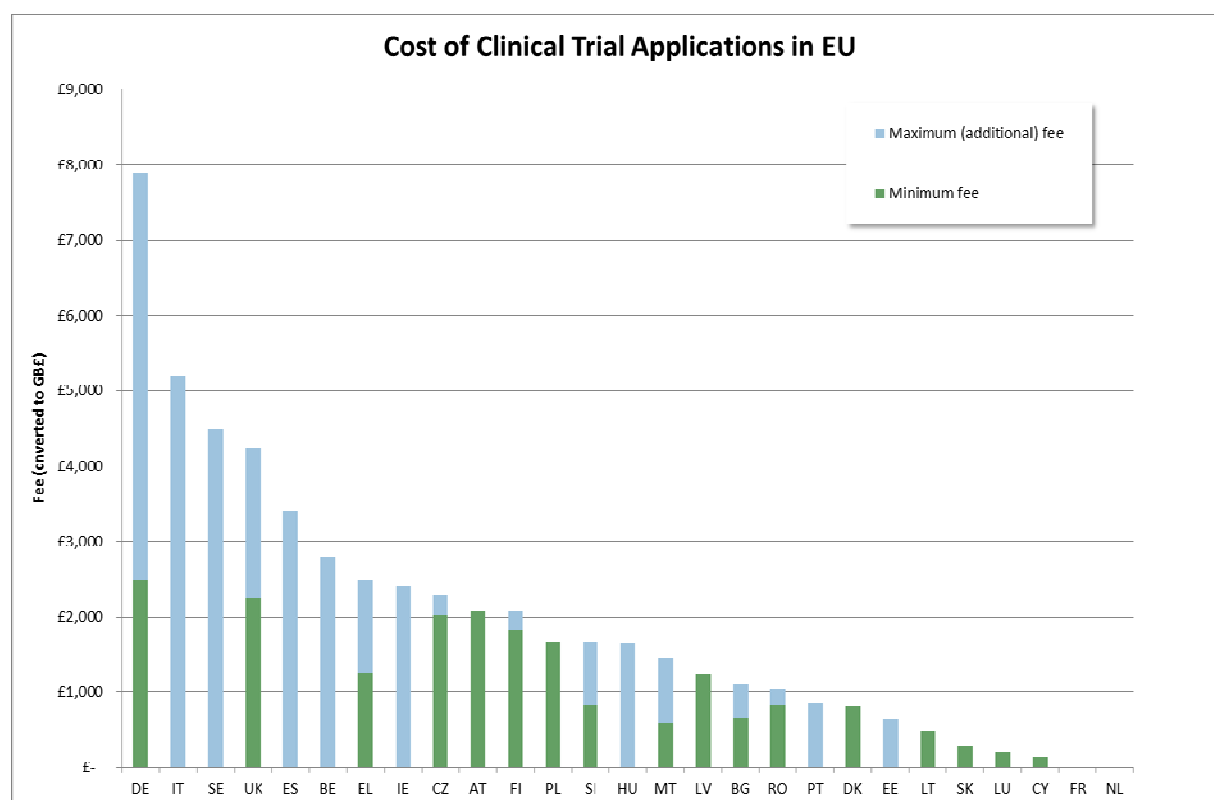


Figure 3: Stacked costs (converted to GB£) for EU27. Green bars are minimum fee; consequently absence of a green bar indicates a fee waiver (typically for non-commercial, see text). Blue bars indication the additional cost of the most expensive CTA (read maximum costs from the axis).

Scientific Advice

Not all national agencies offer formal scientific advice procedures, however data was collected for 16 of the 27 member states. As with other services, these fees are often structured by complexity of request. Four¹⁴¹ of the 16 for which data were collected are excluded from the analysis since their fee structure is based on the number of assessors and hours required to provide advice, making it difficult to include them in the comparison.

The average minimum and maximum fees for the remaining 12 member states (converted to GB£) is £1,982 - £3,631 (range £0 - £6,640). The MHRA charge from £2,378 to £4,849.

¹⁴¹ Czech Republic, Germany, Hungary, and Slovenia.

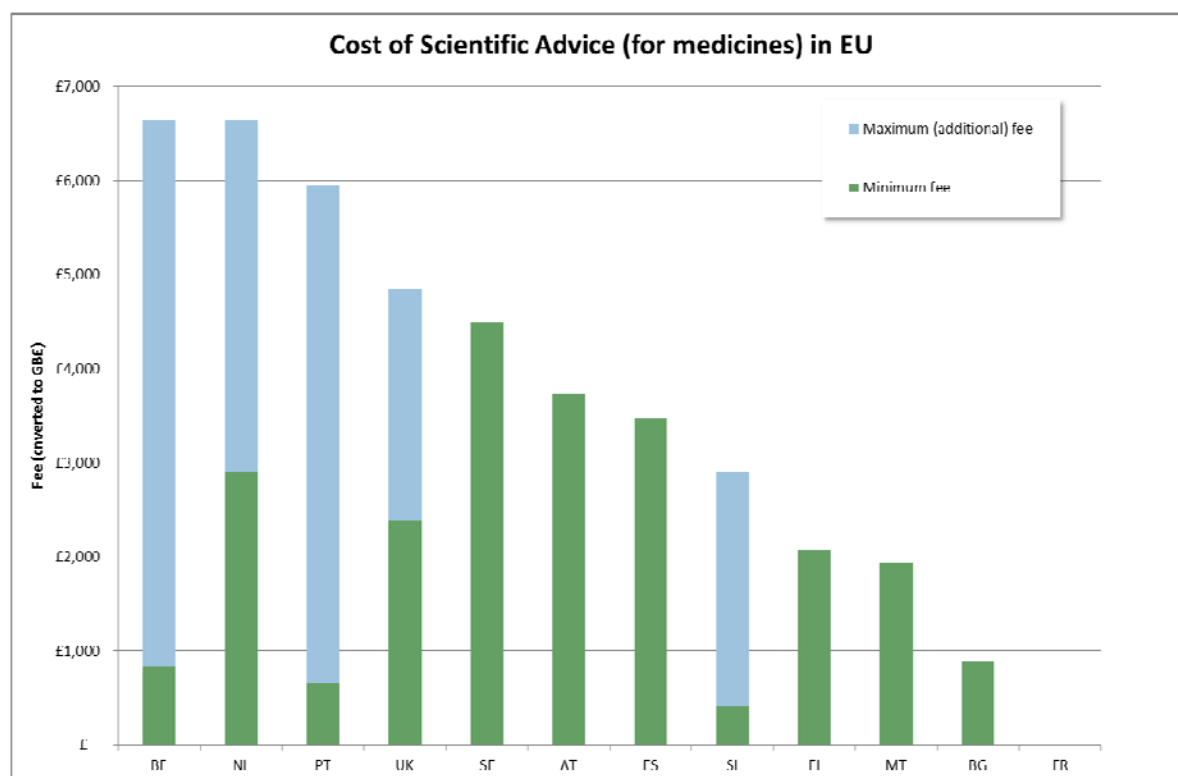


Figure 4: Stacked costs (converted to GB£) for EU12. Green bars are minimum fee; consequently absence of a green bar indicates a fee waiver (typically for non-commercial, see text). Blue bars indicate the additional cost of the most expensive CTA (read maximum costs from the axis).

While the MHRA fee is good value for money, some discounts could be offered for SME's, orphan developers and academics, perhaps by increasing the fees to large companies by a small amount (since these will be a small proportion of all scientific advice given).

To contrast, EMA scientific advice can cost up to around €70,000, but SME's are given a 90% discount (making it similar to MHRA advice in cost) and SME's developing orphan products get advice for free (100% discount). While the option to have national or EMA advice can seem a little baffling, both procedures have advantages and disadvantages which I see as a good thing. The main difference being that the EMA procedure is lengthy, and in most cases written only, whereas national advice is based on a face-to-face meeting allowing for discussion to stray away from the questions set, or to expand the discussion. EMA advice therefore takes more effort to prepare.

It might also be possible to consider a system where developers might be able to receive fee incentives up-front that are paid back (with interest) once the product generates revenue. Payback could be in the form of direct recovery of the loan or discounted product supplied to the National Health Service. Catherine Prescott (Biolartis Ltd, Cambridge UK) has some interesting ideas in this area.

Manufacturing authorisation (GMP)

I was unable to collate adequate information within the time and resources available to me. Furthermore these fees are sometimes relatively complex (application, maintenance and inspections fees) making comparisons more difficult.

The bigger Picture

While it is easy to latch onto fees, these are negligible expenses when compared to the cost of conducting a clinical trial. If we look at the bigger picture and bench mark the UK against other member states with respect to the overall number of clinical trial applications submitted (all phases and types of product), on first glance we look impressive. By this simple measure the UK is second only to Germany in the number of clinical trials applications (Figure 5). However, member states vary considerably in size, so when population is taken into account the UK is revealed as merely average (Figure 6). It's important to comment that the majority of CTA's will be from commercial organisations centred outside the UK.

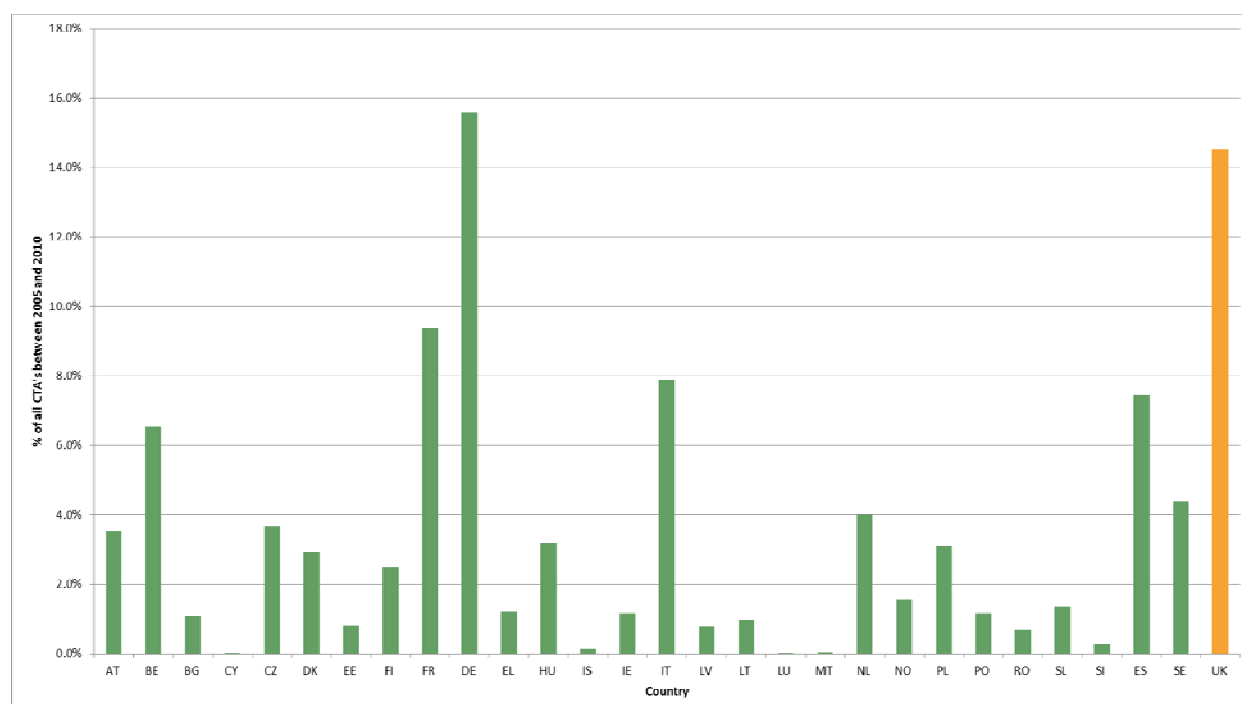


Figure 5: Proportion of the total CTA's submitted (all phases including IV and all medicinal products) within the EU between 2005 and 2010.

Time and resources have limited further analysis, but this raises many questions such as whether some countries are favoured for early or late stage trials. Certain countries such as Belgium stand out as having a disproportionately high number of clinical trial applications compared to their population size. Why is this? These numbers take no account of the number of patients likely to be recruited, so it is possible that more patients are recruited per trial in the UK than say Belgium. This clearly warrants further analysis to identify the reasons.

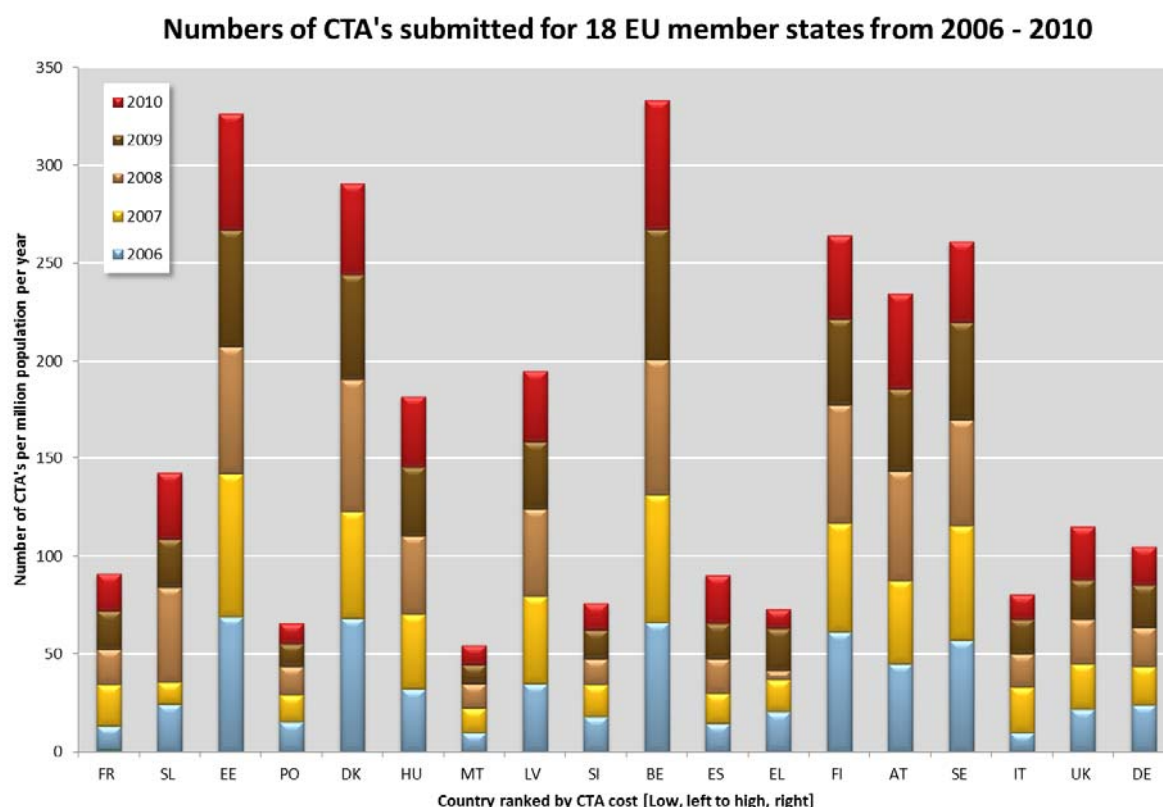


Figure 6: Composite figure using EU Commission data for the numbers of clinical trials applications per member state between 2006 and 2010, normalised to population size

Conclusions

By most fees compared the UK tends to be in the upper range of EU averages. Clearly these data are incomplete and some complexity in fee structures can make fair comparisons difficult. While such fees are relatively trivial when compared to the overall cost of development, for SME's and not-for-profit organisations any savings however small can be helpful. The UK should consider a review of fees for licensing activities and perhaps mirror incentives available in some other member states (and at EMA level) such as fee waivers/reductions for non-commercial sponsors and SME's.

3. In your view, does the current regulatory regime strike the appropriate balance between ensuring standards of safety and efficacy, and encouraging innovation?

Yes, but I often feel alone in this view which likely reflects my unique experience of having worked with the MHRA, biotech and as a consultant. The system is elegant and flexible and my experience of being an assessor at the MHRA within the centralised system is that the assessors across the EU are keen to approve products, and do their best to help developers meet standards. As a scientist I find the decisions primarily science based and reasonable. There are a few requirements that are perhaps based more on paranoia than scientific evidence, e.g. TSE risk, but when charged with safeguarding public health and considering the backlash if things do go wrong (e.g. historic problems with infected blood products, concerns over safety of vaccines etc); this is understandable. The perception that regulators

make unreasonable requests comes primarily from differences of opinion between developers and regulators, and the regulators position cannot easily be conveyed due to confidentiality – without seeing all the data some decision can be hard to understand. I may have disagreed in the past with some of the reasoning during assessment, but cannot think of a time I felt a product should have been approved that wasn't; I have on the other hand been surprised a product was approved. Approval rates for those that submit an MAA to the EMA are reasonable.

Clinical trial approvals I think find a reasonable balance between protecting patients and not putting too much burden on developers. Naturally new science when applied to healthcare will raise questions as to safety; I think the UK is very pragmatic in this regard. The main problem is that by being pragmatic and focussing on safety, clinical trials approvals are very easy compared to MAA, and the inexperienced can mistake this for meaning they are on track with all their development activities. This can be solved by education.

Possible supplementary questions:

- *In your view, are ATMP regulations and the proposed Clinical Trials regulations flexible enough to cope with changes to clinical trials, and with adaptive licensing and reimbursement?*

The system is very flexible, there are no proscriptive rules as to how you demonstrate quality, safety and efficacy, so new approaches are acceptable as long as they are scientifically valid.

There is one particular regulatory gap that doesn't seem to have been acknowledged so far, that of point-of-care or near-patient manufacturing devices. The committee has received some evidence for the value of this, particularly with autologous products. Rather than go the route taken by say Dendreon, where they have to ship donor cells to their central facilities within 18 hours, and following a relatively short and simple manufacturing step have to ship it back to the patient, again within 18 hours. To achieve this in the USA they have had to set up 3 (although one will now be closed) manufacturing sites and develop a computer system that can track the shipments, redirect them when necessary (e.g. bad weather) and alert them if there are delays etc. Based on what is available in the public domain, it seems likely to me the same product could effectively be manufactured by a small local closed-system fully automated device. The problem is the device would be manufacturing a medicine, so it would need to be GMP licensed, it would also need to perform release tests including potency (normally a bioassay) and provide results to a Qualified Person (QP) who could sign off the batch. There are a myriad of other issues associated with GMP and current rules around medicines manufacture. The current legislation for all it is remarkably flexible, did not envisage this situation. There are already devices similar to what I describe (although limited analytics), such as Cytori's Celution and Miltenyi's CliniMACs systems. These already challenge the system, since although their current uses are probably minimally manipulating the cells (meaning they are not ATMP's just cell transplants), if cells are not used for the same essential function (non-homologous use, to use the US term) then they are considered ATMP's. So the same cells isolated by these devices can either be a cell transplant, or an ATMP depending on how they are used. I will avoid a lengthy dialogue about this; it's a very contentious part of the legal definition. Human cells themselves cannot be medical devices, but currently these devices are CE-marked medical devices for manipulating cells. The legal situation remains unclear, yet the approach would be a good solution for some autologous cell products. This is an area

where clarity would enable innovation, but some legislative changes at EU level will be required to enable it.

- *What role does the establishment of common standards play?*

Depends what you mean by standards.

Physical standards: there is a need for more physical standards for this sector, by which I mean for calibration of analytical methods. Each medicine developer is required to develop a product reference material, this is extremely challenging for cell therapy, some solutions are needed. The NIBSC, EDQM, LGC and NIST and USP in the USA have all discussed this with me in the last year at various conferences, as have some of the EU regulators. The NIBSC produces something like 90% of the world's biological reference standards for the WHO; they would be well-placed to take on the more complex job of helping the ATMP community by developing others for them; and perhaps helping developers figure out how to develop their own product-specific reference materials, or alternative approaches. The LGC may also be useful in this respect.

Paper Standards (e.g. ISO, CEN, BSI): I am a member of the BSI's regenerative medicines standards committee, there is a fair amount of activity in this space, but much of it is focused on devices standards. Since human cells (or most human-derived substances) cannot be used in medical devices, many of the proposed standards are not relevant, and could be counter-productive since cell products are regulated as medicines. I personally also have a fear that the wrong standard written too soon would stifle innovation if developers feel obliged to follow it. But there is scope for more standards that find that balance and cover appropriate aspects like quality systems or biomaterials. My perception is this is happening and probably fast enough.

Guidelines and pharmacopoeia can also be considered standards, so many of my previous comments would apply. I think the European Pharmacopoeia has written some monographs on biological active substances that are not particularly useful, or even pointless (deepening on your point of view); I was encouraged more recently to find others agree. They have proposed writing one for Chondrocytes, which I find particularly worrying since I've experienced several companies that misunderstand the purpose of monographs. Personally I think a guideline from the EMA would be more useful.

On the other hand additional chapters or monograph for raw materials commonly used for manufacture of ATMP's would be of value. There has been some discussion around having a system to certify compliance for biological raw materials, akin to the EDQM certificate of suitability for TSE risk. The TSE risk system is really useful to developers and I suspect the FDA find this useful too since they do not have an equivalent. Choosing raw materials causes a lot of anxiety among developers of ATMP's because it's quite complicated and the options can be rather limited – such a system would reduce the paper considerably, especially for clinical trials submissions.

- *How can the regulatory environment be best adapted to meet the needs of areas such as low-risk clinical trials and autologous/small population treatment development?*

I don't think it needs changing because it's already adaptable. Assessors use their judgement as to sufficiency and can balance expectations to risk. When in doubt they have support

committees (clinical trials expert advisory group, or CHM etc). Their approval time metrics are from what I've seen some of the best in Europe. The revisions to the clinical trials directive should hopefully bring other member states in line, and speed up multi-centre approvals considerably. First in man trials are approved (or not) within 30 days, with actual averages nearer to 14 days if I recall the last figures I saw. The current rules say no more than 60 days, for the MHRA there is no clock-stop, but some agencies like Germany use one, which can lengthen approvals further. Higher risk applications, including ATMPs, can if necessary be put on a longer timetable to allow for external advice to be sought. The MHRA does do this in some cases, but certainly not all ATMP's. There is possibly scope for the UK procedure to promise a shorter turnaround for certain applications, but I don't think the effort of implementing this would really be worth it.

- *Do regulators have sufficient expertise in the treatments being developed in order to enable regulatory flexibility?*

Yes

Are we on Track?

Many compare the emergence of cell therapy with that of monoclonal antibodies, I'd like to offer a different more recent comparison. Since November 2005 (7 years) it has been possible to license biosimilar biological medicinal products in the EU. There are currently 12 products authorised, although these actually represent only about 7 products since several were multiple co-marketing applications for the same product (different names). Somewhat like Chondrocelect, the first two submissions were at or around the time of implementation. Biosimilars unlike ATMP's represent a lower risk since the clinical risk/benefit of the active substance is already established; the risk comes from whether biosimilarity can be established such that minimal clinical data is necessary for licensing. It's important to note that the biosimilar paradigm isn't applicable to all biological medicines, for example a biosimilar cell therapy is unlikely to be possible in the foreseeable future, if ever¹⁴².

In comparison to biosimilars, there have been 12 ATMP's submitted to the EMA since 2001; two before the ATMP regulation came into force, 4 are currently under review by the CAT, 2 are approved and 5 were withdrawn during the procedure.

Table 2: List of ATMP products submitted through the centralised procedure (EMA) with outcomes from 2001 to February 2013.

¹⁴² Note: many talk about data protection periods in relation to protection of IP for cell based medicinal products, but actually this is irrelevant since no abridged market authorisation route is applicable. Consequently any copy-cat products must undertake full clinical development.

Consulting on Advanced Biologicals (CAB) Ltd – Supplementary written evidence

Product	INN/description	Indication/s (Therapeutic area)	Company	Submission Date	Opinion	Finalisation Date
<i>Apligraf</i>	<i>Graftskin</i>	<i>Venous leg ulcers</i>	<i>Novartis (Licensing deal with Organogenesis)</i>	<i>Apr 2001</i>	<i>Unknown</i>	<i>Withdrawn 2002</i>
<i>Cerepro</i>	<i>adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene</i>	<i>High grade glioma</i>	<i>Ark Therapeutics</i>	<i>Oct 2005</i>	<i>Negative</i>	<i>Withdrawn Jul 2007</i>
ChondroCelect	characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	cartilage defects of the femoral condyle of the knee	Tigenix	Jun 2007	Positive	Jun 2009
<i>Advexin</i>	<i>contusogene ladenovec</i>	<i>Li-Fraumeni syndrome</i>	<i>Gendux Molecular Limited</i>	<i>Sep 2007</i>	<i>Negative</i>	<i>Withdrawn Dec 2008</i>
<i>Contusogene Ladenovec Gendux</i>	<i>contusogene ladenovec</i>	<i>recurrent or refractory squamous cell carcinoma of the head and neck</i>	<i>Gendux Molecular Limited</i>	<i>Jul 2008</i>	<i>Negative</i>	<i>Withdrawn Jun 2009</i>
<i>Cerepro</i>	<i>adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene</i>	<i>High grade glioma</i>	<i>Ark Therapeutics</i>	<i>Jan 2009</i>	<i>Negative</i>	<i>Dec 2009</i>
Glybera	alipogene tiparvovec (vector = AAV)	Hyperlipoproteinemia Type I	AMT B.V. (now uniQure biopharma B.V.)	2009	Positive	Jul 2012
<i>Undisclosed</i>	<i>Autologous oral mucosal epithelial cells</i>	<i>(Ophthalmologicals)</i>	<i>Undisclosed</i>	<i>2011</i>	<i>TBD</i>	<i>TBD</i>
<i>Hyalograft C</i>	<i>Cultured autologous chondrocytes on hyaluronan based scaffold</i>	<i>(Other medicines for disorders of the musculo-skeletal system)</i>	<i>Anika Therapeutics</i>	<i>2011</i>	<i>Unknown</i>	<i>Withdrawn Jan 2013</i>
<i>Undisclosed</i>	<i>Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF</i>	<i>(Immunostimulants)</i>	<i>Undisclosed</i>	<i>2012</i>	<i>TBD</i>	<i>TBD</i>
<i>Undisclosed</i>	<i>Autologous cultured chondrocytes</i>	<i>(Other medicines for disorders of the musculo-skeletal system)</i>	<i>Undisclosed</i>	<i>2012</i>	<i>TBD</i>	<i>TBD</i>
<i>Undisclosed</i>	<i>Spheroids of human autologous matrix-associated chondrocytes</i>	<i>(Other medicines for disorders of the musculoskeletal system)</i>	<i>Undisclosed</i>	<i>2013</i>	<i>TBD</i>	<i>TBD</i>

To compare to the FDA is a little unfair, since prior to 2009 products could seek national licensing. It is also important to note that a number of earlier products were authorised by the FDA primarily as devices. It is also important to point out that the FDA rules although similar to the EU also apply additional risk criteria which mean that cell transplants (which would be regulated only by the HTA in the UK) involving unrelated donors require a BLA – hence the recent cord blood bank BLA's.

Table 3: List of FDA approved cell-based products

Consulting on Advanced Biologicals (CAB) Ltd – Supplementary written evidence

Product	INN/Description	Type	Indication/s	Company	Type	Approved
Integra Artificial Skin	Artificial Skin Burn Wound Covering	Engineered Skin	Dressing, Wound And Burn, Interactive	Integra Lifesciences Corp.	PMA	Mar 96
Carticel	Autologous Cultured Chondrocytes	Chondrocyte	Repair of symptomatic cartilaginous defects of the femoral condyle	Genzyme	BLA	Aug 97
DermaGraft	Bioengineered Temporary Covering	Engineered Skin	partial thickness burns (mid-dermal to indeterminate depth)	ATS/S&N (now Shire)	PMA	Oct 97
Apligraf	Graftskin	Engineered Skin	venous leg and diabetic ulcers	Organogenesis	PMA	May 98
Epicel	Cultured epidermal autografts	Engineered Skin	Deep dermal or full thickness burns ($\geq 30\%$)	BioSurface Technology (now Genzyme)	HDE	Nov 98
TransCyte	Human fibroblast-derived temporary skin substitute	Engineered Skin	Dressing, Wound And Burn, Interactive	ATS/S&N (now Shire)	PMA	Dec 98
OrCel	Interactive Wound And Burn Dressing	Engineered Skin	Dressing, Wound And Burn, Interactive	Ortec Intermation (now Forticell)	PMA	Aug 01
Provenge	Sipuleucel-T	Immunotherapy	asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	Dendreon Corporation	BLA	Apr 10
LaViv	Azficel-T	Skin rejuvenation	For the improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.	Fibrocell Technologies, Inc.	BLA	Jun 11
Hemacord	Hematopoietic Progenitor Cells, Cord	Cord blood	unrelated donor hematopoietic progenitor cell transplantation	New York Blood Center	BLA	Nov 11
Gintuit	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Engineered Skin	treatment of mucogingival conditions in adults	Organogenesis	BLA	Mar 12
DuCord	Hematopoietic Progenitor Cells, Cord	Cord Blood	unrelated donor hematopoietic progenitor cell transplantation	Duke University	BLA	Apr 12
HPC, Cord Blood	Hematopoietic Progenitor Cells, Cord	Cord Blood	unrelated donor hematopoietic progenitor cell transplantation	Clinimmune Labs	BLA	May 12

Note: The FDA has not yet approved any gene therapies. Unlike Table 2, this table does not include product that may have submitted but refused or withdrawn.

The FDA have yet to approve a gene therapy. It is unclear whether products have started review and been withdrawn since this information is unavailable (to my knowledge). When these things are taken into consideration, the USA is not as far ahead as some might think.

If the products that were/are on national markets are also taken into account, then it is clear there were more cell therapy products available in the EU than the US, but these have had to reapply, leave the market or seek an exemption from MA (e.g. hospital exemption or systems such as the UK's Specials).

The following figure is an attempt (some responses were unclear) to interpret a recent EU Commission survey of member states¹⁴³ asking what products are available nationally. Please note, these numbers do not include the two centrally authorised products, only those that were on the market before the ATMP regulation came into force or exempted from market authorisation (hospital exemption¹⁴⁴ or article 5(1)¹⁴⁵, e.g. UK Specials). Blue bars are where the product was previously available and is in transition (leaving the market or seeking an exemption).

¹⁴³ http://ec.europa.eu/health/files/committee/69meeting/pharm608_atmps.pdf

¹⁴⁴ Article 28(2), Regulation 1394/2007

¹⁴⁵ Directive 2001/83/EC.

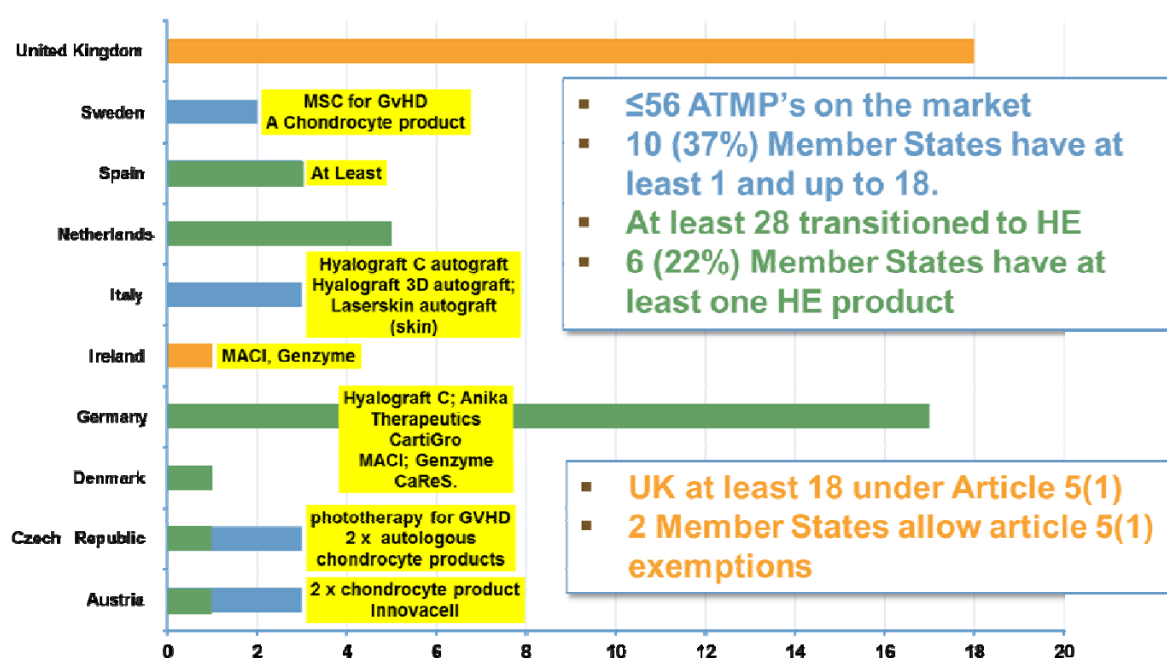


Figure 7: ATMP's available on national markets that do not have a centralised market authorisation.

Note: The above data did not identify all products, so where it says <56 products the actual number is more likely to be around 40, since a number of products were/are clearly available in more than one country. HE, hospital exemption. Article 5(1) is the legal basis for UK 'Specials'.

So the evidence suggests the UK has more ATMP's available than any other member state, with only Germany anyway near. However, these products are only available on a named-patient basis; they have an exemption from market authorisation. Not all member states have chosen to implement article 5(1) (basis for Specials) and at a recent conference a German speaker expressed envy of the UK's Specials system since compared to hospital exemption it is less restrictive. Indeed compared to the German system for hospital exemption, the UK Specials is light touch regulation focussed primarily on manufacturing.

How does the UK regulatory regime compare with other countries – both within and beyond Europe?

Having looked in detail at the FDA system, the EU is broadly similar. More importantly the scientific and regulatory principles applied have been harmonised through ICH covering the EU, USA and Japan, with many other regions following the same principles (and using the guidelines) including Australasia, Canada, Israel to name a few. Most if not all the same principles can be found in WHO guidelines too. I have also heard descriptions of the regulatory regime in Japan, Korea, China, India, Singapore and maybe a few others, and in the broadest sense their approach to regulating cellular therapeutics is similar. Most appear to be adopting something similar to the EUTCD (or US GTP's) and using similar criteria to decide what is regulated as a medicine. Some allow medical devices to include cells, like the USA, but I don't have a clear view on this.

There are lots of nuances between these systems that make development of a global product extremely complicated, even large bio/pharma struggle to stay on top of this. Harmonisation is good up to a point, but if we all harmonise to the highest standards this

can hinder innovation. Sometimes the small differences offer opportunities, especially with new science.

There is definite room for further harmonisation, but this is a slow difficult thing to achieve for obvious reasons. There are on-going efforts to harmonise the PhEur with USP for instance, yet still strikingly few basic methods used by biopharma are yet harmonised, or only partially so. Some of these are tests that apply to almost all sterile products, like endotoxin or sterility. Having to comply with two standards adds burden (although the monographs themselves significantly reduce regulatory burden). I'm not sure what scope there really is to influence this to move faster though.

ICH is considering whether it's time to develop guidelines for ATMP's, but I think the view of some at least is that it is probably a little early yet, we need more products. I'm inclined to agree. But if it's of any comfort I've yet to read an FDA guideline I thought was contradictory to the equivalent EU guideline.

Possible supplementary questions:

- *It has been suggested in evidence to the Committee that having a single regulatory body, as in the US and other European countries, can reduce the cost burden of inspections and licensing, and provide a more attractive proposition for those seeking to develop new treatments and technologies or to establish operations in the UK. Do you share this assessment?*

I think I covered this elsewhere but to summarise, perhaps but I don't really see it as particularly important. The amount of paperwork would probably not alter; the current agencies do not overlap in that respect.

- *A number of submissions to the committee referenced the issue of differences amongst European countries in interpretation of the hospital exemption to the ATMP regulations. How could this be addressed?*

This is a topic that frustrates many, but I think sometimes a few points are overlooked:

National only

This provision is applicable nationally only, you cannot export an ATMP that is exempt under the hospital exemption. Consequently why is there a need to harmonise? It is up to the member state to decide how it wants to utilise this provisions to allow bespoke products to be made for named patients where there is unmet clinical need.

There is already disparity in how article 5(1) of the core medicines Directive is translated (or not) into National Law, yet we do not hear very many complaining about this in the same way. Indeed the UK choses to allow ATMP's to use article 5(1)¹⁴⁶, whereas according to the survey responses depicted in **Figure 7**, Ireland is the only other member state to do this. However, the UK's 'specials' does require that a case is made as to why any available licensed medicines are not suitable to treat the named patient.

Unfair competition

¹⁴⁶ UK 'Specials' system.

While I used the phrase ‘unmet clinical need’, the Regulation does not include this as a requirement. Consequently we already have the situation where chondrocyte treatments exempted under hospital exemption are available on national markets to treat cartilage defects, even though there is a centrally authorised product available. It is unclear therefore whether these exempt products offer something different to ChondroCelect, or whether they are in effect competitor products (whether that is the intention of the manufacturer or not). This doesn’t seem to gel well with a free market. This is in effect (if not intent) unfair competition for centrally authorised products, if it is allowed to continue. It is also not in the best interests of patients since Hospital Exemption products are not required to provide evidence for safety and efficacy. Undoubtedly hospital exemption products will be cheaper, because they’ve not got to recoup the expense of demonstrating safety and efficacy through clinical trials.

This situation therefore needs to be addressed to ensure the current situation doesn’t continue. This unfair competitive situation, if not addressed, will further dissuade investment in ATMP companies.

- *What outcomes from ongoing efforts to harmonize regulatory standards across Europe would be valuable, and should more be being done?*

I think this was addressed adequately elsewhere.

18 February 2013

Abbreviations

ATMP	advanced therapy medicinal product (cell, tissue and gene therapies)
BIS	Department for Business, Innovation & Skills (UK)
BSI	British standards institution
CHMP	committee for human medicinal products (at EMA)
CTA	clinical trial application
EDQM	European Directorate for the Quality of Medicines (Includes the European Pharmacopoeia)
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUTCD	European tissues and cells directive (Directive 2004/23/EC)
GMP	good manufacturing practice
GTP	good tissue practice (akin to EUTCD)
ISCT	International society for cellular therapy
MA	marketing authorisation
MAA	marketing authorisation application
MHRA	Medicines and Healthcare products Regulatory Agency
MSC	mesenchymal stem cells
SME	small and medium size enterprises
TSB	Technology Strategy Board
TSE	transmissible spongiform encephalopathy (e.g. BSE, vCJD)
WHO	world health organisation

Trevor Cook, Bird & Bird – Written evidence

I write in response to your call for evidence to make some observations on the question posed in your call to evidence as to “what role does patenting play in the commercial development of regenerative treatments?”

My own experience of this issue has been as a lawyer in private practice who has specialised in intellectual property, and in particular patent law, since my admission as a solicitor with Bird & Bird in 1977. Since the 1990s my practice has had a particular focus on the life sciences sector, and this has also involved me with the regulatory frameworks that govern the life sciences sector. I have also written extensively on most areas of intellectual property.¹⁴⁷

I must emphasise that the views expressed here are my own personal views and do not represent the views of this firm or any of its clients.

Although methods of medical treatment are not patentable in the UK and the rest of Europe, substances and articles for use in medical treatment, such as pharmaceuticals and medical devices, as well as methods for producing these, can be patented. Thus for example it was possible validly to patent methods for producing the naturally occurring hormone erythropoietin, the use of which in promoting red cell production is identified in the call for evidence.¹⁴⁸

More recently it has been accepted by the UK Supreme Court¹⁴⁹ that the purpose of the patent system is “to provide a temporary monopoly as an incentive to innovation, while at the same time facilitating the early dissemination of any such innovation through an early application for a patent, and its subsequent publication” and that “[a]lthough this is true in any sector, it has particular force in the pharmaceutical field, where even many of those who are sceptical about the value of intellectual property rights accept that there is a public interest in, and a commercial need for, patent protection.”¹⁵⁰ The subject matter of the

¹⁴⁷ In addition to articles and contributions to books too numerous to list these include the following books - *A User's Guide to Patents* (Butterworths 2002, Tottel 2007, Bloomsbury 2011), *EU Intellectual Property Law* (Oxford University Press 2010), *Pharmaceuticals, Biotechnology and the Law* (Macmillan 1991, LexisNexis Butterworths 2009), and *The Protection of Regulatory Data in the Pharmaceutical and Other Sectors* (Sweet & Maxwell 2000) and as a co-author *Practical Intellectual Property Precedents* (Sweet & Maxwell 1998 to date) and *International Intellectual Property Arbitration* (Wolters Kluwer 2010).

¹⁴⁸ See *Kirin-Amgen Inc and others (Appellants) v. Hoechst Marion Roussel Limited and others (Respondents)*. *Kirin-Amgen Inc and others (Respondents) v. Hoechst Marion Roussel Limited and others (Appellants) (Conjoined Appeals)* [2004] UKHL 46. Although the Judicial Committee of the House of Lords found the patent claims that were in issue to be invalid, these were product claims to erythropoietin itself, which were found to lack novelty as erythropoietin had previously been isolated from the body. Thus other claims in the patent, and notably those claims to methods for the production of erythropoietin by the use of recombinant DNA technology were unchallenged, and indeed could not readily have been challenged successfully given Lord Hoffmann's observation at paragraph [132] (emphasis added): “... Standing back from the detail, it is clear that Amgen have got themselves into difficulties because, having invented a perfectly good and ground-breaking process for making [erythropoietin] and its analogues, they were determined to try to patent the protein itself, notwithstanding that, even when isolated, it was not new.”

¹⁴⁹ Lord Neuberger in *Human Genome Sciences Inc v Ely Lilly & Co* [2011] UKSC 51 at [99]. The Supreme Court upheld the validity of the patent, reversing the lower English courts which had, in effect, held the patent to be too speculative validly to cover such a monoclonal antibody. A Technical Board of Appeal of the European Patent Office also came to a similar conclusion as the Supreme Court.

¹⁵⁰ For example some commentators challenge from an economic perspective the value of patents in many sectors but still conclude that patents have value to the pharmaceuticals and biotechnology sectors; see, from the perspective of US patent law, Bessen & Meurer - *Patent Failure How Judges, Bureaucrats, and Lawyers Put Innovators at Risk* (Princeton University Press 2009)

case in which these observations were made was a patent to a biotechnological product, a therapeutic monoclonal antibody, coded for by a gene sequence that the patentee had discovered. The patentee has predicted that it would have some therapeutic utility by reason of the homology of the gene sequence with other sequences which were thought to code for proteins having some physiological effect, but had made such prediction long before any monoclonal antibody had been made, its actual utility identified, and its safety and efficacy as a drug established.

Thus it can be seen that the patent system plays a vital role in the commercial development of regenerative medicine because in the absence of suitable patent protection for a particular regenerative technology, or the realistic prospect of it (because much early stage funding occurs long before any patents that have been applied for are actually granted), the private sector support that is necessary for the commercial development of that technology will not be forthcoming.¹⁵¹

For this reason it is likely that one particular area of regenerative medicine, namely that of human embryonic stem cell technology, will struggle in the future to attract private funding even more so than it has in the past. This is a consequence of Article 6(2)(c) of Directive 98/44/EC on the legal protection of biotechnological inventions (rendering unpatentable “uses of human embryos for industrial or commercial purposes”), as it has been interpreted by the Enlarged Board of Appeal of the European Patent Office and, more recently, by the Court of Justice of the EU.¹⁵² The effect of the expansive interpretations which these decisions have placed on this exception to patentability is not only to render human embryonic stem cell technology in the traditional sense unpatentable in Europe. It also precludes the patentability of synthetic tissue (useful for producing a synthetic cornea or corneal tissue) produced from parthenogenetically activated human oocytes, because of the expansive interpretation by the Court of Justice of what constitutes a human embryo, which interpretation is based in turn on an incorrect understanding as to the nature of such unfertilised oocytes and their scope to develop further.¹⁵³ There has been some ill-informed comment that an absence of patents in the area of human embryonic stem cell technology will encourage research. However the monopoly conferred by the claims of a granted patent is not absolute, and thus in the UK and elsewhere in Europe it is not an infringement of a patent to operate within the scope of its claims where this is done for the purposes of research into the claimed invention, even where this is done commercially or for purposes that are commercial.¹⁵⁴

¹⁵¹ Across industry as a whole (which includes many areas of activity as to which the benefits of patenting are more controversial than in life sciences) venture capitalists favour investing in companies that have already filed patent applications and these companies will do better than others – see Cao & Hsu - *Patent Signalling, Entrepreneurial Performance, and Venture Capital Financing* 2010 - <http://efmaefm.org/OEFMSYMPOSIUM/Toronto-2011/papers/Hsu.pdf>. In the life sciences sector some regulatory exclusivities also exist (such as data exclusivity and orphan drug marketing exclusivity) and can provide a commercial incentive as an adjunct to, or even in some cases, a replacement for, patent protection, and so can play an important commercial role, especially where patent protection may be weak. However in order to operate they need an established regulatory framework under which a regulatory approval is required before a product is placed on the market, and so for example could not be established for medical devices as these are at present regulated in Europe.

¹⁵² Respectively Case G2/06 *Use of embryos* / WARF and Case C-34/10 *Brustle v Greenpeace*.

¹⁵³ See *International Stem Cell Corporation's Patent Applications* GB 0621068.6 and GB 0621069.4 (UK Intellectual Property Office, BL O/316/12 16August 2012).

¹⁵⁴ The precise expression is “experimental purposes relating to the subject matter of the invention.” Much confusion has arisen from the fact that there is no corresponding defence to patent infringement in the USA, although the “Bolar” defence overlaps with it to the extent that the research in issue is directed towards a new therapeutic that will require regulatory approval; see Cook – *A European Perspective as to the Extent to which Experimental Use, and certain other Defences to Patent Infringement, apply to differing types of Research* (Intellectual Property Institute 2006).

The patent system has done extremely well over many years in applying common principles, most notably the requirements of novelty, inventive step and sufficiency, to widely different and, by the nature of the patent system, changing, technologies. Sector specific approaches to patent legislation such as the EU biotechnology Directive, (which dates back to 1998 but the genesis of which was several years earlier) can all too easily lead to unintended consequences, in particular by reason of the use in such measures of terminology that comes over time to assume a different significance, both technically and socially, as technology develops. If the saga of human embryonic stem cell patenting teaches us anything, it is that one should be extremely wary of such legislation, and that that scepticism should also inform one's attitude to sector-specific approaches to patents that fall short of legislation.

28 September 2012

Professor Charles F Craddock, Department of Clinical Haematology, Queen Elizabeth Hospital – Written evidence

Thank you for the opportunity to submit evidence to the House of Lords Select Committee on Science and Technology. I am Director of the Blood and Marrow Transplant Unit at the Queen Elizabeth Hospital, Birmingham and Professor of Haemato-oncology at the University of Birmingham. I am a past President of the British Society of Blood and Marrow Transplantation and am currently Medical Director of the Anthony Nolan and Chair of the UK Strategic Oversight Committee.

The establishment of the United Kingdom as a world leader in clinical research has been identified by the Coalition Government as a major priority. In recent years there has been an expansion of the budget of the National Institute of Health Research to more than £1 billion per annum and a realignment of major funding streams (MRC, CRUK, LLR) to support translational medicine. Simultaneously the wider economic benefits of job creation and inward investment by the pharmaceutical sector accruing from a flourishing clinical trial environment have been identified as important engine of growth by the Treasury and BIS. As a consequence clinical trials were mentioned seventeen times in the Chancellor's 2011 Growth Strategy. The development of an effective clinical trials infrastructure, essential to the delivery of an integrated translational medicine agenda, has been prioritised by US and European Governments and also by the global pharmaceutical industry. However to date most countries have struggled to identify regions with the necessary combination of a suitably sized catchment area coupled with the required clinical trials expertise and basic science excellence. Currently, in common with many other countries, the major challenge to the United Kingdom realising its full translational potential primarily relate to the absence of appropriately funded clinical trials networks in areas such as regenerative medicine where the United Kingdom already possesses exceptional strong basic science and clinical teams.

It is readily accepted that effective delivery of early phase clinical trials is critically dependent on the co-location of high quality clinical teams with experienced trials units. This however is not sufficient to ensure rapid recruitment and delivery of often complex early phase trials and the other key ingredient, namely access to a sufficiently large population of eligible patients, has until recently been ignored in the formulation of translational research priorities. Birmingham houses both internationally renowned clinical and scientific teams and at the same time at the same time serves one of the largest catchment areas in Europe. In 2006 £2.24 million funding was secured from the Regional Development Agency Advantage West Midlands to fund a translational research facility in haematological malignancies and stem cell transplantation. Since its opening the Centre for Clinical Haematology (CCH) has allowed more than 25 novel drug and transplant therapies to be studied in clinical trials and has resulted in more than £18 million of free drug being leveraged from pharmaceutical companies for trial participants. Over and above this impressive record of clinical trial delivery the CCH has also created more than 130 jobs in the life sciences demonstrating the immediate economic benefits which can accrue from funding translational medicine. The CCH has also provided a model for the Trial Acceleration Programme (TAP) funded by Leukaemia and Lymphoma Research (CI Prof Charles Craddock) which was established in 2011. The TAP funds a central trials hub in Birmingham and at the same time supports research nurses or trial coordinators in 13 leukaemia centres across the United Kingdom allowing rapid recruitment to early phase studies from a 20 million population. In its first

twelve months the TAP has rapidly opened two early phase clinical trials for patients with haematological malignancies and plans to open four further studies within the next six months providing an exciting model for maximising national recruitment to early phase clinical trials.

Stem cell transplantation represents an increasingly important treatment option for patients with leukaemia and other haematological cancers. The development of unrelated donor registries and cord blood banks has increased the number of patients eligible for allogeneic transplantation which is now a central component of the treatment algorithm for children and adults with high risk leukaemia. Whilst improvements in transplant technology have substantially improved patient outcomes many patients remain destined to die of treatment complications or resistant leukaemia. In January 2010, the Minister of State for Public Health established a UK Stem Cell Strategic Forum (Chair Prof C Craddock) to advise on options to extend the availability of and improve the outcome after allogeneic stem cell transplantation. In Dec 2010, the Forum published 20 recommendations twenty which were and accepted by the Minister in April 2011. Chief among these were the:

- funding of a 50,000 cord blood inventory in the UK
- establishment of Regional Centres of Excellence for cord blood transplantation designed to ensure high quality patient outcomes
- development of a clinical trials network to hasten the development of new drug and transplant technologies in stem cell transplantation at the same time as fostering interaction with the pharmaceutical and biotechnology industries

Recent advances in molecular and cellular biology have allowed the development of an extensive pipeline of targeted drug or cellular therapies with the potential for improving the outcome of patients after stem cell transplantation. At present no effective mechanism exists within the United Kingdom for the effective and rapid assessment of novel transplant therapies in early and late phase clinical trials. This reflects the relative complexity of transplant trials and, critically, the absence of a co-ordinated network of trial centres with a large enough catchment area to allow rapid recruitment. At the same time the opportunities to integrate the expertise of the UK's world class basic science laboratories so as to optimise biomarker development and trial design are not being grasped. In principle, the centrally imposed structure of the National Health Service (NHS) provides an ideal environment in which to develop an internationally competitive clinical trials programme in stem cell transplantation. The establishment of a national transplant trials programme would accelerate the introduction of new drug and transplant therapies into routine clinical practice and improve patient outcome. Such an initiative would also serve as a major stimulus to inward investment and private sector job creation by the biopharmaceutical industry as highlighted by the Cooksey Report and the Chancellor's recent Growth Strategy.

The British Society of Blood and Marrow Transplantation (BSBMT) has long identified the importance of clinical trials but its impact has been limited, in the main, to retrospective analyses of registry data because of the absence of suitable national trials infrastructure. There is therefore strong support for the development of a national Stem Cell Transplant Trials Network from both the BSBMT as well as the major UK stem cell registries of NHSBT and the Anthony Nolan along the lines outlined by the Stem Cell Forum. Experience from successful international trials networks identify two key ingredients required for the

Professor Charles F Craddock, Department of Clinical Haematology, Queen Elizabeth Hospital – Written evidence

rapid development and delivery of early and late phase transplant trial network within the UK. This would consist of a central hub housing a trial team (of 4-6 trial coordinators and data managers) with specialist expertise in stem cell transplantation allowing rapid work-up and regulatory approvals required and a network of 8-10 major transplant centres with dedicated research nurse funding. It is proposed that such a “hub and spoke” model would secure the delivery of up to 8 early and late phase trials and recruitment of in excess of 400 patients over a 4 year period for a relatively modest investment. Preliminary discussions have identified high level support for utilising CLRN resource to fund research nurses within the individual transplant centres which constitute the trials network. Options for funding the central hub for this network are currently being explored. Effective delivery of such a coordinated national trials network in stem cell transplantation would not only establish a globally significant transplant trials network but as evidenced by the experience with the Birmingham CCH trials programme generate a substantial number of knowledge rich new jobs and inward investment by global pharmaceutical companies.

I trust these observations are of value to your Committee’s deliberations.

20 September 2012

Cytori Therapeutics – Written evidence

Cytori Therapeutics is very pleased to have the opportunity to respond to the Call for Evidence in relation to the on-going inquiry into regenerative medicine. Cytori is one of the world's leading regenerative medicine companies, manufacturing medical devices for the extraction, concentration and storage of adult stem cells derived from adipose tissue.

We thought that it might be helpful to emphasise at the outset that the regenerative medicine sector covers a wide variety of therapies including gene therapy, the use of embryonic stem cells, the use of 'adult' cells derived from third parties (allogeneic cells), and the use of a patient's own (autologous) cells. These different uses and sources each give rise to their own challenges and opportunities which are sometimes markedly different.

Cytori manufactures Celution[®], a medical device which enables stem cells to be derived from the patient's own adipose tissue for therapeutic use. Celution is a closed, automated system which can be used to prepare a regenerative medicine product based on the patient's own cells at the point of care (in theatre, at the bed side, or within a hospital). As the cells are generally extracted and processed within one hour, the Celution device enables clinicians to extract and use adipose-derived stem cells within the same surgical procedure.

Stem cells derived from a patient's own adipose (fat) tissue are recognised as one of the best sources of therapeutically relevant stem cells. There are a large number of clinical trials underway globally investigating various therapeutic applications of such cells, and Cytori is actively pursuing a number of these therapeutic applications with a number of clinical partners globally.

Cytori has also developed a system (known as the StemSource Cell Bank) to allow patients to store their own cells for future use.

We have answered select questions in the Call for Evidence, addressed in turn below.

1. Research Base

How does the UK rank internationally in the field of regenerative medicine?

The UK is a global leader in the application of and research in regenerative medicine. The UK's reputation in this field was a decisive factor in first attracting Cytori (a US-based company) to the UK.

The UK's scientific track record in pioneering scientific advances in regenerative medicine and the basic science underpinning it is well known internationally. Less well known is the fact that, in principle, the UK's healthcare landscape allows for faster and more effective market entry than other systems. The NHS, as a national healthcare programme, presents a clearer path to market entry and coded reimbursement than many other systems in the world. Device adoption and handling within the NHS is also more stratified and rigorous compared to many private systems.

2. Application of the Science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine in the UK and internationally?

Cytori's Celution device has been available for use in Europe since 2006, during which time more than 5,000 patients have been treated using adipose-derived stem cells obtained using the Celution device without any serious safety concerns or adverse incidents.

We have been involved in a number of clinical trials to examine the use of adipose-derived cells in a variety of clinical settings, including:

- The treatment of cardiovascular disease for patients who have undergone myocardial infarction or suffer from chronic myocardial ischaemia; and
- Post-mastectomy breast reconstruction.

More details about our on-going clinical trials are enclosed as Appendix 1 (not published here).

Beyond these trials, we are aware that a number of clinicians are independently using the Celution device to investigate the use of adipose-derived stem cells to assist the treatment of (for example) wound healing, renal failure and peripheral artery disease. We enclose a summary of studies involving adipose-derived cells at Appendix 2.

3. Barriers to Translation and Commercialisation, and International Comparisons

Rather than addressing individual questions in the remaining categories, we thought it would be useful to provide a brief overview of our experience and approach which will answer many of the questions raised.

In our view, the regulatory framework established by various EU Directives and Regulations ensures that autologous stem cells derived from a patient and used within the same surgical procedure are appropriate. Medical device laws require Cytori to:

- ensure that the Celution device satisfies applicable 'Essential Requirements', as set out in the Medical Device Directive, addressing the quality and safety of the Celution device;
- obtain a certificate of conformity from a Notified Body (the organisation which has responsibility for confirming that a medical device conforms to the applicable standards) to confirm that the technical, scientific and clinical evidence supports the conclusion that the device satisfies the applicable Essential Requirements;
- propose specific clinical indications for the Celution device, which are also assessed by the Notified Body;
- establish and pursue a post-marketing surveillance plan (which itself must be verified by the Notified Body) to assess the clinical use of the device in the real world. In the case of the Celution device, Cytori has committed to conducting a number of Post-Marketing Clinical Follow-Up studies; and

- report any serious adverse incidents¹⁵⁵ to regulatory authorities.

Further, the clinicians using the Celution device must do so in accordance with applicable clinical and professional standards.

In our experience to date, the UK regulatory and commercial environment facilitates rather than obstructs the translation and commercialisation of regenerative medicine. As set out above, the framework is demanding, but clear and consistent.

Our positive experience of the UK environment is reflected in the fact that Cytori recently decided to appoint UK-based BSI as its European notified body in preference to our former notified body (which was based in a different European jurisdiction). This decision was made specifically as a result of the regulatory environment in the UK and the approach of this particular UK notified body. We found that BSI was not only more knowledgeable about the application of advanced therapies in this field, but also applied a more contextual, risk-based assessment which combined a focus on patient safety with a practical understanding of the clinical context and clinician-led application of our device.

Similarly, our experiences of dealing with the MHRA and the HTA have also been positive. On the whole, we have found both agencies to be constructive and balanced in their application of UK and EU law in a manner that is both consistent and pragmatic, while balancing risks according to the principles of proportionality. We have had no difficulties or obstacles in the conduct of our UK clinical trials, nor have we encountered barriers to the commercialisation of our product in the UK.

Unfortunately, EU Regulations and Directives are not been implemented or applied harmoniously throughout all EU Member States, and we have found certain other national regulators to be inconsistent and unduly restrictive in their approach to the regulation of regenerative medicine. In this dynamic and fluid field, regulators can adopt an overly restrictive approach, and misapply rules intended for other scenarios or products. In some contexts and countries, this has led to regulatory inertia, with officials unwilling to issue clear and practical guidance, focusing instead on the rigid application of rules. In contrast, the UK has published guidance on some key points of interest to Cytori, and this has greatly helped us shape our plans for the future.

We know that the UK is perceived by other EU Member States as a pre-eminent regulator in this sector. We would therefore encourage the HTA and MHRA to continue to take an approach with European colleagues that pursues a collaborative, risk-based, evidence-led approach which focuses on reducing regulatory burdens and unwarranted bureaucratic barriers wherever possible without ever compromising the safety of patients. This could also have the effect of ensuring that the UK is the preferred point of entry into Europe for companies based in the US and elsewhere.

While good and proportionate regulatory oversight is crucial, a clear route to market is the main driver of technological progress and patient benefit.

In the UK, the existing systems, while not specifically oriented towards new advances in regenerative medicine, nonetheless provide sufficient flexibility in our experience. The

¹⁵⁵ The obligations relating to serious adverse incidents are set out in the Medical Device Directive.

over regulation of regenerative medicine runs the risk of stifling innovation and forcing the technology, the associated companies and their jobs to other, more favorable locations. In our experience, however, the UK has maintained one of the most attractive and facilitative environment in the EU.

The over-regulation of regenerative medicine (or even an inconsistent approach to regulation) runs the risk of stifling innovation and forcing the technology, the associated companies and their jobs to other, more constructive locations. This could also have the effect of depriving patients of the opportunity to access the therapeutic potential of their own cells. We enclose (at Appendix 3) a number of testimonials from patients who have been treated by doctors in the UK with their own cells obtained from the Celution system.

In our experience, however, the UK has maintained one of the most attractive and facilitative environments in the EU. We hope that the Committee will support the regulatory framework and encourage UK regulators to continue to adopt a proportionate and pragmatic approach to the regulation of stem cells.

20 September 2012

Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant, Dr Graham M. Wynne, University of Oxford, Dr Angela J. Russell, University of Oxford and Professor Stephen G. Davies, University of Oxford – Written evidence

Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant, Dr Graham M. Wynne, University of Oxford, Dr Angela J. Russell, University of Oxford and Professor Stephen G. Davies, University of Oxford – Written evidence

[Submission to be found under Dr Angela J. Russell, University of Oxford](#)

Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant, Dr Graham M. Wynne, University of Oxford and Dr Angela J. Russell, University of Oxford – Written evidence

Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant, Dr Graham M. Wynne, University of Oxford and Dr Angela J. Russell, University of Oxford – Written evidence

[Submission to be found under Dr Angela J. Russell, University of Oxford](#)

Professor Stephen B. Dunnett and Professor Anne E. Rosser, Cardiff University – Written evidence

1. We wish to comment on the “barriers to translation”. Specifically we believe that the effective development of novel experimental cell therapies and their translation to first-in-man clinical trial is critically compromised by the absence of adequate funding or appropriate funding streams required to achieve compliance with recent increases in regulatory and legislative requirements associated with clinical use of human tissues. All present funding sources – whether provided by the UK research councils, BIS, NIHR and their devolved equivalents, or industry – are restricted and either requires industrial partnership for economic gain or fundamental innovative discovery research. By contrast, there is an almost total absence of funding streams to support academic/medical school infrastructure and programmes of validation necessary to achieve compliance with the raft of new safety regulation, without which the direct translation of world-class fundamental biomedical science to clinical practice is not possible.

2. We do not challenge the need to maintain the highest standards of safety and quality in taking new therapies to human application. Rather we maintain that raft of recently imposed regulation (EUTCD/HTAct etc) and their implementation (by HTA, MHRA etc) impose standards and procedures that are excessively bureaucratic, time consuming, and costly; in the complete absence of any risk assessment or evidence for their utility or effectiveness; with little consideration for the costs in terms of lost opportunities; and without appropriate funding streams to meet the costs of compliance with regulation (which might, e.g., add ten fold to the costs of a translational research programme).

3. We wish to illustrate our case by the specific example of the fate of the 30 year programme in which we have been engaged in developing fetal neural transplantation therapies for Parkinson’s (PD) and Huntington’s (HD) diseases.

4. One of us (SBD) has been involved since the late 1990s in the experimental development of cell transplantation in the brain in animal models of both PD and HD, among others. I was involved in the very first studies, working with Swedish collaborators who first developed the surgical techniques that now dominate the field worldwide, to show that embryonic brain cells can survive, integrate and function in the brain and can alleviate motor and cognitive symptoms of these neurodegenerative diseases. I am considered a leader in the cell and behavioural neurobiology of cell transplantation, at both national and international levels, and have introduced many of the fundamental principles that over the last 20 years has led to the first clinical trials in both PD and HD.

5. The other (AER) is a clinician scientist, consultant neurologist responsible for the specialist HD and movement disorders research clinics in Wales, and as professor of clinical neuroscience a specialist in cellular and molecular stem cell biology with a research focus on directing stem cells to differentiate into the specific fates necessary for use in clinical cell therapies, ultimately replacing fetal cells as currently required for efficacy.

6. We started working together in 1992 as one of the core programmes of the newly formed MRC Cambridge Centre for Brain Repair, as lead partners in a European consortium organised to translate experimental fetal neuronal cell transplantation to clinical

trial in HD. We established the programmes for longitudinal assessment of clinical research cohorts of HD patients in Cambridge and the programme working with local department of Obstetrics and Gynaecology for ethical procurement of human fetal tissues for research and therapy. Both programmes have been continued in Cardiff since our respective relocation to Wales in 2000 and 2001. The MRC funded our first multicentre UK trial with the first patients operated in late 2000. Ten operations were completed when the EU Tissue and Cells Directive was published in 2003, whereupon the clinical trial was suspended pending compliance with the new regulation, as then advised and subsequently implemented into UK regulation in the HTAct 2004 and administered by the HTA.

7. It has taken 8 years to achieve the point of compliance. At first the false starts and delays were clearly due to an absence of any clear information or guidance for academic and clinical investigators in procedures and protocols that were hitherto only available in large scale medicinal and pharmaceutical industry. Secondly no funding was available to pay for formal professional advisers, and allowing university (or medical school) estates departments to undertake design and construction work in which they had no expertise certainly resulted in further cost overruns due to eventual requirements to completely redo works found on external validation to be incompetently implemented. Subsequent building, licencing, protocol development, documentation and validation work has been undertaken by further research grants provided first by UK Stem Cell Foundation, in partnership with the MRC and Welsh Government (WG), and for the last period 2008-2011 by the WG under their Welsh Office of Research and Development (WORD) programme.

8. Our rebuilding, protocol development, training and documentation progress resulted in the issue on 7 March 2012 of an HTA human use licence (no 22639) to our facility (the 'Cardiff Fetal Tissue Bank', CFTB) to consent procure, process, store, transport and release human fetal tissues to clinical transplantation programmes, which can now resume in Cambridge and Cardiff. Our immediate plans are (i) to resume and complete the HD trial suspended 9 years ago with improved cell preparation and delivery methods, (ii) to progress in 3-4 years to the first-in-man trials of striatal differentiate progenitor and/or embryonic stem cells in HD, and (iii) to act as primary UK source for delivery of tissues into the UK arm of the EU funded TransEuro trial resuming cell transplantation in PD.

9. The CFTB is the sole UK source of ethically sourced and quality-assured human fetal tissue procured to a clinical (as well as a research) grade. It is essential source of tissue not only for the clinical fetal cell transplantation programmes, but also for our ongoing fundamental research programmes in cell transplantation methodology; for understanding the principles of functional integration of human cells in the adult brain environment; and for developmental studies to understand normal striatal development that underpins the ability to direct human stem cells to differentiate into the specific striatal and brain stem lineages required for their use in the next generation of cell transplantation therapies.

10. Hot on the heels of receiving the HTA licence for this exciting programme of work (in which the UK has international leadership and which provide the foundation for the next generation stem cell therapies), the future of the CFTB is now again thrown into question by our failure to renew funding. This is not because we are assessed and found wanting in a competitive funding environment, but because – with an ever increasing focus on strategic planning of all funding agencies – we fall between the initiatives, and are considered ineligible for any existing funding stream that we can identify.

11. As we move towards the CFTB providing a core infrastructure facility, we consider that the WG – as the devolved administration government – is the most appropriate source of support to underwrite a core facility such as the CFTB, on which is founded a combination of discovery science, translation to man of novel therapies, clinical trials, and considerable potential for long-term economic spin offs as cell therapies based on stem cells reach fruition. As an aside, if our facility were to be located in Scotland, we anticipate that we would fare considerably differently with the long term commitment of that devolved government to support future-looking stem cell science.

12. Our research has hitherto been provided by short-term programme and project grants from MRC, UKSCF and WG, in most cases piggy-backed upon our basic discovery science programmes. Our last funding 2008-2011 was funded by WG through their WORD programme, but WG reorganisation of their health funding programmes has abolished both WORD and the Welsh Development Agency, to be replaced by NISCHR, the devolved partner of the English NIHR. With our last grant approaching termination, we approached NISCHR in summer 2011 to ask what would be the appropriate new scheme to continue funding as we approached completion of the new facility and licencing. The eventual advice was that nothing quite fitted but that the i4i initiative was closest. To this we applied, but were rejected, again not because of scientific or strategic appraisal but because we were not operating with an industrial partner (although that was neither required nor useful to achieve the clinical delivery objectives). Further discussion suggested that WG considered our position was more appropriate to research council support than to NISCHR.

13. Helpful discussion with Dr Rob Buckle at the MRC, considering both regenerative medicine and translational stem cell science initiatives, advised that the Translational Stem Cell Research Board was the most appropriate target, and we accordingly submitted an outline application for renewal in February 2012. Since the present grant finished in April 2012 we have been bridging its activities from internal lab research funds, but that fast declining resource will imminently be emptied. In June the MRC communicated that they could not consider funding without an explicit plan for long-term sustainability, notwithstanding the fact that short term grants appear to be the only option. We have spent the summer seeking an agreement between the university and WG to consider underwriting proposals. The University is willing to show its willingness by committing a fourth year of funding to be met from the overheads that would follow a three year MRC award, whereas NISCHR has now indicated that they are fully supportive in principle but there is no scheme in place that could fund such a facility now, and they cannot commit to any options that may arise in future.

14. Following an 8 year programme to establish the infrastructure required by regulation, based on a 30 year programme of fundamental science in which we have been international leaders in defining the field, our facility is now licenced and ready to re-open for business. However, it is now likely that the two trials ready to commence/resume (of which one, the TransEuro trial, has already secured a €13m trial budget) will not be able to progress further due to want of the sustainable core funding to maintain the licence costs, validation staff and support of trained nurses to collect ethical consent.

15. Recommendations. We wish to recommend:

i. that the current inexorable progression away from investigator-initiated open funding streams to strategically defined initiatives with tight conditions, must be reversed. No one

can plan for all future options, and we risk aborting major new opportunities for want of an appropriate strategic funding initiative.

ii. that increased regulation of cell therapies requires longer periods of secure and stable funding that can be achieved by the present focus on short-term target-driven awards. The required infrastructure takes so long to design, develop, build, train and validate, and has to be in place before a clinical trial grant application can be submitted; it cannot be funded retrospectively by full (or even marginal) cost recovery from the projected trials it eventually sustains.

iii. that the criterion for funding, and for funding renewal, must recognise the need for infrastructure that in and of itself cannot be appraised according to the continuous production of new innovations and high impact publications, nor in terms of economic gains. Moreover the outcomes in terms of successful clinical trials or economic spin offs will be realised not by short-term results but over a 5-10 year period. 7-year support is probably the practical minimum for such a facility.

16. In summary, we do not wish to replace peer assessment and competitive funding. Rather our views reflect the frustration that while we believe we are centre stage in the mission to develop UK translational medicine from cutting edge fundamental science to delivering new therapies to patients, the landscape is such that funding of such work seems to be a post-code lottery, and can be effectively excluded by funding strategies and initiatives applied by UK national and regional government and the research councils.

17. This submission is made in our personal capacities as professional experts actively engaged in the field of regenerative medicine.

12 August 2012

Edinburgh BioQuarter – Written evidence

This brief report is restricted to the commercial and financial aspects of the Regenerative Medicine sector in the UK.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

Historically, the UK has enjoyed a strong global reputation in regenerative medicine underpinned by strong academic research, such as the cloning of the first mammal ever (Dolly the sheep) at the Roslin Institute in Scotland by Sir Ian Wilmut or the pioneering work of Sir Peter Medawar on immunosuppression to facilitate tissue and organ transplantation. As with many other groundbreaking technologies that have emerged from the UK, there is now an increasing risk that other countries will begin to overtake the UK through sheer weight of research investment.

Where does the UK have strengths and weaknesses in the field?

The UK has two MRC sponsored Centres for Regenerative Medicine, one in Cambridge and one in Edinburgh. Indeed, the Scottish Government has placed particular emphasis on regenerative medicine as a driver of economic growth - £59m has recently been invested in establishing the Scottish Centre for Regenerative Medicine, the only UK stem cell facility that incorporates academic research, GMP manufacturing and clinical development in one building. Other centres of excellence exist throughout the UK, notably in London and Newcastle. The new Cell Therapy Catapult Centre will undoubtedly add weight as it becomes fully established although its remit goes beyond the confines of regenerative medicine.

There are two key points worth raising in connection with UK weaknesses:

- I. Historically, the UK has focused most of its stem cell research on human embryonic stem cells (hESC) whereas other countries, because of ethical concerns, have tended to work with adult stem cells. As the field develops, hESC are becoming less favoured, with adult and 'induced' stem cells becoming predominant in the development of new therapeutic approaches. In particular, the discovery by Professor Yamanaka in Japan that it is possible to 're-programme' fully differentiated cells back into pluripotent stem cells, so called induced pluripotent stem cells (iPS cells), has revolutionised the sector and changed our views about the applicability of stem cells as therapeutics. A company has been set up in Kyoto to specifically deal with this invention – to date, over 100 licensing deals have been signed. In light of these recent developments, the UK's historical focus on hESC research has placed it at a slight disadvantage.

2. The UK is hugely disadvantaged (particularly by comparison with the USA) with regards to the amount of public and private finance going into regenerative medicine research and translation of that research. The Catapult centre has been established by UK Government to try and redress this balance but the amount of funding (£10m per annum) is relatively modest by comparison with, for example, the \$3bn fund established by the Californian Institute for Regenerative Medicine (CIRM) or the NIH's \$1.3bn annual stem cell budget.

Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

The science is being translated in two main areas: (i) research and development tools and (ii) therapeutics. In terms of research and development tools, stem cells are being used to better model human tissues 'in a dish'. For example, the pharmaceutical industry has been using human liver slices for decades to test the potential toxicity of new drugs in development. Now, using stem cell technology, human liver cells can be re-created in the laboratory, bypassing the need to source human tissues.

With regards to therapeutics, there are undoubtedly numerous currently untreatable conditions and diseases that will benefit from developments in regenerative medicine. A key question is whether the regenerative medicine solutions to these currently untreatable diseases will be commercially attractive to the pharmaceutical industry. There is currently a disconnect between 'big pharma' and the regenerative medicine research base which remains predominantly academic and there is a real danger that new therapeutic concepts are being pursued that big pharma will be loath to adopt. The pharmaceutical industry has grown up around producing chemical powders and pills that can be sold off-the-shelf and supplied to the masses. Big pharma currently plays little part in the small but existing regenerative medicine/cell therapy market which has more to do with isolating, expanding and/or treating cells from an individual patient before re-introducing them back into the same patient (autologous cell therapy) or isolating specialised cells from a donor and transplanting these into another 'matched' patient (allogeneic cell therapy). Adapting these 'specialist-based' therapeutic approaches from their current clinical setting into big pharma's off-the-shelf distribution model will be challenging.

Big pharma is currently assessing the market opportunity and choosing those areas that look to be commercially attractive – these are more likely to be 'small molecule' opportunities rather than cell based therapies. Applications involving cells or tissues may remain within specialist clinics, requiring to be funded privately, or by health authorities and/or health insurance providers. Alternatively, a new generation of biotechnology companies may evolve, unencumbered by existing infrastructure and mindset, that will establish new distribution networks better suited to cell therapy based solutions (national and international blood transfusion services have been doing this for 50 years).

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

The perfect analogy here is the story of therapeutic monoclonal antibodies (mAb). mAbs were discovered in the UK in 1975. Their therapeutic potential was immediately obvious, and the hype was immense but there were numerous challenges getting therapeutic products to market. The first therapeutic mAb was marketed in 1986, but it wasn't until well into the 2000s that the majority of the 30 or so mAb products now on the market were launched. Scientists and the media will continue to add to the hype surrounding the promise of regenerative medicine, but the reality is that it will take 25-30 years before it is making a major contribution to healthcare. In the next 5-10 years, there will be a handful of new treatments, mostly cell based and relatively unsophisticated (islet transplantation for diabetes, retinal cells for degenerative eye conditions, better skin products, use of lymphocytes for cancer treatment, etc). Some of these may herald significant improvements for a small number of patients. But developing regenerative cures for complex degenerative conditions such as Parkinson's disease, multiple sclerosis, cerebral palsy and Alzheimer's disease will take decades.

One major concern is that companies are already being formed (both in the UK and beyond) that capitalise upon the regenerative medicine/stem cells hype to market services and products that prey on the weak, the uninformed and the desperate. A number of companies are already offering to extract stem cells from susceptible individuals and store them, at huge expense, to be used at a later date should they eventually succumb to some disease. There is no evidence that such treatments would be successful. Even worse, some companies are charging vulnerable patients tens of thousands of pounds to inject stem cells with no evidence that such treatments work. XCell-Center, a German company and Europe's largest stem cell clinic, was closed by the authorities last year following an investigation into its practices after the death of a child that had been injected with stem cells directly into the brain. It is important that the regulators stamp out such malpractices which will negatively impact confidence.

Barriers to commercialisation

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

The UK is becoming less attractive as a place to start and grow new biotechnology ventures. The level of available venture capital is an order of magnitude less than in the USA meaning that entrepreneurs have a steeper hill to climb. Many European based life science VC funds now choose to invest in North America – there is safety in numbers. One way to address this problem is for UK Government to kick start the market - investors like investment propositions that have been de-risked with state funding. Examples of where this has worked well are (i) in Medicon Valley, now the largest biotech cluster in Europe which was kick-started by a Swedish/Danish Government backed venture fund, or (ii) the Israeli Government's Yozma project which has seeded the most successful venture capital market outside of the USA, or (iii) the Irish Government's current initiative to invest a total of more than €60million in venture capital funds which establish a presence in Ireland.

Other, more indirect measures that the UK Government could employ to help to move the sector along include: free advice from the UK regulatory authorities (MHRA) on all matters relating to regenerative medicine; match-funding from UK Government for all regenerative medicine pre-clinical and clinical trials; match-funding from UK Government for any VC investments into UK regenerative medicine companies (match funding is already available in Scotland via Scottish Enterprise/Scottish Investment Bank); financial incentives for foreign regenerative medicine companies wishing to relocate to the UK; tax incentives for companies performing regenerative medicine clinical trials in the UK.

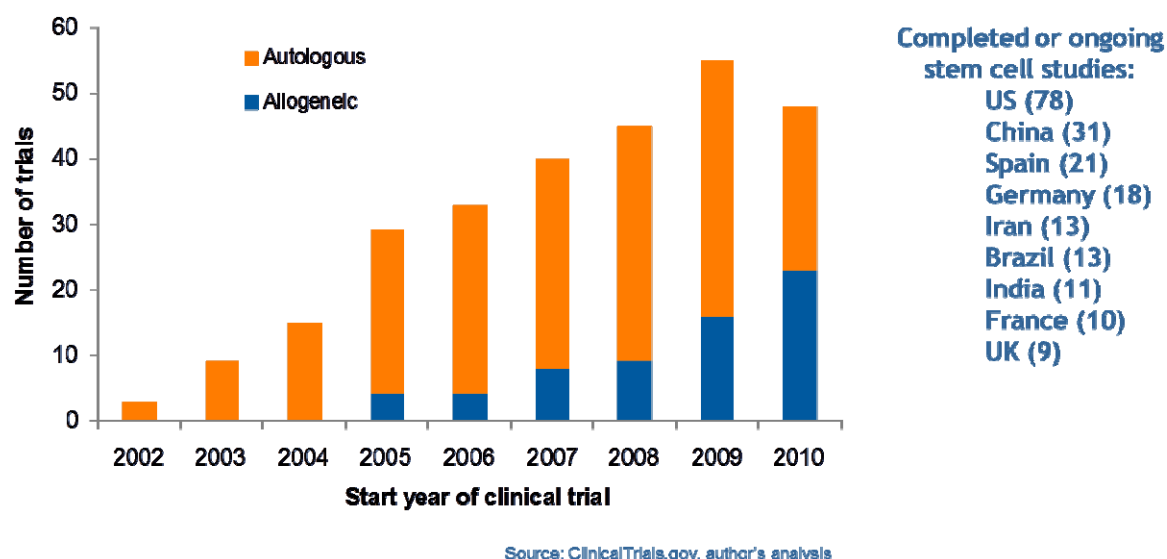
International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

Via the MRC and BBSRC, UK government currently provides £1.15bn annually in research grants covering all biomedical research in the UK. From a commercialisation standpoint, £180m of investment capital has recently been made available to the life science sector through the BioMedical Catalyst fund. More specifically, cell therapy projects will have access to another £10m of translational funding that will become available annually through the newly established Cell Therapy Catapult Centre. Regenerative Medicine research in the UK received approximately £38m from the third sector between 2005-2009; the public sector has invested almost £200m in the field since 2003. Although this level of funding is roughly in line with some of our European competitors, it falls well behind the USA on a per capita basis:

- USA - Via the NIH, the US Government invests \$31bn annually in biomedical research, \$1.3bn of which went into regenerative medicine programmes in 2011. The State of California alone has established a \$3bn stem cell research fund. This year, the NIH launched the NIH Centre for Regenerative Medicine which is expected to attract significant funding (both private and industrial).
- Canada – Centre for Commercialisation of Regenerative Medicine (CCRM) set up by the Canadian Government with an initial investment of \$15M. Already receiving strong industry support.
- Germany – Centre for Regenerative Therapies Dresden receives an annual budget of €8.7M from the German government

To be globally competitive, UK Government needs to start competing with other leading nations with comparable (i.e. per capita) levels of financial support. This shortfall in UK funding is perhaps best exemplified by looking at the current state of completed or ongoing stem cell clinical trials on a worldwide basis - the UK is in ninth position, behind Spain, Germany and France in Europe:



Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

Certain countries do not apply the rigorous ethical and scientific standards that are generally found in the Western World. We need to be aware that poorly regulated clinical trials have the potential to negatively impact the adoption of regenerative medicines.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

The opportunity for unscrupulous marketing of regenerative medical cures, especially to the uninformed or the desperate, presents a key challenge for the sector. The closing of the XCell-Center by the German authorities after the publicised death of a baby highlights the problem. However, we should not assume that the UK is entirely 'safe'. There are already companies in the UK offering to collect and store adult stem cells for paying individuals in the hope that one day such cells could be clinically useful to them. This service overplays the current state of knowledge and preys upon the worried well. UK Government needs to be aware of the issue and legislate to ensure that the public is not being misled. The concern is that malpractice and poor publicity could lead to a public backlash against regenerative therapies. It would be unfortunate if regenerative medicine went the same way as GM Foods.

20 September 2012

Engineering and Physical Science Research Council (EPSRC) Centre for Innovative Manufacturing in Regenerative Medicine – Written evidence

The EPSRC Centre for Innovative Manufacturing in Regenerative Medicine is a collaboration of Loughborough, Nottingham and Keele Universities and industry together with other end users. Its vision is to form a differentiated translational “go to” resource for RM product developers with a focus on manufacturing science, and manufacturing system and process development. Regenerative medicine has the potential to deliver health and wealth – and a new industry. Manufacturing, supply, and managing cost are key barriers to realising this potential. A recent statement of the manufacturing issues for regenerative medicines can be found in D J Williams et al, Precision manufacturing for clinical-quality regenerative medicines, Phil. Trans. R. Soc. A, August 28, 2012, Vol 370, No 1973, pp. 3924-3949; doi:10.1098/rsta.2011.0049.

In order to keep this response focused we have chosen to only make the following comments in response to particular questions.

The research base

- How does the UK rank internationally in the scientific field of regenerative medicine?
- Where does the UK have strengths and weaknesses in the field?

It is important to recognise that UK academic regenerative medicine researchers - when compared to academic researchers in the US - are perceived by North American Industry to be much more product and market led because of our tradition of strong industrially collaborative work as encouraged by the Research Councils, The Technology Strategy Board and the EU Framework Programmes. This represents a significant opportunity to assist in the attraction of inward investments and an important direction in which to continue to develop young researchers.

Barriers to translation

- Are the actions outlined in the Government’s Strategy for UK Life Sciences in their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board’s Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

Translation in this area necessarily relies on national interventions behaving as a dynamic and actively co-ordinated system rather than a static landscape – the Cell Therapy Catapult and other TSB and BIS investments, the EPSRC Centre and other Research Council funded centres, the forthcoming MRC led UK Regenerative Medicine Platform, the MHRA and the NHS and the DH must all work together. A level of co-ordination is required to deliver the eco-system ambition identified by The Rt Hon David Willets in his Life Sciences Strategy Update of 20 August 2012.

Regenerative medicines are frequently made from complex living human materials and under recent ATMP (Advanced Therapy Medicinal Products) regulation that is only now being

interpreted in practice. In particular new regulatory science is required that will inform and enable robust regulatory decisions by both influencing and informing the regulator and assisting the manufacturer in providing the knowledge base to deliver confidence in these products. Any regulatory science or standardisation activity must be managed in such a way that the intent of the work as captured above is delivered. Considering some of the work carried out under the US NIH Regulatory Science programmes, it is clear that some of it has defaulted to technology push or conventional academic curiosity driven research rather than delivering to the intent of the call.

- What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

Facilitation of the appropriate adoption of cost effective regenerative medicines within the NHS must be a major focus to enable UK industry growth. A significant step towards this would be that DH NIHR research programmes explicitly embrace regenerative medicines.

International comparisons

- What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

Healthcare systems are frequently inward looking - the NHS should work with other single payer dominated healthcare systems outside the UK to understand how they are addressing the opportunity that regenerative medicine represents to reduce the burden of chronic disease and return people to productive work.

19 September 2012

**EPSRC Centre for Innovative Manufacturing in Regenerative
Medicine, Cell Therapy Catapult Centre and TAP Biosystems – Oral
evidence (QQ 267-282)**

Evidence Session No. 11

Heard in Public

Questions 267 - 282

TUESDAY 18 DECEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Professor David Williams, Director, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, Loughborough University; **Keith Thompson**, Chief Executive Officer, Cell Therapy Catapult Centre; and **Dr David Newble**, Chief Executive Officer, TAP Biosystems.

Q267 The Chairman: I would like to welcome our three witnesses for the first witness panel. In a moment, I shall invite you to introduce yourselves for the record and to make any very brief introductory comments that you may wish to make. For the members of the audience, the declared interests of the members of the Select Committee are on the list that you have received, as well as the purpose of the inquiry.

Without further ado, starting with Keith Thompson, I would like to invite the witness panel members to introduce themselves.

Keith Thompson: I am Keith Thompson. I am the CEO of the Cell Therapy Catapult. I have been in post for about six months. Immediately prior to that I ran the Scottish Blood Transfusion Service, and prior to that I ran several biotechnology companies here and in the US, all involved with biomanufacturing on a large scale.

The Cell Therapy Catapult is a new initiative, as you know, along with other high-tech catapults run by the Technology Strategy Board. Hopefully, we are going to provide a great

deal of support to develop the industry that the UK deserves to come out of its science base.

Professor Williams: I am David Williams from Loughborough. I lead the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, which is upstream of Keith in terms of its technology. I am not solely an academic. I have seen practice, in particular, in the large-scale manufacturing of drug delivery devices in the commercial world, which engaged me in the scale-up problem significantly.

Dr Newble: I am David Newble. I am the CEO of TAP Biosystems. We are a company that supplies bioreactors and manufacturing systems, and we have been supplying most of the leading regenerative medicine cell therapy companies over the last 15 or 20 years. I have worked very closely with David Williams's group to address some of the challenges of regenerative medicine.

Q268 The Chairman: Thank you very much. I would like to kick off with the first area of questioning. We are very much interested in your views on what kind of infrastructure is needed to develop and support the delivery of regenerative medicine treatments in the UK into the clinic and to commercialise regenerative medicine therapies. We are particularly interested in whether there is sufficient investment—the amount of money available is sufficient; whether there is sufficient leadership; and whether there is sufficient co-ordination across the different actors; and, perhaps linked to that, who should be in overall charge, if any one individual organisation should be.

Keith Thompson, since this is one of the things that the Catapult Centre is meant to be doing, perhaps you could kick off and give us your views.

Keith Thompson: Thank you. In terms of infrastructure, the investment that has happened over the last several years that is coming to fruition now, which has invested in near clinical translational manufacturing space, has been extremely timely. These units, which are dotted about the country—there are about 20 of them—will enable early-stage trials to go into place. In addition to that, a small number of CMOs can operate both at that scale and on a slightly larger scale. Over time, as there is a requirement to get into larger-scale manufacture, perhaps for phase 3 but certainly in market supply, then larger infrastructure, either built internally within companies or for the contract manufacturing industry, will be required. The key issues around this supply stage relate to scale and how they will be delivered. I shall perhaps come back to that with one of the other questions.

In a way, the key objective of translational units, both from the Catapult point of view and from earlier research in manufacturing technologies, is to lessen the requirement on high-grade clean rooms. If you think back to the early days of monoclonals, people struggled with the idea of how they were going to make a monoclonal antibody. They largely did it by hand, in flasks and what have you, and of course those of us who were around when monoclonals first started now see the enormous scale, which, quite frankly, was unimaginable when I first started out in monoclonals. Not only was the scale unimaginable but the productivity was unimaginable. Because the industry feels like this now, most people who are engaged in it are engaged in methods and work that will allow that scale to move further forward, particularly closing the processes so that they do not rely on clean rooms.

The other things that are required to make it happen are not just the manufacturing scale and the facilities that you wrap around it but the analytical tools that will enable what is known in the pharmaceutical trade as CMC—chemistry, manufacturing and control—to show that you can make and control these processes in a reproducible and comparable

fashion. That tools piece is a key part of the landscape that requires developing, both from early stage research and in the kind of development and translational set phase.

Those other underpinning tools and technologies are required to enable the delivery into the clinic, to the patient. Unlike small molecules or large molecules that follow a path through pharmacy that is well known, these will require near patient manipulation. Working on that landscape will be extremely important.

The Chairman: Could you keep it fairly brief, please?

Keith Thompson: Sure; I shall stop now.

The Chairman: Did you want to say anything about leadership and co-ordination—just briefly?

Keith Thompson: The Catapult intends to reach out to all parts of the community, to provide tools, where possible, both to industry and to help pull technologies developed from the regenerative medicine platform run by the research councils, and to get them to a stage where they are robust enough to be used in anger.

The Chairman: Is reach-out similar to leadership, or is it different?

Keith Thompson: You can only be a leader if you can demonstrate that you have the capability of delivering. Therefore, as the Catapult is a new initiative, the leadership will come from the Catapult by demonstrating that it is serving a purpose and delivering benefits.

Q269 The Chairman: Professor Williams, would you like to comment briefly on this general question?

Professor Williams: I shall echo some of Keith's themes to start with. Manufacturing at scale means reaping economies of scale and scope; it is not a technical solution but an economic solution. It requires us to execute our processes under Good Manufacturing Practice, which is a regulatory constraint. So, one of the things that I would like to put on the table is that there is a significant requirement to co-ordinate as we address reproducibility and comparability with the MHRA and the GMP regulator.

There are very significant opportunities for standards work in this area. Scott Steedman of BSI talks about third-generation standards, which enable a business model as an opportunity to push standardisations in this space to give us these economies of scale and scope. The core technological thing that this really hinges on, both in the near patient setting and the scale setting, is the ability, as Keith has said, to give analytical tools that allow us to characterise what a good product is.

I am trying to highlight the fact that there are a number of stakeholders to co-ordinate—people like David (Newble), the academic community, the Catapult, industry and the regulatory and standardisation organisations—which need some manipulation to allow co-ordination and the sharing of understanding, because it is a moving target. Our understanding is evolving with time, so we need to make sure that there are mechanisms for those players in the communities to work together, as we understand better and better what a product is, what the manufacturing environment should be and what the technologies are that will permit the clinical community to adopt the technologies.

Q270 The Chairman: I would like to get a slightly crisper answer to the question that I posed, which is whether there is sufficient investment, leadership and co-ordination. I am hearing various comments, but I am not getting direct answers to those questions. Dr Newble, would you like to try?

Dr Newble: My perspective on this is that manufacturing scale-up is a big part of the challenge of bringing cell therapies to market, but, at the moment, the bigger challenge is having high-value clinician-led early-stage research being carried out that is going to pull those therapies into use with patients. That is part of the reason for setting up the Catapult. My perspective on the way we are structured in the UK is that we have a lot of manufacturing centres, but they seem to me to be quite dispersed across the country.

To get good quality therapies through, the best models that I have seen in those places where I have been working around the world are where you have one or two key centres that are able to produce therapies to support those trials, linked in with clinics that are carrying out some of the basic autologous therapies at the moment, and then you really build up that capability.

At the moment we have centres of it, and we have a lot of the academic-led expertise. We have a lot of the platform technologies in place, but, without that pull and the ability to carry out the trials, then we are missing out and not exploiting the value of the research and the technologies that we have in the UK.

The Chairman: Which countries would you point to as examples?

Dr Newble: I look at two examples. There is a group that we work with in Boston, where there is the Dana-Farber cancer hospital. They started out just supplying cells for haematopoietic cancer therapies; they have built that out and are now supplying a number of different groups that are doing cell therapy early-stage trials. They are looking to expand that, and I think that they are looking to spend somewhere around \$40 million, putting it into that facility to build it and make it a centre of excellence in the Boston hub.

The other centre that I have seen—it is on a much smaller scale—that seems to be quite leading is in the Czech Republic, where there is the National Tissue Centre. It has built a lot of expertise and put some small-scale capability in for producing cell therapies. It is linked into three or four hospitals so that they can try and kick-start the research work that is going on there.

Lord Winston: Which cell therapies are they working on?

Dr Newble: They are working on a range. They have some scaffold production technology in there to support things like bone regeneration and cartilage. They then have a group working on haematopoietic stem cells, and some groups working on mesenchymal stem cells. That is to carry out and support trials in centres around the Czech Republic.

Q271 The Chairman: I wonder, Keith Thompson, whether you agree with Dr Newble that we could usefully learn lessons from other countries and that we are not quite getting it right at the moment.

Keith Thompson: There are a couple of things. The first, which I shall come back to, is the issue of the manufacturing capabilities, if I may. The Catapult has commissioned an in-depth survey of all the manufacturing capability in the UK, not just counting the physical infrastructure but the actual staff, what therapies they have been able to work with and what utilisation rates they have, in order that we can co-ordinate and direct both the

therapies that we are going to want to be manufactured but also inward investors to the right people. It is coming back to that role of co-ordination and analysis.

There is no doubt, as you get a critical mass of expertise and scale, that they do start to feed off each other. That exists in some areas of the UK, like Edinburgh and London and a couple of the other centres.

The Chairman: Do you agree with what we heard from Dr Newble that we could learn lessons—he gave the examples of Boston and the Czech Republic—or do you think that we are ahead of them? Are we behind or ahead?

Keith Thompson: In terms of basic research and the ability to get things into the clinic, I would undoubtedly say that we are at least equal to or ahead of the Czech Republic. They have a particular model that is highly dependent on their interpretation of the regulatory landscape in the Czech Republic, which is perhaps a little more permissive than over here. In relation to Boston, yes, it is a sizeable operation, and scale always brings benefits.

The Chairman: I would like to invite Lord Willis, Lord Cunningham and Lord Patel to speak.

Q272 Lord Willis of Knaresborough: I share your frustration, as I do not feel that we are getting anywhere this morning. The idea is that we are going to conduct surveys and develop new strategies, but the reality is that, in France, half a billion euros is being spent on large manufacturing and the same in a single German Länd. We have seen major developments in the United States, both in California and Boston, and we are likely to miss the boat. What we want from you this morning is for you to say what direction we should be taking in order that we capitalise on the scientific lead that the UK has. Is that direct enough?

Professor Williams: Can I answer the question—

The Chairman: Answer directly and succinctly, please. We do not want diversions; we want an answer to the question.

Professor Williams: I answer from two perspectives. I used to work in a contract manufacturing organisation in device supply to the pharmaceutical industry, and this is very close to that problem. The margins for a CMO are not as high as they are for the big pharma companies that will exploit the final technologies. It is very expensive to build a large facility to make stem cell products. It is very difficult to see a UK company that would be able and willing to make the level of investment required to generate a large facility.

The Chairman: Should that then come from the Government?

Professor Williams: Yes. That is the only way we will get a large facility. The second response is that we have to crack the large facility problem. In my introduction, I said that the core problem is to generate economies of scale and scope. There are other ways of doing that than building a large factory. If we crack the requirement to move away from a large factory, you have a significant competitive advantage.

Lord Willis of Knaresborough: So we should not build a large facility. This Committee should not recommend to the Government that we should have a large facility; we should just have all these little ones, which might get co-ordinated at some time in the future.

Professor Williams: There are two horses we have to back. There is a large facility model, and the alternative, which is not the toy facilities that we have at the moment, is facilities that are able to make, at volume, therapies that reach a large number of patients. My model for this is that, at a conference one day, 25 clinicians will say, “We all need to do that.” We will therefore need a solution to allow all those 25 clinicians to do the same thing in each of their hospitals. That requires us to solve this problem, which we call comparability. It is a standardisation and regulatory interface problem. We have to back both horses.

Q273 The Chairman: You may answer briefly, Keith Thompson. I then want to move to Lord Cunningham and Lord Patel.

Keith Thompson: I shall be as direct as I can.

The Chairman: Please.

Keith Thompson: At the moment, I do not believe that we should build a large-scale facility. The important thing to do right now is to get phase 1 and phase 2 trials through the clinic that are capable of demonstrating clinical efficacy. Without that demonstration, it will not trigger the strategic investments of the order required to put things through phase 3 and in market supply.

I have been in the biomanufacturing industry for an awfully long time, and I have seen many stainless steel palaces built and torn down several years later. That is not to say that we do not want investment in that space. We do, but it has to be the appropriate investment that reflects the kind of technologies that will get us into the clinic.

Lord Cunningham of Felling: Mr Thompson, a little while ago you talked about a critical mass. Is there anywhere in the UK any grouping or cluster that you could describe as having achieved the critical mass required to move forward?

Keith Thompson: Certainly London and the south-east has a very rich cluster. Edinburgh is a good area for this in terms of the translational capability.

Lord Cunningham of Felling: Is that true of the resources going into these clusters, as well as the number of people working in them?

Keith Thompson: Everybody can always use more money; there is no doubt about that. But the key thing that I keep coming back to is that it requires therapies to be driven through the clinic in order to create the future value of both health and wealth for the UK. Without that, it is just building stuff or doing research.

The Chairman: Is that happening?

Keith Thompson: Yes, it is.

The Chairman: Do you feel that there is no need for us to make further recommendations about how phase 1 and phase 2 clinical trials are being delivered through the clinic?

Keith Thompson: At the moment, modest increases in that would be fine. It is more important to work in the regulatory space and the space that supports the clinical trial activity.

Lord Cunningham of Felling: Am I right in saying that you have a budget at Catapult of £50 million over five years?

Keith Thompson: The funding model is a core grant from the TSB. We are expected over time to bring in another £10 million per annum of collaborative R&D and, ultimately, a further £10 million of contract research. We agreed at the TSB board—it still has to go through the final Treasury sign-off—on closer to £70 million. It is a substantial amount of money.

Lord Cunningham of Felling: In the state of California, where the population is smaller than ours, they are investing \$3 billion. It has a GDP not dissimilar to ours, incidentally.

Keith Thompson: That is an awful lot of money.

Dr Newble: I am more in agreement with you. At the moment, the amount of money that is going into the clinician-led studies is far too low compared with other areas in the world.

Lord Cunningham of Felling: Thank you; that is a direct answer.

Dr Newble: For me, the thing that is stopping us developing technologies to solve this problem, as a company that does just that, is not the lack of technology or the lack of will but the lack of people saying, “I need it.” When somebody says, “I need it”—and Organogenesis is probably the leading company in the world—we will go in and design a manufacturing facility to do it, but we are 10 years away from that. The money needs to be funnelled into the clinicians who are actually going to drive the pragmatic decision making about whether a patient will benefit from a therapy or not and whether it should be scaled up in the long run—in my opinion.

Q274 Lord Patel: I have a question related to your question, but I shall move on to the question I had, some part of which has already been answered. Hopefully, it will save some time.

I too was feeling a bit frustrated, as Lord Willis was, and I wonder whether, in your answers, you are trying to be a bit more defensive rather than bold. We would like you to be bold, because we are here to try and help you progress with this agenda of leading the world in regenerative medicine. I suggest that you are being defensive.

You mentioned several times, Mr Thompson, that the key thing is now to get the first and second phase clinical trials done. Compared with the rest of the world, we are nowhere near leading that. Of course, in a minute, you will throw in my face macular degeneration, but, beyond that, I would be grateful if you could list 10 other things in which we might be leading the world. If we are not, what is it that we have to do to get more research into the first and second phase clinical trials?

What do we have to do to think about the delivery systems of various autologous or allogeneic treatment? What do we have to do to be prepared for stage 3 trials and manufacturing? You do a survey, but when will the survey result be available? How are you, as a Catapult, going to lead the world in regenerative medicine?

Keith Thompson: Yesterday, we published the first survey of all the clinical trial activity in the UK. It can be found on our website. This was the first piece of work that I commissioned when I joined the Catapult.

Lord Patel: Can we have that as written evidence?

Keith Thompson: Yes, certainly. It is on the website.

Lord Patel: We would like it sent to the Committee as written evidence, if that is possible.

Keith Thompson: Sure; that is no problem. I have been trailing the clinical trial database to the community, and people have been extremely keen on receiving this to see exactly where we are. It serves a number of purposes. It metricsates where we are now, but it also gives us a base to determine whether the Catapult, through its activities, is de-bottlenecking the pipeline so that more therapies can go through.

We have 24 clinical trials ongoing at the moment in the UK. Only four of them are commercially sponsored. They are approximately equally split between autologous and allogeneic therapies. They have diverse cell types in them; bone marrow cells predominate, followed by T cells. Then we have a range of others, from ES cells through to the various disease categories.

It is my contention that, by increasing this pipeline and making sure that well-developed products get into clinical trial, we will both de-bottleneck the landscape and trigger investments from others. It is a very aggressive strategy that we have.

Lord Patel: What about delivery system development?

Keith Thompson: There are two elements to delivery systems. The first is the distribution from the manufacturing site, and that is for a fresh, live cell—there you have to be relatively close in some cases, though not all, to do that—and a delivery system into the patients themselves. Working with the Blood Transfusion Services, it has been my experience that we have been able to distribute cells through their networks across the UK in a timely fashion.

When I was at SNBTS, we developed both corneal epithelial stem cells and islet cells, and those islet cells—we got that project up and running in two years—have been delivered as far afield as Bristol. That shows just what a network can do. I am in dialogue with NHSBT around adopting projects to prove that cell therapies can be run through the existing network.

The Chairman: Would Dr Newble like to comment on the delivery and geographical location transportation issues?

Dr Newble: Delivery is not a big issue, frankly. I use an international example. I was in Singapore recently. They have a centre of excellence for corneal repair therapy, but they are not worried about delivery because it is cheaper to bring patients to them and put them up in a five-star hotel than it is to build a centre in Vietnam, for example. So delivery is not a problem today.

We need to get more therapies funded. We need to be prepared to fail, and we need to put substantial money behind each of them and quickly build a critical mass of therapies that are in phase 2 studies. If we do not do that, we will be a long way behind the competition.

Professor Williams: We also have to think about supply during the development and clinical trial process. As we go from phase 1 to phase 2, we need to be ready with the manufacturing solutions that match the clinical opportunity and the commercial opportunity.

Q275 Baroness Sharp of Guildford: Can we move on to training and whether you feel that at the moment the training needs, particularly for healthcare professionals and those involved in the manufacture of regenerative treatments, are sufficient? If not, how should they be improved?

Professor Williams: As the academic, shall I lead off with that one? We are very fortunate in the EPSRC world in having doctoral training centres in regenerative medicine that will allow us to create a cadre of professionals who can do the visionary stuff that we have been talking about. In manufacturing, in particular, we have to create a blend of technicians capable of working at the interface, as Keith has described it, around manufacturing excellence and this very challenging stem cell biology. Those animals do not exist; you can try and do it with academics, but young academic researchers do not want to go in that space or stay in it for long, so we need a senior technician cadre to move this along. Without that, we will not be able to make very much progress.

Dr Newble: We do not have a problem in the UK. It is an area where the UK is very much a leader. For example, we have put together a new group developing bioreactors in the last three years, and we have had no problem in recruiting some of the highest quality people around the world that I have come across—a lot of them coming out of Loughborough and University College London. So there is a very strong talent pool. Some of the leading companies around the world often have people with a heritage that leads back to those institutions anyway, so we are often working with British people overseas. I do not believe, certainly on building technologies for biomanufacturing, that there is any kind of problem at all.

Baroness Sharp of Guildford: You do not, therefore, feel that there is a need to train a special cadre of technicians.

Dr Newble: I think there is, but I think we are doing it quite effectively.

Baroness Sharp of Guildford: UCL and Loughborough between them are providing enough.

Dr Newble: I am sure they are. There are others in Manchester that I know of, and there may well be others, but certainly we have not had a problem.

Baroness Sharp of Guildford: Professor Williams, I take it that you do not fully agree with that.

Professor Williams: I would distinguish between the professional engineer who wants to innovate and the senior technician who will get on with the job.

Baroness Sharp of Guildford: The HND-level technician?

Professor Williams: As it were, yes.

Baroness Sharp of Guildford: Who do you think should train those?

Professor Williams: That is an interesting question. It is an uncomfortable role for conventional academic institutions in the current model, but it is a requirement in this space.

Baroness Sharp of Guildford: It could be the college sector through the FE sector. Do you see any collaboration? For example, at Loughborough are you collaborating here and helping to train?

Professor Williams: We have not made that step yet. Perhaps Keith and I should do a deal and do that.

Keith Thompson: May I add to this?

The Chairman: Please do.

Keith Thompson: The sector in cell therapy is a similar sector to that in general biomanufacturing, and the UK has rich talent in that space. I am talking higher up the value chain rather than at the technician level, but I shall come back to that.

I cannot go out right now and hire an experienced biomanufacturing or cell therapy professional very easily who has done it all—who has taken something all the way through to the clinic—but I can go out and hire experienced people from the bio-industry who have done it for biologicals. I can make a mix of those people, with researchers—like those at post-doctoral training centres—and others, and put them together so that they get that value.

One of my objectives is not only to output therapies and the technologies that support therapies but to output people as well. A three-year stint in the Catapult, as therapies move through, should provide cohorts of leadership for the industry as it emerges. I would be very confident that by working hands-on, and by working with Loughborough, UCL and similar places, we will build that cadre of professionals.

The second bit is that, by analogy, for training technicians for the bio-industry there have been many courses set up around the country over the years, precisely in the FE sector, and they have been largely successful. So there is a model to build on from there.

Q276 Lord Dixon-Smith: I want to pick up on something that Baroness Sharp started pushing towards. In global terms in this country, we are a very tight, small community, but, of course, we tend to live in tight, small communities within it. I find myself wondering whether we do not have almost a national psychological problem—I have seen this in other fields—where people do not recognise sufficiently that they are in fact all working together on the same problem and they would have a huge amount to gain by working more closely together, even though they may be in disparate institutions. Partly this has to do with what I would call the imperial nature, which we all suffer from, of our own and our institutional independence and everything else. It seems to me that this is an aspect, particularly in this area, where there should be a much more intense recognition of the benefits of co-operating. It does not mean that you all have to be in one national organisation but simply putting all the work together so that everybody understands what everybody else is doing.

The Chairman: Do you wish to comment?

Keith Thompson: Yes, please, I would like to. There were many first things that I had to do when I started, because there was just me and a mobile phone, but one of them was to reach out to the community and try to establish those sorts of relationships with academic partners and industry. For example, we are due to sign with Loughborough a memorandum of understanding to co-operate on the development of manufacturing technologies. Similarly, I expect to do that with other leading centres around the country. They have all been receptive to working in that fashion. It has been marvellous, really, because I do not feel that we have had to climb up a hill to do it. The reception has been terrific, frankly.

The Chairman: Professor Williams, would you like to respond?

Professor Williams: Lord Dixon-Smith, I hope that you recognise that we are all working together, but there is a very important stakeholder here, because it is a regulated space subject to GMP. The key part of that family that needs to come together is the MHRA, so

we have had significant interactions with very senior MHRA officials in terms of understanding and trying to work out how we can work together with the community.

One of the strongest recommendations that you could make for us is to strengthen that bridge with the regulator and ensure that the regulator has sufficient resource to allow that bridge to be built. That would be a very important step to resolving and tackling some of the opportunities we have.

Q277 Lord Broers: Mr Thompson, how are you setting the strategy in the Catapult? One of the visions for these Catapults was that industry should play a major role in setting the strategy for the Catapult. It should be done with the academics alongside, but the major driver should be industry. Is that the case for this Catapult?

Keith Thompson: Yes, it is. When I was recruited, there was an industry advisory group. On it were Dr Ruth McKernan from Pfizer and Michael Hunt; I think that they have all appeared here. There were also people from GSK, JNJ and Cancer Research UK. In the development of the strategy that was signed off just recently, they assisted in that and fully endorsed it.

Lord Broers: Are they investing in the Catapult?

Keith Thompson: I hope that they will eventually, yes. Through collaborative R&D, we would expect that. Without breaking confidences, there is dialogue with some major pharma at the moment around both collaboration and potentially contract research, but they do not invest as financial investors.

Lord Broers: I do not like the idea of it being contract research. I thought that the idea was that industry did some of the important research within the Catapult—not contracting the Catapult but becoming deeply involved in it and making it a major part of their research platform.

Keith Thompson: That is right. The funding model that the TSB have is essentially to have three streams of work. They have gone out and analysed what works best in other fields. One thing that they have come back with, and we are applying it, is that persistent core funding is required. The core funding that comes in is about a third of that. Another third comes through collaborative R&D, which is precisely the sort of R&D that you are talking about. The last third is contract R&D work, where industry wants us to crack a nut for them. That is the strategy, not just for the Cell Therapy Catapult but for all of them.

Q278 Lord Willis of Knaresborough: There are two things following on from Lord Broers's comments. When we were in California, the one thing that really struck me was that at the very early stage, literally at clinical trials stages 1 and 2, they were bringing industrialists in alongside the academics to develop and commercialise that. Is that something that you struggle to do, or is it something that you are managing quite easily? My second question to you specifically, having just looked at your database of clinical trials that you are supporting, is that only one of them is in fact using embryonic stem cells.

Keith Thompson: That is right.

Lord Willis of Knaresborough: I wonder whether there is a strategy, or is that just the luck of the draw if there are people coming forward?

Keith Thompson: The first question is how we are getting on with bringing industry in. Of course, the industry is quite small in the UK at the moment. We are in dialogue with all of

them and we would hope to be able to announce in the next month or so at least two deals with industry. Bringing them in is happening. We see the SME space as struggling for finance; there is no doubt about that. Therefore, working with them on their problems is extremely important, both to get them over hurdles and to trigger further investment for them.

In relation to ES cells, to be clear, the database is just the database of what is going on now. We have not invested in any trials yet, but we will. This is a legacy issue of what is actually out there.

Q279 Lord Patel: To follow on, and to be quite clear, you said that there was you and a mobile phone. Is that all that there was to Catapult?

Keith Thompson: No. Oh, no, no. We have negotiated the lease and moved into Guy's Tower, on the 16th floor. I have recruited a chief clinical officer, a chief operating officer, other staff, board, plans—the lot.

Lord Patel: The second question was related to you saying that the number of commercial companies is small in the UK. If you believe that we have strength in research that will be taken forward to clinical phase trials, then we urgently need industry to get involved. That means enticing foreign companies to come and work here. How are you going to do that?

Keith Thompson: Getting inward investors is a key part of the strategy. Inward investors can go anywhere, frankly—science is good all around the world—but they require to be helped through the system. What I observed happening when I was running the Blood Transfusion Service in Scotland was potential inward investors developing a good relationship, actually being guided through the regulatory system, which is complex, being introduced to clinicians and being helped on how to get their products into the UK—for instance, part manufactured in the US, thawed out in the UK, and delivered to a patient.

Part of the model that we are setting up to deliver this is to reproduce that sort of environment, whereby we can direct them and help them find the right manufacturing partner, open up with the right clinical centre to deal with their specific disease type and, with a regulatory and clinical trials department that will be sizeable, help them design their studies. By binding them into this network, our objective is to make the UK the go-to place in Europe for cell therapies for inward investors. Again, we will be announcing the first of those inward investors immediately after Christmas.

Q280 Lord Rees of Ludlow: Lord Patel has already asked the question that I was concerned about, which is how you make it attractive for international companies to invest here in Catapult, rather than in Singapore or the US. Is the regulatory framework a deterrent, or do we have advantages to offer?

Keith Thompson: We certainly do have advantages to offer. Frankly, one of the greatest advantages, and one of the greatest difficulties, is the NHS. The NHS as a potential partner to delivering clinical therapies cannot be understated. The Government initiatives to make it easier and faster to carry out clinical trials are something that we welcome, and we intend to leverage them not only for UK indigenous companies but also as a mechanism to draw in inward investors.

The Chairman: I wonder whether Dr Newble has any comment to make.

Dr Newble: The only thing that I wanted to add to the discussion was that the Committee should be careful about believing that there are a lot of overseas companies willing to invest in this space. We do 95% of our business outside the UK, and the problem is the same the

world over. There are not that many companies investing in regenerative medicine, so support from the Government is needed to help get the therapies forward so that companies can invest. Then they will choose the places, but at this point there are not many anyway.

The Chairman: Professor Williams, do you want to add anything?

Professor Williams: Just to return to the NHS a little, we are operating in a country dominated by a single reimburer. That is characteristic of a number of economies, like Canada and Australia. Another place to have on your radar is Toronto, because there is a significant amount of clinical trials going on in Toronto, in terms of its regional leadership and the way that it is using its cluster, to drive both adoption and innovation forward. In Canada, it is a very important target for us to keep watching.

Q281 Baroness Sharp of Guildford: Can I pick on the NHS, and the training issue? We have had a certain amount of evidence that has indicated to us that there is a lack of understanding on the part of NHS R&D staff due to lack of training—for example, leukaemia and lymphoma research said we need to train doctors and nurses to understand stem cell therapies and the process of clinical trials. If we are going to use the NHS, run clinical trials successfully and so on, have we not got to train the NHS staff? Who is going to train them?

Keith Thompson: There is an enormous investment going in through the NIHR—it is certainly hundreds of millions—precisely into this space, where they employ about 3,000 nurses directly to operate in the clinical trials space. The right intentions are there with the NHS, but the key thing is to establish and work with the clinical champions who want to do this. If you have the right clinical champions, and they are given enough space and time to work in clinical research, then you can have this close working relationship that makes things happen. That is the key to it.

When I was in the SNBTS—I apologise that I keep going back there, but I learned so much about how the NHS works from being an insider rather than knocking on the door from the outside—the clinical relationships are absolutely key. In a way, I want the Catapult to be able to work as a quasi-insider in the system, to try to help companies form the relationships and funnels into the clinic. If the Catapult, for instance, works in the ophthalmic space, we will develop those relationships, those pro forma ways of doing things, and we will then be able to offer them to other companies, whether they are UK companies or potential inward investors.

The Chairman: Lord Winston, did you wish to pick up on that?

Q282 Lord Winston: I really wanted the corollary to the first part of the question about the NHS. You argued that the NHS was a great advantage. In a nutshell and just the rest of that sentence, I wonder what the disadvantage is, where you fundamentally see it as a problem.

Keith Thompson: Fundamentally, I believe that, some 20 years ago, something like 15% of all trials in the world were done in the UK. It is down to about 3% now and creeping up. The disadvantages are that it is a bit of a monster to deal with. It can be bureaucratic and, frankly, it can be tough on the clinicians who are trying to deliver these therapies in addition to their day jobs.

Professor Williams: May I add a comment? One of the things that we can do is to give a clear point of contact in the commissioning activity. One of the things that will unlock this is

an understanding of value and price. If you could have somebody within the NHS who had an overview of the commissioning process for cell therapies, that would assist the whole activity very significantly.

The Chairman: We are drawing this session to a close, so I would like to thank the three witnesses very much indeed for their evidence. You will receive in due course a transcript, and that will enable you to make minor corrections to the evidence as you see it written down. We were promised certain documents in follow-up by Keith Thompson. With that, I draw this session to a close. Thank you very much.

European Medicine Agency, Health Research Authority and Medical and Healthcare products Regulatory Agency (MHRA) – Oral evidence (QQ 295-316)

European Medicine Agency, Health Research Authority and Medical and Healthcare products Regulatory Agency (MHRA) – Oral evidence (QQ 295-316)

[Transcript to be found under Medical and Healthcare products Regulatory Agency \(MHRA\)](#)

Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, and Professor Michael Linden, King's College London – Oral evidence (QQ 1-20)

**Professor Charles Ffrench-Constant, University of Edinburgh,
Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks,
King's College London, and Professor Michael Linden, King's College
London – Oral evidence (QQ 1-20)**

Evidence Session No. 1 Heard in Public. Questions 1 - 20

TUESDAY 30 OCTOBER 2012

10.40am

Members present:

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
The Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Professor Charles Ffrench-Constant, Professor of Multiple Sclerosis Research; Director; Theme leader Neural Differentiation and Tissue Repair, Centre for Regenerative Medicine, University of Edinburgh, **Dr Ludovic Vallier**, Stem Cell Institute, University of Cambridge, **Professor Steven Sacks**, Professor of Nephrology; Head of the Division of Transplantation Immunology and Mucosal Biology and Director of the Medical Research Council (MRC) Centre for Transplantation, King's College London, and **Professor Michael Linden**, Professor of Virology, and Director of the University College London (UCL) Gene Therapy Consortium, King's College London, gave evidence.

Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, and Professor Michael Linden, King's College London – Oral evidence (QQ 1-20)

Q1 The Chairman: I would like to welcome our panel of witnesses. This is the first oral evidence session in our inquiry into regenerative medicine. I would like to remind all members of the Select Committee to declare relevant interests before they first speak in the inquiry. The declared interests have been published in the public information sheet. I would like to remind all of those in the room that the meeting is being webcast and therefore sotto voce asides will be broadcast. The broadcasting system often remains on after the end of the session, so be alert to that.

In the first of the two witness sessions that we are holding today, we are very much interested in seeking your views on matters relating to the quality of the science base in the area of regenerative medicine in the UK and how that science might be applied to treating clinical conditions. You have seen some of the questions that we wish to explore with you. Before we kick off with the questions, I would like to invite each of our witnesses to introduce themselves for the record. If there is anything you want to say as a preliminary matter, please feel free to do so. Keep your comments brief because we have quite a lot to get through in the next hour or so. Perhaps I could start with Dr Vallier; please, introduce yourself.

Dr Vallier: I am Ludovic Vallier. I am a Reader in Stem Cells and Regenerative Medicine at the University of Cambridge. I am also the Director of the NIHR/BRC hPSC (human Induced Pluripotent Stem Cells) Core Facility.

Professor Ffrench-Constant: I am Charles Ffrench-Constant. I am Director of the MRC (Medical Research Council) Centre for Regenerative Medicine in Edinburgh.

Professor Sacks: I am Steven Sacks. I am the Director of the MRC Centre for Transplantation, which is at King's College London.

Professor Linden: I am Michael Linden. I am a Professor of Virology at King's College London and the Director of the UCL Gene Therapy Consortium in London.

Q2 The Chairman: Thank you very much. Perhaps I could kick us off by asking each of you in turn to comment on how the UK ranks internationally in research in regenerative medicine and, particularly, what you think are the strengths and weaknesses of the UK compared with other countries. Perhaps, Professor Linden, you could kick off and then I will work along the row.

Professor Linden: First I would like to qualify that what I have to say is probably relevant to gene therapy in particular, which has gone through some developments through which other areas of regenerative medicine probably will go. I have spent a considerable amount of time in my career in the United States and can make something of a comparison in my area between the UK and the United States. I must say that the potential for the field of gene therapy here in the UK is extraordinary. That is based on several aspects which I think should be considered: for example the NHS, which makes it easier to translate clinical studies than in the private environment, in which different sorts of funding need to be found; probably even more importantly, the per capita impact that UK scientists have compared with the rest of the world—I mean UK science and biomedical science in particular—is very high. If you take these two things together I think this is a very fertile ground for the development of novel therapies. It is in a certain sense a unique environment, which should be and is being taken advantage of currently.

Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, and Professor Michael Linden, King's College London – Oral evidence (QQ 1-20)

Professor Sacks: My main interest is transplantation—but beyond solid organ transplantation. Some of us, where I work, have been thinking very carefully about how to transplant cells and make them successful. There are a number of models and actual examples of clinical practice or experimental medicine. I have seen what happens there. It is quite interesting because the history of transplantation is exactly that which is happening with cell transplantations at the moment. There is an initial wave of success but then the limitations become apparent; it is so obvious—always in retrospect—to know what sort of monitoring systems should have been in place to try to learn from experience and build along the way. It is terribly important to make sure that these systems for monitoring and interventions are there right at the beginning. Although I am talking about the transplantation of adult cells, the same thing would apply to some stem cells or poorly differentiated cells as well, so I think that is really important. The potential—as I see it, which is partially from the outside—is very great.

Science in this country has always been terrific; the exploitation of it has not been so great. What I feel is needed is a real quantum leap, which is major investment. There are examples of how this has helped: for example with the human genome, which helped us to be alive and stay competitive. From reading documents, I have a flavour of what we want to be as good as, but if we actually want to lead and dominate, which is a good starting point and a good target, then we have to do something really radical. I know there is a lot of talk about networks, but investment needs to be explored beyond that: having big centres where all of the facilities that we have thought about and heard about can be properly integrated.

Q3 The Chairman: Is that about more resource or about different deployment of the same envelope of resource?

Professor Sacks: Ultimately it is more resource but it is an extension of what I have seen already proposed. Networks and hubs are terrific, but there still needs to be some physicality of colocation for the UK to be a really tough competitor of the US.

Q4 The Chairman: You mean that more concentration than is going on is required.

Professor Sacks: More concentration than is going on is needed—and a real magnet to pull people in, as well.

Professor Ffrench-Constant: The question was, “How good are we and what are our strengths and weaknesses?” How good are we? We have a reputation for being outstandingly good at developmental biology and stem-cell biology. We also have outstanding clinical academics, although that is quite patchy. To try to put some sort of metric on this, though, is quite difficult because citation rates tend to be quite historical. What I did was look at the number of invited speakers to the major international meeting, which is the ISSCR meeting, that is held every year. At the first ISSCR (International Society for Stem Cell Research) meeting there were four out of 45 UK speakers and a decade later, in 2011, there were only four out of 109. Worryingly, many of the four were the same as the ones who had spoken 10 years earlier. At the meeting which has just happened in 2012 there were still only 10 UK speakers out of 157 talks. I think we are perhaps being complacent if we think that our expertise in stem-cell biology is leaving everyone else behind. We are clearly up there with many of the European nations and Japan; the US is obviously the major player.

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In terms of weaknesses, I would agree with the comments of my colleagues. I think there are weaknesses of scale. The regenerative medicine projects largely need to be multi-component; they need to be highly organised. This is a very long endeavour and the rather fragmented and short-term funding arrangements of the UK do not lend themselves to this at the present time. There needs to be a much greater degree of cohesion. I would agree that there needs to be more colocation but there also needs to be more cohesion between the different groups. Part of the problem here is leadership. Academic leadership by its very nature is all about influence rather than power. That often makes it quite difficult to corral people into a very business-orientated model, which regenerative medicine probably needs. I think we need better leadership from pharmaceutical companies coming down into academia and also within the academic community.

Finally, it is very important that we have long-term funding strategies. Three-year or even five-year funding cycles are just too short for this endeavour. I see that as a current weakness.

Q5 The Chairman: To come back on those figures you gave for invited speakers at the international stem-cell research conference, looking at those figures as you gave them, it looks as though that, if anything, on that indicator we are slipping backwards. Is that too pessimistic?

Professor Ffrench-Constant: It would be unwise to read too much into the variation, especially as the geography of the meeting inevitably reflects the balance of the invitees, but I think that in the round they show us that we are definitely not number two behind the US.

Q6 Lord Broers: On this particular topic, if we had 10 papers out of 157, does the ISSCR include industrial application papers as well as science ones and, if so, what was the balance of our 10?

Professor Ffrench-Constant: The ISSCR does include a large number of sessions. I feel a little disconcerted with one of the ex-Presidents sitting here. It does include industrial sessions but I have not included them in my listing; I have simply selected the academic or plenary sessions. There was relatively little industrial input into those sessions.

Q7 Lord Patel: I think Professor Ffrench-Constant would agree that using the sole metric of how many speakers were at the ISSCR international meeting is not strong enough to suggest where the science of the UK is.

Professor Ffrench-Constant: I would completely agree; it is extremely difficult to find metrics. Those metrics should obviously be taken along with the well established metrics of citation rates and things like that. My point was that citation rates do tend to be biased by what happened some years ago. I was trying to find a way to bring to the attention of the Committee a current snapshot. Like any metric, there are many weaknesses and I would not wish to overplay this.

Q8 The Chairman: Could I move on, then, to Dr Vallier?

Dr Vallier: My field of expertise is human embryonic stem cells and human induced pluripotent stem cells (iPS). My comment will be focused on these aspects. I think that clearly the UK is in the top three countries in terms of basic research in this field. The US is first because of its sheer size and the resources that are available there, but I think we

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cannot be complacent because Japan is advancing strongly, especially on iPS and translation. There are also other countries like France and Germany that are doing very well in terms of translation and bringing applications into clinics. Clearly, the excellence of basic research in the UK is based on the environment, a long tradition of funding and the culture of research into stem-cell and developmental biology, which has created a unique network of knowledge and expertise. This means that the UK really is one of the top leaders for basic research.

The weakness, in my opinion, is clearly the translation of this basic knowledge into direct benefits for the patient, which needs to be reinforced, especially in terms of the transfer of this basic knowledge into a clinical product. That is a global challenge; it is not unique to the UK. It is a global challenge for any country that is working in this field, but that is clearly where there are some needs currently.

Q9 Lord Rees of Ludlow: Professor Ffrench-Constant referred to the short-term nature of funding: three to five years. Is that an MRC or a Wellcome Trust issue or anything that we could make representations about?

Professor Ffrench-Constant: Yes. That is obviously an issue for the funders of the Wellcome Trust and the MRC. I think it would be valuable to convince them that longer funding cycles for more ambitious regenerative programmes would be of value.

The Chairman: We will be able to ask them about that when they come to give evidence to us.

Q10 Lord Patel: My question leads away quite nicely from the first question. It is related to it, really, and I would like, if possible, for each of you to answer, for each of your individual areas of expertise, as to what regenerative treatments are currently available, for which diseases. Looking further ahead by five or 10 years, in which areas do you think we are likely to succeed, in your own particular areas of expertise?

Dr Vallier: Clearly, for human embryonic stem cells and human iPS we are at a very early stage of clinical development. We are at the first in human clinical trials. The first clinical application in place is for macular degeneration. Several trials are currently in development for cardiovascular disease and skin disorders, especially in France, and the next round of applications will definitely be for neurodegenerative diseases. My particular interest is liver disease; in the next five to 10 years we ought to be able to do the first clinical trial with human ES cells for liver disease. There is also a very strong push for type 1 diabetes in terms of transplantation of beta cells generated from human embryonic stem cells.

There is a broad panel of applications for human ES and human iPS. Clearly, human ES will come first because in terms of safety and validation there has already been a lot of work done on those cells and iPS still requires more systematic studies. What is important is that there is not one kind of stem cell for every clinical application. There will be a panel of stem cells for a diversity of clinical applications. Human ES cells probably have a broader potential, but other stem cells will be extremely important in the therapeutic panels that will be available.

Q11 Lord Patel: Can I ask if you think there are any stem cell therapies available now for any of these diseases?

Dr Vallier: Yes, haematopoietic stem cells, limbal stem cells and also mesenchymal stem cells are starting to be widely used. Yes, there has been clinical application for a long time.

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Professor Ffrench-Constant: You asked what is currently available. The first thing I would like to say is that there are almost no regenerative drugs available, which I think is a critical long-term goal—medicines that one could actually take that would promote regeneration. There are, as we have heard, a number of cell-based therapies available but it is very important to split them into two groups based on how they might work.

There are the rather small number that are directly addressing the question of cell replacement, where you are directly replacing a damaged cell—like macular degeneration, as we heard about, or using haematopoietic stem cells for bone marrow transplants and limbal stem cells for corneal repair. However, a lot of the mesenchymal stem cell trials that are being done are not cell replacement trials. They are just exploiting the useful properties of these cells in immunomodulation and in protecting other cells within the tissue. I worry that this will limit their long-term use. Ultimately, it would be better to use a drug that had the same effect.

Moving on to what the promise is over five to 10 years, which I believe was the second part of your question, obviously I think cell therapies will become increasingly widely used. I think there will also be a growth in the device industry that effectively provides devices where these therapies can be prepared without requiring vastly expensive GMP (Good Manufacturing Practice) facilities in which to grow them. I think that true regenerative medicines will come through. There are targets which the pharmaceutical industry is currently working on. It is realistic to think that they will come to the clinic over a 10-year timescale.

There is one other thing I would like to highlight, because it often gets forgotten. There is an enormous potential for cell-based platforms for drug screening and toxicology studies using the technologies of regenerative medicine—using iPS cells as disease models or ES cells as a source to generate very large numbers of human cells. The hope is that this will reduce the numbers of drugs that fail in late-stage trials.

Professor Sacks: There are some interesting things going on. I think mesenchymal stem cells for transplantation have produced astonishing first results. We will have to see how well they can be extended. That has a lot of mileage and we will see development in that area. There are other areas in which that can be exploited, because, as you have heard, these cells were studied—we have studied them; other people have studied them—and it was expected to see them to trigger an immune response or a rejection response but these stem cells did quite the opposite. They are useful for suppressing the immune system. You may see that this type of therapy may be useful for other types of transplants to provide immunosuppression. That is how they have succeeded in a particular problem with bone-marrow transplantation. Other people have mentioned islets and hepatocytes as well. They show this initial remarkable success, but people are scratching their heads at the end of two years wondering why they have failed. Once again, they will develop and there is no reason they should not make a step change over five years, providing the right sort of monitoring and interventions are available to deal with them right from the start.

I know in the broader definition of regenerative medicine that we are talking about, molecules that aid stem-cell and cell therapy are really important. Those are there already. They have not really been considered in this background literature, but it is possible to biologically modify stem cells and other cells like these things we are talking about here with islets and hepatocytes, so that they will get past the first stage of recognition by the host. It is really important for all stem cells to be able to implant in particular numbers so that they

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overcome the inflammatory response, which in some cells is inevitable. There are ways to manipulate cells now which can be broadly applied.

It is an interesting thing about transplantation—which I think we will be seeing in stem cell therapy as well as with the things that have been mentioned—that if you can actually get cells to embed at this very early stage, it is very likely that will be evident as a very late impact. In other words, if you do something for the first 24-48 hours to a stem cell to make it more acceptable, that benefit will be seen later on, after the use of these stems cells, let alone having to tackle the immune response, because we do not know whether the immune response will be a problem. Rejection certainly is not a problem for the cells you start out with but, as they differentiate and replace the tissues they are intended to become, it may well be that this rejection, the recognition of foreign tissue in the midst, is more of a problem. I have used that as a vehicle to talk about technologies that have to go alongside these real, concrete examples of things that do exist¹⁵⁶ and hopefully we will develop over the next five to 10 years.

Professor Linden: To answer your question directly, for a front-line clinician, I do not think there is a therapy currently available that is based on gene therapy. That needs to be seen in the context of where this field is. If you look at the maturity of different therapy approaches, small-molecule approaches are probably the most mature ones—the pills that we take every day—and the next one might be antibody-based treatments and then cell-based treatments.

To a certain extent, gene therapy is very immature, if we are looking with respect to its application for a front-line clinician. However, if we are looking at it from a scientific point of view, we have to say that there are very many applications that are at the proof of principle stage in patients after the early clinical studies—Phase 1 and Phase 2 studies. Quite a few of the prominent ones actually came out of the UK; for example, there was a haemophilia study which was published in the New England Journal of Medicine last year; eye disease studies have been published by Professor Robin Ali here in the UK; and, not to be forgotten, Professor Adrian Thrasher's excellent SCID immunodeficiency trial—all of which actually show clinical benefit.

The question—and this question was very well put—and, perhaps, the challenge to this Committee and many other people will be, “How can you make this proof of principle into a front-line therapy?” I think that probably will involve funding bodies such as the MRC and collaborative approaches with pharmaceutical and small biotech companies to actually make this happen. In my view, in the area of gene therapy this is one of the challenges. The proof of principle is there. In terms of proof of principle the UK was leading, together with institutions in the United States. Now the question is: “how we can make these into actual drugs?” I think there are many aspects that can be discussed in this area.

Q12 Lord Cunningham of Felling: There has been some criticism or argument that in the UK our great strength is in basic discovery science rather than in translational science or in converting what we discover into a practical application. That is not restricted to your disciplines; it is a general criticism of fundamental scientific research in this country. The Government has produced its view on this via BIS and they outlined some long-term actions for Government: to reduce the regulatory burden, to effectively fund and promote research.

¹⁵⁶ Note from witness: transplantation of islets and hepatocytes.

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Do you agree with that or have you different views about that? What are the problems? What do you identify as the problems which prevent this translation from the excellent—world-leading in many cases—basic research into a practical application or into products from pharmaceuticals or wherever else?

Professor Linden: I will begin; I am sure there is much to be said after this. In the field of gene therapy at least—maybe it is restricted to this field—the development or translation of bench research into clinical application is a very complex continuum that employs the researcher in the beginning and the pharmaceutical industry at the end stage. The point is that if some of the components in between are not in place and supported well, the end stage will not even begin to engage. In the field of gene therapy right now, sometimes I act as a consultant to pharmaceutical companies; maybe you should ask these people as well, because they are getting ready to get engaged in this field.

For example, the numbers are out there: in 2015, the value of the global gene therapy market could be as much as \$300 million. It is only in the very early stages. Yet these companies are positioning themselves to engage but are not quite ready yet to do so. I think the challenge will be to identify how to ensure the continuous development of a particular therapy from a promising proof of concept into a viable drug, which ultimately will involve very innovative pricing strategies. How do you price a gene therapy for which you have a one-time treatment that might save you a lot of money later on, but on which the person who produces this has to spend a lot of money to get engaged into the development of? How do they get reimbursed? These types of things will ultimately have effects.

In my microenvironment in gene therapy, I see these effects already because you need a lot of a lot of upfront funding, for example, to make a clinical-grade GMP viral vector. This is a very complex production. This upfront funding is not necessarily there; it needs to be gained through, for example, the MRC or the Wellcome Trust, which has, in a limited manner, invested in these types of things. However, early-on engagement of commercial partners will ultimately also be required to make a drug out of an investigative product.

Q13 The Chairman: We are actually moving on to the question of barriers to translation. Professor Linden has given one answer; perhaps I could ask the others to pick that up as well. What are the barriers to translation?

Professor Sacks: I think, Sir, the great case that is quoted is monoclonal antibodies. Even then, one might argue that development has not happened quickly enough. I was involved at an early stage and it was the vision of the inventor that drove it. It was a basic scientist who discovered this technique by accident, ran with it and wanted to be involved in what we now call its translation or application, as has been referred to.

Certainly, vision is important. It is not just the lack of investment and money. I do not think that is the primary problem. If there is a vision that can inspire people that there is something real to be developed, money will follow because people will listen. I would not put that as the primary problem but it is always a problem. He was not put off by barriers that did exist.

We have a discontinuous system. Historically, we have our education system and universities; and we have a health service. They are separate and there are means of bridging the two through bridging funding, which is absolutely fantastic, but there is still a cultural barrier. There is still a gap in actually moving something out from an inspirational beginning to something which is picked up and shared as a vision by the people who eventually use it. That gap is closing and that is certainly important. We are stuck with a

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dual system. It is probably too late to change it, but had we time all over again I can see obviously we probably would have a single system, employer and set of rules, rather than the one extreme of people in universities working on basic research and the other extreme providing health and not really involved in research.

The point I am trying to make and probably will finish on is that context is very important. The fact is that basic science is going on and it is important for these people to see this context—even if they do not wish to push it themselves—once they have got something really interesting. It is being in that context and finding someone to hand over the baton to so that the race is completely finished.

I think there are more restrictions than just that to moving research on. It is also about knowing the right doors to tap on. One can spend years trying to find the right sort of support and the right processes to help with this, because all of the processes and support, in my experience, can take years and years to materialise. The whole process of translation needs to be radically thought through to see if there are areas that can be speeded up. I do not just mean by funding, but by process.

Those are some of the issues and again—sorry, I will stop here—the organisational model is very important. Do we want something where we really believe in virtual networks across the country? Is that realistic? Do we want geographical co-location, so that we can pop in and out of each other's offices and actually bring something together and inspire each other? I think that model is very important.

Professor Ffrench-Constant: I would identify five barriers. In fact, this picks up on what has already been talked about. The first one is partnership; translation really does require partnership. The pharmaceutical and biotechnology industries need to partner with the academic community very strongly to provide the necessary bridge. To be honest, I do not see that happening in the UK to the extent that I see it happening with my colleagues in Germany or the US. I think there are real issues there.

Second—going back to Professor Sacks' point about organisation—I do think this is a major problem. The academic community has historically organised a lot of quite small, self-sufficient groups, which is very good for academic excellence but much less appropriate for product development, which is what we are trying to do here. There needs to be quite high-level strategic leadership to persuade these groups to coalesce into a pathway.

Thirdly, there is regulation. This is something that we have talked about before at another time. The regulations are very difficult, but I not only want to highlight the regulations around human cells but also regulations about the use of animals. This is a major problem for us. Translation often requires being very fleet of foot in terms of the experiments that you want to do to get the major publications which interest the companies. At present, if you have to do an experiment which you have not thought of in advance, which is obviously what happens in research, you need to get your animal licence amended and that can take a very long time indeed. That is a significant delay in the process and one that needs addressing very urgently.

Regarding funding, I would agree. The problem with funding is not the amount of funding; it is the way it is being used. I have already talked about that. Finally, regarding people—and particularly clinical academics—we talked about the gap closing between academics and the NHS. The way in which that gap will close is by increasing the clinical academic community. At the moment it is still too small in this field.

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Dr Vallier: I fully agree with what my colleagues have said. Clearly there is a gap between what we can create in the lab and what needs to be done in clinics. The transfer of a prototype into a clinical product is the main challenge, especially with really innovative medicines like embryonic stem cells or iPS, because basically we do not know what we need to do to reach the clinic. That is really where I think the problem is. We are creating innovative approaches with an unique knowledge and expertise which are complicated to apprehend by regulatory agencies.

Lord Winston: I will come back on a point that both Professor Sacks and Professor Ffrench-Constant have made, which I think is relevant. More and more universities and particularly medical schools have been increasingly exercised by the need for the Research Assessment Exercise. Constantly, a large number of clinic-based departments are being effectively run by non-clinicians, by scientists. Very often, the clinical aspect of the work is in some ways relegated and that vision is absent. Do you think that this has been a problem in trying to get clinical academics to run departments where you can see translation being thought about during the stages of the research?

Professor Sacks: That is an important point. Just to be very specific about it, this business about health-economic assessment is really important, though I would call it prediction rather than assessment. In other words, health-economic cost is usually associated with a fairly advanced clinical trial to see how much it saves and so on, but if one actually tries to go back to the pre-clinical work, to put some sort of scale and value on it, that will actually help to define some of the experiments and the development that will follow. That is looking back, trying—almost like a stock market—to put a price on something before it is actually known what the price is. This is important in terms of its interest and development. That is probably one example of the sort of thing you were talking about.

Professor Ffrench-Constant: You asked the very specific question about clinical departments led by non-clinicians. This is a real issue and, of course, one of the major reasons why this happens is because the clinical workloads are so great for clinical academics that they simply cannot do the very large administrative and leadership roles effectively. The solution is basically to allow them the time. In Edinburgh, I think my bosses do this very well. If you do that, then you can actually get clinicians leading basic science institutes and, I would argue, doing so rather effectively with the respect of both communities.

Q14 Lord Turnberg: Professor Ffrench-Constant, you have set out the barriers very nicely. I wonder if you would like to offer some solutions.

Professor Ffrench-Constant: That of course is a much harder question. We need to devise mechanisms to persuade the pharmaceutical and biotechnology industries to invest earlier in academic products, for which we need a clear awareness in the academic community of what is and is not of potential value to them. We have to both persuade the pharmaceutical and biotechnology industries to invest—one way to do that would be more mechanisms of targeted funding such as that which the TSB provide. Finally, we need to train our young academics to think much more about how you might form links with Biotech and Pharma effectively.

Q15 Lord Broers: The specific question that I am asking is whether you can give positive examples of interdisciplinary work. Is there sufficient collaboration between clinicians, scientists and engineers? If not, how could this be encouraged? We have really been

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discussing this to a certain extent, but I would make an observation. In my world of the physical sciences—I am a microelectronics engineer—the transfer from research to practice is very often done by the people doing it. Scientists can be engineers. I have fantastic reminiscences about Andrew Huxley; he was an engineer in many ways. The same people can do things. Scientists can become practitioners. I hear you saying, “Well clinicians are clinicians; there is no way a clinician can really be a scientist, let alone an engineer.” I would debate that issue. Would you like to comment? The specific question—do not forget it—is that we would like some specific examples.

Professor Linden: First, I would like to go back to maybe answering the previous question and slightly giving a comment also to this one. The development of products in biomedical medicine is actually quite complex, obviously, because we are dealing with a human product. There are advanced therapies regulations; there are drug regulations, very often; in many cases where therapies are being trialled there are paediatric regulations that are involved; and frankly, very often authorities and investigators—both sides—are both on a learning curve. In many senses that is a good thing, because if the interaction is there and the discussion is there one can find solutions to these.

Yet the barriers go beyond a single investigator, clinician or scientist. It addresses—at least in the field of gene therapy—many hurdles that come through regulations that were set up not for this innovative type of medicine but for longer-term medicines. There we must have collaborations between authorities and investigators so that can help move this forward.

The second point is that many of the projects—or those that we are involved in, at least—are quite international, so you will have a gene-therapy approach where a hospital in Sweden, for example, might be involved next to a hospital in the UK, which then means there is a convergence between national frameworks that needs to be addressed in order to make such things possible.

Professor Sacks: These are general points; some examples may follow. One issue is alignment, because you could have a stream of money for forming MRC centres to push basic science towards translation and, at the same time, the very fortunate appearance of reorganised NIHR (National Institute for Health Research) funds. If you can actually align them into a single stream, you complete the spectrum of activity, in theory. In practice, I would suggest that it actually works although it probably has not had sufficient time for us to see that.

Secondly, within that sort of framework, even if it does not exist, I think it is important to have what we call workshops and what others call clusters to bring people from different disciplines together: clinicians, basic scientists, information technology experts and so forth; students, even. It is important to bring them together not just in order to have them together for a nice bit of window dressing, but to focus on a particular problem that they are all going to address. It might be to generate some money; it might be to unravel an experimental plan. The more of this that is allowable, the more we will see people working together. It is very important that people from all disciplines have buy-in and are not just going along to listen and make the odd comment; they are part of evolution of the problem at hand. As I say, there are some good examples in different centres where this is already going on.

Q16 The Chairman: Can you mention one example which is a concrete success story of this sort of interdisciplinary process?

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Professor Sacks: Yes. This is an example where, in order to envisage an inflammatory system being activated, the people who were involved in that inflammatory system—called the complement system—coupled up with people in imaging sciences who had never really thought about transplantation before. The object was simple: to try to devise a new imaging method with a camera held outside the body to see when this system lit up in the tissue when the inflammatory system became activated. With help from the cloning of molecules, this has resulted in a new system that can be used to identify this activation. This has become possible. It is still in animals, but it is ready to be transferred to man. There are other examples, as well.

Professor Ffrench-Constant: Where we are trying to repair a complex three-dimensional structure, interdisciplinarity does become particularly important because we effectively need engineering approaches to either interrogate our therapy or indeed guide it. I point particularly to substrate engineering and also to advances in imaging as being very successful examples of interdisciplinarity in this field. I think that has worked very well. There is an enormous need for much more of it, but seems to me that this is something where the community has appreciated the importance of working with chemists, physicists and bio-engineers, and is doing so quite effectively. There is an outstanding bioengineering group at Imperial College London; that would be an example of people who are doing fantastic work in this area.

Going back to the specific point that was raised, “Why do scientists not get out there and do the business?”, I completely agree with you. My observation, though, would be that those try to do that have to spend so long on the process of trying to get their business off the ground and keep it alive that their science suffers very badly. As a Centre Director, this is something I worry about a lot. I see very bright young scientists that I have in the centre trying to start companies and spending so much time having to work on that company that it definitely affects their primary scientific output.

Dr Vallier: To give you an example of multidisciplinary activity, in Cambridge we have a strong, tight connection between clinicians and biotechnologists. We worked together to show that we can for example hepatocytes for personalised medicine using iPS. At least, what works very well is training of clinicians during their PhD in the stem cell and academic lab. That has developed a very strong interconnection and very strong knowledge. The key problem is that being a bioscientist and a clinician is doing two full-time jobs. To be a leader in one of these fields means that you have to spend all of your energy on one specific job. That is the key problem.

We see these discontinuities. The stem cell field is such a competitive and aggressive field that you cannot just step back from your research for three years, go back to the clinic and hope to be competitive and be a leader in the science at that time. That is one of the key issues: how do you combine your academic life with your clinical life? The translational aspect will not be solved by a clinician who becomes a full-time bioscientist because they will lose their connection with the clinic. They have to remain a clinician at the same time. That is one of the key challenges that I think we are facing at the moment.

Q17 Lord Broers: This is an issue of career development, is it not? Professor Ffrench-Constant, you said you knew a particular scientist. You can be a scientist for 15 years and then you can go and do something else. In many fields, it has been the outstanding scientists who have made the contributions. They do not necessarily have to come back again; life goes on a long time. You can do a lot of things in your life, but you in the medical field—to be a bit contentious—seem to put yourselves very much in boxes.

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Lord Winston: That is because we are continuously learning, I think.

Lord Broers: I think it is the same. If you look at what happened in my field, we went from one transistor to putting 256,000 million of them on one chip. There was a huge amount of science and development, but that was very often done by the very clever people who went on and did that.

The Chairman: Can I ask for just a brief reply, Professor? How do you top that?

Professor Ffrench-Constant: If one had been in science for 15 years and was clearly very established, that is fine. However, when you are two or three years in, just starting your own independent career, and you need your next fellowship in order for the university to give you any form of long-term support, spending half your time trying to set up a company is a very high-risk strategy indeed.

Q18 Lord Dixon-Smith: Chairman, this may be a somewhat tangential question, but I have not heard whether there is—there may well be—a constant liaison with your regulators. I do understand that there is a conflict of interest to a certain extent between what I call pure academia and the financial side of life. If you do not actually have the regulators on side and aware of any potential problems long before they are real problems, you have a very sticky wicket to bat on with both of the other sides.

Professor Ffrench-Constant: I would observe that there is actually a meeting going on today where the community and the regulators are talking. There is certainly a clear understanding of the problems here. When you have a regulatory map that looks like a rather complex underground system, it is actually very difficult to navigate your way through it. I think simplicity is required in order to make these interactions easier.

Q19 Lord Willis of Knaresborough: I have a brief question for Professor Sacks. All of the witnesses this morning have emphasised just how silo-based so much of our approaches to these areas are—both the difference between clinicians and academics and the difference in terms of funding bodies. You mentioned—and I do not know whether it was a slip or I misheard it—that one of the ways would in fact be to pull together both NIHR funding and MRC funding in order to create, as indeed Sir David Cooksey suggested, a single body. Was that a serious suggestion and do the rest of the Panel support it?

Professor Sacks: It was a serious suggestion and it actually has happened on a number of sites. Where the two do exist I think it works very well. It is a logical development, because if you have one packet of money for developing the more basic concept and another packet to bring ideas into practice, then what better way is there than to co-localise them? It is a very efficient way of spending public money, as far as I can see.

Dr Vallier: I would have some concern in terms of how you maintain the balance between basic research and clinical research, because the NIHR have a very clear objective and the MRC have a much broader one, in terms of application and development. I would be concerned that this aspect would disappear if we only focus on a fused NIHR-MRC unit.

Professor Sacks: I was not suggesting it was a total solution, but just as a part of each package – which exists anyway.

Q20 The Chairman: I think we have actually run out of time, so I would like to draw this session to a close and thank our four witnesses very much indeed for their answers. If there are any points that you feel you have not been given time to express, please do feel

Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, and Professor Michael Linden, King's College London – Oral evidence (QQ 1-20)

free to write in and add to your evidence. That would be very helpful to us. In due course you will receive a draft of the transcript for any corrections you wish to make. Thank you very much indeed.

GE Healthcare – Written evidence

Author: Conor McKechnie, Global Public Affairs, GE Healthcare, Corporate evidence submitted on behalf of GE Healthcare

Executive Summary

- Government has taken positive steps to ensure that the significant potential of regenerative medicines is realised in the UK. However, while Government's strategy is a move in the right direction, there are still key challenges to commercialisation.
- To develop successfully, the scientific and clinical communities, investors and financing infrastructure need to communicate better with each other and be closely coordinated for the UK to benefit economically and to develop improved healthcare for patients.
- Patenting is an important mechanism in the development of regenerative medicine. It safeguards the substantial investment made by companies. However, an important balance needs to be achieved between IP protection and access to information for research.
- A strong regulatory system in the UK has supported the development of regenerative medicines well. As other countries continue to invest significantly, the UK has a role to promote and encourage responsible regulatory systems globally so as not to undermine the regenerative medicines industry as a whole.

About GE Healthcare

1. GE Healthcare welcomes the opportunity to provide evidence to the House of Lords Science and Technology Committee's inquiry into regenerative medicine.
 2. GE Healthcare provides transformational medical technologies and services to researchers, pharmaceutical companies, the life sciences industry and healthcare providers around the world. Our broad expertise in drug discovery, biopharmaceutical manufacturing, medical imaging and IT, medical diagnostics, patient monitoring systems, and performance improvement services help our customers deliver better care to more people around the world at a lower cost. Headquartered in Chalfont St Giles, Buckinghamshire, GE Healthcare employs 46,000 people worldwide.
1. The Cell Technologies business of GE Healthcare's Life Sciences division is pioneering the development of new and innovative technologies to help enable the rapidly emerging field of regenerative medicine and cell therapy; these include blood and bone marrow separation products, cell expansion, handling and processing technologies.
 2. Regenerative medicine is one of the most promising areas of emerging technology in medicine, and it comprises a strategic focus area of research and development, investment in talent, infrastructure and commercial business development for the company. Whether working with multipotent cells from adipose tissue, bone marrow, peripheral or umbilical cord blood, or pluripotent embryonic or iPS cells, processing and sometimes growing them for use by clinicians for therapeutic purposes, the regenerative medicine community can rely on GE Healthcare's growing portfolio of stem cell

extraction, culturing and processing tools for a wide number of applications in cellular therapy and research.

3. The GE Healthcare WAVE™ Bioreactor system, for example, is a single-use, closed system for cellular expansion. Used in laboratories worldwide for cell therapy and regenerative medicine research, the WAVE system has significant advantages over traditional cell culture techniques. The system automatically supplies nutrients and removes waste products, enables and simplifies the production of very high density cell cultures, a key factor influencing the likely success of many cell therapies. Being pre-sterilized and disposable, it also eliminates the need for cleaning between batches and reduces the risk of cross-contamination. The WAVE system also reduces the cost of consumables and labour compared with traditional approaches, a factor which will become increasingly important for future cell therapies. It is GE Healthcare's expertise and technologies such as these that are helping bridge the gaps between research, clinic and commercialisation in regenerative medicine
4. As well as the scientific and research expertise GE Healthcare brings to the field, we also bring an in-depth understanding of the issues and technicalities in scaling up, industrialising and commercialising highly-intricate, sensitive and complicated biological and biopharmaceutical processes. As part of the General Electric Company, and under the leadership of some of the world's most effective business people, GE Healthcare brings GE's over 125 years' experience of turning scientific innovation in areas as varied as aviation, energy generation and medical imaging, into commercial success, to the field of regenerative medicine.

Barriers to translation & commercialization

5. The issues faced by the regenerative medicine industry in translation and commercialisation are similar and related, hence we group them together in this submission.
6. GE Healthcare welcomes the actions outlined in both the Government's Taking Stock of Regenerative Medicine in the UK and the subsequent Strategy for UK Regenerative Medicine. We support the positive steps being taken, such as establishing the Cell Therapy Catapult, and see the UK as well-placed to continue to build on its existing expertise in the science and commercial translation of regenerative medicine. However, significant challenges remain.
7. One of key barriers to overcome is how we communicate and bridge knowledge gaps among the different groups involved in the development and take-up of new therapies in the NHS, and among investors in the field. Researchers need better knowledge and skills in the clinical application of their research, and clinicians need a better understanding of the development direction and clinical opportunities presented by the latest research in the field. Likewise, in commercialisation of opportunities, researchers need better knowledge and skills in business to help translate innovation into clinical and commercial success; and the business and investment community needs to better understand the complexities in this emerging field of medicine.
8. Translation from an academic setting to a clinical setting is a well-recognised pathway of progression for a potential new therapy. However, a key challenge for the field of regenerative medicine is moving successful small scale clinical trials to full scale

commercialisation that will bring long term benefits for the patient and taxpayer. The challenges the UK faces in this respect have been the subject of numerous reviews and reports, not least the 2006 Cooksey Report on funding of health research. Many of the challenges outlined in the Cooksey Report remain.

9. Current programmes such as the establishment of the Francis Crick Institute; disease-focused initiatives such as University College London's in age-related macular degeneration (The London Project to Cure Blindness); government investment such as the Technology Strategy Board's catapult programme; collaborations among academia, NHS trusts, research and commercial partners such as NESCI; and many others are all seeking to bridge gaps between research and mainstream use. They should be supported with continued investment and access to skills and knowledge, as well being championed as leaders in their fields globally.
10. Scientists and academics will seek financial support through grants and venture capital to move their discoveries towards clinic and commercialisation. In particular, moving beyond phase 1 and phase 2 clinical trials requires significant resource in both time and capital. The academic community is less attuned to making the health economic and business case for opportunities presented by continued investment and development than is required for informed decision-making by those allocating resources, whether they be healthcare providers, public or private investors.
11. Financiers and venture capitalists that invest in health-related science often have short time horizons in which they aim to recoup their investment. While understandable to an extent, this is not commensurate with an emerging field where therapies may take more than 10 years to reach clinical fruition. Providing business, through information sharing forums, with a better understanding of the risks and opportunities for investing in the field would help overcome the subsequent reluctance to invest.
12. Providing scientists and academics with ready and well-coordinated access to financial and investment advice, professionals qualified in healthcare provision, health economics and pharmacoeconomics, possibly through government-funded resources such as mentors, advisors or consultants could help overcome this. Other novel funding expertise collaborations could work through appropriately qualified and experienced consultancies or with industry partners with in-house expertise. In the long-term, an understanding of business and investment should be seen as a core part of academic researchers' background knowledge and skills.
13. Investment and funding is hugely important in the continued development of regenerative medicine and therefore robust cases for the potential market opportunities of nascent therapies should be developed. However, when a particularly novel therapy, without a clearly established existing market is being progressed, there is often limited understanding in the business community about the nature of the investment and the benefits associated with this. The cell therapy and regenerative medicine community should be supported in its effort to communicate clearly and transparently with the business community.
14. Regenerative medicine holds huge potential for addressing unmet clinical needs. However, in any field or research it is not realistic or practical to take forward every opportunity that could be explored, making a robust approach to prioritisation essential.

This would serve to focus research and translational efforts, as well as investment opportunities.

15. Such a process of prioritisation should examine unmet medical need, predicted disease trends, assessments of risk-benefit profiles of expensive therapies and changes required to current clinical practice required to implement novel therapies. It should also ensure that a thorough and realistic appraisal of the market for a new therapy is always developed: this is central for the business community making investment decisions about which discoveries and technologies to support and take forward.
16. This is a difficult area in which to make strategic choices, as the largest unmet clinical need does not always match with where most progress is being made in research. There is a tension between the speed of scientific progress and the pressing healthcare need. For example, the unmet clinical need in macular degeneration is considerable: a treatment would mean a large patient population (more than 500,000 people have AMD in the UK¹⁵⁷) and health economic benefits, but the science is more advanced in a disease area arguably with less clinical necessity, such as spinal cord injury (approximately 40,000 people in the UK live with paralysis¹⁵⁸), which was the focus of the world's first clinical trial based on human embryonic stem cells (hESCs).
17. Prioritisation by either disease area or therapeutic approach comes with its own advantages and disadvantages. Currently it is more common to prioritise by disease area: this will bias progress towards more commonly occurring diseases that by population size are expensive to treat or which are exceptionally challenging to manage. Prioritising by therapeutic approach may provide a greater opportunity for breadth and therefore chance of encompassing the development of novel treatments for orphan diseases. Either way, each therapy should be assessed separately to maximise use of the right technology and expand on prior technology investment.
18. For example, there are currently numerous unmet clinical needs for new therapies to tackle the predicted surge in neurodegenerative diseases resulting from our increasingly ageing population. Furthermore, rising obesity levels have led to increasing cases of diabetes. There are also numerous rarer diseases, for example endocrine cancers, that require significant new research and development if successful therapies are to be developed. However, uncertainty over future treatment policies and the likely financial return from low volume medicines is hindering commercial development work.
19. Government should convene a multi-stakeholder forum to assess these needs with a view to signalling to industry and academia those areas that are a priority focus for the UK and which would be supported through R&D financing and procurement policies. In turn, industry could focus and channel resources into developing therapies for these specific diseases, including those rarer diseases which the policy environment is prepared to support.
20. Ultimately, GE Healthcare believes that to truly achieve critical mass in the commercialisation of regenerative medicine Government should seriously consider establishing a 'silicon valley' or 'silicon roundabout' in regenerative medicine in the UK.

¹⁵⁷ Information Leaflets - Macular Disease Society <http://bit.ly/PSiRJD>

¹⁵⁸ <http://www.apparelyzed.com/statistics.html>

As a first step, we recommend Government look at building on the existing model of Centres of Excellence to develop one or two areas in the UK for companies to physically co-locate as commercial opportunities around new therapies grow. Crucially this would include access to expertise in business and commercial requirements for successful translation, opportunities for knowledge and infrastructure sharing.

21. While we welcome Government's strategy for the life sciences industry, we feel this may be put at risk by the on-going drive to reduce costs. For example, The Department of Health (DH) is currently consulting on '*proposals to transfer functions from the Human Fertilisation & Embryology Authority (HFEA) and the Human Tissue Authority (HTA)*.' The DH's preferred option is to transfer their functions to the Care Quality Commission (CQC) and the Health Research Authority (HRA). Neither the CQC nor the HRA currently have the necessary expertise to carry out the functions of the HFEA and HTA and address the ethical and scientific challenges that often arise. The cost savings enabled by these proposals are relatively small in comparison with the potential negative impact on regenerative medicine in the UK. GE Healthcare encourages the Committee to review this proposal and like us, also respond to DH's consultation on the future of these two organisations.
22. For translation of regenerative medicine to be successful, there are still numerous technological challenges to be overcome. Furthermore, even in therapy areas of significant progress, there are communication challenges and a need to think about new ways of working in the medical community. See Box 1 for some example of these challenges and Box 2 for an example of an area where good progress is being made.

Box 1 - Technological challenges

- Effective and efficient harvesting of cells and cell concentration for therapeutic application from large volumes
- Expansion of adherent cells for allogeneic and autologous therapies to allow scale up and scale out of existing clinical approaches
- Small volume expansion (<250ml) in an effectively closed, single use bioreactor system
- Cold chain and logistics tracking of cellular therapeutics so that the treatment reaches the appropriate patient in the right place, right time and right condition

Scientific / Technological challenges (and long-term health economic impact)

- Cord blood expansion
- Red blood cell precursor expansion / manufacture

Communication and opportunity uptake (including current and future health economic impact)

- Raising the awareness of the benefits and availability of cord blood stem cells as an earlier choice in the treatment of patients in the UK otherwise requiring a live bone marrow donor
- significant funding to support public cord blood banks, collection and processing

Box 2 - Harnessing the potential of cord blood

Stem cells can be sourced from umbilical cord and placental blood in a non-invasive, post-birth procedure. Once a sample is collected, the stem cells can be isolated and have the potential to be used as an alternative source of cells in bone marrow transplants for the treatment of leukaemia where there is a lack of a suitable matched bone marrow donor.

Clinicians and researchers have been aware of the potential of cord blood stem cells for some time and, as a result, there is now a growing network of public and private cord blood banks for the long term storage of samples, for future use by donors identified by correct matching of the cells or by family of the donor.

Because of the link to an existing market (bone marrow), industry has been quick to understand the potential, and therefore investment has followed.

Even in this well-progressed area, technological and communication challenges remain, and significant funding is still required to support public banks, collection and processing (see box 1).

23. We believe that the regulatory system in the UK allows for clinical trials to be carried out in a safe and controlled environment. GE Healthcare does not see any significant challenges which should be drawn to the Committee's attention, although we will be closely monitoring the development and consequences of the proposed revision to the EU Clinical Trials Directive published in July, to ensure it does not impede the current regulatory environment.

What role does patenting play in the commercial development of regenerative treatments?

24. Patenting is an important mechanism in the development of new technologies and therapies. They are essential in safeguarding the significant investment made by companies in the life sciences sector. While GE Healthcare supports the use of patenting we recognise there is a view within the wider scientific community that patenting prevents access to new products and information and impacts their ability to conduct further research. We would like to stress to the Committee that at GE Healthcare this is not the case.
25. For on-going academic research, any scientist is free to use our technologies for research and discovery without incurring any liability for royalty fees related to any subsequent discoveries. GE Healthcare believes that other commercial organisations should be encouraged to take a similarly collaborative approach to IP sharing with academic researchers. GE Healthcare manages a system which delicately balances the need for IP protection without hindering scientific discovery and progress, and translation into commercial benefit.
26. The patentability of technologies derived from stem cells, specifically hESCs, is an area of significant concern for all stakeholders in the field, as these cells are of critical importance in regenerative medicine research.

27. In October 2011, the Court of Justice of the European Union (CJEU) decided in the *Brüstle v Greenpeace*¹⁵⁹ case concerning the patentability of inventions involving hESCs. The lack of clarity arising from this decision, and subsequent decisions by the European Patent Office and the UK's Intellectual Property Office drive additional uncertainty in the field and could have consequences for scientists researching in the field with a view to commercialisation of technologies, as well as for the investment community which typically demands solid IP protection for technologies in which it invests. A clear ruling on the IP issues in the field, grounded in good science by the relevant European and UK authorities would go a long way to reducing this uncertainty.

International comparisons

28. The regulatory, legislative and clinical framework already in place in the UK is very effective and allows for development to flourish in a way that is ethically and scientifically sound.
29. It is important to look at regenerative medicine from a global perspective. Many companies, GE Healthcare included, operate internationally and need to do so in an equitable global marketplace. That is, a marketplace which is well-regulated and that ultimately does not compromise patient safety.
30. It will be important that the UK's positive yet controlled environment is replicated in other geographies to ensure that the international reputation of regenerative medicines is not compromised. There is a clear reputational risk to the regenerative medicines industry if its practice is undermined by weak regulation in other parts of the world. Emerging economies for e.g. in Asia are investing significant sums of money into research and development however, in GE Healthcare's view without the appropriate safeguards in place. GE Healthcare would like to see global best-practice regulation of cell-based therapies based on clinically accepted standards of practice (i.e. clinical trials), with the necessary powers to protect patients. The UK's regulatory and legislative framework for regenerative medicine and cell therapy provides a good example that the UK should encourage other countries in the early stages of developing their regulations to consider as a model.

20 September 2012

¹⁵⁹ Judgment in Case C-34/10 *Oliver Brüstle v Greenpeace* <http://bit.ly/OEacGa>

Genetic Alliance UK, Consulting on Advanced Biologicals (CAB) Ltd and LGC – Oral evidence (QQ 330-342)

Evidence Session No. 15

Heard in Public.

Questions 330 - 342

TUESDAY 15 JANUARY 2013

Members present:

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Alastair Kent, Director, Genetic Alliance UK, **Dr Christopher Bravery**, Principal Consultant, Consulting on Advanced Biologicals (CAB) Ltd, and **Dr Julian Braybrook**, Director of Strategy, Measurement Research, LGC.

Q330 The Chairman: Good morning. I would like to welcome the three witnesses in our first panel this morning to this inquiry into regenerative medicine, and I would like to invite you to briefly introduce yourselves for the record. If you would wish to make any opening statements, please keep them very brief and then we will move straight on to the questions. Perhaps I could start with Alastair Kent.

Alastair Kent: Thank you. Good morning. I am Alastair Kent. I am the Director of the Genetic Alliance UK, which is an alliance of over 150 patient organisations that support families affected by genetic disorders of all types. Our membership ranges from common complex disorders to very rare conditions caused as a result of changes in single genes. Our members see this area as being one of huge potential in terms of delivering innovative interventions that will change the course of many of the most horrible conditions that can afflict us, and we welcome the opportunity to be here to present the perspective of the patients and of the families who stand to gain from the appropriate encouragement and regulation of one of the most exciting areas of biomedical research, one of the areas that offers, perhaps for the first time in human history, the opportunity to intervene and to

change the natural history of diseases which have blighted the lives of families forever. Now we see that we have this opportunity to look at how we can change that, improve things for the better and take away the threat of inherited diseases in an increasing number of what are currently very rare conditions.

Dr Christopher Bravery: My name is Christopher Bravery. I am currently an independent consultant who focuses primarily on the area of regenerative medicine, but hopefully I can bring you an interesting perspective, since I have worked in biotech, including a cell therapy company; I have also been an assessor at the MHRA, working primarily within the European system. I was a member of the Cell-based Products Working Party at the EMA until about five years ago when I left, so I was involved in writing the core guidelines for Europe, but also drafting the technical requirements that came out as Directive 2009/120 and also aspects of implementation of that regulation within the UK, and then I have moved into consulting. Hopefully I have seen this industry from many different angles, particularly around the regulation of the medicines.

Dr Julian Braybrook: I am Julian Braybrook. I am currently Director of Strategy leading LGC's measurement research activities and within those its designated function as a national measurement institute. LGC has been working in and around the area of regenerative medicine for probably up to 15 years, applying various aspects of measurement science and also assisting with setting up guidance, standards and pre-standards associated with regenerative medicine. I am probably here today because I also chair the British Standards Institute regenerative medicine committee, which has produced a number of publicly available specifications or pre-standards, if you like, relative to or for the regenerative medicine community.

I would like to make a couple of points. The issues that we are discussing here are largely the same the world over. Really what we should be looking for or talking about is how we can support the bringing of regenerative medicine products to the point where they can gain investment. The reason behind that is companies will tend to gravitate to a place where they can actually get things done and make things happen. Therefore, if the UK maintains its probable current lead, then it offers a huge opportunity for the regenerative medicine industry within the UK.

The Chairman: Thank you. Is that enough?

Dr Julian Braybrook: Yes.

Q331 The Chairman: Thanks. Perhaps we could move on to the first question. We are really interested in how the regulatory system for regenerative medicine works in the UK. We have heard a number of comments from witnesses that the system is too complex with too many regulators involved. For example, we have been told it can be “daunting”; “there is significant duplication, redundant regulatory burden ... and major delays”. We wondered what your perception of this is. Perhaps you could briefly answer. Give us your overview reaction to those sorts of comments we have had. Alastair Kent, would you like to kick off?

Alastair Kent: Yes. Clearly it is a complicated area and, for many patients and families, the apparent plethora of bodies involved would have to be satisfied in terms of getting a good piece of science through into an intervention that will be able to benefit patients with a life-limiting disease, which can be confusing. However, the various agencies that exist which have an interest in this field have actually developed a degree of expertise and insight into the issues that does not overlap significantly. The problem is more one of communication

than actual complexity in practice, so that the relationship between the HFEA, the HTA, the MHRA and so on is seen to be one of duplication whereas, in reality, it is about looking at having the critical mass of expertise in order to address the relevant aspects—the relevant parts of the spectrum—in order to get a coherent picture across all the issues that are raised.

The Chairman: What would you like to see the regulators doing to communicate more?

Alastair Kent: I think it is incumbent upon the regulators to present their role more effectively in lay language to a lay audience. Often, many of the issues that come up for consideration by regulators arise from research in academia or from small companies that may have very limited experience of going through the regulatory process; and there is a need for clarity of explanation and, also, outreach and support for organisations that have good ideas, potentially good products, bringing them through the system in a way that makes it clear what the hurdles are that they will have to overcome and what the standard of proof is that will be required of them, in order to satisfactorily negotiate those hurdles.

Q332 The Chairman: Has the Stem Cell Toolkit been useful in providing guidance?

Alastair Kent: I cannot comment on that, other than from a very lay perspective, where those of our members who have patients who have been involved in clinical development, through clinical trials or whatever, are aware of it. Whether they have found it helpful or otherwise, I cannot comment.

Dr Christopher Bravery: I ask myself the question that maybe we should benchmark ourselves against other member states, because I understand you have a lot of evidence where people have said, “We have three different agencies and it is very complicated dealing with all these different agencies. Should we only have one?” You might be interested in this—unfortunately it is based on a 2008 survey by the European Commission of member states’ competent authorities, so it is potentially a little bit out of date. If you look at how member states deal with medicines, medical devices, organ transplantation, tissues and cells, reproductive cells and blood, how many agencies do they need to achieve all those parts of the regulation? The average is two; the UK has three. There are three countries that have four agencies to cover those activities. 40% of the member states only have one agency. An interesting question might be to ask, say, Belgium or France for instance if having a single agency is better, compared to, say, Italy or Poland, which have four: “Is this worse in your country?”

I am not really convinced that having three different agencies is a huge problem, particularly when I hear views from my US clients that the jurisdictional issues within the FDA can cause a lot of complications and difficulties. It is not necessarily a problem. You can move them under one banner, but we have to be wary that changes also cause more upset to industry, because they get used to a system and then they need to move on.

Yes, it is complicated: the science is incredibly complicated; the levels of regulation we need are very complicated. The real issue to me is one of education. We have an unusual situation where advanced therapies, particularly cell therapies, are being taken up within academia in a way that we do not see with other product categories. It is a natural extension of transplantation to move into fiddling around with the cells and trying to make them more effective with what you are doing in transplantation, and then they become medicines. We need to work on regulatory science. I did a quick web search for the term “regulatory science”, “university” and “course”, and in the US there are a few courses for regulatory science. The UK leads Europe in areas of pharmaceuticals. We host the

European Medicines Agency; we have key positions within that agency, but there is not a single course in the UK for regulatory science. Even broader than just regenerative medicine, are we really supporting regulatory science and understanding? There is a shortage of regulatory professionals. I am phoned a lot for jobs, because there are not many people around and there are even fewer that have expertise in advanced therapies. It is figuring out how to educate, and I see a big difference between newer organisations embarking on development and established ones, by far. I have clients that are in the top-20 pharmaceutical companies that are looking into advanced therapies.

Q333 The Chairman: Do you have a view about whether, as I asked Alastair Kent, the regulators could communicate more effectively with scientists and small companies?

Dr Christopher Bravery: I think they have done a phenomenal job. If you look at what proportion of the work advanced therapies are for the European Medicines Agency, about 4% or 5% of registered orphan products are advanced therapies. 4% or 5% of scientific advice procedures at the EMA are for advanced therapies, and about 2% of market authorisations in the last couple of years are for advanced therapies, and yet they have undertaken an enormous amount of outreach work; they have written a lot of new guidelines; they have set up new committees and working parties. The MHRA has been equally proactive in this area and I think they have done a really good job, but it is a case of those developing needing to educate themselves or acknowledge that they need to educate themselves.

The Chairman: How do you explain the difference between your perspective, which essentially, summarised in a sentence, is that things work pretty well, with the witnesses who we have had and who have written in—big organisations like the British Heart Foundation, NHS Blood and Transplant, UCB Pharma as well as the Cell Therapy Catapult—which are saying that the regulatory process is daunting and complex? Are they just not getting a grip on it and it is up to them, or are you being a bit too complacent?

Dr Christopher Bravery: I think it comes back to acknowledging there is a discipline of “regulatory”; it is a discipline. What I find with earlier-stage organisations—I am going to use that broadly because I am covering all sorts of things—is they do not have that expertise in-house. They do not really acknowledge that they need to get it in at the beginning. They need people who understand the system to guide them through it. That is what I do as a consultant.

The Chairman: The complexity of the system gives you a living. It is very straightforward if you are in that business.

Dr Christopher Bravery: Indeed. Yes, I have been accused of that as a self-fulfilling prophecy or whatever before, but actually I do what I do because I am passionate about developing advanced therapies and I want to help people get them to market. My motivation is not generating income actually, but you have to acknowledge that it is highly complicated. In about 2005, there was a BBC *In Business* programme, where Jean-Pierre Garnier, the CEO of GSK, likened getting a medicine to market to putting a man on the moon. It takes about the same amount of time and the same amount of money. That is perhaps an overly ridiculous example, but if you were going to embark on developing a commercial airliner, you would not doubt that it was going to be very complicated, cost you a lot of money and there would be a lot of regulation around safety. Some people underestimate what they are trying to achieve in developing a medicinal product for a market potential of 500 million Europeans.

Dr Julian Braybrook: Mine is obviously much more of an observation. The regulatory regime that we have is a mixture of legacy and evolution. If you think about the fact that we have a plurality of regulators, we have a mixture of European Directives and regulations that have been brought into UK law and we have cross-reference into the pharmaceutical standards, there has to be an acknowledgement that this brings with it a number of complexities. The point I possibly would make is that, whilst we could be critical of the regulations and how they have come about, actually, we have a very robust regime within the UK that is the envy of many countries around the world. The message that that gives, if we can articulate that correctly and demonstrate that it works in the best way that it can, is probably the biggest point to make.

Lord Winston: Do you think that the United States, which has a clear record of translating this kind of work into clinical practice much quicker than we have, is successful at doing this because its regulatory system is different?

Dr Julian Braybrook: It would be too simplistic to say yes. Within something as large as the FDA, you have a number of competing interests and a number of competing views. Whether you have separate entities or entities that have been brought together, because of the diversity of the range of products that are concerned here—and Christopher has already indicated that—that in itself means that you will always have that present, whether you have a single or a multiple entity. I am not sure that they are that much better at it. They have supported it and thrown more money at regenerative medicine, certainly in some of the states and that probably does help.

Q334 Lord Willis of Knaresborough: May I ask a couple of brief questions? First of all, Dr Bravery, the number of regulators that you gave across Europe, that work was actually done in 2007 and published in 2008, so it is actually the best part of six years old. I just wondered whether it would be possible to let the Committee have an update on that.

Dr Christopher Bravery: I had to rely on that survey to generate it so, without a survey of that nature, it would be a lot of work to try to put that together to double-check those numbers.

Lord Willis of Knaresborough: Do you not have good friends who you could ask?

Dr Christopher Bravery: I could try and do that for you, yes.

Lord Willis of Knaresborough: The thing that struck me when you were giving incredibly expert evidence to the Committee is that, like most regulators who know the system, they know the system, but the companies or the science groups that we are dealing with here are often very small, embryonic—if you will pardon the pun—groups that do not have the sort of expertise, which you say they should have, in order to be able to work through the process. The question the Lord Chairman asked you earlier was how in fact these regulators could communicate better and offer support to those small organisations, so they get their products through the system much faster and therefore into patients.

Dr Christopher Bravery: I can reflect on my own personal experience of working at the MHRA, and what I would say is that, actually, it was fairly difficult to go out into the public and give talks. If the conference, workshop or whatever was a for-profit, the MHRA requires a turnout fee of about £1,500 plus all your expenses. Because this is a small industry still, the conference organisers will not pay that. If it is not for profit and if you, the individual who wants to give the talk, fight within that system, you will be allowed to go, but

it is difficult to do that. Having said that, the MHRA, compared to other agencies, is more prominent on the conference circuit.

What I think we have been doing outside of the agency, with the BSI committee of which I am also a member, we wrote a PAS which lays out very simply, in about 70 pages—which sounds a lot but there are a lot of nice figures and diagrams—the basic system and how you go through it for both the EU and the US. To respond to Lord Winston's comment about the US system being different, it is actually not very different at all; it is remarkably similar and there was some deliberateness to that, as they have evolved the regulation. More importantly, we regulate through principles, not through very many rules. There really are not very many rules. They are scientific principles, and those are harmonised through ICH. None of those ICH guidelines are specific for advanced therapies, but they convey the principles by which we regulate and they are harmonised across a huge amount of the planned.

Q335 Lord Willis of Knaresborough: Can I just stop you there, because you are becoming really complicated again? My question really was: what advice can you give the Committee, other than this fee waiver? Is there any other way in which we can actually support these young companies, young scientists, in order to be able to get this stuff to Alastair Kent's patients?

Dr Christopher Bravery: The Stem Cell Toolkit perhaps should have been broader than that. It should be "How do I develop regenerative medicine and cover things more broadly?" because I think perhaps that means certain people do not look at it. The regulators themselves provide a lot of guidance, but all of us find it difficult to find it, even myself, when I do it for a living.

The Chairman: Sorry; say that again.

Dr Christopher Bravery: It is difficult to find the guidance if you do not know where to look for it.

Lord Willis of Knaresborough: This is my point.

The Chairman: I thought earlier on everybody was saying that you are communicating extremely well.

Dr Christopher Bravery: They are if you know where to find the information. Trust me: this is not unique to the UK or anywhere else. If you look at the FDA website, it is very hard to navigate too.

The Chairman: Just let me be clear in my own mind. They are communicating well, but it is very difficult to find where they are communicating.

Dr Christopher Bravery: If you do not know where to look, yes. It is a Catch-22, I absolutely agree, which is why we wrote things like the PAS, because the PAS identifies where you—

The Chairman: Sorry; what does that mean?

Dr Christopher Bravery: The publicly available specification.

The Chairman: Who writes that?

Dr Christopher Bravery: The British Standards Institution wrote that. It is like a roadmap for how you develop a cell-based product.

Q336 The Chairman: I have to say at this point I am a little bit confused, because I heard earlier on from all three of you that everything is fine and dandy; there is great communication, a simple regulatory system. Then I suddenly hear, “Well, it is jolly difficult unless you know where to look.” That does not sound to me like a straightforward simple regulatory system. What am I meant to be taking away here at the moment?

Dr Julian Braybrook: Let me jump in for a second. I am not quite sure I said it was simple. I did acknowledge it was complex, but I was saying that we have what we have, and we can make it work. It is looking at the measures of how we can make it work more optimally that is important. As far as the regulator communicating; they have done a lot of that. What we have been trying to do within the BSI committee, and we have produced three of these specifications so far, is to simplify the system as much as possible to, first of all, make people aware of common terms or terminology and what the issues (regulatory, testing, ethics etc) are going to be if they want to embark on this. The second thing is to make sure that they acknowledge upfront what it is they need to consider, rather than to plough ahead, meet some regulation that they had not quite realised and then be forced to go back and repeat work. There is some data we can discuss later around the issues of getting measurement wrong or repeating measurement. That is really quite critical in some of these evolving areas.

PAS 83 specifically addresses the product lifecycle and regulatory guidance for developers. There is also PAS 84 that looks at simplifying terminology, because there are some differences in terms internationally. There is also PAS 93, which is characterisation of human cells for clinical applications. These are beginning to lay out the early stages of what could be standards. The difficulty is, where you have a regulation, standards do not officially have a place. Regulations are law and that is what you do. The difficulty is where you get, with all the right intentions, a regulation that leaves too many things uncertain, then that is where problems may arise. I would hazard a guess that some of the issues here are indeed because, with the best intention in the world when they first wrote the regulation, they were slightly naïve in their understanding and belief that it could be interpreted so simply by others, and that actually there is the need to assist people far more perhaps through that process than was first imagined.

The Chairman: You are now slightly changing the story to say there is a need to help people navigate through.

Dr Julian Braybrook: I have always said that, because that is why we have produced the documents that we have. What I was saying earlier was that we have the system that we have. Even if you go back, think about changing it and bringing things together, I am not sure, because of the variety of products, that actually you are going to change the complexity of the issue. You are certainly not going to go back and redraft the regulations.

Q337 Lord Cunningham of Felling: Complex and difficult regulations can also be very expensive, particularly for start-up businesses and SMEs. The Committee has received a fair amount of evidence that suggests that the costs of gaining regulatory approval and compliance are onerous, prohibitive even to some companies as I have described, SMEs and start-up companies. I would like to ask each of you if you agree with that—that that is the real world for these small businesses. If you do agree with it, what actions do you think could be taken to improve the situation and reduce the costs?

Alastair Kent: We have to remember that an awful lot of the products that are coming through are addressing conditions that are very rare and about which relatively little is known. If you simply apply the regulations as they stand now, it is expensive, time-consuming and very difficult to generate the volume of evidence of efficacy and safety that is required by the current procedures. What I think we would like to see, as representatives of patients and families, is the opportunity to engage at a much earlier stage in the process to explore with the regulatory authorities and the SMEs, the academic groups or whatever, the process by which the risks and benefits associated with a particular possibility are assessed and whether or not it is a reasonable risk to allow a family to take to opt to participate in a development process, with the expectation that that would bring things to the point where families were able to benefit at an earlier stage in the development, but with a concomitant obligation to take a part in reporting the effectiveness, the outcomes, the benefits and the downsides that came from being able to access that product, that intervention.

If we do that, it would result in patients getting things that were potentially very beneficial sooner and, therefore, at a lower cost in the development process. It would also indicate much more quickly those products which, whereas they might be safe, were not actually delivering a great degree of benefit to patients, in terms of the impact of their experience of living with the condition under investigation.

Dr Christopher Bravery: I have been told recently by one of my clients that the cost of their facility licence, a tissue establishment licence in Germany, was something in the order of tenfold less than the equivalent UK licence, but I have no hard figures on that. It could be worth considering to ease some of the costs, but these would be relatively low costs in the grand scheme of things; for instance the European Medicines Agency, if you are a registered SME, you get a 90% discount on the cost of scientific advice. Now EMA scientific advice can cost as much as €70,000, so it brings you down to about €7,000. If your product is orphan-designated and you are an SME, you get that advice for free. The MHRA charges about £5,000 for scientific advice, or their top whack is in that region, but there is no mechanism for them to give discounts. There are also incentives at EMA level for things like GMP inspection and authorisation, etc. Again, the UK does not offer any incentives of that nature.

Lord Cunningham of Felling: Sorry, you said that the UK does not offer incentives of that nature.

Dr Christopher Bravery: No, there is no fee reduction, so if you are GlaxoSmithKline or you are an academic group and you formally apply for scientific advice, you will be charged the same amount of money. There are also no additional benefits to orphan designation within the UK, and there could be some sort of additional incentives if you are designated, maybe some tax incentives or whatever. This is outside of my area of expertise, but that is an opportunity, because very few member states do offer incentives for orphan products.

The cost of regulatory compliance is very hard to detach from the cost of development because, when you are assessing a medicine, you are assessing the entire development and all the evidence that has gone towards the risk benefit and the quality of a product. How do you detach that from development because, in essence, they are the same thing? Really what you are doing is reviewing development. The real additional cost to industry is of preparing the paperwork for the regulators but, unless you do not regulate, you are stuck with that situation and it takes a lot of time to prepare the documentation, but then that has some additional benefits. It really brings a rigour and an organisation to the company, and

makes sure that they really are staying on top of things. Really the two things are very difficult to separate, but you could offer some cost savings on things like licensing.

Q338 The Chairman: You have alluded to this tenfold difference that one of your clients has referred to. Do you know what the cause of that was?

Dr Christopher Bravery: Unfortunately, I could not find the numbers. I think maybe I was told and did not write them down or I lost the email but, in my head, I think it was something in the region of €600 for that licence in Germany and £6,000 in the UK, which to me was quite shocking. My client mentioned it to me because they were quite surprised by the disparity. Adding to that, actually going back to the question of complexity, the German system is possibly slightly worse because that facilities licence is actually dealt with on a regional basis, so there are a lot of different people you have to seek out, but that could be looked at.

Dr Julian Braybrook: LGC does not bring products to market, so I cannot really comment directly on the actual cost, but where I can offer some insight lies with the cost around the uncertainty surrounding the data that is required to establish the quality, safety and efficacy of the regenerative medicine products. What we have tried to do as an organisation, under our national measurement role, is to look at where we can provide assistance and guidance that will support common standards ultimately but, actually, we use our measurement expertise to support initiatives that help technologies get from point A to point B faster. There are a number of ways in which we have done that. Most of these are supported through collaborative exercises funded by the Technology Strategy Board and their regenerative medicine policy. Here, what we are trying to do is to look across the chain of regenerative medicine and look at the value at the various points within that, in terms of development, manufacture, assessing the quality and optimising the process at the end. Some of that work has been completed by some groups, and some of that work is still outstanding.

Q339 Lord Rees of Ludlow: Dr Braybrook mentioned that there was no difference in the hurdles required from a big company and from a start-up company. I wonder also if there is a reason why there should be perhaps slightly different levels of requirements for a potential blockbuster as compared to some development that would only be of benefit for a small number of patients, of the kind that Mr Kent is concerned with. Should there be, in some sense, a slightly easier pathway for something where the long-term commercial benefits are much lower than in other cases?

Dr Julian Braybrook: It was Dr Bravery actually.

Dr Christopher Bravery: I would love to respond to that actually because, although the legal structure and the description of the procedures that you go through for regulation are exactly identical, it is a scientific opinion reached by the assessors and they do factor these things in. A good example is the recent approval of the first gene therapy in Europe for Glybera. I have to consult my notes, because I always forget the disease. This is for lipoprotein lipase deficiency. Now, the prevalence of this means there are only about 1,000 individuals across the whole European Union who will be suffering from this disease. They studied only 27 patients to obtain an exceptional circumstance market authorisation from the EMA. It is possible to balance the ability to collect the data, the ability to generate the data, with the need to make the product available. The system is remarkably flexible in that respect, and at the MHRA, I have to be cautious how I say this because they might tell me off if I express it badly but, in essence, you do, to some degree, take into account the

organisation you are dealing with. If you are dealing with a large pharma, you expect them to do it properly. If you are dealing with a small company, you help them to understand where they need to improve things, but you may be a little bit more sympathetic to what they have in hand when you are deciding whether or not to approve their clinical trial or whatever.

Lord Rees of Ludlow: The size of the company is a separate parameter from the prevalence of the disease, is it not?

Dr Christopher Bravery: Indeed, you are weighing all those things up and, with the clinical trial in particular, you are just asking yourself the question: is this putting patients at unacceptable risk or are the risks acceptably managed at this stage, for this number of patients?

Alastair Kent: Without wishing to disagree with the principle of what my colleague has said, I was a patient representative on the committee for orphan medicinal products of the European Medicines Agency for six years, and then later a representative on the advanced therapies committee. Very often, discussions of safety of applications that came forward were predicated on the assumption that this was an unacceptable level of risk that patients would not be prepared to take. As a patient representative, one of our key roles was frequently to say to the professional regulators, the representatives of the national competent authorities, “Have you asked? Have you checked that this risk is not acceptable?” given that in the vast majority of cases we were dealing with diseases for which there was no licensed intervention. We were talking about a condition that reduced the quality and quantity of life for those affected quite significantly, and where the opportunity to intervene to change that might be seen as providing a significant benefit from the patient family perspective, when perhaps from an objective external view this was perhaps not a great step forward.

Q340 The Chairman: Dr Braybrook, you have referred both in your oral evidence and written evidence to the de-risking of products by the National Measurement Institute. Can you give us any examples where that has proved effective?

Dr Julian Braybrook: Yes, I am happy to do so. I mentioned four areas through the value chain and horizontal activities. If we take some examples of what we have been doing and how that has been taken up that might answer your question. I should just state that those four or five areas came from the original sandpit meeting, when the concept of the TIC, as it was going to be called, now the Catapult, as it has developed into, and were identified as areas of common need from that meeting.

On the product development side, we have been working both with UK and European regenerative medicine companies and with other national measurement institutes to address aspects around cell behaviour, particular markers and marker expression on cells within regenerative medicine products and also to look at the levels of proteins, both on the cell surface and within the cell. To give you a specific example within one UK company as a result of the work we did, they were able to prove validation of their new product and use it to gain seed funding, which gave them another year’s money, when they were facing this ‘cliff face of funding’ we all hear about. On the back of that, they have now launched a three-dimensional matrix, which is for sale, and we are now working with them on a particular form of chemical that will allow the cells to develop in a particular way. I have to be suitably vague here, but that is a very clear example under product development.

Under product manufacture, we have been looking at real-time methods to help identify cell shape, number and quality during cell manufacture. Particularly we adopted the approach that was, at the time, either frowned upon or ahead of the game, depending on which way you want to look at it, real-time monitoring of large-scale (three-dimensional) bioreactor-based manufacture. We took the view at the time that to get large pharma and biopharma interested in this area, this was the nearest thing that they would immediately see advantage to—if they could relate to the ability to actually take products forward using a scalable technology, they were more likely to invest at an earlier stage. We are still discussing some of those aspects with particular companies, especially around a neural regenerative medicine product.

On the quality control side, we have been looking at the quality of cells for a particular transplantation, a human transplantation. Here we have been working with UK SMEs, academic institutes within the National Health system and cell transplantation centres. We have a technology that we believe is robust, and we are now taking this forward through a clinical study to prove it, and then that will provide the potential for a service back into the NHS or within the NHS probably more likely. I can say this is for pancreatic islet transplantation.

Finally just an example on the optimisation side; I have hinted at it already. This is again through a number of academics and one particular UK-based bioprocessing company trying to develop this toolkit, which will allow the cell manufacture and the costs associated with cell manufacture to be identified, and would perhaps give options for different technologies to say, “If this is technology A, you should consider option A or B for its manufacture.” That is all based around being able to work out the unit scale and unit cost of manufacture.

The Chairman: Baroness Perry, I think the point you were going to raise has already been covered to some degree.

Q341 Baroness Perry of Southwark: Indeed, yes. My question really relates to the balance that exists between the quite proper need to safeguard patients and make sure the trials are safe and also the need to encourage innovation. I think, Mr Kent, you gave a very good example from your own experience of being an advocate for patients who would rather like the balance to be tilted more in allowing innovation, rather than simply following the safety rules. Is the system too rigid or is the balance just about right?

Alastair Kent: It is not about whether we should allow the system to be tilted into a more relaxed approach to safety. It is much more that we should have a system where the safety issues are explored with the patients on whom they will impact, because there will be situations where you have risks that are unacceptable to patient in terms of the potential benefit. I am thinking, for example, of the case that some of you may be familiar with, of a few years ago, where a gene transfer trial for children with severe combined immune deficiency resulted in a number of cases of those children getting leukaemia as a result of insertional mutagenesis. Now, one of the mothers of one of the children who was affected was heard to say, “Yes, this is a serious outcome and I wish it had not happened, but you have to remember that I now have a child with leukaemia whereas, without the work, I would have had a dead child and I know which I prefer.”

On the other hand, there have been trials proposed where the risks that patients had been asked to take on board have been such that they have not been willing to do it and, as a result, the development of the medicine has not proceeded. I am thinking of a trial that was proposed for a particular form of a mucopolysaccharide disease which, in itself, although it

had serious effects, allowed people to live lives of reasonable normality and quality. The patients who were asked to enrol in the trial felt that the likely benefits that were anticipated were not such that the risks were ones that they were prepared to contemplate. It is about a process of openness and negotiation, and having the opportunity to give comfort to the regulators that, if they allow something to proceed that has got the support of the patients, they will not be pilloried if the uncertainty is such that things go wrong in the long term.

Baroness Perry of Southwark: Is that really not asking for flexibility? Is there a feeling that there is a one-size-fits-all approach by the regulators that mitigates against flexibility?

Alastair Kent: There is a perception of that, certainly. Patients do not get to look at the standards that are imposed across different disease areas, because you only ever have one disease when you are invited to participate in a clinical trial. You cannot say whether it would have been different if you had had a different disease, but there is a perception that the height at which the bar is set is the same for everybody. Perhaps in terms of diseases that are rare diseases for which less is known than some of the complex conditions, generating the evidence necessary to get you over that bar is disproportionately more expensive.

Q342 Earl of Selborne: If we are to seek to learn lessons from other regulatory regimes overseas, and Dr Braybrook has addressed the American comparison with this country, where could we learn the most as to how we might develop the regulatory regime which is fit for purpose?

Dr Christopher Bravery: To be honest, it is very difficult to have the level of understanding of different regimes to really answer that question very effectively. What I have heard over the last few years is a series of talks from other countries about their evolving regulation of cell and gene therapy products, and they are all, in a very broadest sense, following a very similar approach to Europe and the US. As alluded to before, these principles on which we regulate are fairly well harmonised, but of course the devil is always in the detail. For instance in Japan, clinicians preparing small numbers of cells or whatever for treatments is considered outside of the legislation for pharmaceuticals, but a company doing exactly the same thing would be regulated. Obviously a lot of clinicians see that as a desirable outcome. I have no particular view actually on that.

I feel we are moving towards the same point. Sometimes I feel this is not necessarily a good thing, because I think the differences sometimes between regulatory systems can offer opportunities to new science. The risk of harmonising too much globally is you all harmonise to the highest point. We see that within Europe a little bit. As other people, I think, referred to, you can gold-plate your interpretation of directives. The problem is then, when you are working within Europe for a centralised market authorisation, you have to rise to the highest standards to keep all the member states happy or you are taking a bit of a risk. I am not sure I can really clearly answer that, in a sense.

Earl of Selborne: You refer to the need to harmonise within Europe, and clearly we do not have a harmonisation at the moment. We have heard that there are different interpretations, for example, of the hospital exemption for the advanced-therapy medicinal products. That gave concern to the manufacturers of some products that their market would have been undermined. You have referred to the cost difference, which of course is a different issue for regulation, but I suspect that one leads to another. What would you like to see develop on EU harmonisation, if this is an unsatisfactory situation?

Dr Christopher Bravery: Application of the European Tissues and Cells, the way that it is run, the expectations, definitely needs dealing with. As I alluded to, there are going to be at least 30 different competent authorities you are going to have to deal with. Particularly with an autologous cell therapy product, if you were marketing to all member states, you would be dealing with tissue establishment licensing in all member states. This seems a huge amount of additional paperwork and it would not really even be science-led; it would be duplication of the paperwork.

What they are proposing with the clinical trials is fantastic if it happens how it reads, because it really does solve a lot of those problems, but the European Tissues and Cells needs a lot more work. Otherwise, regulators around Europe have harmonised considerably over the last five years or so in their approach to advanced therapies. Obviously some member states have a lot less experience than others, but the work of the EMA's committees, bringing together key people from those member states to discuss and write guidelines and so on, is harmonising them quite well. There is actually work going on between the EMA and the FDA, and now Health Canada actually, which have bi-monthly meetings discussing issues around advanced therapies. This is a form of soft harmonisation amongst the regulators, and there is a broader regulators' forum that basically includes the whole world and anybody who wants to join in who is a regulator, that sort of thing. I do not know any more detail than that. So, there is work going on amongst the regulators to try to harmonise their approaches too.

In some ways, the UK has quite an interesting balance. Again another recent European Commission survey, the UK's response to that identified that we have 18 advanced therapies available under our specials system here in the UK. That is more advanced therapies than any other member state has available. Germany is the only one that comes close to us with 17; they are all under hospital exemption. I had a German stand up at a conference recently and tell me that they really wished that they had our specials system in Germany. I said, "Lobby the Government, because it comes from Article 5.1 of 2001/83. You just need to implement it into national law. You could do the same thing." He said, "Well, maybe we should, yes, because it is a really great system. It is so flexible." If you are a patient looking for a treatment for which there is no licensed product available, the specials do offer you that option to have these unusual therapies, but we have to remember that they are untested and we do not really know the safety or efficacy of them. They are available on a named patient basis and we do have that flexibility. I think the UK uses more unlicensed medicines than almost any other member state.

The Chairman: Thank you. We are running out of time and I would like to thank the three witnesses very much indeed for their comments this morning. You will in due course receive a draft of the transcript for you to make minor editorial corrections. If there are any other points you wish to make to us in writing, please feel free to do so. They will become part of the published evidence. Dr Bravery, you did say that you would have a stab at giving us an update on comparative EU regulatory regimes. Also, if you are able to provide any more documentation on the difference in cost in Germany and the UK for licence approval that would also be very helpful to us. Thank you very much indeed.

Government – Written evidence

This memorandum has been prepared by the Department for Business, Innovation and Skills (BIS) and the Department of Health (DH).

1. The Research Base

How does the UK rank internationally in the scientific field of regenerative medicine?

1.1 The 2011 BIS/DH report *Taking Stock of Regenerative Medicine in the UK*¹⁶⁰ established that the UK retains a leading position, in Europe and globally, in the science and commercial translation of regenerative medicine.

1.2 According to evidence collected for a BIS study International Comparative Performance of UK Research Base, the UK is a leading country according to percentage of publications in the top 1% most cited papers globally (2006-2010) for neuroscience (17%), medicine (16%), pharmacology toxicology and pharmaceuticals (13%)¹⁶¹ – ranking behind only the US. These are all areas of relevance to regenerative medicine research.

1.3 However, the UK cannot be complacent because of the rapid pace of change in emerging technologies and because regenerative medicine has been identified as a strategic priority by many countries.

Where does the UK have strengths and weaknesses in the field?

1.4 UK Regenerative Medicine research is world class for a number of reasons. Public funding into science respects the Haldane principle¹⁶². It therefore provides the academic community the freedom to support the best science based on excellence. Government investment supports a network of Regenerative Medicine Centres of Excellence. Underpinning both research and innovation is a strict but permissive legislative and regulatory framework.

1.5 Regenerative Medicine is a ‘step-change’ technology and will only become a reality if ways can be found to overcome complex challenges such as the manufacture, transportation and patient delivery of therapies. The cost of new treatments may also challenge existing models of funding, reimbursement and commissioning. The UK is addressing these challenges through actions from the *Strategy for UK Life Sciences*¹⁶³ and *A Strategy for UK Regenerative Medicine*¹⁶⁴.

¹⁶⁰ *Taking Stock of Regenerative Medicine*, 2011, Department of Business, Innovation and Skills and Department of Health.
<http://www.bis.gov.uk/assets/biscore/innovation/docs/t/11-1056-taking-stock-of-regenerative-medicine>

¹⁶¹ Numbers in brackets indicate the percentage of publications in the top 1% cited papers

¹⁶² Haldane principle - the Government's role is to set the over-arching strategy, while researchers themselves establish detailed priorities and apportion funding on the basis of peer review.

<http://www.publications.parliament.uk/pa/cm201011/cmhansrd/cm101220/wmstext/101220m0001.htm>

¹⁶³ *Strategy for UK Life Sciences* 2011, Department of Business, Innovation and Skills.

<http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-1429-strategy-for-uk-life-sciences.pdf>

¹⁶⁴ *A Strategy for UK Regenerative Medicine*, 2012, MRC et al.

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008534>

1.6 A key UK advantage over other countries is that investigators are able to explore the full spectrum of potential regenerative medicine interventions, including both adult and embryonic stem cell based approaches¹⁶⁵, which as well as offering distinctive options for therapeutic development according to disease area, provide important cross-fertilisation of biological understanding.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

1.7 Public funding for Regenerative Medicine, as defined in this inquiry, comes primarily from the Research Councils (RC's), the Department of Health (DH), the Technology Strategy Board (TSB) and the Devolved Administrations. Research support is also provided through the charitable sector, notably The Wellcome Trust, British Heart Foundation and Cancer Research UK.

1.8 The RCs and the TSB recently published *A Strategy for UK Regenerative Medicine*¹⁶⁶, including commitments of £40 million to deliver the Strategy including through the UK Regenerative Medicine Platform (£25m) and the Cell Therapy Catapult Centre (ca. £10m p.a.).

1.9 Translational clinical research is supported through the National Institute of Health Research's (NIHR) Biomedical Research Centres (BRCs) and Units (BRUs). These are currently running 14 research programmes which involve significant cutting edge translational research into regenerative medicine across a range of disease areas.

2. Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

2.1 Haemopoietic stem cell transplantation is firmly established as a curative therapy for patients with leukaemia and other haematological malignancies. Pancreatic islet cell transplantation for the treatment of type 1 diabetes mellitus and limbal stem cell transplantation for re-growth of corneal epithelium are also undertaken. Cell therapy products which represent the largest proportion of available treatments include cartilage and skin repair products as well as products to treat bone, adipose and blood disorders.

2.2 To date only one product, Chondro Select, has passed through the European Medicines Agency (EMA) centralised authorisation procedure for Advanced Therapy Medicinal Products (ATMP). The private healthcare provider BUPA has adopted the product through its clinical decision algorithm. A gene therapy product (Glybera) recently received a positive opinion from the European Medicines Agency (EMA) and it is expected that European Commission authorisation will be granted in the near future.

¹⁶⁵ Human Fertilisation Act 2008 <http://www.hfea.gov.uk/134.html>

¹⁶⁶ A Strategy for UK Regenerative Medicine, 2012, MRC et al.
<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008534>

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

2.3 We anticipate significant progress over the next few years using a range of cell types e.g. human embryonic stem cells, induced Pluripotent Stem cells (iPS cells), direct reprogramming of different cells, adult stem cell trials as well as in gene therapies¹⁶⁷. Research is also being carried out on stem cell transplantation to combat retinitis pigmentosa and age-related macular degeneration, which are the leading causes of blindness.

3. Barriers to translation

Are the actions outlined in the Government's strategies sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

3.1 The actions outlined in the three documents¹⁶⁸ collectively address what Government and the research community have identified as the key barriers to the therapeutic and commercial use of regenerative medicines. They address issues identified from research through to patient delivery, including regulatory burden, effective public funding, and international promotion. Although good progress has been made in implementing these, many are long-term actions.

3.2 In addition to the Regenerative Medicine Platform and the Cell Therapy Catapult Centre (see *A Strategy for UK Regenerative Medicine*) funding is also available to innovative small and medium sized companies (SMEs) and academics developing solutions to healthcare challenges from the TSB and Medical Research Council's (MRC) joint £180 million Biomedical Catalyst. The first awards announced in August totalled just under £10 million.

3.3 The legislative framework that applies to ATMPs has been in place since December 2008¹⁶⁹. In order to provide clarity surrounding the regulatory framework, the MHRA has published comprehensive guidance and provides tailored advice for products that may be classified as ATMPs¹⁷⁰. Regulatory and scientific advice for ATMPs is also available from the EMA¹⁷¹. Finally, DH and the MRC have published the Stem Cell Tool Kit¹⁷², which provides on-line guidance on the regulatory pathway.

3.4 To accelerate innovation and to increase the probability of success, the British Standards Institution published three cell therapy and regenerative medicine standards in 2011/12¹⁷³. Although downloads of the technical guides (PAS83 and 93) from the BSI website have been fairly limited (73 and 342 since publication), 'users' are not restricted to

¹⁶⁷ *Taking Stock of Regenerative Medicine*, 2011, Department of Business, Innovation and Skills and Department of Health. <http://www.bis.gov.uk/assets/biscore/innovation/docs/t/11-1056-taking-stock-of-regenerative-medicine>

¹⁶⁸ *Taking Stock of Regenerative Medicine*, 2011, Department of Business, Innovation and Skills and Department of Health; *Strategy for UK Life Sciences*, 2011, Department for Business, Innovation and Skills and Office for Life Sciences; *A Strategy for UK Regenerative Medicine*, 2012, MRC et al.

¹⁶⁹ Regulation on ATMPs, Regulation (EC) No 1394/2007

¹⁷⁰ <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>

¹⁷¹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000265.jsp&mid=W_C0b01ac05800b378a

¹⁷² <http://www.sc-toolkit.ac.uk/home.cfm>

¹⁷³ <http://shop.bsigroup.com/en/Browse-By-Subject/Regenerative-Medicine/>

the UK and come from the majority of countries active in regenerative medicine. Additionally, over 2,250 hard copies of the Cell Therapy and Regenerative Medicine Glossary¹⁷⁴ have been distributed in the UK and internationally. This indicates that the UK is leading in setting standards in the international arena.

What difficulties are encountered when conducting clinical trials and how could these be overcome?

3.5 Regulation of clinical trials is harmonised at European level. The European Commission recently published proposals for a revision of the current European clinical trials regulatory framework (2001/20/EC). The proposals are for a Regulation, rather than the current Directive, and the Commission's central aim is to ensure that the rules for the conduct of clinical trials are identical throughout the EU. Negotiations on the proposals for review of the Clinical Trials Directive are expected to commence in autumn 2012.

3.6 The Government's Plan for Growth highlighted the need to improve clinical trial start up and cost effectiveness. Progress on commitments aimed at improving the clinical trials environment has taken place on a number of fronts. The NIHR Research Support Services framework has been launched to facilitate consistent local research management. The Health Research Authority has been established to protect and promote the interests of patients and the public in health research, helping to streamline regulation and improve the cost effectiveness of clinical trials. The NIHR will be making research funding to NHS Trusts conditional on meeting benchmarks, including a 70 day benchmark to recruit first patients for trials; performance will affect funding from 2013.

Difficulties encountered when conducting translational research within the NHS and how could these be overcome?

3.7 The NIHR supports Translational Clinical Research through the NIHR Biomedical Research Centres and Units (BRC and BRU's). One example of partnership working with industry is The London Project sponsored by Pfizer running at Moorfields and the Institute of Ophthalmology NIHR BRC.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

3.8 In order to improve outcomes for patients and deliver value for money, 'Innovation, Health and Wealth'¹⁷⁵ was launched in December 2011 to drive the adoption of innovation at pace and scale across the NHS. This listed some 30 actions to improve innovation in the NHS, the oversight of delivery will be the responsibility of an Implementation Board, chaired by Sir Ian Carruthers.

3.9 According to work undertaken by the TSB's 'Value' project¹⁷⁶, the current pathway for adoption of innovative and disruptive health solutions in to the NHS is clear, but poorly

¹⁷⁴ <http://shop.bsigroup.com/Browse-by-Sector/Healthcare/PAS-84/>

¹⁷⁵ http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131299

¹⁷⁶ https://connect.innovateuk.org/web/136128/articles/-/blogs/the-final-report-of-the-tsb-funded-value-project-has-just-been-published-and-is-available-for-review?sessionId=C61E6999D512E06363679794AC78190C.MekushUdbew4?ns_33_redirect=%2Fweb%2F136128%2Farticles

understood and utilised by both the industry and the NHS. NICE have recently developed capacity in the Scientific Advice Programme to offer more generic advice in the form of training workshops to companies. They have yet to receive requests for advice on regenerative medicine products from smaller companies.

4. Barriers to Commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

4.1 In an area of high uncertainty including the science, the technologies, the route to market and indeed the market itself there are likely to be high levels of variation between individual market estimates. That said, UK Trade & Investment values the global regenerative medicine industry at just over £500 million, and estimates that it will be generating revenues of over £5 billion by 2021. It is extremely difficult to estimate what share of this market UK business will capture but given our leading position in the field we are well placed. This is of course the reason why we have a Regenerative Medicine Strategy and are investing particularly in the translational space.

4.2 Wider social benefits of the regenerative medicine industry in the UK include the employment of 15,000 people in knowledge-based research and manufacturing jobs¹⁷⁷. The improvement in health of approximately 1 million people per annum will lower healthcare spending and improve quality of life. Although there has been no definite study into the rate of return to investments in regenerative medicine, current medical studies put the rate of return on cardiovascular disease research at 9% and mental health at 7%. Including wider societal benefits, the rate of return could be as high as 40% for cardiovascular research¹⁷⁸.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

4.3 The Regenerative Medicine Programme and new Cell Therapy Catapult aim to support the commercial development of regenerative medicine therapies and the delivery of these highly innovative products to patients. Over this last year alone, the TSB has committed some £2 million in support for four regenerative medicine projects to progress to clinical studies. Additionally, projects received £6.5 million of funding from TSB (£3.9m), and MRC/BBSRC/EPSRC (£2.46m) to support the development of manufacturing technologies or the development of safety/efficacy assays.

4.4 More generally, the TSB supports the commercialisation of new technologies in sectors such as healthcare through the Small Business Research Initiative. It also provides support for proof of concept and of market activities, and the development of prototypes within businesses and universities through the Smart Awards (previously known as Grant for R&D).

4.5 Many individual companies do not possess the specialist skills and knowledge required in connection with innovation. Most also struggle with access to specialist technical

¹⁷⁷ Finbarr Livesey, Enabling the Emergence of the Regenerative Medicine Industry in the UK, p.1
<http://www.ifm.eng.cam.ac.uk/cig/documents/Workingpaper3.pdf>

¹⁷⁸ Medical Research: What its worth? Estimating the economic benefit for Medical Research in the UK.
http://www.wellcome.ac.uk/stellent/groups/corporatesite/@sitestudioobjects/documents/web_document/wtx052110.pdf

facilities or services, due to high costs. TSB-funded projects such as Collaborative R&D projects and Knowledge Transfer Networks enable the exchange of information and skills between academia and industry within particular technology areas.

What role does patenting play in the commercial development of regenerative treatments?

4.6 Patents are seen as an incentive to innovate, particularly in fields where development costs are high, such as in regenerative medicine. However, they do not offer any guarantee of feasibility, quality or commercial merit. External factors relevant to the commercialisation of a patented invention include governing regulations, the existing market and competition.

4.7 In regenerative medicine, the route from patenting to commercialisation differs according to the type of invention. For example, the progress of clinical trials may be more involved for therapies as opposed to devices. This makes it difficult to make direct links between trends in patented technology¹⁷⁹ and trends in commercial development.

4.8 Moreover, an invention need not be patented to be marketed. If a product cannot be reverse engineered by competitors, or only with considerable investment, then secrecy, or the data protection associated with marketing approval requirements, may provide sufficient commercial advantage. Even so, as is the case of many start-up firms, a granted patent may be the most significant asset they hold in terms of demonstrating potential for investors. This is why concerns were raised in response to the Court of Justice of the European Union's ruling on the Brüstle vs. Greenpeace case. The application of this ruling reduces the availability of patents in the UK and other member states for inventions that involve stem cells derived from human embryos. The UK Government has secured agreement that the European Commission will report on the impact of the Court's ruling at the end of this year.

What business models are most appropriate to support the development of regenerative treatments?

4.9 The TSB funded three projects to support the development of regenerative treatments by exploring potential business models, adoption and reimbursement, manufacturing and supply relevant to the sector. The reports from two of these projects ('Value' led by Biolatris, and 'Realise' led by the Scottish Stem Cell Network) have been submitted separately as evidence to the inquiry.

What are the barriers to securing finance to develop such treatments?

4.10 Access to adequate financial capital on a timely basis is seen as a significant barrier to the regenerative medicine industry. The uncertainty over clinical efficacy and adoption by the health system, feeds into uncertainty in future margins, cost of goods and reimbursement.

4.11 The Government provides support for companies investing in research and development (R&D) through the R&D Tax Credit. In total, over £1 billion of support was

¹⁷⁹ See for example the Intellectual Property Office's patent landscaping report published in 2011 at <http://www.ipo.gov.uk/informatic-regenmed.pdf>

provided through the Small and Large Companies schemes in 2009-10. In Budget 2011, the Chancellor of the Exchequer announced that the level of the Small Firms R&D Tax Credit would be increased to 200% in April 2011 and to 225% in April 2012.

4.12 Government programmes that support venture capital investment to businesses, in all sectors and from early to later stage investments, include the Enterprise Capital Funds programme and the UK Innovation Investment Fund. In addition, tax incentives such as the Enterprise Investment Scheme and Venture Capital Trusts provide incentives for investors to provide equity finance for individual companies or to invest in venture capital funds.

4.13 UK Trade & Investment has developed a detailed proposition of UK's capabilities in regenerative medicine. This is being used to better promote the UK's regenerative medicine industry, generating potential international investment leads.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

4.14 There is no national policy specifically on the pricing of regenerative medicines. For branded regenerative medicines supplied to the NHS, pricing is currently controlled by DH through the Pharmaceutical Price Regulation Scheme (PPRS). This aims to balance a reasonable price for the NHS and a fair return for the industry to enable it to research, develop and market new and improved medicines.

4.15 Although PPRS has provided stability over time, it has not been considered to promote sufficient innovation or access. A much closer link between the price the NHS pays and the value that a new medicine delivers to patients and to society is needed. In view of this the Government will introduce value-based pricing from January 2014 to provide a broader assessment of a medicine's value, taking into account factors such as unmet need and wider societal benefits.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

4.16 Delivery systems are an additional concern. NHS Blood and Transplant (NHSBT) already provides a diverse range of specialist services in human tissue and cells such as the collection, Good Manufacturing Practice (GMP) production, storage and delivery of viable cell therapies. The Department of Health is working closely with NHSBT to ensure these services are an integrated part of strategy development. NHSBT will be providing a separate response to the inquiry.

5. International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

5.1 Nearly all the leading regenerative medicine countries are investing heavily in Translational Research Centres, but with mixed approach to their business models (all public sector funding, part public/private). Canada is focusing its National Centre on the lower risk cell therapy technologies with a view to delivering commercial return within 3 - 5

years. Germany, has established its centres of excellence at multiple geographies as opposed to there being a single national centre.

5.2 Some Governments have chosen to focus public sector support on technologies adjacent to existing national industrial strengths or on the countries research strengths. The US' Centre for Regenerative Medicine is focused on iPS cell research and similarly Japan has recently (August 2012) announced plans to create a clinical-grade set of iPS cell lines.

5.3 A number of countries have a strategic intent to develop deep international collaborations. There are bilateral links (e.g. between Germany and China), and multilateral links (e.g. the US, Germany, Canada and Spain have formed the 'Regenerative Medicine Coalition'). Following the creation of the cell therapy centre, the UK is exploring deeper international collaborations.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

5.4 The European Commission developed the legislative framework that applies to ATMPs in order to harmonise the regulatory framework across the EU. This followed concerns expressed in the UK and elsewhere in the EU that the lack of regulatory clarity was holding back investment and progress in developing new innovative technologies/products in this area.

5.5 Products categorised as ATMPs are subject to the centralised procedure under which EU-wide marketing authorisation is granted by the European Commission following assessment by the European Medicines Agency (EMA). Under the Regulation, there is an exemption for ATMPs which are prepared on a non routine basis and used within the same Member State in accordance with a medical prescription for an individual patient (the 'hospital exemption'). It is also possible to supply ATMPs as unlicensed medicines ("specials") to meet the special clinical needs of an individual patient under the direct responsibility of the clinician where an equivalent licensed product is not available. To date, the MHRA has not authorised any sites to manufacture under the 'hospital exemption'. However, many of the sites engaged in the development of ATMPs in the UK hold a manufacturing specials licence.

5.6 The European Commission has committed to review the operation of the ATMP Regulation by 30 December 2012. The review will include an assessment of the impact of technical progress on the application of the legislation.

5.7 The UK's strict but permissive legislative and regulatory framework has attracted researchers from countries seen to have more restrictive regulations.

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

5.8 The UK has taken an early international lead in setting technical standards and in establishing a common nomenclature. This work has been led by the British Standards Institution who recently updated and published a set of three cell therapy and regenerative medicine standards.

5.9 In cases where tissue or cells are to be used in a medicinal product, the donation, procurement and testing of these are covered by the Tissues and Cells Directive (2004/13/EC), transposed into UK law by the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and the HTA is the competent authority. Processing activities such as work in derivation laboratories leading up to a point where a Master Cell Bank has been established with a reasonable expectation of clinical utility in a medicinal product will be covered under the Tissues and Cells Directive. Thereafter, medicines legislation applies with the MHRA and the EMA as the national and European regulators.

5.10 Both the MHRA and HTA play an important role in influencing EU policy development and representing UK interests within an EU regulatory framework for regenerative medicine. They work closely together and are in the late stages of formalising working arrangements in a memorandum of understanding.

5.11 From April 2013, the National Institute for Biological Standards and Control (NIBSC) will become part of the MHRA. The integration will provide a number of specific opportunities to strengthen UK capability, including harnessing NIBSC input for scientific advice and specialist aspects of regulatory assessment, supporting innovative product development and rapid follow up of potential adverse events.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

5.12 The risks UK citizens face are considerable if they go abroad to acquire unregulated treatment that has not complied with internationally recognised clinical trials processes. The Department of Health recommends that patients who are considering involvement in private stem cell therapy or enrolling on a private stem cell research trial discuss their participation with their GP or consultant. The Government also supports the work of the International Society for Stem Cell Research to introduce guidelines for those considering paying for private stem cell therapy.

18 September 2012

Annex I

HOUSE OF LORDS SELECT COMMITTEE INQUIRY INTO REGENERATIVE MEDICINES - MHRA CONTRIBUTION ON REGULATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

1. The legislative framework that applies to advanced therapy medicinal products (ATMPs) is laid down at European level. The Regulation on ATMPs, Regulation (EC) No 1394/2007, entered into force on 30 December 2007 and applied from 30 December 2008. The Regulation was developed by the European Commission in response to concerns expressed in the UK and elsewhere in the European Union that the lack of regulatory clarity was holding back investment and progress in developing new innovative technologies/products in this area. The Regulation resulted in harmonisation of the regulatory framework that applies to ATMPs across the EU.

2. The Regulation groups together three categories of medicinal products called ATMPs – those categories are tissue engineered products, gene therapy and somatic cell therapy products. The Regulation also covers combination ATMPs – such products incorporate a medical device (as laid down in Article 1 (2) (a) of Directive 93/42/EEC or an active implantable device in accordance with Article 1 (2) (c) of Directive 90/385/EEC.

3. The ATMP Regulation did not change the definition of medicinal product but introduced specific requirements tailored to the nature of ATMPs. The Regulation also established the committee for advanced therapies (CAT). The CAT comprises members from EU Member States and brings together multi disciplinary expertise as well as representation from patient organisations. Products categorised as ATMPs are subject to the centralised procedure under which a centralised European marketing authorisation is granted by the European Commission following assessment by the European Medicines Agency (EMA).

4. In order to obtain marketing authorisation, applicants need to provide adequate evidence of safety, quality and efficacy. To date, the European Commission has authorised one ATMP under the centralised authorisation procedure (a product called Chondro Celect). A gene therapy product (Glybera) received a positive opinion from the European Medicines Agency in July 2012 – it is expected that authorisation from the European Commission will be granted in the near future.

5. Under the Regulation, there is an exemption for ATMPs which are prepared on a non routine basis and used within the same Member State in accordance with a medical prescription for an individual patient (the ‘hospital exemption’). The hospital exemption was included in the Regulation in recognition of the small scale developmental activity that takes place in hospitals in this area. It was considered that in such situations it would not be realistic for a hospital to apply for a full marketing authorisation. The provision was therefore included to allow some flexibility for development activity within individual Member States. The exemption is however tightly drawn so as not to undermine the incentive for companies to invest in achieving a marketing authorisation.

6. The Regulation stipulates that manufacture of ATMPs under the hospital exemption must be authorised by the Member State (the MHRA for the UK). In addition, traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to ATMPs with a centralised marketing authorisation. To date, the MHRA has not authorised any sites to manufacture under the hospital exemption. In addition, it is also possible to supply ATMPs as unlicensed medicines (“specials”) where the product is supplied under the derogation that applies under Article 5 (1) of Directive 2001/83/EC (the main European medicines Directive). Under the derogation, an unlicensed medicine may be supplied to meet the special clinical needs of an individual patient under the direct responsibility of the clinician where an equivalent licensed product is not available. Many of the sites engaged in the development of ATMPs in the UK hold a manufacturing specials licence.

7. In cases where stem cells are to be used in a medicinal product the donation, procurement and testing of the cells are covered by the Tissues and Cells Directive (2004/13/EC). Processing activities such as work in derivation laboratories leading up to a point where a Master Cell Bank has been established with a reasonable expectation of clinical utility in a medicinal product will be covered under the Tissues and Cells Directive.

The Human Tissue Authority (HTA) is the competent authority for the Tissues and Cells Directive. Thereafter, medicines legislation applies with the MHRA and the EMA the national and European regulators. The MHRA and the HTA work closely together in this area and have held joint advisory meetings with organisations from the ATMPs sector, carried out joint inspections of sites in this area and also collaborate on other matters of mutual interest. This working arrangement is in the late stages of being formalised in a memorandum of understanding.

8. MHRA currently plays a key role in Europe in the regulation of ATMPs. From April 2013, the National Institute for Biological Standards and Control (NIBSC) will become part of the MHRA. This integration will present a number of opportunities for collaboration that will strengthen the UK's capability to further support the development and regulation of regenerative medicines.

9. NIBSC established and continues to operate the UK Stem Cell Bank, a key component of the UK's strategy to lead the development of regenerative medicine. NIBSC's role is to support translation of the scientific promise of regenerative medicines into clinical therapies by providing to the research and development community well characterised, quality assured and ethically sourced stem cell lines, by developing and sharing practical expertise in growth, characterisation, standardisation and control of cells for therapeutic use, and by helping to establish a scientifically robust and practical regulatory framework to underpin the field. NIBSC is the world leader in developing the tools for measuring the safety and efficacy of biological medicines, with unrivalled infrastructure and expertise. It has extensive networks both nationally and internationally.

10. The merger will provide a number of specific opportunities to strengthen UK capability, including harnessing NIBSC input for scientific advice and specialist aspects of regulatory assessment, supporting innovative product development and rapid follow up of potential adverse events.

GUIDANCE ON THE ATMP REGULATION

11. Guidance on the Regulation is available from both the EMA and the MHRA. The EMA's Innovation Task Force provides regulatory and scientific advice for ATMPs that are intended to be placed on the EU market. In addition, the MHRA has undertaken a wide range of initiatives in order to support the sector and provide guidance on the regulatory framework including:

- publishing comprehensive guidance on the MHRA website;
- developing advice arrangements on product classification specifically tailored to products that may be ATMPs;
- contributing to the UK regulatory route map for stem cell research and manufacture which was produced in 2009 and updated in 2012;
- providing advice and guidance to individuals and organisations ranging from researchers at academic institutions and representatives of professional bodies through to multi-national pharmaceutical companies;
- keeping abreast of developments in the field of regenerative medicine and the convergence with other emerging technologies such as nanotechnology and the possible impact on the regulatory framework;

- hosting workshops as well as meeting with individual investigators/sponsors at regulatory meetings;
- hosting with the EMA an open meeting of the London Regenerative Medicine Network on ATMPs in April 2011; and
- hosting a joint symposium with the Drug Information Association in November 2011.
- The MHRA will be hosting a conference on regenerative medicines on 30 October 2012.

REVIEW OF THE ATMP REGULATION

12. The European Commission has committed to review the operation of the ATMP Regulation by 30 December 2012 (this is laid down in Article 25 of the ATMP Regulation). The review will include an assessment of the impact of technical progress on the application of the legislation. The UK will have the opportunity to contribute to this review.

CLINICAL TRIALS REQUIREMENTS FOR ATMPs

13. Regulation of clinical trials is harmonised at European level and clinical trials on ATMPs must be conducted in accordance with the principles laid down in the Clinical Trials Directive (2001/20/EC). The MHRA is responsible for authorising clinical trials and inspecting and issuing the manufacturer's licence for any investigational ATMP in the UK.

14. The European Commission has recently published proposals for revision of the current European clinical trials regulatory framework. The Commission has indicated that the number of clinical trials conducted in the EU decreased by 25% between 2007 and 2011. The number of clinical trials of ATMPs in the EU has been increasing. A similar increase has been seen in the UK.

- 10 trials were conducted in 2009 **(of which 2 were conducted in the UK)**.
- 11 trials were conducted in 2010 **(of which 3 were conducted in the UK)**.
- 66 trials were conducted in 2011 **(of which 8 were conducted in the UK)**.
- 61 trials have been conducted to date in 2012 **(of which 6 have been conducted to date in the UK)**.

15. One of the areas included in the Commission's proposals for review of the clinical trials legislation is to introduce a co-ordinated assessment where trials are conducted on a multinational basis though the authorisation of clinical trials would remain a national competence. Negotiations on the proposals for review of the Clinical Trials Directive are expected to commence in autumn 2012.

Government–Department of Health (DH), Medical Research Council (MRC), Wellcome Trust and British Heart Foundation (BHF) – Oral evidence (QQ 42-63)

Evidence Session No. 3

Heard in Public

Questions 42 - 63

TUESDAY 6 NOVEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
The Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Professor Dame Sally Davies, Chief Medical Officer and Chief Scientific Adviser, Department of Health (DH), **Sir John Savill**, Chief Executive, Medical Research Council (MRC), **Sir Mark Walport**, Director, Wellcome Trust, and **Professor Peter Weissberg**, Medical Director, British Heart Foundation (BHF), gave evidence.

The Chairman: I should like to welcome the first witness panel this morning with the usual reminder that the session is being webcast and that sotto voce comments are picked up by the microphones. The declaration of interests that Members have made is available to the observers in the note that you have on the chairs. I remind Members who have not spoken before in this inquiry, if they speak for the first time, to declare any relevant interest before they do so. First of all, I invite the four witnesses to introduce themselves for the record, starting with Sir John Savill and moving along the row. If there any points that any of you wish to make as part of your introduction, please feel free to do so, but please keep them brief because we have quite a lot of question-and-answer to follow.

Sir John Savill: I am John Savill, currently serving as chief executive of the Medical Research Council. I also work at the University of Edinburgh.

Government—Department of Health (DH), Medical Research Council (MRC), Wellcome Trust and British Heart Foundation (BHF) – Oral evidence (QQ 42-63)

Professor Dame Sally Davies: I am Sally Davies, the Chief Medical Officer and Chief Scientific Adviser to the Department of Health, and I direct the R&D budget for the NHS NIHR.

Professor Peter Weissberg: I am Peter Weissberg, medical director of the British Heart Foundation. We have made a major commitment to regenerative medicine and research recently.

Sir Mark Walport: I am Mark Walport, director of the Wellcome Trust.

Q42 The Chairman: Let me kick off. What we are trying to build at this point of the inquiry is an understanding of who is funding what. Please look at the funding in terms of basic research, different elements of translation from preclinical to stage 1, stage 2 and stage 3 clinical trials—so that whole block—and finally the commercialisation and delivery to patients. We have received a lot of numbers in different bits of written evidence, but they are quite confusing to say the least, so we are trying to bottom out from you, who represent the principal funders of research in regenerative medicine. Can you give us some numbers? How much do you spend? I will go along the line, starting with MRC.

Sir John Savill: Can I just address the point that you have made? The document “A Strategy for UK Regenerative Medicine”, includes a stock-take of public sector funding, which I believe you have, published in March. It shows that there are 353 projects with an annualised spend of £72 million. Of that, £37.7 million is from the MRC; that is, 52%. The other major players in this are BBSRC, which contributes £12.8 million; EPSRC, which contributes £11.3 million; TSB, which contributes £8.8 million; and then a number of other funders, including NIHR, ESRC, the Scottish Government and STFC. So the public sector figures were analysed as recently as March, but obviously they do not include very important contributions, particularly from the Wellcome Trust and the British Heart Foundation.

Q43 The Chairman: To be clear, the total annual public sector spend is £72.6 million divided over 353 projects, so that is £0.2 million annual spend per project. How is that partitioned along the different stages of basic through translation to application?

Sir John Savill: Again, this is a developing science in the life sciences. In the physical sciences, great use is made of technology readiness level assessments, from early discovery through prototype to adoption. Those TRL assessments can be transposed on to biomedical science. The same document has a very useful graph, which again you will have seen, that shows that by far the largest investments are in the very early stages of discovery science, with only a small number of projects in the translational pipeline at this stage. This simply reflects the state of the art.

Professor Dame Sally Davies: Since that, we have been looking more closely at what our infrastructure is spending, so I can now add to that. In our NIHR biomedical research centres and units, we are spending about £9 million a year in this area. Clearly, it is a very broad area. There is at least one programme grant of over £1.5 million at University College and about £1.5 million going to NHS Blood and Transplant.

The Chairman: Is this part of the £72 million?

Professor Dame Sally Davies: No, this is in addition, because, through the summer, we always update our figures.

Sir John Savill: To explain that a bit more for the Committee, I have recently visited Birmingham, where NIHR supports a clinical research facility and a cell therapy facility. The

infrastructure, the nurses and the cell therapy experts are supported by NIHR. The research that the other public sector funders include in that £72 million relies heavily on the NIHR infrastructure at the translational stage.

Q44 The Chairman: Coming back to Dame Sally, is the £9 million a year that you are investing more at the translational end, or can you give us a breakdown across it?

Professor Dame Sally Davies: It is a minimum level of what we are putting in because it is such a broad area. It is difficult. It is the NHS infrastructure in general for the research that others fund. We are directly contributing to some things; for instance, the gene therapy factor IX study at University College. We have contributed to the vector development facility and the research, and in the work which I think that you have heard about at Moorfields, we will play a major part along with two private sector people.

Q45 The Chairman: Let me now ask the two charity funders what the figures are. I know that you are representing the British Heart Foundation, Professor Weissberg, but I wonder whether you have a general figure for charities other than the Wellcome Trust.

Professor Peter Weissberg: I am afraid I cannot give you a much more general figure for global charity spend, although I suspect that, between the Wellcome Trust and ourselves, we capture most of it. We estimate that we have so far committed about £40 million—that is not per annum; that is the total over the past few years—into regenerative medicine. That includes fundamental science and developmental biology which feeds into regenerative medicine, but at least two-thirds of that is aimed specifically at a regenerative medical outcome.

Q46 The Chairman: If you annualise that, is it £40 million over, say, five years?

Professor Peter Weissberg: No, it would be over about three years, I think.

The Chairman: So roughly 12 to 13 per year.

Professor Peter Weissberg: But we have made a very specific call for funds. We have a fundraising appeal at the moment called Mending Broken Hearts. It was launched last year and the intention is to raise an additional £50 million over and above our annual spend of somewhere around £100 million a year on cardiovascular science across the board. This is an additional £50 million that we wish to spend over the next five years in regenerative medicine. To pre-empt questions that may come along later, I shall explain how we are spending the money. We have just received applications for two centres of cardiovascular regenerative medicine.¹⁸⁰ We have made sure that the applicants are collaborative, not competitive, so we have encouraged universities to talk to each other about complementary skills before making their application. For example, Edinburgh and Glasgow have put in a joint application, as have Oxford and Cambridge. We have partnered with the Medical Research Council around its regenerative medicine platforms bids and made sure that any or all we give is linked to one of those. So there is a very strong element of joined-up thinking here in trying to get added value.

Q47 The Chairman: So just to try to nail the numbers in my mind, your current spend on regenerative medicine is around £13 million and you are going to add to that another £10 million a year through Mending Broken Hearts?

¹⁸⁰ Note from witness “We have just received three applications for up to two centres of cardiovascular regenerative medicine that BHF is seeking to fund.”

Professor Peter Weissberg: Approximately, yes.

The Chairman: So it would be £23 million per year over the next few years?

Professor Peter Weissberg: Yes, but the figures are not set in stone. We flex it according to the quality of the applications that come in.

The Chairman: And that is largely at the basic research end of the spectrum?

Professor Peter Weissberg: Pretty much all of it. We have one or two small proof-of-concept clinical trials that we are supporting. I am afraid that, in my field, cardiovascular regenerative medicine and myocardial regeneration, our view is that the science just is not ready yet to be translated. Despite the fact that numerous clinical trials have been done with bone marrow cells, none of them has really delivered on the initial promise and the science underpinning them is not always that robust. We are very keen to get the basic science right before launching into clinical trials.

Sir Mark Walport: We fund the full spectrum of research, from basic research all the way through to clinical trials. We also fund public engagement. For example, our recent exhibition, “Superhuman”, at the Wellcome Collection is not unrelated to regenerative medicine. In terms of the quantum, we are talking about roughly £70 million, depending on the precise definition of regenerative medicine, committed at the moment.

The Chairman: Is that annual?

Sir Mark Walport: No, that is not annual. Again, because we do commitment accounting, we write it all down in the year that the grant is made, but you can divide it roughly by four to get the annual spend. In terms of the division of that activity, about £40 million of that is on basic stem cell research and the rest is on various applied elements.

Q48 The Chairman: Some of the written evidence that we have had indicates a lack of funding at the more translational end. The Scottish Government, for example, said that, “there is a continuing market failure between very promising academic research data and early stage clinical proof of principle which will attract larger scale investment. Most countries competing in this space are now providing second phase public-sector funding in order to build their regenerative medicine industries of the future. The Scottish and UK Governments will need to do the same if they want to build on the investment made thus far”. What do you think of that?

Sir John Savill: I am happy to address that; I might have written it myself when I worked for the Scottish Government a couple of years ago. That experience was salutary for me, because I observed translation initiatives that I do not think reached their full potential because they did not address the need to link the basic discovery research to the translation research. As the Committee will know well, the UK Government, through TSB, have committed £50 million to what is now called a “catapult” centre in cell therapy. That is not exclusively regenerative medicine cell therapy but, by and large, that is the main target. The new chief executive has made it clear that he wants that resource devoted to what he calls pathfinder trials, which demonstrate a particular principle in the field. He has the means to commit £50 million to support pathfinder studies. The research councils have responded together, particularly MRC, EPSRC and BBSRC, with a £25 million initiative in the shape of a regenerative medicine platform. That is now being structured so that it addresses key questions in the field; for example, immunological reaction to heterologous cells and the seed-and-soil issue of the substrates on which cells might prosper. So I think that in fact the

public funding is there to address the translational agenda, but clearly it has to be highlighted.

Q49 The Chairman: Would anyone else like to comment on whether there is enough money in this translational space?

Sir Mark Walport: It is always a balance, of course, between enough money and enough good proposals, so one has to look at the push as well as the pull. Because we have a technology transfer division, we are able to fund in the area of translation. We have just announced a new translation fund which brings together two of our funding streams in technology transfer. The first theme highlighted is called Restoring the Body, so that is a pretty clear invitation for funding in this area. As you may know, we have also set up on the investment side of the Wellcome Trust a fund called Syncona, which has money to invest in biomedical translation in various forms. So I believe that the money is there. You have to look at both sides.

Q50 The Chairman: I am going to ask other Members of the Committee, Lord Dixon-Smith, Lord Willis and Lord O'Neill, to come in in a moment, but I wonder whether, Dame Sally, you have anything to add from the NIHR perspective on whether there is funding in the translational area.

Professor Dame Sally Davies: It is always very difficult to judge. We have a variety of routes. The BRCs and the BRUs decide locally, having passed peer review, what the balance of their portfolios is and they have chosen to put quite a significant amount in this area. We also have jointly between the MRC and ourselves the Efficacy and Mechanism Evaluation programme—phases 0, 1 and 2A perhaps. We have a phase 2 trial of gene therapy for cystic fibrosis in that, funded by the MRC, which is very expensive. The charity could not afford it, but, between us, we thought that it was important to take it forward. So there are routes.

Q51 Lord Dixon-Smith: Can we try to translate the resource involvement in a different way? It is very easy to do it in money terms. What is it in human terms? I can imagine that this is a difficult question to answer, because many people spend some parts of their lives—maybe small, maybe large—in research and some in medical practice. But it would be interesting to me at any rate to know what the human involvement is.

Sir John Savill: That is a very good question. What I have heard is spend of the order of £100 million. Broadly speaking, if you divide 50,000 into that, you would get a figure that equates roughly to the number of people involved. I would think that we are talking about somewhere between 1,000 and 2,000 researchers in the UK who are currently supported in this area. That is an inexact figure; I do not have the data; but most funders' experience is that each head costs roughly £50,000 to £75,000 per year depending on the form of funding. So that is a pretty considerable response.

Lord Dixon-Smith: That is very helpful.

The Chairman: Does anybody wish to gloss that?

Professor Peter Weissberg: Only to add that one of our initiatives is to try to entice scientists into the regenerative medicine field, particularly the cardiovascular regenerative medicine field, because we have a wealth of very good scientists, but they are not all focused on regenerative medicine. Part of our initiative is to try to entice some of them to refocus their attentions away from what they happen to be doing at the moment on to

cardiovascular regenerative medicine. There is an element of capacity-building at the basic science level to get the good science done.

Q52 Lord Willis of Knaresborough: I first declare an interest as the chair of the AMRC, which I should have done last week when I asked a question. I address my question particularly to Mark Walport and it is on the issue of a national strategy. We have heard about disparate elements coming into regenerative medicine. Even at £100 million, it pales into insignificance compared with what is happening particularly in the United States. None of you has mentioned, for example, the Office for Life Sciences. Who is actually co-ordinating this from on high? Who hovers over it to make sure that we get the best drive? It did seem that when the life sciences strategy came out this was going to be one of the very rich fields. I am at a loss to see who is driving it from the Government's point of view.

Sir Mark Walport: There is no single, overarching national strategy. Indeed, one would have to think from the charity perspective about the extent to which that would be valuable. You could argue that you would need to write it for all sorts of different areas, of which this is just one. The funders around this table work together extremely closely. The Office for Strategic Coordination of Health Research, or OSCHR, is a body where topics such as this are discussed and which again brings together the research councils and the Department of Health. I am a non-executive member of OSCHR. If you look at the evidence of our funding partnerships, the Wellcome Trust funds with NIHR through the Health Innovation Challenge Fund; we fund partnerships with the Medical Research Council—for example, the stem cell centre in Cambridge. We have just announced a big induced pluripotent stem cell partnership in which Fiona Watt, your adviser, plays a principal investigator role. So if you look at practice on the ground, you will see that we work together extremely well without a guiding hand from above.

Lord Willis of Knaresborough: Do I take from that that it would not be helpful to have a guiding hand from above?

Sir Mark Walport: My personal opinion is that it would not add a lot of value because we work together very effectively anyway. But it would be interesting to hear what others think.

Professor Dame Sally Davies: Can I pick it up from the government perspective? What we do not want is bureaucracy; what we do want is alignment and debate, so that good applications get funded and get moved, for instance, from the MRC to us or vice versa, depending on which is the key funder in that area. The OSCHR plus bilaterals have shown that it works pretty well. The other bit that we have is the UK Clinical Research Collaboration, where MRC, industry and many people have a seat. So we have a number of co-ordination mechanisms, and I would argue that we do not need more bureaucracy.

Sir John Savill: Perhaps I may make a general point and a specific one. The general point is that, in my view, science works best grass-roots up. Most of the funders represented at this table listen very carefully to what scientists in the field want to do and we see their applications. We have to be ruthless about the quality of applications that we fund, which does not always make us popular with our friends and neighbours, but nevertheless we listen very carefully to what the scientists want to do. Much of the strategy in the UK is driven by our excellent scientists. There is some strategic push. I think back to Sir John Pattison's report, published in about 2006, in which he argued that we needed five or six centres each spending about £10 million. Well, we have got that now. For what it is worth, we have published *A Strategy for UK Regenerative Medicine* involving the public funders.

Currently, there is a sensible mix of benign overview about where we should be going, with pressure up from the scientists themselves, which is really good for British science.

Q53 Lord O'Neill of Clackmannan: In some respects, what I was going to ask has almost been covered, but you did make the point about the bottom-up approach. How often do research projects get hawked around between the four of you? Is this a time-wasting process? Do people make simultaneous applications and take up your time, or am I perhaps being a bit oversimplistic? You are telling us that there is a benign view from above and, obviously, you are not necessarily the best people to ask what the view is like from below, but do you think that, from below, people perhaps spend more time than they should trying to secure funding for their programmes after they have had an initial rejection?

Sir John Savill: I think that we have all had a few. It is the John West principle: John West fish are best because of what they reject. Broadly speaking, at the moment, the MRC is supporting about 20% of proposals. In the field, I think that most people think that that is about right. Members of our boards go away at the end of a board feeling that the applications that should have been funded have been funded. All of us around this table will have had applications rejected. They are made better by working harder on them. We have to accept that there is what some people would regard as waste. Whenever we defend ourselves in a spending review, the Treasury taxes very hard over, “Well, surely, this represents waste”. Well, it is the John West principle. You only get the best if you reject a lot of what comes. With regard to the bigger issue of whether grant applications are hawked around, in a very sensible way they are when there are large applications. Mark referred to a very important programme on induced pluripotent cells that he might like to cite as an example of how we can work together co-ordinately to fund very big, ambitious proposals.

Sir Mark Walport: I think it depends on the scale of the proposal. Small, response-mode applications, for a project grant, programme grant, a fellowship or one of the Wellcome Trust Investigatory Awards, are all reviewed competitively. I do not think that any of us allow people to make simultaneous applications except for the most junior fellowships. Those are done in competition and the applicant may end up taking them to two or three funders. When it comes to the larger grants, those are much more co-ordinated and I think that research funders play a much more catalytic role. If you look, for example, at the induced pluripotent stem cell grant, which is a £12 million grant from the MRC and the Wellcome Trust, you will see that we played there a very active catalytic role. We assembled the community; there were at least three meetings when the proposal was discussed; and, to some extent, we nurtured it through the application process. When it came to the crunch, it had to defend itself against other grants at our Strategic Awards committee, but there was a high degree of catalysis in that process. So, for the big grants, there tends to be catalysis and they do not have to make repeated applications, though they are not guaranteed success. For the smaller grants, I think what Sir John Savill has described is exactly right. There is a competitive element, and it is one of the strengths of the British system that we have a plurality of funders. People have asked, “Well, wouldn’t it be better if we all threw it into a single pot?”, but that would give you only one chance, whereas in the model that we have at the moment, you get more than one.

Professor Peter Weissberg: I echo both those responses. I agree with John that a lot of what is presented to us in responsive-mode research is really not fundable research; it is not good enough. That is not my view; it is the view of the reviewers and the committees. When it comes to the bigger money—the larger sums and the multiples of millions—it is

almost unheard of for us not to talk to the MRC and perhaps the Wellcome Trust as well, and Sally if it is appropriate and clinically orientated, to decide before we go ahead with receiving applications as to how we are going to handle them. We have a fairly sophisticated, if unwritten, protocol whereby we receive applications very often jointly; we review them jointly; and we then commit money to them as independent organisations. But a lot of joined-up thinking goes on for the higher-value grants in this field.

Q54 Lord Turnberg: I should declare an interest in that I am scientific adviser to the Association of Medical Research Charities, of which the BHF and the Wellcome Trust are both members. What does your organisation consider to be the funding priorities for regenerative medicine? Is your funding co-ordinated? We have talked about co-ordination. Reading your written submissions, I found them extremely helpful, but it did seem that, as an applicant for a grant to one or other of you, I would be faced with a plethora of potential funding mechanisms, through platforms, challenge funds, catapults and translation funding. There seems to be rather a lot of them. Perhaps you could explain a little more about the relationship between them. Some criticise the MRC for focusing too much on cell therapies at the expense of research on other treatments such as biologics and tissue engineering. How do you respond to such criticisms? Perhaps you could deal with the question in two parts.

The Chairman: Do you want to deal with the first part of the noble Lord's question, on the plethora of funding opportunities and how the researcher navigates their way through?

Professor Dame Sally Davies: I could start. Are they not lucky that they have all sorts of opportunities? The savvy, good researchers have watched this accretion and understand what the funding streams are for, and that some of them are only a one-off. It is very interesting that, when we set up a new stream of funding, it always takes two or three rounds before the researchers get what we are after. I wanted to highlight the role of programme managers in all our organisations—the TSB and the other research councils—so that researchers can and do ring up and say, “I want to do this. Is it appropriate?”. They get guidance. I know that, between ourselves and the MRC, they shift applications, let alone advice, between the two and into our shared challenge with Wellcome. So advice is there for them, but the savvy ones have no problem working around it.

Q55 Lord Turnberg: Do you think there should be some central advisory mechanism? If someone has an idea and they want to pursue it in the area, which would be the best route to take?

Professor Dame Sally Davies: No, because they would be out of date almost immediately. They need to go to the funder, who will tell them what they are thinking and whatever the strategy of the council or the NIHR is at that time.

The Chairman: Does anyone else wish to come in or do you agree with Dame Sally?

Sir Mark Walport: Only to agree with Sally and to make the point that the Wellcome Trust is an independent funder. We work very effectively with the other funders in the UK, but one of our great strengths is our independence. The idea of a single co-ordinating body where you could go for advice for all grant mechanisms in the UK is probably not the ideal solution. Sally is exactly right that people phone us up.

Sir John Savill: The reason why I recently went to Birmingham is that the MRC engages in regular strategic dialogue with the major research-intensive universities and medical schools. I will visit them annually, or one of the senior staff will visit them. Again, we frequently say,

“Well, that idea would be great for the British Heart Foundation. Why don’t you speak to Peter Weissberg?” or, “That would be good at the Wellcome Trust”, so there is a lot of interchange between the research programme managers that Sally referred to, people at chief executive/director level and the scientists who are interested in this field. It is impossible not to interact with them, as you know.

Lord Turnberg: So good researchers know where to go.

Professor Peter Weissberg: That is exactly what I was going to say. If you were naive about the field and looked at the morass of things available, you would be confused. On the other hand, we do not really want people who are naive about the field, because they will not do a very good job. I suggest that all the key players know well in advance, before the calls come out, what is on the horizon, because, by and large, they have been engaged in discussions about how to shape calls for funding to suit their needs. I agree with what John said: we talk to researchers a lot and, if we sense that there is a particular need out there, we will often coalesce funding in a way to satisfy that need. That is driven by the researchers rather than the funder, but to somebody going to the website, it will look like a call out of the blue and it does not evolve that way.

Q56 Lord Cunningham of Felling: I should like to ask Professor Weissberg how what he said earlier about the importance of attracting new and better scientists and researchers to this area fits with what he has just been saying. You almost made it sound like a rather cosy system which nobody else could break into.

Professor Peter Weissberg: We have a particular problem in cardiovascular research in the UK in that, for some years, we have lagged a bit behind the rest of the world having been well at the forefront for some time. There was a job of work to be done there to capacity-build by getting young scientists into the cardiovascular research field. Our remit is cardiovascular research, so, of course, we are focused on that. We are the major funder; we fund about 51% of all the non-commercial cardiovascular science in the UK. So we see it as our job to entice young scientists into our field. On this occasion, we are majoring on regenerative medicine, but not totally, because we fund the whole panoply of cardiovascular science. There is an issue for us in that there are not enough good people at the very top of the tree in cardiovascular science at the moment. We do not have a surfeit of world-class applicants for our chairs. We have to search around the world and place people. I am concerned about capacity-building in the next generation. We put a lot of money through research centres of excellence and this programme into PhD studentships, young scientist fellowships and intermediate fellowships to give them a career pathway. That is beginning to pay off now, so I would suggest that, as a result of one of our initiatives, we now have some 120 or 130 new researchers being trained in cardiovascular science coming through the pipeline who will be the leaders in the next decade or so. I do not think that what I have said is inconsistent.¹⁸¹

Sir Mark Walport: This is absolutely at the cutting edge of science at the moment. This is where cell biology and molecular genetics is in the forefront. It is very important not to take too narrow a view of what regenerative medicine is. I do not think that Sir John Gurdon, who won the Nobel Prize three weeks ago, thought that he was doing regenerative medicine. Indeed, I do not think that Shinya Yamanaka, when he developed his induced pluripotent stem cells thought that he was doing regenerative medicine. Much of what we

¹⁸¹ Note from witness: Inexperienced young scientists need to be trained by experienced leaders in the field who know how to access appropriate research funding for them, so the way to capacity build is to provide funds for leading scientists to recruit and train new talent in the field.

fund with Cancer Research UK at the Gurdon Institute is cell biology at the cutting edge, as is much of what happens at the Sanger Institute. For example, a recent experiment in which Sanger researchers collaborating with Cambridge researchers took a skin cell from a patient with a deficiency of an enzyme inhibitor, alpha-1 antitrypsin, corrected the gene defect and turned it into a liver cell. This is absolute cutting-edge science that gets published in the very best journals. One has just to be a bit careful. The basic science here, which still has to be done at a very high level, is very attractive; a lot of the smartest young scientists are going into it. The challenge is how much of this science is actually ready for translation. I think there is a danger of overhyping this. Peter Weissberg might want to come back on this, but it is unlikely that we would have funded some of the early studies injecting stem cells into the circulation in the hope that they would regenerate the heart, because they seemed to us to be premature. The question is more: how much of this science is ready for translation? Of course, there is one example; you asked about funding by other organisations. Bone marrow transplantation is probably the most spectacular success of regenerative medicine in which the UK has played a leading role, and that has been going on for many years.

Professor Dame Sally Davies: We continue, both ourselves and the MRC, to fund exploration in that area. I just wanted to highlight a programme of NIHR research professorships that we have, involving early in their career, cutting-edge, translational research scientists. In the first year, we awarded eight, and it is going to be five a year, each for five years. They are getting a very supportive package. Among the first eight is Professor James Bainbridge at Moorfields, who is doing its gene therapy. So we are trying to build from the young people as well for this nation.

Q57 Lord Cunningham of Felling: If I could just ask a supplementary question in view of what Sir John Savill said a while ago about the number of people engaged by this spend. How quickly is that number growing? Is it growing at all?

Sir John Savill: I think that it has grown very fast over the past seven or eight years. When John Pattison published his report and said that we should be spending £50 million, everyone thought, “Wow, that is a lot of money” and we have doubled it. So I would say that the science, particularly the transitional clinical science, has developed seriously over the past five, six or seven years. The issue that Peter was highlighting is one of translation. It is getting people who have the expertise to understand the heart in the human to want to do regenerative medicine. Perhaps I may personalise that from the point of view of the University of Edinburgh. We have a bright young chap; he did his PhD; he is a clinical cardiologist; he understands how to cannulate the heart for diagnostic and therapeutic purposes. He did a PhD funded by the BHF in cardiovascular pathophysiology. He is now training as a clinical scientist in cell therapy. He has been enticed into the field. So getting clinical scientists who want to make a difference to patients is part of the translational pathway. The BHF is making a very good fist of it in the cardiovascular area. I should say, Mark, that I do not remember the BHF funding work of the kind you described.

Sir Mark Walport: No I didn’t say they did.

Professor Peter Weissberg: I was just going to say that we have not.

The Chairman: Could I ask Sir John to respond to the second part of Lord Turnberg’s question?

Sir John Savill: I thought I might have been off the hook. It is a very legitimate point of view. You might think that if you look solely at the MRC strategy. That strategy is set out in our delivery plan, agreed with government, and there is a major focus on stem cells and

discovery science. If you looked at the MRC, Wellcome Trust and BHF centres of excellence, you might have a similar view. At Cambridge, Edinburgh, Imperial and places such as that, you might think that there is a strong focus on stem cells and cell therapy, but that overlooks the contribution made by the EPSRC, the BBSRC and the Technology Strategy Board. They have made major investments in advanced manufacturing facilities in Leeds, Loughborough and other centres of excellence that address the issue of the substrates on which cells might be grown before transplantation into a human, and the substrates that might be used in an interdisciplinary regenerative medicine approach that would encourage autologous cells to fire up again and restore and regenerate tissue. So I emphasise that the MRC is only half of the public sector spend. A lot of the other half focuses on those areas that your question implies might be being underdone. I do not think that they are.

Sir Mark Walport: We have two partnerships with the EPSRC in the medical engineering space. At Imperial College, we have a centre for medical engineering solutions in the management of osteoarthritis, and at Leeds, we have a partnership: engineering solutions for an ageing population with musculoskeletal and cardiovascular disease. I pick up John's point that regenerative medicine goes a long way past cell therapy.

Q58 Lord Dixon-Smith: I have a slightly peripheral question. Is there a relationship between NIHR and NICE, which of course has an interest in outcomes?

Professor Dame Sally Davies: NICE, the National Institute for Health and Clinical Excellence, is one of the customers of our evidence output. We invite it to tell us what its key research evidence needs are and put them into our programme. In this particular area, I am not aware that we have many products beyond stem cell transplants and everything that it will have looked at.

Lord Dixon-Smith: It seems to me that there should be a relationship between what I would call the customer—

Professor Dame Sally Davies: There is.

Lord Dixon-Smith:—and those who are proposing the research. You have just said that there is not.

Professor Dame Sally Davies: No, I have just said that it is the customer for the evidence output and we invite it to tell us what its specific needs are so that we can commission the appropriate research.

Lord Dixon-Smith: Okay, that is fine

Professor Dame Sally Davies: Often, what it asks us to do is on research—but that is a minefield.

Q59 Lord Turnberg: Just a quick question on co-ordination. None of you has mentioned industrial involvement or co-ordination with industry. That may be a big question and I am not sure that we have got time to answer it fully. Could you comment briefly on interaction with the industry? Are we at the stage where we need to talk to it?

Sir John Savill: That is a helpful question, because that is a strong feature in the UK, although we are probably reaching a stage where small and medium-sized enterprises in this area no longer need the help that they have had. There has been a UK stem cell network that has supported small companies. In my own bailiwick, I know well that there has been a Scottish stem cell network. Obviously, the funders speak regularly to big pharma. Pfizer has

an investment in this through a small company called Neusentis based in Cambridge. We also speak regularly to the industry association that represents a lot of the companies in this area. Many of those discussions were seminal in persuading government to put more money into TSB so that MRC could partner it in an £180 million biomedical catalyst fund which we hope will pick up some regenerative medicine as well as other good ideas. The relationships with the companies are very important.

Professor Dame Sally Davies: There are set-piece meetings of the Ministerial Industry Strategy Group where industry, Ministers, I and others sit. R&D does come up. There is the UK Clinical Research Collaboration, which meets three times a year, where industry associations are invited, plus others, and where they can bring issues up. From our perspective, we leave it to the researchers to build specific bridges. If you take the example of Moorfields, it has a partnership with Advanced Cell Technology from the US and Pfizer. So there are project partnerships and then strategic discussions.

The Chairman: I would like a brief comment from Sir Mark and Professor Weissberg, and then I shall turn to Lord Patel.

Sir Mark Walport: On the iPS consortium, again, industry was actively in discussions about setting that up and it will be one of the major users of the induced pluripotent stem cells.

Professor Peter Weissberg: I simply want to add a note of caution, in that, because we would all like to see this science translated into man—that is certainly the case in my field of cardiovascular medicine, where we are trying to create new myocytes, which, five or six years ago, would have been said impossible, but now looks potentially biologically tractable though it is still a long way off—there is huge public pressure on us to fund clinical trials when they are just not ready to be done yet. One of our problems is trying to hold our fire so that we do not make the mistake of ruining the field by rushing too quickly into clinical trials which come out as damp squibs and people think that this is fantasy and not fact. It is biologically tractable, but it takes a lot of biology before we get to where we need to be. I speak purely from a cardiovascular perspective; there are other areas that are more advanced than that.

Q60 Lord Patel: My question focuses primarily on initiatives and processes set up for translational research. Have the new initiatives and processes improved translational research in regenerative medicine? Have they helped people who want to do clinical trials, or early-phase and late-phase clinical trials, and is there support for academia and the NHS to translate research into effective medicine?

Sir John Savill: Again, if I can respond on behalf of members who sit round the OSCHR table, an obsession for members of the OSCHR for the past five years is how we ensure that the increased investment that came in with the 2007-08 spending review delivers for the nation. Around that table, we feel that the life sciences strategy that was mentioned earlier by Lord Willis is a significant advance in the Government's thinking about how to take the translational agenda forward. I refer you to the point that Peter Weissberg has made: the proof of the pudding is in the eating. We are not ready to eat it yet, but it is looking jolly tasty. The investment that has gone into the translational pathway is very impressive and, I think, puts Britain in a world-leading position.

Lord Patel: From fish to pudding, John, is pretty healthy.

Professor Dame Sally Davies: The NIHR started six years ago with the biomedical research centres and units. In the first round, the international panel thought that we had some decent partnerships between the NHS and academia. It recommended funding and we

funded generously. The second round was completed last summer and its contracts started in April this year. That was a different kettle of fish. It was very exciting to see the partnerships between basic translational and NHS in order to pull things through and the quality of the science. The international panel recommended that some people who had biomedical research centre status and funding be dropped, so it was a very competitive field. But it is beginning to pay off: we have made major contributions to gene therapy at Moorfields; Leber's congenital amaurosis; and the factor IX gene therapy at University College, with six patients done. So there are things happening. It is a very exciting area, with people collaborating much more than they used to.

Q61 Lord Patel: So you think that the new initiatives to promote collaborative translational research are the way forward and that we have got it right?

Professor Dame Sally Davies: I think that people need to compete to get the funding. There are different ways of doing it. There are the very big projects, where you start with a collaboration and you build it with peer review as you go into it, or there are smaller ones where there needs by definition to be some competition to make sure that we fund the best. But then it is important that people, once they have the money, collaborate with the right others. Increasingly, researchers are collaborating.

Lord Patel: So networks of research scientists working across the UK is a better model than researchers collocated?

Professor Dame Sally Davies: I was not commenting on that at all; I think that it is horses for courses. In some subjects, you need collocation; in others, you need more distant networking and collaboration.

Sir Mark Walport: It is important to say that we are not complacent about this area. It is rapidly evolving; there are always things that we can do to be catalytic. A good example of an initiative is the Catapult being set up at King's. That will be important because it clearly has a powerful catalytic role in trying to get from the bench to the bedside. But it is important to say that we are not complacent. Our role is to catalyse; there will be new initiatives and groupings; and we will facilitate that happening.

Q62 Lord Patel: ABPI suggested in its evidence that there was a funding gap between early-phase and late-phase clinical trials. Would that be a fair comment?

Sir Mark Walport: That is a generic problem. I am not sure that there is any evidence that that is especially an issue for cell-based therapies. There is a question about what the business models will be for the bespoke cell-based therapies. The way that bone marrow transplantation has evolved, most of the business opportunities are around the equipment and paraphernalia for doing it rather than the stem cells themselves. So quite what the business models will look like is uncertain.

Sir John Savill: The biomedical catalyst, which, again, was a plot hatched at OSCHR, really sought to address that. From the point of view of industry, there has been a gap in terms of small companies getting the development funding that they need to do the proof-of-concept work and proof-of-mechanism work in humans. To some extent, we hope that that will be plugged by the biomedical catalyst. I see this more as an observation on the state of venture capital investment in the UK for small companies than as a criticism of public funding in translation. I should just like to reiterate one point that Sally made: the reason that we feel reasonably confident, but not complacent, about the transitional pathway is the feedback that we get from international reviewers. The large grants that we have been talking about

always have international review. The significant investments that Sally made, getting on for £900 million, again, have high-quality international peer review. Experts from across the world are telling us that what we are doing looks good.

Q63 The Chairman: We are coming to the end of our time, so perhaps you could keep your final comments brief. You have given us a pretty positive picture of the funding landscape, in terms of the increased volume of support, the recruitment of new blood into important fields related to regenerative medicine and the balance between basic and translation and commercialisation. Should we take away from this that nothing needs to change, that it is steady as she goes and that we have got it right, or are there things that you feel should be changed?

Sir Mark Walport: Clearly, one has to look at this in terms of the overall science budget. So the critical issue will be to maintain and, hopefully, increase the overall science budget. At the moment, if spending in one area is increased, it will have to be at the expense of funding in another, and it would be equally easy to see how you could have inquiries in a number of areas of science at the moment and ask similar types of questions. The big issue will be the overall science envelope. A second question will be this balance of how much TSB funding is available—TSB is the obvious funder missing from this table—and that will be a very important component of science funding as well. The issue is perhaps less about looking tightly within stem cells and more about looking at it in the context of the broader science spend. I think that there will be a balance to be struck.

Professor Peter Weissberg: I am optimistic about the way things are going. The direction of travel in the UK in the past five years has been extremely good. My biggest concern would be potential legislative changes over the horizon, which could slow us down. If the European decision on clinical trials gives us the wrong answer, we could be in real difficulties in prosecuting the things that we want to do. Patient data and all the issues which are at the moment being considered could slow down a movement in the right direction. I think that everybody is facing in the right direction at the moment and I am quite optimistic, provided that nothing gets in the way and turns us back.

Professor Dame Sally Davies: I think that we started well, but we know that there is a problem with venture capital. There is also a problem for start-up companies of vector production and that kind of technology issue. I echo Mark's concern that, if we really want this and other areas to work, we are going to have to continue to invest in them. Even a stable state, which in the present economic circumstances would be potentially generous, would be damaging to this and other areas. We will need to continue to invest, particularly if we want to see growth building on the investments to date.

Sir John Savill: I am not sure that there is a panacea, but the key issue is what we can do as a society to drive economic growth as well as health gain from the research that we have been talking about. Again, I think that that probably requires additional targeted investment beyond what we are very fortunate to have had protected by the coalition Government. Medical research spending in particular was protected, having been increased in 2007. We are very grateful for that, and one has to be realistic, but we need more investment to get the right growth ecosystem in this area.

The Chairman: Thank you. On that note, I should like to draw this session to a close and thank you all for your comments. You will receive in due course a draft of the transcript for you to make comments on. If there is anything else you wish to say to us, please feel free to send in comments in writing, which will form part of the published evidence base. Thank you very much indeed.

Government, Headquarters Surgeon General, Ministry of Defence – Supplementary written evidence

I have been asked to respond to you on behalf of Headquarters Surgeon General, regarding a request for information by the Lords Science and Technology Committee about MOD investment into regenerative medicine research.

I can confirm that the following areas are being explored as part of the National Institute for Health Research (NIHR) Theme 3 (Reconstructive and Regenerative Medicine):

Traumatic Brain Injury –identification of brain injury by psychological tests and biomarkers.

Ocular Trauma – treatment of injuries arising from operations.

Cranio-Facial Reconstruction –with the Healing Foundation.

Composite Tissue Allograft –at an exploratory stage.

The MOD has committed £10M, in collaboration with the University Hospital Birmingham Foundation Trust, which includes elements of regenerative medicine.

9 January 2013

Government – Further supplementary written evidence

This supplementary memorandum has been prepared by the Department for Business, Innovation and Skills (BIS) and the Department of Health (DH).

1. This note sets out the geographic distribution of research capabilities, business activities, national infrastructure and networks relevant to Regenerative Medicine in the UK. Research capabilities evidence draws on work undertaken by UK Trade & Investment and the Medical Research Council (MRC). The geographic distribution of businesses developing regenerative medicine products used the Department for Business, Innovation & Skills (BIS) Bioscience and Health Technology database.
2. Regenerative Medicine Research capabilities clusters are found across the UK and include the East of England, the North of England, London, the Midlands, Oxford and Scotland. This does not mean of course that regenerative medicine research is not happening elsewhere. Details of these research clusters are provided in Annex 1 and the National Institute for Health Research (NIHR) Biomedical Research Centres (BRCs) and NIHR Biomedical Research Units (BRUs) conducting Research in Regenerative Medicine in Annex 2.
3. Our analysis identified 40 businesses whose primary purpose is to develop regenerative medicine products. The geographic spread of this business activity largely matches research clusters as shown below;
 - East of England – Cambridge area 8 companies)
 - Yorkshire (York, Leeds, Sheffield) – 8 companies
 - Scotland – Edinburgh region – 5 companies
 - Manchester (including Wilmslow in Cheshire) 4
 - London 3 companies
 - Cardiff 2 companies
 - Aberdeen, Abingdon, Birmingham, Bristol, Daresbury, Durham, Guildford, Keele, Leicester and Nottingham each with one company
4. Infrastructure
 - The Cell Therapy Catapult and UK Regenerative Medicine Platform (UKRMP) have been established to bridge the gap between academic invention and real life commercial products. The industry-led Catapult will address technical issues relating to the quality, safety and efficacy of cell therapies in pre-clinical studies and carry out clinical trials as well as develop effective manufacturing processes for these novel products. It is located in London within the NIHR Biomedical Research Centre at St Guy's and St Thomas' NHS Foundation Trust and King's College London. The academic-led UKRMP will be based upon a network of 4 to 5 geographically distributed research hubs that will provide a technology platform to address the translational barriers upstream of commercial development
 - The UK Stem Cell Bank is based at the National Institute for Biological Standards and Control at Potters Bar, Hertfordshire. The Bank was established to provide a

repository of human embryonic, foetal and adult stem cell lines for research use. It has now accepted the first UK 'clinical grade' hES cell lines which are expected to support the oncoming stream hESC-based clinical trials for novel regenerative therapies.

- The National Health Service Blood and Transplant Service (NHSBT) operates eight Good Manufacturing Practice (GMP) facilities capable of manufacturing regenerative medicine products. These facilities are based in; Liverpool, Oxford, Birmingham, Bristol (two facilities at Langford and Filton), Sheffield, Leeds, and Southampton. The facilities have a total of 31 GMP compliant clean rooms. From these facilities NHSBT provides a national service and is capable of providing an international service upon request. NHSBT managed GMP compliant clean rooms represent approximately 50% of the cell therapy manufacturing capacity of England.
7. Networks_ There are at least three geographically discrete regenerative medicine networks and other networks like Health Science Scotland have strong interests in this area as part of their broader remits. In addition, the HealthTech and Medicines Knowledge Transfer Network has a special interest group in Regenerative Medicines and the National Clinical Human Embryonic Stem Cell Forum is an informal group of practitioner stakeholders in the area of pluripotent stem cell production for therapeutic use.

London Regenerative Medicine Network - the world's largest cell therapy and regenerative medicine network with in excess of 5,500 members representing all the stakeholder groups including: the general public, patients, patient advocates, students, scientists, engineers, clinicians, charities, government organisations and business people.

Regener8 provides industry members with easy access to the research expertise available within the Northern eight universities and academic members with the capabilities needed for successful translation.

Mercia Stem Cell Alliance (previously the North West Stem Cell Network) – is a network of scientists, clinicians and industry collaborators from across the North West region to facilitate the development and promotion of stem cell research in the region.

The National Clinical Human Embryonic Stem Cell Forum focuses on the procurement, manufacture and storage of human embryonic stem cells but also considers induced pluripotent stem cells and the manufacture and use of cell lines as advanced therapy medicinal products.

16 January 2013

Annex I

East of England

The Cambridge Stem Cell Initiative draws together researchers from 25 stem cell laboratories in Cambridge to form a world-leading centre for stem cell biology and medicine. The Initiative provides state-of-the-art equipment and expert advice in the following eight Core Facilities: Bio-Informatics, Cloning Services, Flow Cytometry, Gene Services, Histopathology, Imaging Facility, Information Technology Services and Tissue Culture Facility. At its core is the Wellcome Trust – MRC Stem Cell Institute established in July 2012 through the merger of previous MRC and Wellcome Trust centres.

The Cambridge Biomedical Campus is a NH R Comprehensive Biomedical Research Centre (BRC) and part of the Cambridge Academic Health Science Centre. The BRC houses the Induced Pluripotent Stem Cell (iPSC) Core Facility and provides a mix of stem cell, cardiovascular, state of the art imaging and phenotype research in close proximity to Addenbrookes Hospital Cambridge.

The Babraham Institute is a centre of excellence in epigenetics and regenerative medicine. It also has a large Biocubator. Approximately 400 people work at the Institute and 350 people in the (commercial) Biocubator with a number of these companies active in the regenerative medicine area.

University Campus Suffolk has established a regenerative medicine product development laboratory at their campus in Ipswich. The laboratory space is used in commercial collaborations and for their PhD research programme.

London and Cambridge. The new Wellcome Trust-MRC **Human Induced Pluripotent Stem cell Initiative (HiPSCI)**, based at Kings College London and the Sanger Institute in Cambridgeshire, will provide underpinning support for the development of iPSC-based disease models and drug screening platforms for both the academic and commercial sectors, and in the longer term clinical tools. It will link to the recent EU Innovative Medicines Initiative (IMI) StemBANCC award led from Oxford, which brings together a major consortium of academic, clinical and pharmaceutical partners to create iPSC-based drug development platforms.

London

The Imperial College Tissue Engineering and Regenerative Medicine Centre (TERM) – is based at Chelsea and Westminster Hospital and is a collaborative enterprise between translational biological research and material science. The Imperial College Hammersmith site is also home to the **MRC Clinical Sciences Centre** which represents one of the major MRC investments in stem cell biology/differentiation.

University College London Centre for Stem Cells and Regenerative Medicine – Launched on 24th April 2009, the centre brings together 185 researchers from several faculties, specialised hospitals and institutes across UCL, including the London Centre for Nanotechnology and the MRC National Institute for Medical Research (NIMR) which houses a number of stem cell-based research programmes.

Kings College London- the **Cell Therapy Catapult** is located in the NIHR Biomedical Research Centre at St Guy's and St Thomas' NHS Foundation Trust and King's College London. KCL also leads the new national iPSC platform, (HIPSCI), and provides one of MRC-funded derivation centres providing clinical grade hESC lines for the UK SC Bank.

Midlands

The **Loughborough-based Engineering & Physical Sciences Research Council (EPSRC) Centre for Innovative Manufacturing in Regenerative Medicine** carries out research, tests and implements ideas in clinical and industrial settings creating next generation platforms for manufacturing regenerative medicines. The Centre is a partnership between **Loughborough, Keele and Nottingham**. The **Institute for Science and Technology based at Keele University** has developed expertise in orthopaedic applications of Regenerative Medicine. The **Wolfson Centre for Stem Cells, Tissue Engineering and Modelling (STEM)** based at the **University of Nottingham** has particular expertise in treating fractures with cellular and tissue therapies.

Oxford

The **Oxford Stem Cell Institute** links 42 research groups across the University and undertakes research on embryonic stem cells, adult stem cells, hematopoietic stem cells, and cancer stem cells. It has links to the **MRC Molecular Haematology Unit in Oxford** which focuses on research on blood stem cells and related disorders.

North of England

Regener8 (www.regener8.ac.uk/home.html) is a partnership hosted by the University of Leeds and includes researchers based at North of England's 8 main research-intensive universities- **Newcastle**, **Durham**, **York**, **Sheffield**, **Manchester**, **Liverpool**, **Lancaster** and **Leeds**.

Newcastle Bio-Manufacturing Facility produces clinical grade stem cells and derived cellular products.

The **EPSRC-funded Innovation and Knowledge centre in Medical Technologies in Leeds** is based around the Universities integrated multi-disciplinary medical engineering centre and seeks to deliver innovation right across the medical technology spectrum – from implantable devices through to regenerative therapies that can be enhanced with autologous stem cells.

Manchester and **Sheffield** each host an **MRC-funded derivation centre** providing clinical grade hESC lines for the UK SC Bank.

Scotland

The **MRC Centre for Regenerative Medicine (CRM)**, based in the University of Edinburgh, is a world leading research centre that studies stem cells, disease and tissue repair. The Centre is based at the **[Scottish Centre for Regenerative Medicine](#)**

(SCRM) Building, on a site shared by the Royal Infirmary Hospital and the University's Clinical Research facilities. With new state-of-the-art facilities and team of scientists and clinicians, the Centre translates scientific knowledge to industry and the clinic. The Centre was formed in 2008 and is a conglomerate of the Institute for Stem Cell Research (ISCR) and the College for Medicine and Veterinary Medicine.

Annex 2

NIHR Biomedical Research Centres (BRCs) and NIHR Biomedical Research Units (BRUs) conducting research in Regenerative Medicine (England)

NIHR BRCs

NHS Organisation Total= 6 BRCs Running 9 programmes	Academic Partner	Research Themes
Cambridge University Hospitals NHS Foundation Trust	University of Cambridge	Transplantation and Regenerative Medicine
Great Ormond Street Hospital for Children NHS Trust	University College London, Institute of Child Health	Stem and Cellular Therapies
Guy's and St Thomas' NHS Foundation Trust (2 programmes)	King's College London	Transplantation; Translational Genetics
Imperial College Healthcare NHS Trust (2 programmes)	Imperial College London	Surgery and Technology (which includes a component on Cell Therapies)
Moorfields Eye Hospital NHS Foundation Trust (2 programmes)	University College London	Gene Therapy; Regenerative Medicine and Pharmaceuticals
University College London Hospitals NHS Foundation Trust	University College London	Cellular and Gene Therapy

NIHR BRUs

Priority Area Total= 5 BRUs Running 5 programmes	NHS Organisation	Academic Partner	Research Area
Cardiovascular Disease	Barts & The London NHS Trust	Queen Mary University of London	Cardiovascular Regenerative Medicine
Cardiovascular Disease	University Hospitals Bristol NHS Foundation Trust (UH Bristol)	University of Bristol	Cardiovascular Regenerative medicine
Gastrointestinal Disease	University Hospitals Birmingham NHS Foundation Trust	University of Birmingham	Liver Regeneration, Repair and Stem Cells
Musculoskeletal Disease	Leeds Teaching Hospitals NHS Trust	University of Leeds	Biomaterials and Regenerative Interventions
Musculoskeletal Disease	Oxford University Hospitals NHS Trust	University of Oxford	Orthopaedics

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Evidence Session No. 17

Heard in Public

Questions 357 - 366

TUESDAY 26 FEBRUARY 2013

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Rees of Ludlow
Lord Patel
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Rt Hon Earl Howe, Parliamentary Under-Secretary of State and Government Spokesperson, Department of Health, and **Rt Hon David Willetts MP**, Minister of State for Science and Universities, Department of Business, Innovation and Skills (BIS).

Q357 The Chairman: I would like to welcome the Ministers to this final evidence session in our inquiry into regenerative medicine. We have a number of questions that we would like to put to you in drawing our evidence to a close. I will invite you in a moment to introduce yourselves for the record. It goes without saying that the occasion is being webcast, so what we say is on the record and sotto voce asides will also be picked up. Without further ado I invite the two Ministers to introduce themselves, perhaps starting with Earl Howe.

Earl Howe: Thank you very much, my Lord Chairman. By way of introductory remarks, it is perhaps useful for me to say that, as a Health Minister, I am involved day to day with many aspects of health that relate to regenerative medicines, from the research dimension right through to regulation and, indeed, how we can spread innovation throughout the NHS. If we reflect on where we are with this agenda, we can point to a number of ways in which this country has benefited from strong support for the development of regenerative

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medicines. In that context, for me, the regulatory system that we have got in this country—which I would characterise as robust but facilitating—has a lot to do with it. That is partly why we are recognised as world-leading in embryonic stem cells, for example, and the system ensures that only research of the highest quality—both scientific and ethical—is carried out here. The more I have read on this subject, the more I think that regenerative medicine has the potential to play an increasingly vital role in delivering the next generation of healthcare, particularly in areas of unmet medical need. We are in a strong position, with world-class research, very high-quality infrastructure, an active commercial sector and, we must not forget, a single-payer healthcare regime to go with that, in the form of the NHS.

The Chairman: Thank you very much. Science Minister?

David Willetts MP: Thank you very much, Lord Krebs. Obviously my responsibilities are universities and science. We can take great pride in the excellent science that we have been conducting in regenerative medicine and cell therapies, with Nobel Prizes for Martin Evans at Cardiff and John Gurdon at Cambridge reflecting that. We fully understand that the challenge is to translate that into patient care and also into commercial and business opportunities. That is what we try to do in BIS through supporting the Cell Therapy Catapult, for example.

Q358 The Chairman: Thank you very much. I will kick off, perhaps addressing this in the first instance to Earl Howe. You paint a very positive picture of the potential future of regenerative medicine treatments within the healthcare system. At the same time, we have heard in our evidence sessions that there are a number of barriers to getting from where we are now to where we would like to be in delivering regenerative medicine treatments, including: barriers to innovation in the NHS, as reflected in the Nicholson report and the TSB review; the absence of a national policy on pricing for these treatments, which would be rather different in nature from conventional treatments, as highlighted by the House of Commons Health Select Committee in its report; and the question of whether we have sufficient infrastructure, for example, in provision of GMP products. I wonder whether you could come back and amplify your opening statement by saying what sort of steps are being taken by the Government to address the various obstacles that might be there to inhibit the development of regenerative medicine treatments and also perhaps, as a supplementary, give us your view on how soon you think such treatments will be widely available on the NHS. Are we talking five years, 10 years or further out?

Earl Howe: I would observe, first off, that the healthcare system in the UK has already been delivering some regenerative medicines successfully for a number of years—in fact, for decades—if one looks at things such as tissue transplantation and, more recently, stem cell transplantation, through to medicines such as erythropoietin. The definition of regenerative medicine is quite a broad one, and bone marrow transplantation falls under that definition. Now we are seeing induced pluripotent stem cells coming to the fore. For new, innovative therapies, the spotlight is very much on the recommendations contained in the report called *Innovation Health and Wealth*, the purpose of which, as I am sure all Members of the Committee will know, is to identify and find ways of overcoming the barriers to the spread of innovation in the health service.

First on my list, were I to look down the recommendations of that report, I would single out the concept of academic health science networks. We see establishing those networks as a unique opportunity to align clinical research, informatics, education and training, innovation and healthcare delivery as a way of translating research into practice, not just in

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one place but in many, and at an accelerated rate. That work, which we can perhaps come back to, is proceeding at present.

We can also point to the work of NICE in their technology appraisal guidance, which provides the NHS with really robust evidence-based guidance on the clinical effectiveness and cost-effectiveness of drugs and, indeed, other technologies. For example, NICE has appraised the use of autologous chondrocyte implantation for the treatment of cartilage injury. My notes say that this is a regenerative technology, so it does fall under the scope of this inquiry. NICE concluded that the evidence is, at the moment, insufficient to recommend its use except in the context of further research, but it plans to consider the need to update the guidance this year, pending the publication of expected trial data on the technology. I see NICE as facilitative in that context. It also operates a scientific advice service, which it charges for, advising pharmaceutical and medical technology companies, including those who intend to manufacture regenerative medicines, on their early plans for product development, so that the organisation can prepare the evidence in a relevant way for when they eventually submit proposals to NICE and other assessment bodies. NICE operates the initial stages of the topic selection process for its technology appraisal programme, and we expect that it will continue to consider the suitability of regenerative medicines in that appraisal process. The clinical guidelines that NICE prepares for whole conditions or pathways of care very often look at medicines. Regenerative medicines in particular could also be considered as part of that, where it is relevant.

I would also mention NHS Blood and Transplant, which already provides quite a range of specialist services in respect of human tissue and cells, such as the collection of tissue and cells, good manufacturing practice—which you mentioned—and storage and delivery of cell therapies. We are working closely with NHS Blood and Transplant to ensure that those services are an integrated part of the way that strategy is being developed.

You asked me how soon I thought these kinds of treatment would be widely available. Stem cell transplantation is firmly established in the NHS as a curative therapy for patients with leukaemia and other blood cancers. We can point to that as something positive. The transplantation of cells for diabetes, and the corneal epithelium in the eye, are also established in the NHS. Outside this country, I know there is work going on, particularly in the United States, with a number of cell therapy products, including cartilage and skin repair products, as well as products to treat bone adipose and blood disorders. My notes say that only two products have received marketing authorisation in Europe: ChondroCelect and Glybera, which is a gene therapy product. One can hope that, quite soon, what is happening in America may well be available here.

The Chairman: Thank you very much. I do not know whether David Willetts would like to add anything to that.

David Willetts MP: No.

Q359 Lord Patel: As a supplementary to that, from what we know now about regenerative medicine, in the early phase, the major block is going to early phase translation. Big pharma—and small pharma—are not prepared to go there unless they are fairly confident that the therapy is going to be successful. The cost of early phase translation is significant. The issue here is who should be responsible for funding or helping people with that early phase translation. We learn from other parts of Europe and from the United States that they have a mechanism to enable that to happen. From the evidence that we

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have had so far, we do not seem to have that. The Catapult may be one way, but the budget for the Catapult would not indicate that it is big enough for it to be able to do that.

The Chairman: This may be one for the Science Minister. How do we stimulate innovation?

Lord Patel: We can spare the noble Earl.

David Willetts MP: Of course, there are very large standing budgets elsewhere. Like this Committee, I have been to the California Institute for Regenerative Medicine and was very impressed. They say they have to \$3 billion to spend but, on the other hand, they seem to have a one-off \$3 billion: it is not totally clear what the successor arrangements will be, although I accept that \$3 billion is not a bad start. When you look at what we have been doing, we inherited from the previous Government a regenerative medicine platform within the TSB, which we have added to. Indeed, we added a further £20 million to regenerative medicine as part of the Autumn Statement's £600 million announcement. We have the TSB Programme. We have got the Catapult, which I am sure people might want to ask further about. It is one of our seven Catapult centres and is absolutely aimed at translational medicine, linking up the research with actual patient care in Guy's and elsewhere. Although as yet, sadly, only one project has been funded, our new biomedical catalyst can be available for funding regenerative medicine projects right through to clinical use. In the next round of allocations I am advised that we may see several more projects. I cannot match the scale of the \$3 billion but we are using all the instruments at our disposal—the TSB, the Catapult model and the biomedical catalyst—to try to link up the research base and clinical practice.

Earl Howe: I would add to that the funding which comes at the truly translational end, from the NIHR. I have got a long list of projects currently being funded by the NIHR in centres of excellence around the country, including Cambridge, Great Ormond Street and so on. There is quite a lot of money there, all told: over £45 million at the moment, in a number of projects. We are, I hope, addressing the question that you asked. However, I would just say that we have been very strict about the projects that we fund from the Department of Health. No preference is given to particular areas of research. Every proposal has to compete on the basis of the quality of the science within that proposal. We think that that is appropriate, as I hope you will, against the background of what is, inevitably, a cash-limited budget.

The Chairman: Could I just get clarification of the £45 million you referred to? Was that exclusively for regenerative medicine translational research? Or was it more general?

Earl Howe: It is more general. For example, Cambridge University Hospitals NHS Foundation Trust, in collaboration with the University of Cambridge, are looking at a project involving transplantation and regenerative medicine; Great Ormond Street are looking, with UCL, at stem and cellular therapies; and Guy's and St Thomas's are looking, with King's College London, are looking at translational genetics. It is a range of projects.

The Chairman: Would it be possible for us to have a note on how it breaks down into regenerative medicine and other treatments?

Earl Howe: Yes.

Q360 Lord Turnberg: I want to continue on this theme of translation. We are, as you say, pretty good on the basic science side but the thing is how to translate all this and how

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the Government can facilitate that. I have a specific question about the design and running of large clinical trials. Expertise is not freely available and it is quite a difficult area. What supportive roles can you play in facilitating that side?

Earl Howe: There are two ways in which we can do that. One is through advice and one is through streamlining of regulation. On the advice front, on a general level, we have the National Institute for Health Research—the NIHR—and the Research Design Service, the RDS, which offers researchers access to support when they are developing and designing high-quality research proposals. That can cover any aspect relating to preparing grant applications for applied research across the piece, including statistics, quantitative and qualitative research techniques, clinical trials, health economics, epidemiology or whatever it happens to be. That is a good all-round service.

The MHRA already provides support to sponsors of clinical trials, in the form of scientific and regulatory advice. Although I think it is primarily seen as a benefit to academics and to small to medium-sized enterprises who need their hands holding in this area, there may also be a need for this kind of advice for larger pharmaceutical companies who are moving into the field of regenerative medicine.

On regenerative medicine specifically, I think that if Sir Kent Woods were sitting here, he would say that he encourages early engagement with the MHRA on the part of investigators and sponsors. The MHRA have provided advice to investigators at the time of grant applications to funding bodies and will continue to do that. A new initiative for the MHRA, which you may have heard about, is the setting up of the Innovation Office, which is coming on stream quite soon, in March. The point of that will be to foster and support innovation over the whole range of development and manufacture of medicinal products and the development of medical devices. It is expected that a significant number of queries will be in the field of regenerative medicine. I think it is important to say that the MHRA has had initial contact with the Cell Therapy Catapult, to support the regenerative medicines sector.

As regards streamlining regulation, we have now got the Health Research Authority, whose purpose is, I suppose, twofold: to protect and promote the interests of patients and the public with research but also to help to streamline regulation and improve the cost-effectiveness of clinical trials. Although it has only been going for a short while, I am aware that it is doing a number of things which will help to reduce the burden of administering clinical trials. I can give you further and better particulars of what it is doing if you would like me to.

Lord Turnberg: I am surprised you did not mention the academic health science networks as helping facilitate development.

Earl Howe: I mentioned them earlier but of course they are not in existence yet. The proposals are still being evaluated but I can give you some encouraging news on that front, which is that the proposals are of high quality. There has been an enormous amount of enthusiasm on the ground for this concept, despite the fact that we are going through a time of change in the NHS. There is wide recognition of how powerful a concept this is.

Your question related to what support we could give to the design and administration of clinical trials. Broadly, I think I have answered that, but if we are talking about how we can encourage the spread and uptake of the results of clinical trials, when we have them, you are absolutely spot on. These networks will do just that. The whole point of them is to accelerate the pace at which the NHS can take advantage of these new techniques.

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The Chairman: Thank you. I will turn to Lord Broers, to pick up on a theme that Lord Patel touched on.

Q361 Lord Broers: We are on the same topic with this question really. My question is: what can the Government do to stimulate investment by the private sector in regenerative medicine? Presumably, this is one of the functions of the Catapult. Perhaps more generally, we are all aware of a lot of government programmes that stimulate innovation; you named a number of those in your report. Would you like to comment on the relative emphasis that you think is being placed on regenerative medicine as against all those other priorities that we have in the innovation space?

David Willetts MP: We see regenerative medicine as having a very high priority. We inherited from the previous Government an assessment by the TSB that it was a very important area of medical technology. Hence, there was already a platform which was delivering funding on a significant scale. I think that between 2009 and 2011, the TSB invested in 76 projects in regenerative medicine. If I may say so, when the Chancellor and I set out the eight great technologies where we see Britain as having a distinctive research lead plus opportunities to grow substantially, one of those eight great technologies was regenerative medicine. We are absolutely clear that it is very significant. That is why, out of the seven Catapults, one of them is, as this Committee knows, in this very important area.

Lord Broers: It is the international comparison that we are concerned about. I might ask you about the Catapults. Do you see Catapults as unlimited in size? If this turns out to be a very effective and important field, will we really be encouraging industry to get into the Catapult in a large way? The Catapults at the moment are running on a sort of £10 million annual budget, are they not? Would you see regenerative medicine—say the cell therapy one—growing above that?

David Willetts MP: We would not rule that out. The funding model for the Catapult was roughly based on Fraunhofers, although each nation does it themselves. One-third of the funding is from public money and one-third from bidding for projects, and with the other third we are looking for co-investment from business and other partners. The more that business steps up to the plate, you would find plenty more investment from us. The Cell Therapy Catapult was one of our first decisions, after advanced manufacturing, and as I think this Committee knows, it is now established at Guy's. It has not yet moved into its full, final set of facilities—those are being refurbished—but it is up and running.

There is this question of international challenge, which we are very aware of. There is a global race, as we say in the Government, and we keep a very close eye on the kind of very large initiatives launched in France. I talked earlier about the California initiative. When I was over in California meeting the people at the centre in San Francisco, without being complacent, what I took some encouragement from was that when I asked them where the other international centres of activity were and where they would look to as a place that they would partner with and take seriously, they were absolutely clear—I think that this has been brought out in what they have said to this Committee as well—that they saw the UK as a very serious partner. When I asked them, as independent objective observers, whether we were falling behind France or Germany, that was not their view. But you must never be complacent and we have to make sure we are up with the best.

Q362 The Chairman: One of the points they made to us was that we have a huge natural advantage with the NHS as a structure for translation into the clinic. But they did also—as I am sure they did to you—point out that, because of the high risk involved in

Government – the Rt Hon Earl Howe, Parliamentary Under-Secretary of State and Government Spokesperson, DH and Rt Hon David Willetts MP, Minister of State for Universities and Science, BIS – Oral evidence (QQ 357-366)

regenerative treatments and because we are exploring quite new territory compared with conventional drugs, the likelihood of pharmaceutical companies taking up the reins of funding this are quite low until you have got to a pretty advanced stage in clinical proof of concept. If you start from basic research, here, to people being treated, in a way, the valley of death has moved over in this direction when it comes to regenerative medicine. As you are aware, their model is to fund people with ideas to take their ideas right through to the clinic and establish FDA approval to carry out clinical trials. Only after that has happened do they envisage the private sector coming in. Are there lessons of that model for us in the UK?

Earl Howe: It is precisely for that reason that the NIHR has committed £800 million to biomedical research centres and units. That is a large sum by any standards. Those BRCs and BRUs are currently running 14 research programmes which involve translational research in regenerative medicine. That segment of the funding is around £9 million. I went to Moorfields a while ago, where they have achieved the world's first successful gene therapy for Leber's congenital amaurosis, which, as I am sure you will be aware, is a very distressing condition which causes progressive deterioration of vision and blindness in young people. If ever there was centre of excellence that we can point to, I always think of Moorfields. It is a genuinely world-class operation.

Lord Rees of Ludlow: This is just a question on Catapult centres. If you compare this particular one with the other six, it is more likely to be able to draw on philanthropic input to supplement the commercial sector. That will come obviously from medical charities but also from special charities for particular diseases. Does that give it a head start in terms of building up its scale compared to other Catapults?

David Willetts MP: That is a very important point. I am not aware, immediately, whether they receive philanthropic support and, if so, how much, but I will check that point out and perhaps provide a note to the Committee if there is philanthropic support. It is a very fair point.

Q363 Lord Patel: Could I follow up a bit more on what the Lord Chairman said? I have no question at all that as a Government you are committed to progressing with regenerative medicine and the whole area of life sciences. Clearly, we want to see that we lead the world, because we have top-class science. That is why places such as the California Institute for Regenerative Medicine think so highly of us. From the evidence we have got, it is not about what investment is going in—including the NIHR, biomedical centres, the Catapult, the Medical Research Council and others putting money in—but that there seems to be a lack of co-ordination or of one body having the intelligence out there to say which of the science is now likely to go to translation and who will take the lead. That is exactly what the CIRM in California is good at doing. Also, we need to recognise that early phase translation costs money, both in meeting the regulation fees and in providing money for early translation. If that is not available, because the therapy seems not to be ready or to be too risky, then others will steal a march on us. If you take the example of California, the institute itself is already looking at 11 or 13 early phase translations. Here, we know of three maybe, including the gene therapy one. The question is whether we have got the strategy right in terms of co-ordination et cetera.

David Willetts MP: We—or a TSB research council—published last year this document, *A Strategy for UK Regenerative Medicine*, which in turn drew on earlier work. We have tried to set out a strategy. I accept there is more to do on regulation and making that user-friendly,

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which is a regular message that we hear and the Department of Health hears. We are working on that. I think perhaps the issue which you are raising, which I completely recognise, is the manufacture of these cell therapies. That is why the value of death is potentially so broad and deep—the manufacturing challenge. Whereas in more conventional pharmaceuticals the manufacturing, at least of small-molecule drugs, is a well established procedure—it is an innovation but at least it is familiar—manufacturing cell therapies is a challenge. The fact that you can make something work in a lab does not mean that you can necessarily manufacture it on a scale necessary for clinical treatments. We completely understand that. That is why one of the functions of the Catapult will be to help work alongside on the manufacturing challenge. It is why there is excellent work under way elsewhere in the country on manufacturing, for example in Scotland, in Edinburgh's bioquarter. I assure the Committee that we are investing in new technology. We are not sitting back and expecting the commercial sector to take on much greater risk and uncertainty than they are willing to bear. We fully understand there is a legitimate role for government and public support in cracking the challenge of manufacturing techniques.

Earl Howe: NHS Blood and Transplant represent about 50% of the cell therapy manufacturing capacity of this country, with their clean rooms. There are eight GMP facilities capable of manufacturing regenerative medicine products. Unfortunately, I have not visited any of them but I am told that Liverpool is one of the most important ones. That really does comprise, I believe, an important national service. They say as well that they are capable of providing an international service as well, if they are asked to do that.

Lord Broers: On this general topic, it is as much a matter of the image of what we do. That is what Lord Patel is perhaps getting at as well. It is co-ordination. The UK is superb in this field but we are in Liverpool, Edinburgh, Oxford, Cambridge and London—we are not seen as a single cluster that big pharma must be involved in. That is what I am worried about and I wonder whether the Government can just help. It is not really a matter of money, it is a matter of gathering together some image of the UK as one single cluster and not a distributed cluster all over the place, so that people like Pfizer will not go away, because they will not be able to go away and still be competitive in certain fields. We are doing well but there is more we could do somehow to represent ourselves as an overall facility and cluster rather than a bunch of hot spots.

David Willetts MP: That is a very fair point. To be frank with the Committee, the process of setting up the Cell Therapy Catapult was quite a long and fraught one. One issue was this competition about where it should be. There were several strong bids, which the Technology Strategy Board had to assess. It became clear by the end that what we really needed was a centre. The decision was London and Guy's but that it should be the centre of a network. We did not want Edinburgh or Cambridge to feel they were somehow losers and did not have any role in this. We see the Catapult as a national resource linking up to those other centres. But there may be more we could do here and if there is advice from the Committee, we would certainly take account of it.

Q364 Lord Willis of Knaresborough: I want to come back to this whole issue of regulation and Earl Howe will not be surprised at that. I think we are all agreed that the breakthroughs in terms of regenerative medicine are not likely to come from large, traditional pharma but from small research groups, often academics, for example creating small SMEs. Whether we are successful or whether we fail depends on driving those through this whole process.

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If we take the issue of embryonic stem cells, a small SME coming out of, perhaps, a university, would, to get phase 1 or phase 2 clinical trials up and running, have to encounter in regulatory form: first of all the HFEA; then the HTA; then the Home Office for an animal licence; and then the MHRA, as well as the new organisation which is supposed to streamline this, the HRA, which is basically the National Research Ethics Service. If they want to move on from there, they would have to get something from NICE, and if they are going into Europe they would have to get support from the EMA. For a small organisation, that is mind-blowing. We have the opportunity, Earl Howe, of bringing the regulatory framework together in a seamless organisation. But the Government blew it. They said, “No, we will keep all these different little bodies”. Organisation after organisation has told this Committee that this is a problem and a challenge; yet we are not doing it. At the same time, we are spending literally millions on back-office functions for all these regulators, which create costs for the research programmes themselves and take money out of the system. Surely we can do better?

Earl Howe: I am aware that this concern has been expressed, that there is a kind of maze that you have to navigate in terms of regulatory oversight. It is very much with that in mind that the MHRA offers the service that it does, which I referred to earlier and which I think is well appreciated. I hope that you have gained a sense from your evidence sessions that the regulators do work very closely together. For example, the MHRA and the Human Tissue Authority do so; they have carried out joint inspections. We in the Department of Health, along with the regulators, have worked very hard to produce a regulatory map, in particular for stem cell research and manufacture. We are not ducking the issue that you have, rightly, highlighted. But “bringing it all together”, is perhaps a phrase that one would need to break down a little bit.

Q365 Lord Willis of Knaresborough: May I, with your permission, try to help you, as I always do? I think the Committee would accept that many of the functions of each of the regulatory authorities are, in themselves, important. They are there for a purpose but have built up a little like Topsy, and as new demands have come on through research, we have developed new regulatory regimes. The idea that they all need to have a chief executive, finance operations and media operations, all on top of that, just seems to me, as a very simple Member of your Lordships’ House, to be an incredible waste of resources, which we could be spending on the very things that you want them spent on; whether in the Catapult or on making sure that there are more hand-holders to actually bring these people through, as we saw in America.

Earl Howe: It was very much with that thought in mind that, following the recent consultation on what we should do with the functions of the HFEA and HTA, where the consultation came back and told us that we were on the wrong track—

Lord Willis of Knaresborough: They would say that, wouldn’t they?

Earl Howe: They said that we should not be parcelling out this function to the CQC. They were unhappy with that. What we are now proposing is a workstream to look at whether it makes sense to bring together the HFEA and HTA in a much more tangible way, along the lines you have suggested, or even more closely. However, we have been down this path before, with the proposals a few years ago for RATE, as it was called, and Parliament made its opinion very clear on that proposal at the time.

Lord Willis of Knaresborough: We have moved on.

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Earl Howe: We have moved on, I agree with that. We are in a different place now and we need to look at that sort of idea again very carefully, for exactly the reasons that you have articulated.

Lord Willis of Knaresborough: Can I just ask the Science Minister one question? The Minister—or his department—is responsible for the central admin and resource centre, which is now based in Swindon. Could you say whether the idea of having a super-centre is actually going to happen? Would they come under BIS's auspices and would they be taking on the central admin and organisational functions from organisations such as the regulators?

David Willetts MP: The suggestion is that Swindon is performing so well and achieving such high efficiency—

Lord Willis of Knaresborough: I am not saying that, your department is saying that.

David Willetts MP: Is the suggestion that Swindon is achieving such high efficiency and popularity that other people can look at her and ask Swindon to deliver services for them as well?

Lord Willis of Knaresborough: I understand the Treasury is thinking of that. Is that true?

David Willetts MP: I would not rule it out. It has been a very traumatic and painful process but I think we now have got this resource for, as you say, a lot of the back-office functions for the science and research community. If people made an absolutely persuasive case that it could help with the pay and rations for other members of the wider research community, I would not rule it out. I think we would be advised by the Department of Health on that.

Q366 Lord Wade of Chorlton: We are talking about regulators. We interviewed some of them, and we must remember that a regulator is appointed to regulate. That is what they do. If you want to change regulators, you cannot expect them to be more flexible when you have appointed them to regulate a particular thing. If government wants regulators to change, it has to change the regulations. That is a government role and I think you are expecting too much of regulators, in many ways, to adapt to changing circumstances, which regulators, by their very nature, do not do. I agree entirely with the arguments of Lord Willis that you should look seriously at this because you will not reorganise it. But the Government has got to meet the challenge. Maybe I am wrong, but I thought that we appointed Parliament and government to make the decisions; not to try to listen to a lot of people who want to try to hang on to their jobs. We have made so many mistakes in government over doing that. Do it.

Earl Howe: I would say in our defence that, at the outset of the current coalition government, we had an arm's-length body review, which in my department resulted in a wholesale shrinkage of the number of arm's-length bodies.

Lord Wade of Chorlton: I agree with all that.

Earl Howe: It was a very serious rationalisation. We decided to keep some bodies going. For example, we felt that it did not make sense to merge the MHRA with anyone else, although we are amending its functions in minor respects. But I take your point. It is incumbent on any Government to keep looking at this area. I mentioned the HFEA and HTA, which we do still think are two bodies where sensible rationalisation could take place. I do not think that arm's-length body reviews should be regarded as one-off exercises to be done once every 20 years. One should look constantly at the scope for this, because money

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matters and is in short supply at the moment. I can reassure you that we are not complacent on this. It is up to government to do this; it is not for the regulators themselves to propose their own destiny. But I would just pay tribute though to many of the regulators for the way in which they have brought in efficiencies to the way that they operate, often by collaboration in a very sensible way.

The Chairman: On that note, I would like to draw the session to a close and thank both Ministers for their very helpful contributions. There were a couple of points on which I think Earl Howe offered to send in further information. One was on this £45 million investment in translational research and how it breaks down. I think you also offered to send some notes on reducing the paperwork associated with clinical trials.

Earl Howe: Yes.

The Chairman: If we could receive those, that would be very much appreciated. If there are any other points that either of you feel we ought to take note of, please do not hesitate to write and give us some further information. In the mean time, thank you both very much indeed. You will receive a transcript of course to correct in due course.

Government – Further supplementary written evidence

This supplementary memorandum has been prepared by the Department of Health (DH).

Additional information for the House of Lords Science and Technology Select Committee Inquiry into Regenerative Medicine following Earl Howe's appearance in front of the Committee on 26 February

National Institute for Health Research – Regenerative Medicine programmes and funding

The National Institute is investing a record £800 million in biomedical research centres and units. These are currently running 14 research programmes which involve significant cutting edge translational research in regenerative medicine across a range of disease areas, attracting over £9 million per annum (as shown in the tables below).

List of Biomedical Research Centres (BRC) and Biomedical Research Units (BRU) conducting research in regenerative medicine (England)

NIHR BIOMEDICAL RESEARCH CENTRES

NHS Organisation Total= 6 BRCs running 9 programmes	Academic Partner	Research Themes	Funding 2012-17 Total: £38,711,860
Cambridge University Hospitals NHS Foundation Trust	University of Cambridge	Transplantation and Regenerative Medicine	£5,399,424
Great Ormond Street Hospital for Children NHS Trust	University College London, Institute of Child Health	Stem and Cellular Therapies	£11,517,285
Guy's and St Thomas' NHS Foundation Trust (2 programmes)	King's College London	Transplantation; Translational Genetics	£6,702,486
Imperial College Healthcare NHS Trust (2 programmes)	Imperial College London	Renal Medicine and Transplantation; Surgery and Technology (which includes a component on Cell Therapies)	£10,122,030
Moorfields Eye Hospital NHS Foundation Trust (2 programmes)	University College London	Gene Therapy; Regenerative Medicine and Pharmaceuticals	£3,508,096
University College London Hospitals NHS Foundation Trust	University College London	Cellular and Gene Therapy	£1,462,539

NIHR BIOMEDICAL RESEARCH UNITS

Priority Area Total= 5 BRUs running 5 programmes	NHS Organisation	Academic Partner	Research Area	Funding 2012- 17 Total: £6,977,542
Cardiovascular Disease	Barts & The London NHS Trust	Queen Mary University of London	Cardiovascular Regenerative Medicine	£1,455,073
Cardiovascular Disease	University Hospitals Bristol NHS Foundation Trust (UH Bristol)	University of Bristol	Cardiovascular Regenerative medicine	£1,429,557
Gastrointestinal Disease	University Hospitals Birmingham NHS Foundation Trust	University of Birmingham	Liver Regeneration, Repair and Stem Cells	£611,232
Musculoskeletal Disease	Leeds Teaching Hospitals NHS Trust	University of Leeds	Biomaterials and Regenerative Interventions	£427,280
Musculoskeletal Disease	Oxford University Hospitals NHS Trust	University of Oxford	Orthopaedics	£3,054,400

Support for clinical trial design and administration

The **National Institute for Health Research (NIHR) Research Design Service (RDS)** offers researchers access to support in developing and designing high quality research proposals. The RDS provides expert advice to researchers on all aspects of preparing grant applications for applied research in health and social care, including statistics, quantitative and qualitative research techniques, clinical trials, evidence synthesis, health economics, epidemiology, public and patient involvement, ethics and governance.

The **Medicines and Healthcare products Regulatory Agency (MHRA)** already provides support to sponsors of clinical trials in the form of scientific and regulatory advice. Although this is primarily seen as being of particular benefit to academics and SMEs, there may also be a need for this type of advice for larger pharmaceutical companies who are moving into the field of regenerative medicine.

The MHRA **encourages early engagement with investigators/sponsors** working in the field of regenerative medicine and has provided advice to investigators at the time of grant applications to funding bodies. The Agency will continue to do so.

A new initiative for the MHRA is the setting up of the **Innovation Office** (expected by the end of March 2013) to foster and support innovation over the whole range of development and manufacture of medicinal products and the development of medical devices. It is expected that a significant number of queries will be within the field of regenerative medicine. The MHRA has had initial contact with and looks forward to future engagement with the Cell Therapy Catapult to support the regenerative medicine sector.

The **Health Research Authority** (HRA) has been established to protect and promote the interests of patients and the public in health research, helping to streamline regulation and improve the cost effectiveness of clinical trials. The HRA is doing a number of things, which will help to reduce the burden of **administering** clinical trials.

Firstly, it is working to streamline the approval process for health research through unification of functions and processes wherever that is possible without additional legislation; and through co-ordination where it is not. The HRA has brought together functions relating to research ethics committees and it is collaborating with other regulatory and advisory bodies to create a unified approval process for the approval of health research and promote consistent and proportionate standards for compliance and inspection. This will build on the Integrated Research Application System (IRAS) to bring together the bodies involved in approving and advising on research behind the scenes. The unified approval process aims to:

- reduce the impact of regulation on research-active businesses, universities and NHS Trusts; and
- improve the timeliness of decisions about research projects and hence improve the cost-effectiveness of their delivery.

Secondly, since its establishment in December 2011, the HRA has halved the timelines for the first three studies that have gone through the Gene Therapy Advisory Committee (GTAC) by working in partnership with the Medicines and Healthcare products Regulatory Agency (MHRA) and relying on their expertise.

Thirdly, the HRA has established a collaboration and development steering group involving key partners to oversee a programme of work to improve national regulation and local governance of health research, and researchers' experience of them. This includes work to identify duplication in the approval of research in the NHS at a local level and working with NHS trusts to speed up the approval processes in the UK. The HRA is undertaking a feasibility study and pilot work to look at removing duplication by streamlining elements of research ethics review and of NHS trusts decision-making into a single review.

Fourthly, in response to requests made during its engagement with researchers, the HRA is organising an event to look specifically at access to advice on navigating regulatory and NHS research governance processes, to explore whether or not there is a gap in getting access to it.

13 March 2013

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[Transcript to be found under Government – the Rt Hon Earl Howe, Parliamentary Under-Secretary of State and Government Spokesperson, DH](#)

Government – Further supplementary written evidence

Further supplementary evidence from the Department for Business, Innovation and Skills (BIS) following David Willetts oral evidence on 26 February 2013

Philanthropic Funding

The Cell Therapy Catapult has been in discussion with a number of medical charities who are already actively engaged with projects using regenerative medicine and cell therapy. In particular the Cell Therapy Catapult has recently signed a Memorandum of Understanding with the UK Stem Cell Foundation (UKSCF) with the purpose of working together to progress promising stem cell projects to commercialisation.

The UKSCF is a charity that focuses specifically on raising funding for translational stem cell research in the form of projects with potential to enhance or lead to treatment of a wide range of conditions and diseases. Since its establishment in 2005, UKSCF has enabled over £15million to be invested in stem cell research projects in the UK through a combination of fundraising, co-funding and collaboration.

19 March 2013

Iva Hauptmannova, Head of Research and Development Royal National Orthopaedic Hospital (RNOH) NHS Trust – Written evidence

I. Barriers to Translation and Commercialisation

I.1 General:

Translational research in regenerative medicine is held back by confusion in regulatory requirements, and by the constant use of application of medicinal trial paradigms on regenerative medicine. An application of some areas of Clinical Trials Directive to regenerative medicine is unhelpful (perhaps its interpretation in the UK should be clarified as this problem does not seem to occur in other countries within the EU).

Long term follow up of patients without centralised monitoring is also an issue.

I.2 Example to support this statement: In 2009, shortly after ATIMP legislation came into effect we sought advice from the MHRA on a clinical trial looking at use of autologous mesenchymal stem cells (MSCs) for non-union fractures. Initial advice stipulated that autologous MSCs did not fall under the ATIMP legislation. Following a submission to REC, another contact was made by the MHRA to correct the initial advice and to request full submission for MHRA authorisation, this led to withdrawal of original REC application, full re-working of the submission to REC and submission to the MHRA. This led to 12 months delay in trial initiation. The study was approved as phase II randomised controlled trial.

In 2011 another advice was sought from the regulators as part of submission for funding to account for funding of MHRA regulated study. Autologous MCSs were being considered, manufactured processed remained the same as on previous occasion, but different part of the musculoskeletal system was being treated. The advice provided was to conduct phase I safety study for use of MCSs (Essentially stipulating that aspirin for headache can be licensed, but aspirin for toe ache requires new phase I study).

Discussions and different approaches to QP release on stem cell products, where Clinical Trials Directive is applied rigorously (QP sign off for each batch), increase cost unnecessarily.

Currently each trial in regenerative medicine has to request funding for long term follow up of patients. This can be costly and difficult to implement and will make future use of such therapies very expensive.

I.3 Conclusion:

The usage of drug trial paradigms on phases of development is very unhelpful and better guidance should be developed based on type of regenerative therapy – stem cells, gene therapy, autologous stem cells vs. allogeneic. Review and application of the regulation should take place to provide better clarity. This includes overlap between MHRA and HTA powers (HTA procurement licence required for biopsies and donor testing but manufacturing for clinical trials can only be done under MHRA GMP licence).

Central register of patients in regenerative medicines studies, which could support flagging and long term safety issues would be beneficial.

2.1 Barrier to conducting stem cell treatment in the NHS:

Lack of understanding of NHS R&D staff due to lack of training leads to costly delays in setting up of regenerative medicines studies.

2.2 Example:

MCS trial in non-union fracture, set up time nearly 18 months (2 site approvals, 1 REC approval, 1 MHRA authorisation). 1 of the sites took 18 months due to confusion as to what was under HTA and what was under MHRA powers. As well as overall lack of understanding of regenerative medicine.

3. Overall comments

Providing efficient and effective support for regenerative medicines would enable better evaluations of such therapies, reduce time spend on regulatory processes, which adds to the overall cost of the developed product (developing more efficient system, which can support safety, but is not bureaucratic). Better and clear pathways for development of ideas in regenerative medicine, regulatory advice and support, which enables speedy evaluation of specific ideas to determine their potential, better trained support staff would enable UK to become better place for development of regenerative medicines.

Disclaimer: where the views within this letter are not fully aligned with the views of the organisation as a whole those should be perceived as the views of the individual.

18 September 2012

Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil,
University of Sheffield – Written evidence

**Professor John Haycock, Professor Stephen Rimmer and Professor
Sheila MacNeil, University of Sheffield – Written evidence**

[Submission to be found under Professor Stephen Rimmer, University of Sheffield](#)

Health Protection Agency (HPA) – Written evidence

The Committee invites submissions on the following points, with practical examples where possible. HPA has only answered the questions that are relevant to us:

The research base

- 1.0 *How does the UK rank internationally in the scientific field of regenerative medicine?*
- 1.1 UK scientists continue to provide significant and regular contributions to international scientific conferences on regenerative medicine and stem cell research, which is good evidence of the high ranking assigned to UK academics in regenerative medicine.
- 2.0 *Where does the UK have strengths and weaknesses in the field?*
- 2.1 Clearly the UK has scientific strength in the areas of haematopoietic stem cells, developmental biology, tissue engineering and human embryonic stem cell biology. We defer to input from academic stakeholders to provide a detailed response on UK research strengths.
- 2.2 The UK also provides an environment in which researchers and other key professionals can work together not only in scientific collaborations but also to develop consensus expert opinion to present to regulators. For example the human Embryonic Stem Cell Coordinators Organisation (hESCCO) was formed by staff from different assisted reproduction centres to establish a consensus on criteria for informed consent for donation of embryos. More recently the National Clinical human Embryonic Stem Cell Forum engaged Medicines and Healthcare Regulatory Agency (MHRA) and Human Tissue Authority (HTA) on the need to seek changes in the European Union Tissues and Cells Directive and the HTA has now drafted a paper to take some of the key issues forward to the next revision of the Directive.
- 2.3 The UK also has key national assets in the form of professional organisations which can support the development of the UK regenerative medicine. Such organisations include NHS Blood and Transplant (NHSBT), Scottish National Blood Transfusion Service (SNBTS), UK Biobank and HPA National Institute for Biological Standards and Control (NIBSC) which houses the UK Stem Cell Bank (UKSCB). The UK Stem Cell Bank has established a leading role amongst stem cell resource centres and is recognised internationally for its expertise in quality assurance and governance.
- 2.4 The UK has also provided coordination for some well known international collaborations such as the International Stem Cell Initiative (1, 2) and the International Stem Cell Banking Initiative (3, 4) both funded by the Medical Research Council (MRC) led International Stem Cell Forum.
- 3.0 *Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?*
- 3.1 In the UK the MRC, Technology Strategy Board, UK Stem Cell Foundation, Engineering and Physical Sciences Research Council (EPSRC) and Biotechnology & Biological Sciences Research Council (BBSRC) have together made major

contributions to funding for regenerative medicine. The British Heart foundation and Wellcome Trust have also emerged to make significant contributions as has the UK Stem Cell Foundation. Currently the Technology Strategy Board (TSB) is providing significant funding which is also contributed to by the Biotechnology Research Industry Club. In addition the 'Catapult' is set to progress the development of industry-academic collaboration to deliver new regenerative medicines. Additional funding is also provided by specialist charities which are coordinated through the Association of Medical Research Charities.

- 3.2 We anticipate that funding will be needed to facilitate collaboration between sources of high quality starting materials (such as UK Stem Cell Bank), leaders in standardisation (e.g. NIBSC, National Physical Laboratory - NPL, Laboratory of the Government Chemist - LGC) each playing to their strengths, and health-service production units (NHSBT and SNBTS, which could also provide clinical trial support) to help kick-start the development and delivery of new cell therapies.
- 3.3 Internationally the Joint Diabetes Research Foundation has supported stem cell research and the Californian Institute for Regenerative Medicine (CIRM) has made significant funding available for both basic research, development of new PIs and development of new therapies. Both organisations have provided support for UK researchers although CIRM funding is constrained by a requirement for funds to be spent within California. There are also other private international funding organisations which support regenerative medicines such as High Q and its associated activities CHDI Inc and HP Therapeutics.

Application of the science

- 4.0 *Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally?*
- 4.1 There have been both dramatic and incremental developments. High profile projects such as the Pfizer/University College London collaboration to treat blindness and similar projects in the US and elsewhere look set to deliver exciting results in the near future. However, the majority of clinical current clinical trials utilise 'mesenchymal stromal cells' (or mesenchymal stem cells) which have the capacity to generate cells representative of a range of tissues.
- 4.2 Other improvements in materials and equipment are also providing a background of enabling technologies that will help to accelerate the delivery of new cell therapies. Promoting coordination between these groups and clinicians and academics wishing to get new ideas developed is essential.
- 4.3 An important current difficulty for the field is the progression of cell-based medicines to advanced stages of regulatory consideration without having completed key and sometimes basic elements required to meet regulatory approval. There is a clear and urgent need for companies to have access to early stage high quality advice on the application of regulation and regulatory science.
- 5.0 *Which treatments are available on the NHS or through private healthcare?*
- 5.1 HPA NIBSC is not involved directly in patient treatment and defers to stakeholders with experience in this area

- 6.0 *What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?*
- 6.1 The next 5-10 years will see results from a series of clinical trials for new cell therapies. Whilst the withdrawal of Geron from cell-based medicines was a blow for the field it does not appear to have been due to failure of the therapy. Obviously further investment in the field will depend on their success or at least lack of adverse events. However, first impressions from some products moving to clinical trials are promising.
- 6.2 The issue of cell metrology and control of cell differentiation will remain challenging for some time and early products may be inefficient since manufactured cells will not always meet acceptance criteria and the knowledge base will need to be built on improving *in vitro* culture processes.
- 6.3 Haematopoietic stem cells have been used in the form of bone marrow transplant to cure childhood leukaemias for a number of decades and are funding an increasing range of applications. Umbilical cord blood is increasingly being used for therapy and is of particular value as it can be used in mismatched recipients. Mesenchymal Stromal Cells are used in the majority of current clinical trials but their efficacy has yet to be determined. These sources of cells are constrained by the numbers of cells available from individual donors and whilst cell number can be expanded by *in vitro* culture the hazard of genetic abnormalities arising in cultured cells, and the consequent risk of malignant cell populations, mean that careful validation and control of such scale up will be necessary.

Barriers to translation

- 7.0 *Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?*
- 7.1 The Government's actions outlined in the document 'Taking Stock of Regenerative Medicine in the UK' provides a comprehensive approach to drive UK success in the regenerative medicines field. However, the regulators' role should not only be to ensure that regulation is clear but also to facilitate discussions between key stakeholders to ensure that those bringing cell therapy products to market do so in the most efficient and effective way to avoid delays in development due to inappropriate approaches. The regulators might also support the industry through the provision of expert guidance on specific regulatory science issues of central importance to the delivery of safe and effective regenerative medicines.

In particular:

- 8.0 *What difficulties are encountered when conducting clinical trials and how could these be overcome?*
- 8.1 HPA NIBSC is not involved directly in clinical trials and defers to stakeholders with experience in this area

- 9.0 *What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?*
- 9.1 HPA NIBSC does not conduct translational research within the NHS and defers to stakeholders with experience in this area
- 10.0 *What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?*
- 10.1 HPA NIBSC is not involved directly in patient treatment and defers to stakeholders with experience in this area

Barriers to commercialisation

- 11.0 *What is the current and potential future, commercial value of the sector to the UK economy? What is its value to society?*
- 11.1 Whilst commercial stakeholders can provide relevant expert advice on these issues it is clear that the potential for health economic benefit is huge especially where long term cures and improvements in quality of life can be achieved by a single intervention to replace long term repeat treatment. The advent of induced Pluripotent Stem Cell (iPSC) technology and rapid developments in reprogramming, mean that personalised cell therapy is now a possible future aspiration but the ability to deliver economic health benefits to the broader public has yet to be established.
- 12.0 *Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?*
- 12.1 HPA NIBSC is not involved directly in commercial product development and defers to stakeholders with experience in this area.
- 13.0 *What role does patenting play in the commercial development of regenerative treatments?*
- 13.1 Whilst HPA NIBSC expertise in the area of patenting is limited, the presence of strong and clear patents generally supports the development of new medicines. However, currently there is a well recognised patent thicket in the regenerative medicine area which is complex and will require careful analysis and possibly collaborations between the holders of IP to establish the most effective routes to establishing or using the existing intellectual Property rights (IPR).
- 13.2 This will clearly be relevant not only to cell differentiation protocols but also to developments in bioprocessing for cell therapies, efficient transport and storage systems and new diagnostic/analytical technology. The value of patenting cell cultures with unqualified potential is not so clear.
- 14.0 *What business models are most appropriate to support the development of regenerative treatments?*
- 14.1 Whilst industrial stakeholders will have clear views on the development of a mature regenerative medicine industry, the coordination between national assets such as NHSBT, SNBTS and HPA NIBSC/UKSCB must be well coordinated with industry to provide the most effective, safe and broadly capable support for the early development of cell therapy products.

15.0 What are the barriers to securing finance to develop such treatments?

15.1 HPA NIBSC is not involved in financing new products and defers to stakeholders with experience in this area

16.0 Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

16.1 HPA NIBSC is not involved in financing new products and defers to stakeholders with experience in this area

17.0 What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

17.1 HPA NIBSC is not engaged in such activity and defers to stakeholders with expertise in this area.

International comparisons

18.0 What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

18.1 HPA NIBSC defers to stakeholders with expertise in this area

19.0 How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

19.1 There is a tendency to utilise either a US or European models for regulatory frameworks and there is also increasing coordination between these two. However, there are issues such as degree of traceability for the original cell starting material, need for virological screening data on donors, which are managed differently under different regulatory jurisdictions. Seeking harmonisation will be crucial. European Union Tissue and Cells Directives (EUTCD) requirements do not meet the exact requirements of all Advanced Therapy Medicinal Products (ATMPs). However, some of the more significant issues are now being presented by the UK to enable the necessary changes to the EUTCD.

19.2 There is also significant variation in implementation of regulations even within Europe. In the UK the MHRA engages manufacturers in discussion on the best routes to deliver of products and is prepared to this should be a model for regulatory engagement that is promoted across the European Union (EU) and elsewhere to avoid the spread of a box-ticking approach to meeting regulations.

20.0 Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

20.1 There is effort being applied to provide international regulatory coordination (e.g. International Conference on Harmonisation (ICH), European Medicines Agency-Food and Drug Administration (EMA-FDA) joint conferences. ICH has a role to play and it will also be valuable for WHO to facilitate the discussion across a broader range of countries since numerous developing countries in SE Asia and South America are focusing on regenerative medicine for economic growth.

20.2 Independent dynamic 'standards setting organisations' could also play a valuable role in supporting the development of best practice guidance and examples include the

American Type Cell Culture (ATCC) Standards Development Organisation and National Institute of Standards and Technology (NIST) activities on cell line identification and the International Stem Cell Banking Initiative. The latter is coordinated by the UK Stem Cell Bank and has delivered guidance on stem cell banking developed by experts from 22 countries, which has been translated and published in Japanese and a Chinese translation is in preparation.

- 20.3 The HPA NIBSC is planning to launch a new initiative to develop standards and reference materials for cell-based medicines in 2013. This will bring regulators, industry and clinical academics together to discuss the key issues in safe and reproducible delivery of cell-based medicines with the intention of holding a series of focused meetings to make practical progress in this area.
- 21.0 *What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?*
- 21.1 Whilst this is an area in which HPA NIBSC is not directly involved it is clear that the potential hazards in travelling for foreign treatment include lack of follow up, potential exposure to unsuitable tissue and cells (with consequent infection and cancer risks) and absence of formal clinical trials procedures to protect patients. In addition, the failure of many private therapeutic services performed outside of clinical trials; fail to publish patient outcomes in peer reviewed journals making it difficult to use their experience to progress the field. There is probably more to be done through patient lobby groups and charities possibly with the support of the Association of Medical Research Charities in the UK.

25 September 2012

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Health Research Authority, Medical and Healthcare products Regulatory Agency (MHRA) and European Medicine Agency – Oral evidence (QQ 295-316)

Health Research Authority, Medical and Healthcare products Regulatory Agency (MHRA) and European Medicine Agency – Oral evidence (QQ 295-316)

[Transcript to be found under Medical and Healthcare products Regulatory Agency \(MHRA\)](#)

Health Research Authority – Supplementary written evidence

This memorandum has been prepared by Dr Janet Wisely, Chief Executive, Health Research Authority.

I am pleased to be able to provide, as requested, the operational guidance and announcement of the new arrangements for GTAC. As I described in the session it is early days but the first three applications completed under these new arrangements have been approved at days 76, 68 and 58 respectively. Compared with an average of around 130 days under previous arrangements, we will aim for further improvement but believe this to be an impressive start.

The HRA has set out a vision and ambition to make the UK a great place to do research, where more money invested in research goes into carrying out relevant, good quality research. We recognise we need tangible metrics to measure success and I was struck by the question from Lord O'Neill and the reference to efficiencies not just within regulators but also for the wider community. We certainly recognise the importance of this. We have set out aims including those listed below, and feel these are fully consistent with what the committee members were urging us to achieve:

- Researchers find it easier to do high-quality, ethical research
- Less resource is invested in getting studies started
- The NHS appreciates the benefits of health research

The HRA has set out an ambitious programme of work, and recognises that it needs to deliver tangible improvement and ensure that success is relevant, recognised, appreciated and valued by all HRA stakeholders. The HRA is addressing the main findings of the Academy of Medical Sciences review that reported national regulation and local governance of health research are too complex, and scattered across too many bodies. Specifically the HRA has set out a series of projects that include HRA assessment for NHS approval and initiatives that will remove duplication within NHS approval and the ethics review in particular.

18 January 2013

Attachment I

NRES Standard Operating Procedures

Gene therapy

6. Under the Clinical Trials Regulations, all clinical trials of investigational medicinal products for gene therapy must be submitted to GTAC.

7. Gene therapy medicinal products are defined in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC) as follows:

“... [a] gene therapy medicinal product means a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.”

Note: currently trying to come up with a clear list of what else needs to go from a policy angle with help of MHRA.

NRES Operational guidance – issued November 2012

Purpose

- 1.1 This policy defines the new arrangements for the Gene Therapy Advisory Committee (GTAC).

2. Ownership and Responsibilities

- 2.1 The Director of Operations owns this policy and is responsible for its development and implementation, and for reviewing it regularly to ensure that it remains appropriate and up to date.

3. Scope

- 3.1 This policy applies to the RECs identified by the Appointing Authority to review gene therapy and novel therapy and all REC staff, including temporary staff and secondees, who process applications requiring GTAC review

4. New Arrangements

- 4.1 On 25 October 2012, The Health Research Authority (HRA) Board, in its capacity as the Appointing Authority for the Gene Therapy Advisory Committee (GTAC), agreed new arrangements for ethics applications to GTAC.
- 4.2 From 30 November 2012, GTAC will no longer operate in its current form and will be closed. The NRES Committee, London-West London will become the Gene Therapy Advisory Committee and will be renamed, London-West London REC and Gene Therapy Advisory Committee.
- 4.4 The Chair of London-West London REC and GTAC can transfer applications for ethical review to NRES Committee, South Central – Oxford A, NRES Committee, North East – York and Scotland A Research Ethics Committee.
- 4.5 The application should be booked directly to the chosen REC with the formal transfer subsequently being confirmed by the Chair (Vice Chair/Alternative Vice Chair) of the West London REC and GTAC taking place.

5. Booking Applications

- 5.1 Bookings should be made to the chosen REC through the Central Allocation System (CAS) and applications and supporting documentation submitted to the REC in the standard format.

- 5.2 Once the booking has been made, the application and supporting documentation should also be sent to the REC Co-ordinator for London-West London and GTAC.
- 5.3 The West London REC and GTAC Chair (or designated officer) should receive a copy of all applications and formally authorise (by email to the REC co-ordinator) that the application(s) may be transferred. The transfer may be transferred only to a REC recognised by UKECA to review such applications.
- 6. Peer Review**
 - 6.1 The responsibility for ensuring that adequate peer review is provided will rest with the sponsor.
- 7. Pre application advice and submission**
 - 7.1 There will no longer be a requirement to seek pre-application advice from the NRES.
 - 7.2. Pre application advice can be sought from Professor Andrew George. Initial contact should be made by e-mail via nrescommittee.london-westlondon@nhs.net and marked for the attention of Andrew George.
- 8. Categories of application to be submitted to GTAC.**
 - 8.1 Legally, all gene therapy applications must be submitted to the GTAC that is able to transfer to designated RECs.
 - 8.2 Applications that involve cell therapy submitted to the MHRA Clinical Trials Expert Advisory Group must also be submitted to London-West London and GTAC, South Central-Oxford A, North East-York or Scotland A Research Ethics Committee.
 - 8.3 To be included at a later date. The MHRA will identify the category of studies that this applies to.
- 9. Ongoing Studies**
 - 9.1 After 30 November 2012, all documentation relating to ongoing studies should be submitted to the REC Co-ordinator for London-West London and GTAC via nrescommittee.london-westlondon@nhs.net.
- 10. The role of the MHRA**
 - 10.1 All gene therapy and cell therapy applications for Clinical Trial Authorisation will be assessed by the MHRA and, where appropriate, will now be submitted to the MHRA Clinical Trials Expert Advisory Group for review. This review will assure the RECs that appropriate scrutiny of the safety of the study has been carried out.
 - 10.2 The REC will raise any concerns directly with the MHRA under the terms of the Memorandum of Understanding

Attachment 2

HRA announcement – 6th November

New arrangements for the Gene Therapy Advisory Committee (GTAC)

The Health Research Authority (HRA) Board, in its capacity as the Appointing Authority for the Gene Therapy Advisory Committee (GTAC), agreed new arrangements for ethics applications to GTAC at its Board meeting on 25 October 2012.

From 30 November 2012, GTAC will no longer operate in its current form and will be closed. The NRES Committee, London - West London, will be the Gene Therapy Advisory Committee, and renamed London - West London and Gene Therapy Advisory Committee (London - West London and GTAC). At least two members of the current GTAC will transfer to this new group. The Chair of London - West London and GTAC can transfer applications for ethical review to either NRES Committee, South Central - Oxford A or NRES Committee, North East - Northern and Yorkshire . An additional REC may be identified at a later date.

The HRA believes that these changes will improve the service offered to researchers. As well as providing an opportunity for ethical review across a wider geographical area, we will now be able to offer at least 30 meeting dates per year, and are confident that this will improve timelines for ethical review. The new processes mean that the review of applications will follow NRES Standard Operating Procedures, with clear roles for the MHRA and RECs, and that any concerns will be addressed through the Memorandum of Understanding between the HRA and MHRA.

What do I need to do?

Booking Applications

In future, you may book an application through London - West London and GTAC, South Central - Oxford A, or North East – Northern and Yorkshire (based in York). Bookings should be made via the Central Allocation System on **0845 2704400**. Once a booking is accepted, you should be in a position to submit your application to the REC within four days. Additionally, when the booking is made, the application and all supporting documentation should be emailed to Andrea Graham at nrescommittee.london-westlondon@nhs.net.

If your application is valid, you will be sent an acknowledgement within five days of receipt and arrangements subsequently made for you to attend the REC meeting.

If you experience difficulty in booking a slot please contact Mrs Sheila Oliver, on **07824 406749**

Peer Review

Historically GTAC would send applications for external peer review. In future, as with all other NRES RECs, the responsibility for providing peer review will rest with the sponsor. The HRA will seek to work in partnership with other organisations to determine whether it is possible to develop some agreed standards. For more information, see the [NRES document – Science v Ethics](#).

Pre-application advice and submission to GTAC

You are no longer required to seek pre-application regulatory advice from GTAC. The MHRA will continue to provide this service to commercial companies, and will consider requests for advice from academic researchers.

Professor Andrew George, who will transfer to London - West London and GTAC, is available to provide advice to applicants before submission of their applications for ethical review. Initial contact should be made via nrescommittee.london-westlondon@nhs.net and the email marked for the attention of Andrew George.

Categories of applications to be submitted to GTAC

Members of the research community have requested clarity on the type of application that needs to be submitted to GTAC.

- Legally, all gene therapy applications must be submitted to a GTAC that is able to transfer to two designated RECs.
- To make it easier for researchers and sponsors to identify other studies needing review, other applications that involve cell therapy that are submitted to the MHRA Clinical Trials Expert Advisory Group must also be submitted to either London - West London and GTAC, South Central - Oxford A or North East - Northern and Yorkshire.

Ongoing studies

If you have submitted any documentation – for example a Notice of Substantial Amendment – to the current GTAC and are awaiting a response, please contact Nischintha Cherodian at the HRA (ncherodian@nhs.net). Please continue to submit any documentation that requires review by the current GTAC to Nischi by 30 November 2012.

After this time, please submit all documentation to Andrea Graham at nrescommittee.london-westlondon@nhs.net.

The role of the MHRA

All gene therapy and cell therapy applications for Clinical Trials Authorisation will be assessed by the MHRA and, where appropriate will now be submitted to the MHRA Clinical Trials Expert Advisory Group for review. This review will assure the RECs that appropriate scrutiny of the safety of the application has been carried out. The REC will raise any concerns directly with the MHRA.

Cell Therapy Catapult

The Health Research Authority is liaising with the Cell Therapy Catapult to determine if it can help provide advice to researchers and facilitate access to a network of peer reviewers for cell therapy (somatic cell or tissue engineered) products. The Cell Therapy Catapult has been established to grow a strong, sustainable cell therapy industry in the UK with access to finance, clinical and technical expertise to enable the UK's global leadership in the development, delivery and commercialisation of cell therapy. We will keep you advised of progress.

HealthTech and Medicines Knowledge Transfer Network (Health KTN) – Written evidence

The HealthTech and Medicines KTN response to the Call for Evidence for the House of Lords Select Committee on Science and Technology Regenerative Medicine Inquiry ¹⁸²

HealthTech and Medicines KTN Background

1. The HealthTech and Medicines Knowledge Transfer Network (Health KTN) ¹⁸³ is funded by the Technology Strategy Board to support and accelerate business innovation in the (human health) life sciences sector. It focuses predominantly on technology and innovation, which requires an assessment of the main knowledge transfer needs, including barriers and solutions to innovation challenges, as well as support to businesses to access technology, partners, funding and markets to move their developments to a commercial success. The Network is inclusive and open to all UK life science businesses, as well as the academic, clinical and other stakeholder organisations who can support the overall goals around knowledge transfer. Regenerative Medicine is a key priority area for the Health KTN

General Comment

2. The Health KTN welcomes the opportunity to respond to this call for evidence. The responses focuses mainly on the questions pertaining to challenges and barriers for this emerging sector in the UK – this reflects the activity we have undertaken in recent years where we have brought different aspects of the regenerative medicine community from industry, academia and the clinic together to discuss key knowledge transfer issues and barriers to innovation, and to ensure uptake of the funding available for this sector through the Technology Strategy Board and other funding mechanisms.

3. Broadly speaking from an economic perspective this is a global sector. Ensuring an overall environment that sends the message that the UK is the best place to research, develop and deliver RM therapies will benefit patients through access to new treatments and the UK economy through increased investment and business opportunity for the wider supply chain.

Barriers to translation and commercialisation

4. The key areas, as recognised by the Committee, remain as access to finance, regulation and routes for adoption and reimbursement for regenerative medicine treatments. Recognition of and support for the full supply chain in terms of enabling tools and technologies - as indicated in the Strategy for UK Regenerative Medicine ¹⁸⁴ - is also crucial to ensure that innovation in tools and platform technologies can have a bearing on commercialisation potential for therapies.

5. Renewed emphasis on funding for translation as cited in the UK Strategy document is an acknowledgment of the sector's need, expressed through different channels in recent years.

¹⁸² <http://www.parliament.uk/documents/lords-committees/science-technology/RegenerativeMedicine/CfERegenerativeMedicine.pdf>

¹⁸³ <https://connect.innovateuk.org/web/healthktn>

¹⁸⁴ http://www.innovateuk.org/_assets/rm%20strategy_a4-full_final%20low%20res%5B1%5D.pdf

The regulation is still largely untested and complex and a dual approach is needed of enabling navigation of the process as it stands and simplification of it where possible will be welcomed by the community.

6. Examples from a technological point of view some of the barriers with respect to clinical trials are cited as:

- Availability of appropriate animal models
- Funding streams that support animal studies essential for toxicity and safety data to progress to clinical trials
- Basic research in terms of mechanisms of action, in both the disease area and how treatment works
- As for broader fields, the right patient population recruitment and ensuring their understanding of the clinical trial process
- Identifying the best delivery approach
- Identifying the right cells and products and knowing source and provenance
- Scale up for manufacturing and bioprocessing of products

www.innovateuk.org/healthktn

7. Further barriers include the availability of the right clinician and the opportunity to engage early with them at an early stage in the process. Clearly, ensuring that a product or service serves unmet medical need, or is relevant to the clinical setting and will have a significant impact, are key to successful translation and subsequent commercialisation. Workload constraints and funding to collaborate can hamper progress of research into the clinic. Therefore mechanisms to enable early industrial engagement with clinicians to scope collaboration as a matter of course will drive more translation and further development.

8. There is a need for a more holistic view of the value of regenerative medicine treatments in terms of the reimbursement model and the longer term cost savings that can be brought to bear for the NHS for a potentially higher upfront cost - ie making a sound health economics case for support, adoption and reimbursement. This is not a simple process and needs early involvement of health economists particularly when the treatment is not an extension of an existing patient pathway but rather a disruptive and new route for treatment.

9. The TSB funded projects in the area of Business Models and Value Systems are now completed or in the process of completing. These resources now provide a toolbox approach to translation and commercialisation (eg REALISE¹⁸⁵) and an in depth analysis of various case studies on aspects directly relevant these issues, examining both private and public healthcare provision (eg VALUE¹⁸⁶).

10. To bring a therapeutic product all the way to market requires significant investment and a long timescale. This level of finance is not widely available through venture capital sources for biotech ventures in the UK currently, let alone regenerative medicine with a perceived higher risk profile and unclear route for adoption and reimbursement.

¹⁸⁵ <http://www.sscn.co.uk/PublicAccess/AboutUs/Projects/ProjectRealise/tabid/145/Default.aspx>

¹⁸⁶ http://www.biolatris.com/Biolatris/News_&_events_files/VALUE%20Executive%20Summary.pdf

11. The forthcoming anticipated changes to NHS structure through the Innovation Health and Wealth Report¹⁸⁷ should take steps to enable a more level playing field for adoption of regenerative medicine therapies, where change is needed in the emphasis from cost to clinical outcomes. For this particular sector, the ability to refer to an active home market will be an essential step to leveraging investment through the demonstration that there is a route to market and reimbursement.

12. The continued direction of public funding and support through mechanisms such as the now closed TSB-led RegenMed Programme 2009-2011, the Cell Therapy Catapult¹⁸⁸, the Biomedical Catalyst (BMC)¹⁸⁹ and the forthcoming UK Regenerative Medicine Platforms (RMPs)¹⁹⁰ will be welcomed by the community. Investment in research centres across the UK is crucial to the maintenance of UK prominence in the field.

13. This support is a part of the equation to unlocking the type of investment needed to bring products to market. In times of economic constraint the Government can influence funding mechanisms, fiscal policy, proportionate application of regulation and ensure the NHS is utilised as the rich resource that it is for the benefit of UK patients and more broadly the growth of the UK regenerative medicine sector.

20 September 2012

¹⁸⁷ http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf

¹⁸⁸ <https://catapult.innovateuk.org/cell-therapy>

¹⁸⁹ <http://www.innovateuk.org/content/competition/biomedical-catalyst.ashx>

¹⁹⁰ <http://www.ukrmp.org.uk/>

Julian Hitchcock, Counsel, Lawford Davies Denoon – Written evidence

I am a lawyer at the specialist life science practice, Lawford Davies Denoon (LDD). I have expertise in intellectual property and regulatory matters relevant to stem cell science and advanced therapy medicinal products. I am a former Executive Director of the East of England Stem Cell Network (EESCN), advised the UK National Stem Cell Network (UKNSCN) on intellectual property and am a member of the Government's Emerging Science and Bioethics Advisory Committee (ESBAC). I have a strong interest and involvement in the translation of life science technologies, especially in the stem cell and regenerative medicine arena, and campaign on translation matters at a European level through the CellFate network¹⁹¹.

Summary

Is the UK in a position to facilitate the translation of knowledge from world-leading research to treatments and to benefit from the commercial opportunities that they present?

Yes. However, translation is a competitive process: the fact that a technology is developed in a particular location does not guarantee its translation there. The UK has the opportunity to acquire intellectual capital from less competitive countries, but states that are more facilitative will gain more value from UK innovations than the UK itself. The UK should aim to maximise the value of its returns from the entire stack of technologies attributable to a platform, not merely the platform itself. The special commercial characteristics of the emerging sector need to be distinguished and addressed: regenerative medicine is a world away from most other technologies, where products get to market very fast indeed without extensive regulatory compliance and with far less risk

Weak links between UK government and the EU compromise responsiveness to significant European opportunities (for example, the UK's position as a portal for new therapies to enter Europe) and threats (for example in the *Brüstle* case: see below). Unless Government compensates sectors according to the level of regulatory burden, less regulated sectors will always attract more investment. The regulatory burdens being so high, territories with easier access to venture capital will begin with an advantage. Lack of coordination between regulators can have a similar effect.

Research base

What are the UK's strengths and weaknesses in regenerative medicine research?

Data is available on citation rates, which places certain UK centres, for example Cambridge, Edinburgh and London at the lead in impact indices.

The UK is fortunate in having the support, not only of the Research Councils, but the Wellcome Trust. However, a significant funding stream, under the EU Horizon

¹⁹¹ www.cellfate.com

2020 programme is threatened. This was prompted in part by the ideological decision of the Court of Justice of the European Union (CJEU) in *Brüstle v Greenpeace* and in part by erroneous statements as to its impact by members of the stem cell community. This highlights an extremely poor understanding, not only of patents, but also of sources of commercial value in regenerative medicine in general.

Application of the science

See comments below on technology transfer offices.

Barriers to translation

In my EESCN capacity, working under the Chairmanship of Dr Hermann Hauser and in partnership with Professor Austin Smith, I sought to create an “ABC” (Academic, Business, Clinic) culture by holding regular meetings. It was clear from these that many clinicians were conservative and not motivated to participate (with notable exceptions). The UK National Stem Cell Network also failed to foster this culture. EESCN was unable to secure funding for the establishment of a Regenerative Medicine Enterprise School: despite great interest, funder requirements were unrealistic. Life science training, and regenmed enterprise in particular, require specialist training.

Patents

The “Hinxtion Group” and others have claimed that the subsistence of stem cell patents impedes (“chills”) research. This was doubtless true in the past, when research royalty rates for the use of human embryonic stem cells (hESCs) was high, although I suspect it is no longer the case. There is an exemption under the UK *Patents Act 1977* in connection with experimental purposes relating to the subject matter of an invention. Though possibly an imperfect provision, it seems to work. I understand from the UK Intellectual Property Office, which consulted upon the whether the provision is fit for purpose, that there is little evidence of a chilling effect.. However, insofar as the Hinxtion claim is correct in the context of human embryonic stem cell work, the CJEU’s *Brüstle* decision has come as an unexpected solution: it purportedly (sic,- see below) invalidates patent claims which rely upon uses of fertilised human eggs (or their equivalents) for industrial and commercial purposes (which is deemed to include research). Bizarrely, and in stark contrast to the claims made by scientists, the *Brüstle* case created a European research haven.

Extremism

Embryonic stem cell research was, in *Brüstle*, chastised as an assault upon the dignity and integrity of *ex vivo* fertilised eggs, on which ground patenting of such cells (and their equivalents) was prohibited. However, the very aim of regenerative medicine is to restore bodily integrity so as to protect the dignity of real, suffering, legal persons. Degenerative disease threatens everyone, and everyone has a legitimate expectation that the outcome of research in regenerative medicine may offer some relief to these conditions. By removing incentives to develop regenerative medicine, the *Brüstle* decision is therefore an assault on the dignity of all UK and EU citizens. As such, the decision conflicts with (among other things) the EU Charter of Fundamental Rights, which prevents the use of rights under the Charter to impede those of others who are protected by it. The alternative analysis, that the Court

(outside the Charter) itself created the rights now accorded to cells, is no more reassuring.

The UK needs to be a great deal more diligent in defending hESC research from challenge at the level of the European Parliament and Council of Ministers. I am concerned that the motivating principle in *Brüstle v Greenpeace*, which subversively equips fertilised human eggs (and their equivalents) with personhood, threatens other areas. As noted below, certain MEPs are using *Brüstle* to block EU funding for research using existing cell lines. I would urge the government, through the UK Intellectual Property Office and otherwise, to distinguish the *Brüstle* case. A legal analysis in support has been provided as an Annex. The government should review the EU Court's attempt to personify, and create rights for, cells to the detriment of the rights of real people, with the utmost concern.

Patent Folklore

A further barrier to translation may be described as “patent folklore”. The serious misunderstanding about the impact of *Brüstle* by many in the field (i.e. that the case had removed all prospect of an economic return and that young scientists would be wise to leave Europe), which was briefly fostered by some patent attorneys, has already had a palpable knock-on effect: the JURI committee of the European Parliament recently used this claim to advise MEPs to oppose funding of research involving human embryonic stem cells under the Horizon 2020 funding programme: i.e. that taxpayers should not fund research having no economic benefit for the developer. If EU funding is withdrawn as a result of this misconception, this may represent a considerable shot in the foot by the people most in need of funding.

My colleagues, James Lawford Davies and Alex Denoon and I have written to George Freeman MP raising our concerns about the damaging effect of this patent folklore. The reality is that the UK and Europe are slightly advantaged by the *Brüstle* decision, because of the freedom to operate position in the EU is more favourable than that in other jurisdictions (including the US). UK researchers enjoy exactly the same opportunities to patent as researchers anywhere else in the world, with less burden on research. Furthermore, non-patent exclusive rights in cells and cell lines last longer than patents. Furthermore, embryonic subject matter is but a small part of the overall endeavour of regenerative medicine. The value in plastic, metal, glass, software and bioactive factors (e.g. those that determine cell fate) dwarfs the value in original embryonic IP. Unfortunately, efforts made to correct the impression of disaster only convinced investors that there was “disagreement” in the sector, which then became a reason for not investing. There is an urgent need to demythologise *Brüstle* and to educate researchers, businesses and investors about where the value actually lies. Unless this happens, grant applications and bids for commercial funding will be compromised and junior researchers may leave the UK for allegedly more friendly research destinations.

Regulation

Regulation is both necessary and an inevitable barrier to translation. Because advanced therapeutic products, like other medicinal products, cannot be placed on the market until they have been approved to the high regulatory standard expected of them, their period of market exclusivity is extremely limited when compared to, say a patented dishwasher. Although a “supplementary protection certificate” (SPC)

scheme purports to compensate for the period of patent life lost in seeking an authorisation to market medicinal products, the total period of exclusivity falls short of the period that would be available to the dishwasher. The inadequacy of SPC compensation has led some in the biotechnology and pharmaceutical sectors to call for an extension to the patent term. As advanced therapy medicinal products are especially highly regulated, it might be argued that the case is especially strong in their case. This would require international support, however, and consideration should also be given to quasi-intellectual property rights, that prevent third parties from using data submitted in support of an original application for authorisation.

The overall framework of UK regulation in this sector is European, which is necessary in order to sustain a competitive market. Although a key piece of EU legislation, the *Advanced Therapy Medicinal Products Regulation* (Regulation 1394/2007 EC), does not require national implementation, there are nevertheless discrepancies in the manner in which national competent authorities apply the discretion that is devolved to them, leading to disparities (for example in connection with a “hospital use exemption”). There are concerns of regulatory creep and views have been expressed that the existing framework mistakenly treats the patient’s own cells as a medicine: in effect denying treatment and exposing clinicians to serious liabilities.

Where national legislation applies, the UK is fortunate in its legal regime under the Human Fertilisation and Embryology Act, which permits responsible research under a licence scheme. I hope that research licences will be expedited once research licences fall to the new HRA.

Barriers to commercialisation

Is Government providing sufficient incentives in the current commercial climate to attract investment in this high-risk area? If not, what more should Government do?

More significant than the transient commercial climate is the enduring climate of regulation, which is cited by most investors as the leading disincentive to life science investment. Because regenerative medicine is concerned with the most highly regulated products on the planet, the level of commercial disincentive is higher than for most sectors.

Under Dr Hauser’s Chairmanship, EESCN was an early advocate of what has become the “Catapult” centre in cell therapies. It is far too early to assess its success, but I strongly support its philosophy. The Technology Strategy Board is working well to support the sector generally.

My colleagues and I would encourage the HRA to advocate research and to work proactively to shepherd/chaperone researchers through the regulatory framework. Given that the competitiveness of the translation process itself is so decisive, we suggest that such a facilitative environment, which helped to pull technologies through the system, would give the UK a significant competitive edge.

What role does patenting play in the commercial development of regenerative treatments?

Patents per se are undoubtedly important, but their role has been exaggerated, not least as a result of a preoccupation with the *Brüstle* case (see above). Rights in cell

lines promise greater value. A comparison may also be made with immunological medicines: when Milstein and Köhler isolated monoclonal antibodies (mABs) in the late 1970's, no patent was claimed, leading to censure from (inter alia) the UK's new scientist Prime Minister, Margaret Thatcher. Despite this, subsequent layers of technology, which were patented, more than made up for the loss: Humira is now one of the world's most commercially successful medicinal products. Indeed, most of today's "blockbuster" drugs are mAB based.

The 2005 Pattison Report suggested that consideration should be given to the use of patent pools: a point reiterated by the Hinxton Group. In 2009, I took this forward at the prompting of a leading player in the field, by holding a stakeholder conference. The Vine Street conference found no appetite for a stem cell patent pool ([here](#)), chiefly because of uncertainty about key platform technologies. However, because of the pace of development, it would be wise to revisit this approach. Government could play a facilitative role.

What business models are most appropriate to support the development of regenerative treatments?

One cannot be prescriptive about the whole sector. However, the regenerative medicine mantra, "the process is the product", holds true in many cases: the opportunities for service models is considerable. One model, which EESCN presented to the former Secretary of State for Health, Andrew Lansley, concerned a national cell therapy centre in which "low hanging fruit" regenerative medicine therapies were provided to NHS patients, with costs being subsidised by stem cell tourists.

On balance, I am disappointed by technology transfer offices, some of which in my experience, have deterred inventors. To some extent, this comes from a bias in favour of licensing and the constraints of working in a higher education context. As a result of the nascent nature of the sector, technology transfer officers with a good understanding of this sector simply do not exist. An idea raised at the Vine Street conference, in preference to patent pooling, was a common national clearing house for regenerative medicine IP, an idea which the Committee may wish to consider.

International comparisons

How do regulations that govern the development of regenerative medicines in other countries and at a EU level impact on the development of regenerative medicine in the UK?

The UK cannot readily impose a more straightforward regulatory regime to that elsewhere in the EU. The same is true of other EU states. The effect is to secure an even playing field. However, states can implement EU and national laws in more user-friendly ways, foster more proactive, business-lead cultures and be more proactive at the European level (EU and competent authorities of other Member States). The UK could optimise the existing legal framework by, for example: coordinating agencies, funding and the HRA; encouraging the use of existing regimes such as the conditional marketing authorisations; adopting a flexible approach to clinical trials of stem cell therapies; and by providing commercially helpful guidance

from NICE. We would also suggest that care is taken to monitor and prevent “regulatory creep”.

Unethical stem cell tourism is certainly a blight, which may affect numerous UK citizens. However, higher regulatory standards are in my view likely to attract more stem cell tourists than lower ones because of the greater assurance as to quality, safety and efficacy. As such, as legitimate therapies emerge there should be an improvement.

20 September 2012

Professor Anthony Hollander, University of Bristol and Azellon, Smith & Nephew and Intercytex Ltd – Oral evidence (QQ 81-127)

Professor Anthony Hollander, University of Bristol and Azellon, Smith & Nephew and Intercytex Ltd – Oral evidence (QQ 81-127)

[Transcript to be found under Intercytex Ltd](#)

[Written evidence to be found under Azellon Cell Therapeutics](#)

Professor Anthony Hollander, University of Bristol and Azellon – Supplementary written evidence

During the hearing on Tuesday 13th November, those of us being interviewed were asked if the scale of funding through TSB and Catapult were adequate and how we would wish George Osborne to spend any additional funds made available to regenerative medicine. I do not feel I gave a considered enough answer at the time and wish to add a little more here.

1. TSB funding is limited both in scale and in timing (dependent on a call being made in the regenerative medicine field at the right time). The further limit is the requirement for matching of funds. The UK industry would benefit from more funding being made available with some degree of response-mode funding (ie applications assessed at any time, not just when a call has been published), especially where a project has previously been funded. I would support an increase in funding through TSB in this way.
2. The Catapult is limited to backing just two companies/projects. I believe that a primary aim of the Catapult should be to increase the chances of early winners being proven, through intensive support in a range of ways. The risk of backing just 2 companies in this way is the high risk of failure for either or both. Increased funding allowing 4 – 6 companies to be supported through the Catapult would obviously increase our chances of success being demonstrated and thereby galvanizing the field
3. I believe there is also room for increased funding of regenerative medicine projects through MRC, to ensure that early stage work continues to thrive and stimulate the industry in future.

17 November 2012

Human Fertilisation and Embryology Authority (HFEA) and Human Tissue Authority (HTA) – Oral evidence (QQ 317-329)

Evidence Session No. 14

Heard in Public

Questions 317 - 329

TUESDAY 8 JANUARY 2013

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Peter Thompson, Chief Executive Officer, Human Fertilisation and Embryology Authority (HFEA), and **Dr Alan Clamp**, Chief Executive Officer, Human Tissue Authority (HTA).

Q317 The Chairman: I would like to welcome our second witness panel, consisting of Dr Alan Clamp and Peter Thompson. In a moment, I would like to invite you to introduce yourselves for the record, and if you wish to make any brief opening statement please feel free to do so. Then we will move straight into the questioning on the matters of regulation of regenerative medicine research. Perhaps, Dr Clamp, you could kick off.

Dr Alan Clamp: Thank you. My name is Alan Clamp. I am the chief executive of the Human Tissue Authority. We work to ensure that human tissue and organs are used safely and ethically. We regulate across a number of sectors but, in terms of the interests of this Committee, that most relevant is our work under the European Union tissues and cells directives, which involves using tissue for patient treatment. In this area, we work very closely with the MHRA, who you have just heard from, and with the HFEA. My final point would be that we believe, as you might expect, that effective regulation does support good practice and high-quality science, which ultimately leads to better healthcare.

Peter Thompson: Hello. I am Peter Thompson. I am the chief executive of the Human Fertilisation and Embryology Authority. As I have no doubt that we will explore in questions, our role in your subject is narrow. We are effectively limited to the regulation

and use of human embryos or human admixed embryos to derive embryonic stem cell lines, some of which may be relevant to regenerative medicine, but this is a very small part of our responsibilities.

Q318 The Chairman: Thank you very much. You are aware that we are interested in whether or not the regulatory process is complex and burdensome to small companies or to academics wishing to seek approval for the clinical application of their knowledge in relation to regenerative medicine. I wonder if you could give us your view on the opinions that we have had from witnesses that the regulatory process is too complex, with too many organisations involved. Could you tell us whether you agree with that and, if you do not, justify the current position?

Dr Alan Clamp: Well, I would have to agree that the regulation is complex. Actually, there is some merit in talking about the complexity of the science, but it is certainly true that the legislation that underpins those regulations is very complex, and it is important to get it right, because it is about patient safety. But I would hope that, as a regulator, we do a good job of ensuring that there is no additional complexity. A lot was said in the first part of this session about clarity, about regulators leading people by the hand through the complexities, and about the route map that Kent Woods mentioned, which is the stem cell toolkit, which has recently been revised. I do believe that it is the job of the regulator to bring that clarity to the complexity. Feedback from our stakeholders suggests that, for the small part of the process that we regulate, we do that well, but I am sure we could always do more.

Peter Thompson: I, perhaps unsurprisingly, echo what Alan has just said. It clearly is a complex pattern of regulation which has built up over time, and I can well see why anybody embarking on this would not find it as straightforward as it ought to be. There has clearly been a recognition of that in the past, and efforts on it—Kent Woods referred earlier to this Department of Health-led work on a sort of stem cell map. Can more be done in that area? Perhaps. The key thing here is that, given that we have got this historic pattern of different bits of law and different regulators, the task ahead is to actually bring that together in such a way that our respective responsibilities are dispatched as seamlessly as possible, and that those people who are wishing to develop therapies are as clear as possible about that framework. We take the view—and frankly we have an even smaller part of this responsibility than the HTA—that there is a great deal that the individual organisations can do within the framework that already exists to make this as easy as possible.

Q319 The Chairman: Your two responses seem to be more sympathetic than we had in the first witness panel towards some of the critical comments that we have heard made. Those have said that there is significant duplication, redundant regulatory burden, sequential approval and major delays, which I think the previous panel more or less rejected. To caricature slightly, they said that it was the fault of the people out there rather than the fault of the regulator. Just to be clear in my mind, are you taking a position—either both of you or one or the other of you—that has some degree of sympathy with the critical comments that we have received in the evidence?

Peter Thompson: I am sympathetic to the extent that I think it is Government's responsibility to make this easy, not people out there's responsibility to somehow cope with whatever the complexity is. I start from that point of view. I quite understand that, were I in an SME or something, this would look pretty daunting. That said, I noted the oral evidence comments made from Roslin Cells and others, who seemed to me to be saying that there was reasonable evidence that the regulators that are responsible for this complex pattern were trying to deliver a regulatory regime that made sense from start to finish, and the issue

was more about the extent to which that regime was clearly explained so people understood what these processes were. I understood that some of your questions beforehand talked about sufficient hand-holding and the like, rather than, if you like, “What you have got is a patchwork of regulators here who can’t manage to work together in such a way that they just put up unreasonable barriers”.

Dr Alan Clamp: I would echo Peter’s point. Also, it is worth bearing in mind that this is a regulatory pathway for which we have different responsibilities at different times. It is difficult, in the face of some of the quotes on issues that you have given us to see exactly where the issues are. But it appears that a number of them are around clinical trials, for example, which is not an area that either of us regulates.

The Chairman: Lord Broers, and then I would like to turn to Lord Willis.

Q320 Lord Broers: I would like to ask you whether you are aware of any formal mechanisms, or you have them yourselves, for getting feedback from researchers and small companies. We are in an era when polling our customers is a standard procedure. In universities, we used to just give lectures and imagine we had done well. Now we ask the students whether we did well. Are you asking small companies and researchers whether your systems work well?

Dr Alan Clamp: We certainly do in terms of those establishments that we regulate and inspect—it is a fundamental part of the inspection process; we are looking for feedback on that—and in other areas where we have been involved, such as with Roslin Cells, ‘upstream’, as it were, when they were looking to set up new processes. We do get very positive feedback about that. Yes, it is something that we are always looking to get feedback on. Incidentally, given that both our organisations have recently been subject to a consultation about their futures, a number of research organisations have responded to that. I have not been privy to all the responses about the HFEA but, in terms of the HTA, those that have been willing to share their consultation responses with us have been very positive about our response.

Q321 Lord Willis of Knaresborough: I know what your positions are about the abolition of your authorities, so we will not go there, because that would be foolish. What I would ask you, however, is: if in fact the department did decide to go ahead with its original proposals, or its declared position, what would be the difficulty, do you think, in transferring those research elements to the HRA or other appropriate bodies?

Dr Alan Clamp: The preferred option of the Government in terms of the Human Tissue Authority was to transfer all of our functions to the Care Quality Commission. We have always been quite clear that what is important for us is that our functions are carried out effectively and efficiently, so if the Government made that decision our response would be that we would work with CQC and the other organisations represented here to make sure that those functions are carried out as well as they need to be. In terms of research, I think the HFEA have a bigger remit in terms of project approval—so over to Peter.

Peter Thompson: The position effectively under the law is that, if you want to do research involving human embryos, you need a licence from us. That can only be granted against a series of tests that are set out in the HFE Act, so we cannot duck those kind of tests. The Government’s preferred option with us is that the treatment side of what we do—that is the regulation of IVF clinics for treatment purposes—would go to the Care Quality

Human Fertilisation and Embryology Authority (HFEA) and Human Tissue Authority (HTA)
– Oral evidence (QQ 317-329)

Commission, and our human embryo research approvals and licensing would go to the Health Research Authority.

The difficulty would be this: embryos for research come from IVF treatment. Most research involving human embryos actually takes place in organisations, the majority of which are clinics that do both treatment and research. Our special focus is the embryo. We are interested in the embryos that are, in this case, taken from women involved in treatment. We are interested in the consents that are given, so that the women understand that they are donating them for research, and what they know about that. We can then track that embryo very neatly, from something that is given in treatment to its use in research, often within the same establishment. Now if the licensing of embryo research is given to the HRA, you draw a line between treatment and research. The clinic that does both treatment and research will have to be inspected and licensed by the CQC, and also be inspected and licensed by the HRA, so they would gain two regulators rather than one regulator.

Clearly, if the human embryo research is only being undertaken in a research establishment—that is one that does not have any IVF responsibilities—the treatment clinic would have CQC regulation, and then the research facility would have HRA regulation.

What you would also lose is that continuity with following the embryo through. I can see why on the one hand, from a research function, it looks initially attractive, but in terms of research involving human embryos it actually makes matters possibly more complicated. It is also a pretty small area of research. At the moment, we are required by law to license by individual projects. We have 24 research project licences. That covers research undertaken at 22 centres, and only four of those projects are in the territory that you are interested in today—that is the derivation of stem cell lines from human embryos.

Q322 Lord Willis of Knaresborough: What worries me, if I am honest with you, is that when there was last a problem in terms of licensing research, which was really on cytoplasmic hybrid embryos, the HFEA went running right for cover. It did not actually make any decisions; it basically threw its hands in the air and said, “Help us, department. Help us, Parliament. We can’t make a decision”, even though it had all the powers necessary to make those decisions. My worry is purely about the research, because I actually regard IVF as being a very established treatment now, rather than an area of continuous research, though I accept that there is research going on in that area. It is the same on knees, really—research as well replacements. That is the bit that worries me—that what we are wanting to do is to have a research-intensive regulatory system which understands the research and has that as its prime focus. That seems to me an advantage which would be gained if in fact it all came into the Health Research Authority. Would you accept the premise?

Peter Thompson: I see exactly where the argument is going but, given that the Government is not proposing, as I understand it, to change the substance of the law, the Health Research Authority would still have to make research approvals against the tests that we have to make. So it is not like it has suddenly got a different focus. Clearly, if you go right back to Warnock, there is this belief enshrined in the original HFE Act and then the revised Act in 2008 that the embryo is of a special status—that is a different kind of tissue from skin or other kind of tissue—and, accordingly, most of the tests that we have to apply are actually on the face of the primary legislation.

Lord Willis of Knaresborough: But Dr Wisely and her colleagues are not imbeciles.

Peter Thompson: No, of course they are not.

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Lord Willis of Knaresborough: They are very sensitive people who are just as capable of doing this as you.

Peter Thompson: I am not suggesting they are not, but I do not believe that there is evidence that the HFEA falls shy of approving research. I do not think it is anti-research. I got a sense from you that you thought, in some way, that it was uncomfortable with regulating research.

Lord Willis of Knaresborough: Well, it was, when you were dealing with admixed embryos. It was uncomfortable, and you ran for cover.

Peter Thompson: There were issues at the time; this is before my time, I must freely admit.

Lord Willis of Knaresborough: It always is.

Peter Thompson: As I understand it, there were some real contentions about whether or not—

Lord Willis of Knaresborough: Do not—

Peter Thompson: Oh, let us not go into the details. You can use the time better.

Lord Willis of Knaresborough: My point is that this is such an exciting area of development that anything that gets in the way of driving it forward is going to put the UK on the back foot. We have a wonderful opportunity here to do something about it. Maintaining regulatory systems because they have worked in the past does not seem a very acceptable answer.

The Chairman: Okay, I think we should move on at this point. I turn to Baroness Sharp.

Q323 Baroness Sharp of Guildford: Well, I really want to come back to the area that we started on, in terms of regulation and so on. As you said, this is a very complex regulatory pathway for companies to pursue. Many of those pursuing it are either academics themselves or small new companies, facing the problems of coping with this pathway. One of the things that certainly Dr Clamp suggested was that both of you deal with a little bit of this pathway but you both feel at the moment you are actually dealing with it relatively well. Do you feel that there is nevertheless a need to facilitate some early dialogue with the companies developing regenerative therapies in the UK and at EU level? Are there lessons that can be learned from the way in which you do things that others might follow? Are there ways in which you could in fact simplify this regulatory path and avoid some of the duplication? You are very much at the early stages of it, but could you avoid some of the duplication that perhaps comes later on?

Dr Alan Clamp: I think perhaps there is, as was mentioned earlier, an awareness issue. One challenge that we have is that people know to come to us. That is something that we need to look into to make sure that it is clear. I suspect that the Health Research Authority is a good place to start, and could perhaps form a triage function to point them in our direction early in the process. You ask whether we have experience of an approach that works. The Human Tissue Authority has always worked on the basis of regulation by advice and guidance where it can. It does not mean that there are no teeth, but we prefer to use a growl and a bark rather than a bite. Because we have got used to providing that advice and guidance and walking people through processes when we can, that has turned out to be very effective, and actually very cost-effective for us. Then what we find is a compliant sector—so it is a bit like preventive medicine. Yes, as a regulatory approach we have a lot of

experience and, yes, we can walk people through it. For example, we flag up MHRA requirements very early on in the process, even though researchers may not be aware of them. Our challenge is making sure that everybody feels that way and knows that we are there to do that service.

Baroness Sharp of Guildford: Do you feel that the tool kit that has been developed picks up these ideas that you have developed?

Dr Alan Clamp: That is a very good example. It was refreshed last year and works well. Perhaps it could be a model both for communication and in terms of content for how we work in other areas.

The Chairman: Peter Thompson, do you want to add anything?

Peter Thompson: Very little, if only to say that the toolkit is very much better than it was. The first draft looked like a wiring diagram and, frankly, was quite off-putting. The online version is much better in the way that it takes you through the steps. Listening to the prior session and the comments now, I wonder whether more energy ought to be put into getting people sufficiently knowledgeable to know to go to the toolkit in the first place. Maybe it is good once you are there, but more energy needs to be put into—there was talk about upstream—further upstream engagement so that people are aware that there are these ways in. To echo Alan's point, we have a good relationship with what is a small, discrete sector. Lots of people, well before they make a formal application, are talking to us about the shape of these things. That is clearly the way to go.

Q324 Lord Dixon-Smith: I speak as a total lay man in this field, but it seems to me that the field will be permanently open to what one American Secretary of State described as “unknown unknowns”. Someone is going to apply to research a solution to a particular problem and find that they have got the answer to something else. How are you going to handle that?

Dr Alan Clamp: One of the ways in which we try to handle that is to make them aware that it is a possibility and to make them aware of what they would need to do if they wanted to go down that route. The point of entry into the process for regenerative medicine is either with the human embryonic stem cell lines with the HFEA or with other cell lines through the HTA. So we try to be clear from the start of the process—we keep using “upstream” and “downstream”—about the need to do it. That is the example that I just gave about flagging up to organisations that, if there is any intention or possibility of this developing into something which is a useful medicinal product, they need to start thinking about quality and safety early on. We regulate procurement and testing; we would then hand on the process to the MHRA. If organisations are aware of that early enough, we can work with them and essentially pass them on to the MHRA. It is helping them look at the possibilities and, I suppose, future-proofing.

Lord Dixon-Smith: Is there a free market, as you might say, between different research groups? If somebody comes along asking to look at a particular problem and thinks that they have a solution to it, and you find that three other groups are already working on that at the same time, what do you do? This is a commercial market and you obviously cannot give away the stage of development of other research groups. I can imagine that this must happen quite often, because the problems are common across a very wide area.

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Dr Alan Clamp: Yes. We publish all our inspection reports and we are conscious, particularly with commercial organisations, that there are sometimes sensitivities around what we might put in them in terms of information that they may even want redacted because it is commercially sensitive. We would not make a judgment on a fourth entrant into a market; we would provide the advice and guidance that we had been put there to provide rather than try to give any commercial advice which is not part of our remit or expertise.

Lord Dixon-Smith: So you see your role essentially as being to help them forward rather than throw logs in the track.

Dr Alan Clamp: It is to make sure that what they are developing is safe and high-quality and therefore will have some clinical utility or potential clinical utility.

Lord Dixon-Smith: Okay. It is a worthy ambition. The trouble is that we have heard so much which indicates that it works the other way.

Q325 The Chairman: I wonder whether we could turn to the ATMP regulations and the proposed clinical trial regulations. We are interested in whether they are flexible enough to cope with changes to clinical trial design, particularly in relation to adaptive licensing and reimbursement. What is your view on that?

Dr Alan Clamp: I would at this point have to hold my hands up and say that that is very much a question for the MHRA in terms of clinical trials, because it is not something that we regulate. We are involved in that initial procurement and testing, and possibly even some of the early processing stages before we pass that on. We try to make sure that the legislation moves with the science, and there are a couple of examples where we have gone to the European Union and said, “We’re looking for some changes to the regulations to facilitate this process”. One recent example would be around the HTLV testing of stem lines, which is being implemented this year. In terms of the clinical trials, it is not an area where I or my organisation would have the expertise to give you a full answer.

The Chairman: What about the HFEA?

Peter Thompson: I am afraid that it is not a very satisfactory answer, but we are in exactly the same position. We have supported the HTA on the example that Alan gave, but this is very much MHRA territory.

The Chairman: Okay, thank you. I should like to move on Baroness Hilton.

Q326 Baroness Hilton of Eggardon: You have mentioned the European Union and the international scene. To what extent is that an additional complication for you? Do you provide people with advice about how to manage their research on a European scale or are you totally confined to the UK situation?

Peter Thompson: The particular projects that we currently license are all within the UK only. It is not as if we have had applications that are collaborations from companies in different parts of the EU. That has not arisen so far.

Dr Alan Clamp: In terms of the tissues and cells directives, we have the same piece of legislation across Europe. However, there is not full harmonisation. Some countries choose to impose higher standards in some areas than others. I should point out for the purposes of this meeting that the UK is not one of those countries.

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Baroness Hilton of Eggardon: Oh really? We have a reputation for gold-plating European regulations.

Dr Alan Clamp: Not in this case. The directives are quite prescriptive but there is no gold-plating in the UK. However, there is in other countries. Some of that comes back to a point that was made earlier about different definitions of medicines and devices. To a large extent there is good harmonisation under the tissues and cells directives, but where—I have just mentioned an example—we see an opportunity to facilitate a more permissive regime or a more effective regime in terms of testing, we have worked with the European Union on that.

Q327 Lord Patel: My point is not related to this question; I want to go back to the licensing issue, particularly as regards embryonic stem cells, or embryo research for that matter. You said you have 25 licences.

Peter Thompson: 24.

Lord Patel: Am I right in thinking that none of them is related to developing treatments?

Peter Thompson: There are four projects related to deriving embryonic stem cells for human application.

Lord Patel: Correct, but none is going to be used for treatment.

Peter Thompson: I do not think that that is yet defined.

Lord Patel: Okay. Secondly, you do not regulate any research on fetuses?

Peter Thompson: No.

Lord Patel: So you do for embryo research but not for foetal research?

Peter Thompson: That is right.

Lord Patel: So that is an anomaly then?

Peter Thompson: It reflects the historical origins of parliamentary and public concern about assisted conception.

Lord Patel: If the embryonic stem cells are created outside the United Kingdom and are brought in for research in this country, do you regulate them?

Peter Thompson: Once the embryos have become disassociated to form stem cell lines, they become the responsibility of the HTA.

Lord Patel: So the HFEA does not have a role then?

Peter Thompson: No.

Lord Patel: But if research was done on those embryonic stem cells, might we have a completely different regulatory authority overseeing whether or not that research was ethical?

Dr Alan Clamp: We would not be looking at whether the research was ethical or not. In terms of the—

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Lord Patel: There would be another regulatory authority sitting behind you looking at that aspect of it.

Dr Alan Clamp: The HRA, yes. We would be looking at the quality and safety of those cells that were already imported.

Lord Patel: So now do you understand why people say that there is complexity of regulation and lack of total co-ordination? What is a researcher going to do? Will he have to go through each one of you?

Dr Alan Clamp: As I think I said in my opening remarks, that is an example of our working closely together and taking people through that process. At present no organisations have gone all the way from the embryonic stem cell lines through the part that is regulated by the HTA and gone on to become an ATMP, so we work at that interface with the HFEA and at the other interface with the MHRA. The regulations are very clear. We would hope that we are very clear. In terms of feedback from researchers, we do not have any particular issues with that. As regards the ethical approval for the whole thing—I can see that that is another area to be looked at—again we are working closely with the HRA to try to make sure that those things are lined up but in terms of the regulatory pathway, that works well.

The Chairman: Lord Willis?

Q328 Lord Willis of Knaresborough: I was going to make exactly the same point. But, in terms of the embryo, the research you can only keep in vitro for 14 days; then it has to be destroyed. It then gets passed up if any cell lines have been developed, as we have heard. Can you not see that those two processes could be combined?

Peter Thompson: I can well—

Lord Willis of Knaresborough: I know the law says not—do not get me wrong—but we are not looking at that. We are looking at making some recommendations about moving forward. Can you not see that?

Peter Thompson: I see exactly what you are driving at. I am also saying that we have responsibility, for good or ill, for the regulation of research involving human embryos in general, of which this is a small subset. There then comes for the Government quite tricky choices as to whether you treat research involving human embryos differently from research involving stem cells derived from human embryos. I readily admit that this is complex. I think that what I am trying to say, and what Alan is trying to say, is that within that complex regime we are determined to make this as straightforward as possible. So, for those four research projects, we will in future do joint inspections. Equally, we are keen that all research applications can go through the IRAS [Integrated Research Approval System] system so that they can make one application rather than several applications, and so on. So, if you like, within the particular range of responsibilities that we have been given, we are determined to make this as straightforward as possible. We start from the premise that there are people out there making the application, not a kind of, “Well it’s complicated, get used to it” attitude. I can well see how, if you are trying to work your way through that, you need some hand-holding and some help, and we are determined to make the best of that.

Q329 Lord O'Neill of Clackmannan: Mr Thompson, you have just admitted that you are, at the end of the day, a creature of statute and that you are totally dependent on that.

Peter Thompson: Yes.

Lord O'Neill of Clackmannan: Do you not think that it might well be the case that, rather than have statute, what we really require are amendments to the law and a provision whereby this would be capable of change by statutory instrument? We are talking about what seems to me, as a lay man, a very dynamic science, which is rapidly changing, and the average opportunity the legislature has to change this kind of law is very limited. Therefore, should you not be, as a collective body—that is to say your board and whatever—going to the Government and saying, “Look we cannot really do the job that we are now expected to do because the science has moved on but the legislation has remained static and we need a more flexible system to accommodate this”? I appreciate that matters of health and safety are perhaps diminished in significance if they become the creatures of secondary legislation, but if secondary legislation is the means whereby more effective forms of regulation can be introduced, surely that would be the road to go down. Have you given any thought to that?

Peter Thompson: What I would point to on that—clearly the Act is a mixture of things in primary, such as the test we need to employ in terms of an embryo, and other bits that are in secondary. I appreciate that you have had submissions and that I have not seen all those submissions—is that we have not had feedback from the sector which says, “The law you have to operate here is the problem”. I believe that if the authority had had representations from people saying, “Look, I am very keen to do research involving human embryo-derived stem cells, or even human embryo research more generally, but the law that you, as an organisation, have to operate is so restrictive that it is making my life difficult”—we have not had those applications but I am sure that if we did have them—we would look seriously, as an authority, at whether or not there was something we could do about it.

Lord O'Neill of Clackmannan: But, with respect, we would not anticipate researchers having a lot of time to pause and reflect on matters which are almost akin to constitutional law. Certainly my experience as a Member of Parliament was that the kind of people who came to see me saying that something was wrong with the system were not then looking back to find out the legal basis for it. That is your job, because by definition you are a creature of statute. There is understandable frustration from bureaucratic approaches. I do not blame you, and I am not using the word “bureaucratic” in a pejorative sense, but the ordinary public just know that it ain't working as well as it could. They do not necessarily know the reason for that but the evidence we have had would suggest that there is frustration there. You are the kind of people who really ought to be able to interpret that frustration and explain to people that it is beyond your capability but then say that, if it is serious enough, the Government should be looking at means of legislating to accommodate what are now changed circumstances and changed science.

Peter Thompson: I understand your point. Perhaps I could take one example. One of the four research projects—and this is not a matter of secrecy because it is in our annual report—is Roslin Cells Ltd, which I understand came and gave you oral evidence. When I read that evidence—if I read it correctly—they appeared to suggest that the regulatory regime was not a fundamental problem. I am not trying to sound complacent. I do not know about the various submissions that you have had and I would very much want to understand where in this process the particular problems are and therefore what the solutions are. Clearly, the amount of research currently involving material derived from human embryos is really very small indeed. I am not at all clear that that is where the fundamental problems are.

Dr Alan Clamp: Can I just give another response to the same question? It does not relate to this particular area, but what you described does happen. For example, at the Human

Tissue Authority, we have had things pointed out to us that essentially, as you say, are not working. We have looked at where we can look at regulatory policy, how we apply the regulations and what flexibility we have. We have had establishments come back and say, “That is helpful, but it doesn’t solve all the problems”, and now we are at a stage where we are proposing those regulatory changes. It is not in the area of regenerative medicine but it does happen.

The Chairman: I would like to draw this session to a close. I think that we have covered the points that we wished to raise. If there are any further points that you would like to make to us in writing after the session has finished, please feel free to do so, and of course you will shortly receive a copy of the transcript to make any minor editorial changes that you wish. With that, I would like to thank you very much indeed for your co-operation this afternoon.

Human Fertilisation and Embryology Authority (HFEA), Medical and Healthcare products Regulation Agency (MHRA), NHS Health Research Authority and Human Tissue Authority (HTA) – Supplementary written evidence

Human Fertilisation and Embryology Authority (HFEA), Medical and Healthcare products Regulation Agency (MHRA), NHS Health Research Authority and Human Tissue Authority (HTA) – Supplementary written evidence

[Evidence to be found under Medical and Healthcare products Regulation Agency \(MHRA\)](#)

Human Tissue Authority (HTA) – Written evidence

Author: Dr Shaun Griffin, Director of Communication and Public Affairs

Context – Arm’s-Length Bodies Review consultation

1. In order to set this response in context, it is of value to note that the Department of Health (DH) is currently consulting on the future of the Human Tissue Authority (HTA). The three options detailed in the consultation document are:

Option One

2. Transfer all Human Fertilisation and Embryology Authority (HFEA) and HTA functions to the Care Quality Commission (CQC), with the exception of HFEA functions relating to research that will transfer to the Health Research Authority (HRA); and abolish the HFEA and HTA.

Option Two

3. Transfer all HFEA and HTA functions to CQC with the exception of HFEA functions relating to research that will transfer to the HRA and a limited number of functions that would transfer elsewhere; and abolish the HFEA and HTA.

Option Three

4. HFEA and HTA retain their functions but deliver further efficiencies.
5. Option one is identified as the Government’s preferred option.
6. The HTA believes that option three, to retain the HTA as a separate organisation and to make further efficiencies, is, subject to clarification of the further efficiencies expected, by far the best option for the regulated sectors and the public as a whole. It is our view that this option would continue the effective and efficient regulation of human tissue and organs by the HTA, minimise the risks associated with the use of human tissue, and protect public confidence. The HTA therefore supports option three.
7. The HTA is of the view that the specialist knowledge and experience we have developed in regard to the implementation and application of EU legislation in the area of regenerative medicine further supports option three.

HTA response to inquiry questions

8. Responses to two questions in the ‘international comparisons’ section are set out below.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

HTA remit in regulating regenerative medicines

9. The HTA's remit in relation to the regulation of regenerative medicines is well defined. Under the European Union Tissues and Cells Directives – transposed into UK law by the Human Tissue (Quality and Safety for Human Application) Regulations 2007 – the HTA licenses establishments that remove, test, process, store, distribute tissues or cells that will (or may) be used to treat patients. In the case of regenerative products manufactured using human tissues and cells, the HTA regulates the procurement and testing of the tissues and cells and the Medicines and Healthcare products Regulatory Agency (MHRA) regulates the further development of the advanced therapy medicinal product (ATMP) into the resulting [regenerative] medicinal product.
10. The HTA's oversight of early stages in the development of regenerative medicinal products is a crucial step in ensuring that quality and safety standards are met and that the resulting product will meet the requirements necessary for eventual authorisation of the product onto the market.
11. To provide some context, the number of establishments jointly regulated by the HTA and MHRA in this area is approximately 15. The sector as a whole includes some 200 establishments licensed by the HTA to use other tissue and cells for patient treatment – such as heart valves and corneas – that will not be processed into regenerative medicinal products, and therefore do not link with the remit of the MHRA.

Collaborative working and support for the sector

12. The close working relationship that the HTA and the MHRA have established – for example by conducting joint inspections and issuing joint position statements – ensures that the impact of regulation on the development of regenerative medicines in the UK is enabling. Through collaborative working, the HTA and MHRA provide assurance to our shared stakeholders in the regenerative medicine field that the systems and processes they have in place during the development of a product are compliant with both UK and EU regulatory requirements.
13. The HTA works closely with a number of other organisations who have an interest in the development of regenerative medicines. For example, the HTA is a member of the UK Stem Cell Bank Steering Committee and the UK Clinical Stem Cell Forum. Effective engagement with our stakeholders in this dynamic area of healthcare ensures we are able to horizon-scan effectively and respond proactively to issues, particularly where regulatory barriers may be perceived.

Regulation supports future market authorisation processes

14. Ensuring that medicinal products are safe is a fundamental prerequisite before they can be authorised for use: robust regulation provides the assurance that this prerequisite is met. The HTA is aware that regulation in this innovative area is complex and we have worked collaboratively with a number of organisations to provide clarity about

regulatory requirements and access to advice and guidance. An excellent example of this approach is the successful development of the UK Stem Cell Tool Kit which provides clear guidance on the regulatory pathways that must be followed in developing a regenerative product derived from stem cells. A case study below provides an example of how we have supported an establishment.

15. In November 2011, Roslin Cells Ltd, moved to new, larger state-of-the-art premises within the Scottish Centre for Regenerative Medicine and worked with the HTA throughout this process to ensure that they had the appropriate licences in place whilst the move from one site to the other took place. The move required months of preparation and planning to ensure cells, assets, staff and processes were moved successfully into the new premises. The HTA worked with MHRA to arrange for a single inspection to be carried out by the two regulators to provide Roslin Cells with advice and guidance about ensuring compliance with the requirements of both HTA and MHRA.

Influencing EU policy development and representing UK interests

16. Influencing EU policy development and representing UK interests is an important role performed by UK regulators working within an EU regulatory framework. An example is the recent initiative taken by the HTA to find a practical and robust solution to difficulties experienced by those working with human embryonic stem cells (hESCs). As the possibility of developing medicinal products derived from hESCs comes closer to being realised, so too does the imperative for ensuring the products will meet all EU and UK regulatory requirements. For some time, the HTA has been aware of difficulties in ensuring that all cell lines derived from embryos are fully compliant with the virology testing requirements of the legislation. The HTA has been discussing with EU colleagues the possibility of revising current legislation to align it with scientific developments. The proposed revisions reflect developments in the testing for virology markers in the cell line derived from the donated cells rather than having to test the donors of the embryos. If the proposed revisions are accepted and implemented, it would significantly ease the current difficulties of producing compliant hESC lines and could also impact favourably on the development of other cell-based regenerative products.

Regulation and public confidence

17. Surveys carried out by Ipsos MORI on behalf of HTA show that regulation impacts favourably in engendering public confidence and trust, which in turn leads to a greater willingness to donate tissues and cells.

Summary

18. In summary, regulation has the potential to impact favourably on regenerative medicine for the following reasons:
 - it provides essential safeguards for ensuring quality and safety
 - regulatory oversight ensures that EU standards are being met, which in turn supports any future market authorisation process
 - regulatory bodies can and do represent UK interests at a EU level

- knowledge there is regulation leads to greater public confidence and therefore an increase in the willingness to donate

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

19. EU countries are governed by the same legislation for the development of regenerative medicines. The key principle behind EU-wide legislation is to harmonise practices across Member States. The HTA's experience of regulating under EU legislation is that the principle of harmonisation is attainable to a point but may be unachievable in its entirety due to the principle of subsidiarity. EU laws do ensure that there is a consistency across Europe in applying a set of minimum standards as set out in the legislation; however, Member States can and do apply higher standards to some practices – when this occurs harmonisation becomes fractured.
20. The UK provides a permissive environment within which translational research occurs. For example, unlike a number of EU countries the UK allows research on embryos and cells lines derived from embryos. The comprehensive regulatory structure in place in the UK, covering as it does the regulation of embryos, provides an assurance of the safe and ethical use of those embryos, which in turn supports the permissive environment. During the cell line derivation process the embryo is dissociated and it is at this processing stage that the HTA regulatory remit begins and the HFEA's regulatory remit ceases. The HTA regulate the procurement and testing of embryonic stem cell lines intended for patient treatment under the Human Tissue (Quality and Safety for Human Application) Regulations 2007, and the embryonic stem cell lines must be compliant with the HTA standards.

Representing UK interests at an EU level

21. While recognising that harmonisation may be an ideal, it is important to recognise the role that regulators have in ensuring that UK interests are represented at an EU level. In particular regulators can identify areas where clarification may be required around a particular minimum standard, and ensure that it is applied in a more consistent fashion across the EU.
22. The HTA has successfully represented UK stakeholders at an EU level in seeking clarity around provisions within EU legislation relating to the testing requirements for the Human T-lymphotropic virus (HTLV). By working closely with the EU and the European Centre for Disease Control (ECDC), a revision to the wording in the Directives has been agreed by all Member States and will be implemented in 2013/14. The revision should result in a more harmonised approach to applying the legal requirements.
23. It is important for all those involved in regenerative translational research to be confident that they are working with a set of harmonised standards that apply to all equally. Regulators have a significant role in ensuring that UK developers are not disadvantaged by inconsistent practices and when appropriate develop proposals for legislative change, so that the law keeps pace with science.

Summary

Human Tissue Authority (HTA) – Written evidence

- Within EU there are harmonising laws that cover the field of translational research
- The principle of subsidiarity may detract from the ability to achieve full harmonisation
- Regulators represent UK stakeholders at an EU level and can affect and drive change to the benefit of UK, including ensuring consistent application of EU laws.

3 September 2012

Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA)
– Oral evidence (QQ 317-329)

Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) – Oral evidence (QQ 317-329)

[Transcript to be found under Human Fertilisation and Embryology Authority \(HFEA\)](#)

Human Tissue Authority (HTA), Human Fertilisation and Embryology Authority (HFEA), Medical and Healthcare products Regulation Agency (MHRA) and NHS Health Research Authority – Supplementary written evidence

Human Tissue Authority (HTA), Human Fertilisation and Embryology Authority (HFEA), Medical and Healthcare products Regulation Agency (MHRA) and NHS Health Research Authority – Supplementary written evidence

[Evidence to be found under Medical and Healthcare products Regulation Agency \(MHRA\)](#)

Imperial Innovations, Apax Partners and Cenkos Security – Oral evidence (QQ 170-195)

[Transcript to be found under Cenkos Security](#)

**Intellectual Property Office, Lawford Davies Denoon and Professor
Peter Andrews, University of Sheffield – Oral evidence (QQ 196-213)**

Evidence Session No. 8

Heard in Public

Questions 196 - 213

TUESDAY 27 NOVEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl Selborne
Lord Turnberg
Lord Willis of Knaresborough

Examination of Witnesses

Witnesses: **Sean Dennehey**, Acting Chief Executive, Intellectual Property Office; **Alex Denoon**, Partner, Lawford Davies Denoon; and **Professor Peter Andrews**, Arthur Jackson Professor of Biomedical Science and Co-Director of the Centre for Stem Cell Biology, University of Sheffield.

Q196 The Chairman: I would like to welcome our three witnesses for this morning's session. Thank you very much for coming to join us. In a moment, I will ask you to introduce yourselves for the record, and if you wish to make any brief opening comments, please feel free to do so—but please feel free to keep them brief. For those here who are observers, the purpose of the inquiry and the declared interests of the Members of the Committee should be available to you. I would like to invite Alex Denoon to start off by introducing himself.

Alex Denoon: My name is Alex Denoon. I am a lawyer who works a lot in regenerative medicine, focusing particularly on intellectual property and regulation.

Sean Dennehey: My name is Sean Dennehey. I am the acting chief executive of the Intellectual Property Office, which is an executive agency of the Department for Business, Innovation and Skills. The IPO has responsibility for granting UK patents, trademarks and registered designs; responsibility for policy in those areas and the area of copyright; and for outreach and awareness in those fields.

Professor Peter Andrews: I am Peter Andrews, Professor of Biomedical Science in the University of Sheffield. I have worked on embryonic stem cells since they were first derived. We received the first lines in the UK from Jamie Thomson in 1999, and before that I worked on the malignant equivalent of those cells which come from a strange cancer called the teratocarcinoma, and I have carried out quite a lot of the basic underlying work that led up to ES cell work. In Sheffield, we set up a spin-out company, Axordia Ltd, that subsequently was bought up by Intercytex, which then failed. The IP and cell lines from Axordia went to Pfizer.

The Chairman: Thank you very much. I would like to start off by asking each of you about the importance of intellectual property in the commercialisation of regenerative medicine. We have heard conflicting evidence, with a number of submissions suggesting to us that protection of IP was fundamental; but others have argued that the complexity and know-how inherent in developing a treatment will provide sufficient protection to attract investment. I wonder if, starting with Alex Denoon, you can give us your assessment of the importance of IP protection.

Alex Denoon: I suspect we are years away from knowing the answer to that question. The business models for these products are simply yet to be determined. Intellectual property is a crucial element in the mechanism to reward investment in life sciences generally, but it may well be that the regulatory protections and barriers will be much more of a barrier to entry and deliver much more protection to innovators in the sector. I also think it is worth stepping back a bit and mentioning that there is an enormous diversity of potential regenerative medicine therapies. If we are thinking about an embryonically derived neural progenitor cell for treating spinal trauma, that has a very different business model from the use of a patient's own autologous cells within the same surgical procedure. The business models for those two will have very little in common with one another. Your ability to get patents on a patient's own cells is a non-sequitur. You would not bother trying to get a series of patents for each set of patent cells. So at the autologous end, you will be much more interested in patents around divisors, biomarkers and so on. At the other end, whether it is adult or embryonically derived, you will be very interested in patents on the composition itself. However, there is no one-size-fits all. It really will depend, and it will take a while before we find out. It is also worth reiterating the regulatory barriers; once someone gets a marketing authorisation for an advanced-therapy medicinal product, no one else using that data can get a generic of that line for a finite period of about 10 years. Even if, at the end of that 10-year period, someone wanted to use that data to get a generic approval, it will be virtually impossible to convince a regulator that your generic neural progenitor cell derived from an embryonic stem cell line is much the same as the one already on the market. I just do not think that there is a simple answer to this. Intellectual property is a vital element, but it will not be the sole tool to reward investment in the sector.

Sean Dennehey: Clearly, Alex is expert in the field, and the Intellectual Property Office, when considering these questions, takes careful notice of what stakeholders acting in the field are actually saying and doing. The received wisdom is that patents support innovation by incentivising invention by giving inventors exclusive periods of protection, exclusive rights during the period of exploitation and, importantly, facilitating disclosure of new ideas so that others can build on them. However, as in every other field of technology, having a patent is not a necessary or sufficient requirement for commercial success. A whole range of other considerations come into play. I suppose that a number of people who have given evidence to this Committee and who commentate in this area regard the ownership of a granted

patent as a sort of token of the worth of the invention concerned. That may sometimes be a token made of base metal. It is necessary to look beyond the ownership of the patent itself to see what it can bring.

Professor Peter Andrews: It is actually rather a mixed bag. One thing that is clear from my experience of trying to set up a spin-out company, is that when you go to investors they look for patents. Therefore, when you are setting up a company, you spend a lot of time running around trying to invent things that you can patent. When we set up Axordia we produced all sorts of patent applications, which took an awful lot of effort. One was granted in China and the rest have now gone the way of most other things. It was an important exercise in trying to secure investment, and clearly venture capitalists, VCs, like that, but, in practice, it did not help us very much. One of the clear things with patenting is that the object is to allow disclosure of inventions and knowledge, which is what we need to pursue science. One of the dangers is that if you cannot patent things, certain discoveries and developments may become rather less publicly known and impede the development of science. On the one hand, patenting is important from that point of view; whether it is actually important in practice, I do not know, but I can see that theoretically.

The Chairman: Could you just say why it did not help you very much in the end.

Professor Peter Andrews: All the patents were based on various ideas that we had. One of the problems was getting enough funding to then develop the ideas encompassed in the patents. Then at some point there is always the issue of weeding out those that have a lower priority than others. It depends on how successful you are at persuading the VCs to give you the money to pursue the patent.

Lord Patel: That was exactly the issue. I know that you are a top researcher in embryonic stem cells and, therefore, issues about patenting. You might be not less involved with but less focused on patenting. However, what we heard previously was that if there were no patents, then venture capitalists are less likely to invest, or that individual researchers will go to spin-outs sooner than they needed to.

Professor Peter Andrews: That seems to be the perceived wisdom, and it was certainly our experience in trying to set up a spin-out company. I cannot test the reality of it, in a sense.

Q197 Lord Dixon-Smith: If there is an investor fixation with the idea of patenting, what could or ought to be done to try to overcome that if, in fact, the reality of this is that patents are not really a clinical issue?

Alex Denoon: We made a suggestion to George Freeman and a number of players to try and see whether it might be possible to prepare a brief note explaining, with a buy-in from a variety of stakeholders, paths to market, and ways in which you might be able to protect your investment and secure income streams for reward, with a view to trying to put that out in the public domain and, in particular, to make that available to researchers seeking grant funding or, in due course, venture capital funding, and with a view to saying, “Look, there is a more nuanced situation here”. Physical ownership of the cell line itself does not expire when the patent expires. So long as you can retain control of your cell line and license it out to people sequentially, there are, in fact, a number of very valuable cell lines out there in the world that are still valuable long after the patents expired. Perhaps we could try and put forward a note explaining the different business models, with buy-in from bodies such as the Wellcome Trust, the British Venture Capital Association, BIA, PWC and, possibly, the IP office, with a view to saying, “There are models to think about here”. We would not be saying, “Abandon the patent office”, or “Abolish patenting in the sector”. Let

us think about this in a way that might help people to address that issue, particularly researchers seeking that early-stage funding.

Q198 Lord Cunningham of Felling: This is a question principally for Mr Dennehey, but if other witnesses want to add their thoughts, that is fine. Is it possible to be definitive about what is patentable across the full range of regenerative medicine—gene therapy and tissue engineering—or not?

Sean Dennehey: Definitive is a very strong word, in the sense that it implies a guarantee in the answer, which is going a little further than I am prepared to go; but I am happy to respond to the question. Most areas of regenerative medicine are patentable. In the focus on the post-Brüstle discussion, it is easy to lose sight of that. In the appropriate European Union biotechnology directive (98/44/EC), there are specific exclusions laid down arising from inventions that are considered contrary to morality. This includes uses of human embryos for industrial or commercial purposes. The human body and any of its natural elements are not patentable. However, materials isolated from the human body, such as cells or isolated genes and their use in therapy, are patentable. Methods of medical treatment or diagnosis are not patentable, to ensure that the actions performed by a medical practitioner do not infringe a patent. Methods of tissue engineering, such as culture techniques, delivery methods or cell scaffolds, are also patentable. The proviso is that the general requirements for patentability are met—that is, that the invention is new, inventive and has some industrial application.

Lord Cunningham of Felling: Perhaps you can give us specific examples of things that have been patented.

Sean Dennehey: I certainly can; in fact, I have a number of patents here that I would be happy to write to the Committee about and share. Examples of patents granted in the UK include: a peripheral nerve-growth scaffold, which includes poly epsilon-caprolactone; human-induced pluripotent stem cells; biocomposite skin substitutes for wound healing; collagen matrix for supporting cell growth; multipotent stem cell from human adipose tissue; or method of decellularisation of a membranous sac or bladder, prior to transplant. I would be happy to write to the Committee with examples.

Alex Denoon: Perhaps I may make a brief point here regarding Professor Coffey's development at UCL using Professor Andrews's original embryonic stem-cell line for the treatment of macular degeneration. A lot of the therapies that are going to be developed using regenerative medicine or cells will involve novel delivery systems, novel scaffolds or novel mechanisms for monitoring exactly what is going on. Without trying to steal thunder from the IP office, patents on those kinds of delivery systems would be very conventional and, subject to the normal requirement, would be very readily patented. Perhaps I can give another example of that. Tigenix, which had the first marketing authorisation for an advance-therapy medicinal product for treating knee pain and to regrow cartilage in the knee does not have any patents on those cell lines because they come from each patient. There is a series of autologous patients. However, the company holds a variety of patents around delivery systems, and monitoring and culturing systems. They are more likely to be the more valuable patents in this sector, rather than the patents on the lines themselves.

Q199 Lord Cunningham of Felling: Is uncertainty about this a problem with respect to determining investment—uncertainty about the ability of people to protect their intellectual property?

Sean Dennehey: The first thing that I would say is that patenting is not an exact science, whether in this field or any other. The legal books are full of case law determining very nice and fine points. It would therefore be a mistake to assume that life is complicated in the field of regenerative medicine in a way that it is not elsewhere. The challenges are different, and that is partly because there are potentially large benefits to be gained, both in terms of society from the research, but commercially for businesses—and because the technology is so new and the establishment of the rules that apply in practice around patenting of these technologies are emerging. The fact that many people would not have predicted the outcome of the Brüstle case is indicative of that. In commenting on Alex's earlier suggestion of better guidance, I suggest that that is certainly something that the Intellectual Property Office would be keen to look at and collaborate with others on, because in the absence of hard and fast rules, giving clear guidance on which people can make subjective but soundly based judgments must be a way forward.

Professor Peter Andrews: In terms of an example about investment without patent protection is the investment from Pfizer in Professor Coffey's studies in London to transplant RPE cells for macular degeneration. That is based essentially on a cell line that we produced in Sheffield, which actually belonged to our spin-out company, Axordia. Perhaps through not very good business sense, it ended up in the hands of Pfizer. However, it owns the cell line, which has been developed to a clinical standard and has gone through large numbers of tests and so on. Coming back to Alex's point, once that goes into clinical trials and if that is successful, I should have thought that with certainly Pfizer investing in and promoting that it would be much more difficult for someone to come up with another cell line to do the same sort of work with, or indeed any other similar application. For example, in Sheffield, another of my colleagues is working on developing auditory neurones from human ES cells, with the potential that that could be used for transplantation for treating deafness at some point in the future. He is doing that work with the same cell line, Shef-1. If the work with Pete Coffey goes ahead, works and there are no unforeseen consequences, then that cell line will become particularly valuable for pursuing that particular work. That is without any patent.

Q200 Lord Cunningham of Felling: Just one final question on a matter to which you referred a moment ago. Is the Brüstle-Greenpeace decision something to be concerned about or not?

Sean Dennehey: That is a question that I would answer by saying that the initial reaction to the decision does not appear to have been sustained. Having followed with some interest the evidence that has been given to the Committee so far, it is possible to discern a broad range of opinions that regards that decision as not a disaster, for a number of reasons that we may come on to. The more balanced view is that having a patent, as we said earlier, is helpful in securing funding but not essential. Clearly from the perspective of encouraging activity in a particular field, one would ideally want patenting to be available in that field. The balanced view is that other stem cell research using induced pluripotent stem cells or adult stem cells, offers alternatives as technology evolves. It is therefore quite possible that Brüstle will become a footnote in the history of this technology before too much longer.

Professor Peter Andrews: Perhaps I may comment, not directly on the consequences for patenting. There was a large concern, certainly among my colleagues, about the tone of and the way that that judgment was delivered. It appeared to imply a sense of immorality and non-ethical standards for working with human ES cells in general. I know that the judgment did not specifically say that, but there was that kind of tone and implication. There was some

concern that this was a ripple effect and a thin end of the wedge whereby these sorts of arguments could be used by other people to undermine our ability to work with human embryonic stem cells much more generally, irrespective of the patent issue. So there was a general concern in the community from that point of view.

Alex Denoon: Any uncertainty is unhelpful, but I cannot think of a single project that has been abandoned or has failed to progress as a result of the decision itself, for the variety of reasons that we have discussed. However, it is interesting that the opponents of embryonic stem cell research in the European Parliament are trying to use the decision to justify withholding funding for embryonic stem cell research in the Horizon 2020 project. They say either that this is immoral and should not therefore be funded, or that it cannot be commercialised and should not, therefore, be funded. Both are polar opposites. Rest assured that a number of people are trying very hard to resist that amendment to Horizon 2020. However, the ripple effect is probably more important than the direct effect on specific cell lines. It is worth mentioning that Oliver Brüstle's patent would expire long before any therapy got to market. I think it was 15 years into the life of his patent when the Court of Justice knocked it off.

Q201 Lord Turnberg: I wanted to just follow the questioning on the Brüstle case. I was interested in reading your written submission, in which you seem to be suggesting at one point that the ruling was rather more helpful than otherwise, and that developing stem cell lines may be liberators from the tyranny of a 20 year-old patent life. That suggests that it might be helpful in encouraging researchers in the field, rather than the opposite.

Alex Denoon: I apologise for having conveyed the impression that the decision was helpful. I think for the reason I mentioned previously, a cell line itself can generate enormous revenues and can be hugely commercially valuable, as well as scientifically and clinically valuable, long after the patent on the cell line expires. As regards, the conventional model, with pharmaceuticals running to the end of their patent life, whether extended with an SPC or not, and then dropping off a cliff in terms of the value that can be generated using that pharmaceutical because of generic entrants reducing the price by 90%, I suspect that that will not happen with a lot of these cell products. The original patents that Professor Andrews derived many years ago will expire long before those therapies get to market, but will continue to be used. I think that regenerative medicines and cell-based therapies offer wonderful opportunities for recovery of investment in the sector. That is why I think that patents are important but not crucial. I apologise—if I conveyed the impression that the Brüstle decision itself was helpful, I unreservedly retract that. However, the sector has the opportunity to be liberated from that model of having to replace your product line every 10 years.

Q202 Lord Patel: Because of the discussion that has been going on, I want to explore the question I was going to ask in three different ways. My key question was going to explore the barriers to obtaining patents—for individual researchers to meet the costs, to establish a better understanding of what patent time-limits are and how to fund them, and for universities to have the necessary support for their researches. But in the context of our discussion, I also want to explore certain issues, particularly with Alex Denoon and Peter Andrews. Peter, you created the line that will be used by Pete Coffey and others to test whether the treatment for age-related macular regeneration would work or not. If it does, then, on the basis that there will be 3 million people in this country alone who might benefit, that line is extremely valuable. However, Alex, you said that it is not important to obtain patents on the lines, and you cannot do that anyway. Let us hope that the line that Peter

Andrews created is the only one that works for this treatment—in which case, it would be enormously commercially beneficial. That will not be the case if any embryonic stem cell line will work for the treatment. If you say these cells are not patentable, how are we as a country and you, Peter, as a creator of the line, going to hold on to these lines? Those are interlinked questions.

Professor Peter Andrews: I should actually say that the cell line was derived by my colleague Harry Moore, not myself. It is clear that other human embryology stem cell lines will make retinal pigment cells, so it is not the unique property of that cell line. I think the value comes from all the work that goes into developing and justifying its use. As far as I can understand, if someone wants to come and use another cell line for exactly the same treatment, they will have to invest an awful lot of money in confirming the provenance of that line, that it does not carry various pathogens that we do not know about that have not been tested for, or that it has not acquired genetic changes that interfere with safety. There is a whole range of work that has to be done to make the cell line of the whole treatment acceptable to the regulators for transplanting to people. It is that body of knowledge related to that cell line which will make it valuable. I do not think that it will stop other people coming along and creating things with another cell line, but it is nevertheless a barrier to other people coming in. One of the problems is that it is not that difficult to make enough retinal pigment cells and go through the hoops to treat 10 or 20 patients in a clinical trial. It is a much bigger jump to trying to work out how to treat 10,000, 100,000 or 1 million patients. There is a major area of development and I cannot see many other people jumping in with new cell lines to try to develop other cells for that purpose until someone has reached a point to show that the whole thing can be taken through. That is not going to take two years; we are talking about five or 10 years, at least.

Alex Denoon: If I have a patent on a particular cell line—the Pete Coffey cell line—that would not prevent someone else trying to generate their own cell line and go forward with it. A patent on my cell line would not necessarily inhibit someone else developing their own. However, it would make it much harder for them to produce a generic version of that cell line. I do not think that we are exposed to generics in this sector because the regulators have struggled. Only about half the monoclonal antibodies that have been submitted for approval as a generic or a bio-similar have been approved. If you consider the complexity of two different versions of Herceptin, and you cannot even be confident that they are similar, creating two different versions of an embryonically derived RPE cell simply will not happen. You may have parallel competition, but the absence of a patent on your particular cell line would not have stopped someone else generating another one afresh. Going back to the barriers to entry, universities really struggle for sufficient funds to file the patent, prosecute it and, crucially, enter the national phase 30 months or so afterwards, depending on the route they go. They often run out of money not at the initial filing stage, but after they file at some later stage, when the fees increase dramatically.

Q203 Lord Patel: How do we overcome these barriers to patenting, costs and so on?

Sean Dennehey: Perhaps I may comment on this general question. The costs involved in obtaining a patent can vary considerably, depending on the strategy that has been adopted. For example, to obtain a patent from the UK Intellectual Property Office would cost £230 in official fees. A study by Professor Ian Hargreaves published in 2011 indicated that when you added on to that the time spent by the individuals in a university or a company, plus the advice of patent professional attorneys, the total cost would then come to something like £20,000 or £21,000. There is a difference between the official fee and the total fee.

However, a good deal of university research relies on applying for an international patent application, which immediately takes you into much more expensive territory, but brings with it the ability to defer substantially decision points in terms of whether to proceed with a patent application or not. There is a balance to be struck here, and this is Alex's area of expertise rather than mine, but looking out more generally from the regenerative medicine area, many companies are now saying that being more discriminating in the territories in which they seek protection is a more cost-effective way of getting patent protection that actually delivers what they need—for example, by not necessarily seeking protection in every state of the European Union, but cherry-picking key states. Therefore, there are strategies for managing cost, and it may be that not all universities are as sophisticated in their patenting approaches as they might be.

Q204 Baroness Perry of Southwark: The story that we have been hearing of the need to have a lot of patents in place before you go and get funding and so on obviously raises the question: are there just too many patents out there? Is there what has been called a thicket of existing patents, whereby it is difficult for someone to find their way through to a niche where they can get a unique patent for themselves? Is that a genuine problem?

Sean Dennehey: It is a very interesting question on which the IPO has been doing a good deal of research. We have published one report and we have another that is currently under peer review. What I would say is that in the area of regenerative medicine there are relatively few patents around at the moment. The patent informatics report, which the Committee has seen, indicates that there are many patent holders who each have very few patents. In an emerging technology such as this area, I would suggest that patent thickets are not an existing problem; however, it may be that they will become one. In our emerging research, it is not so much the number of patents that is significant but the extent to which the claims or monopolies of the patents overlap and, therefore, the extent to which—I use a simplistic analogy—the brambles are entwining rather than able to be parted. The evidence in other areas of technology suggests that sometimes lots of patents give rise to significant market-entry barriers, but they do not do so in other areas where you might expect them to be a problem. It is a sophisticated question, but my current observation is that in the area of interest of this Committee, patent thickets have not become a problem yet.

Q205 Baroness Perry of Southwark: How does an academic researcher who is reaching that point get advice? I understand that your office has now backed away from giving advice. Where do they turn? How do they get advice on what the existing patents are and finding their way through the thicket?

Sean Dennehey: The office that I currently lead has not backed away from giving advice of an appropriate nature to anyone who comes to us.

Baroness Perry of Southwark: I should not have said advice, but you will not do the search for them.

Sean Dennehey: In terms of pre-filing searches, no, we no longer do that. That is absolutely right. We give anyone who asks us for it general advice on the nature of the patent environment, and because obtaining a search on a patent application is so cheap, an easy and quick alternative for anyone who wanted that sort of search is to make a patent application, because we provide a search in 90% of cases within four months of being asked, and there is no need for the person applying then to disclose their invention, because they can then immediately withdraw it. It is also worth saying that one of the reasons we

withdrew the service that we used to provide was that there are other commercial providers in the marketplace and other considerations therefore came into being.

Baroness Perry of Southwark: Can Professor Andrews comment on that, having been through the process?

Professor Peter Andrews: In terms of trying to assess other patents, we had a very good patent agent who we dealt with through the University of Sheffield and who gave us a lot of good advice. It occurs to me that there is one aspect of patents which is interesting in this area because some patents can occasionally be disrupted to the whole area. It is arguable that the original patent that was obtained from Wisconsin for embryonic stem cells was more deleterious to the field than the stance of the United States Government in the 1990s on working with embryonic stem cells. That was largely because that patent claimed ownership of embryonic stem cells, full stop. That meant potentially that people trying to get embryonic stem cell lines, as they did, from Wisconsin had essentially to hand over a lot of potential IP. I have heard of some people who probably did not get embryonic stem cell lines in the States because of those requirements. We were fortunately in a somewhat favoured position because Jamie Thomson was a colleague and we obtained the stem cell lines before a lot of this evolved. However, it was potentially a problem that hampered in the early days access to cell lines, just because of kinds of requirements that they had to sign up to.

Alex Denoon: As regards the patent holder in Wisconsin, although I am not a research foundation, the licensing strategy was changed. Initially, it was fairly restrictive and onerous, but it was subsequently decided to take a less onerous line and a lot of the sensitivity was addressed with that change.

Professor Peter Andrews: Yes, I think that that resulted from negotiation with the NIH that essentially forced that.

Q206 Earl of Selborne: Continuing the theme on the support available to patent applicants, I think we have covered the role of the IPO and university IP offices. What role should the cell therapy catapult play in this respect?

Sean Dennehey: I am happy to offer a comment, although, strictly speaking, this is outside the remit of the Intellectual Property Office. I am sure that my colleagues in the wider BIS department would be happy to advise the Committee on this point. None the less, the catapult centres are absolutely there to provide the hands-on and close support in these technical areas, and there are a number of catapult centres. The one based in London is, I understand, only in the process of being set up and I am therefore not in a position to say how Guy's and St Thomas' trust will be able to work in this area, I am afraid.

Q207 Earl of Selborne: Perhaps I may ask Mr Denoon: in the evidence of your firm, Lawford Davies Denoon, you refer to a patenting clearing house. What do you mean by that and what would it fulfil?

Alex Denoon: It would be there with a view to helping inventors try and work out what is patentable, what might not be patentable, and to provide a sense of the landscape. It would provide some kind of rule of thumb or preliminary guidance by saying, "Actually, this area is simply way too patented" or, "There have been huge disclosures here already, so thinking about thinking about patenting there is unhelpful, but thinking about patenting in these areas may well be more helpful". The clearing house would try to give some overview of the position, not really to address the specifics of any invention but to help weed out some of

the more extreme positions and help people realise whether or not it is worth paying the patent attorneys who can assist. Patent attorneys in the UK do a very good job, assuming you can find the funds to pay them. Whether at a catapult level or some other level, people understand the patentability, breadths and weaknesses of patents in this sector.

Q208 Earl of Selborne: Finally in the area of support for patent applicants, we have in April 2013 the patent box coming in, which gives fiscal support. How relevant will that be?

Sean Dennehey: It would be interesting to see how it develops. Stakeholders to whom we have spoken have expressed considerable interest in the opportunities that it provides for a reduced rate of corporation tax to support businesses that rely on patents for their income. The arrangement is being phased in over five years. However, the fact that it is dependent on having a granted patent is resulting, we believe, in increased numbers of filings at the Intellectual Property Office across a whole range of technologies. Therefore, we are expecting that the new arrangement will make a difference. I do not have any particular insight as to whether, in the field of regenerative of medicine, there is a disproportionate interest, as compared with technology as a whole.

Alex Denoon: I would say that it is important where the company that holds the intellectual property is going to be incorporated, rather than where the research is done or the clinical trials are conducted. However, I know some companies that are very interested in being in the UK that were not previously going to be based in the UK because of the patent box, but it is not really impacting on the research itself.

Q209 Lord Willis of Knaresborough: Perhaps I may ask a question from ignorance, rather than anything else. You established that with an embryonic stem line it is going to be difficult to create a generic, for obvious reasons, and the cost of creating a generic would be as much as creating an original line, and therefore there is no point in creating a generic. Secondly, you said that the barrier to entry into this field in terms of creating a new stem line is hugely expensive because of the regulation of procedures, not simply the of the patenting. Is there any way in which you can protect ownership other than by patenting?

Alex Denoon: Yes.

Lord Willis of Knaresborough: Why bother with patents if there is a better way?

Alex Denoon: In part, because you want to have patents around the periphery in order to be able to license.

Lord Willis of Knaresborough: I understand that, but what about in terms of the lines themselves?

Alex Denoon: A number of hybrid donor lines were generated in the 1980s and are still very valuable because you had tight control over the line itself, and you said, “These are the terms upon which I am going to allow you access to it”. That would apply even to relatively boring things such as yeast or in more conventional agricultural or horticultural areas. Lines themselves can therefore be valuable. That was my point about being liberated from the tyranny of the patent period, because you are not going to have that drop-off, so long as you become the gold standard. My only fear about stating that too strongly is that we simply do not know—we do not have the successful embryonic stem cell therapy product on the market, and it is not going to come for a while. We are not going to have these blockbusters, so I do not want to say definitively that this will be the model. However, retaining ownership of that line and, I suspect, making it available to others in a controlled way, but disseminating the line in the way that Sheffield has done, and having lots of

researchers work on it, is a good thing and is more likely to generate the confidence and standing that one would expect. I can send you through some supplementary material in relation to a number of cell lines that are enormously valuable—the HeLa cell line in particular.

Professor Peter Andrews: I suppose the hybridomas that we made back in 1982 in Wistar in the United States are producing antibodies that are widely used for defining human embryonic stem cells. They are owned by the Wistar Institute, which licenses them to all sorts of companies and they are generally available. Wistar continues to make money out of them from the licence.

Q210 Baroness Hilton of Eggardon: If we could look at comparisons with other countries, do they have approaches that are more supportive and generate more invention, or do we have nothing to learn from the rest of the world?

Sean Dennehey: My comment would be no—in terms of neither the patenting framework nor the support that is given to universities or businesses in this field. In terms of the patenting framework, although it is fair to say that in the United States, for example, there are not constraints based around morality in the same way as there are in Europe, and although there is clearly a substantial body of activity in the United States in this area, we would not put that down to the patenting environment, but wider factors. In terms of the support given by government and funding of research, certainly in the UK, recent reports in relation to regenerative medicine and the evidence that was submitted by the Department for Business Innovation and Skills, I would strongly argue that the support available in this country is as good, if not better, than anywhere else in the world. However, I can see that that opinion is not necessarily shared around this table.

Baroness Hilton of Eggardon: You provided us with a table on some research that you carried out on inventiveness in various countries as regards levels of patent applications. It suggested that we are not quite as inventive as one would expect us to be.

Sean Dennehey: It is certainly true that the report we submitted to the Committee showed that we are not as inventive as we would like to be; that is absolutely right. The extent to which the position of the field of regenerative medicine is different from life sciences research generally is actually quite small. Looking at population sizes¹⁹², Israel, for example, comes out perhaps surprisingly high in the analysis, but relatively few additional patents would need to be granted to UK researchers to make quite a big difference. This is a situation where the small size of the data set can have arguably misleading consequences; but, none the less, the data say what the data say.

Professor Peter Andrews: I do not have any insights at all.

Alex Denoon: The availability of funding is the hugely determining factor here. The UK Intellectual Property Office does a good job.

Q211 Lord Patel: I was the one who shook my head when Mr Dennehey commented on whether research in this country is supported at the level of other countries. It is not so much the basic research—although I like your comment and Professor Andrews’s comment about that—but I wish to know whether support is needed beyond that for translation, including for IPO issues. Are the commercialisation and legal issues that need to be faced, supported or not?

¹⁹² Note from witness: i.e. overall level of patented invention expected for each country

Professor Peter Andrews: I am going to talk specifically about embryonic stem cell work with regard to regenerative medicine, as opposed to regenerative medicine in general, because that is what I know about. The issue there is that we have a long way to go in terms of basic research to provide the infrastructure to underpin products. Clearly, we need a pipeline of work that covers funding for the basic research that will eventually give rise to products. There is a large effort at the moment to put money from the research councils and elsewhere into the translational activities to support activities to move work through to applications. I am still concerned that we must recognise that the basic research to generate the ideas that will go through the pipeline still has to be strongly supported.

Sean Dennehey: This is where the catapult centre strongly comes into play, because it is designed, when it is up and running, to fill the gap between research and exploitation by introducing finance, expertise and the ability quickly to move research through to commercialisation. To the extent that I recognise that there is more to be done, I would argue that the catapult centre is poised to fill that gap.

Alex Denoon: I would say that the commercial translation infrastructure is relatively weak in the UK, particularly for regenerative medicine, partly because we do not have many role models to follow in terms of products getting through. However, very early on in the development of a potential therapy, you have to make a lot of crucial decisions about regulatory pathways and reimbursement models. Ignoring the opacity of that for the time being, there is very little maturity in relation to understanding the ramifications of the decisions made early on. You might choose a particular route to market that ends up becoming unviable, simply because you had not realised the ramifications that were going to come your way later on. Many other countries are a lot better at understanding, working out and implementing these strategies than we are in terms of trying to get the basic research through therapies.

Lord Patel: Perhaps you can give an example.

Alex Denoon: If you have a cell line that has a potentially broad set of therapeutic indications, there is an interesting decision as to whether you go for the orphan indications, the rarer indications early on, or whether you go for the larger indications. That has its own regulatory pathways. Orphan drug designation can be a very attractive pathway as a sequence of small orphan designations; but that means that you are not going to be treating large populations. Orphan drug designation has the benefit of relatively small patent groups during your phase two or phase three clinical trials. Going for a broader indication means that you are going to have to raise a lot more money and conduct trials over a much longer period in order to get the power in your statistical analysis. Simply at a level of choosing which of the various indications are available to you, working out which of those to pursue is crucial to the business model that you are pursuing, the amount of funding that you are going to need, or whether or not you are going to patent certain things.

Lord Patel: As you said, other countries were better at developing those models. Will you please give us examples of which countries?

Alex Denoon: Primarily in the United States, the technology transfer offices in universities have more experience, are more sophisticated and have more money to throw at the opportunities. As a general rule, very few of the technology transfer offices or universities in the UK have much experience at taking these kinds of products through, understanding the nuance about which product to take forward, and knowing which therapy to pursue.

Q212 Lord Rees of Ludlow: Following up this general question, in academia is it not a good thing to have collaboration between universities, and even international collaboration? The aim of the catapults is to promote closer links between different universities and companies. Hopefully, there will be more than just two or three companies. Although those are clearly good things in the abstract, will they not make the situation much more complicated in handling all the patenting and so on? Can you comment on whether this is as much of a potential tension as it seems to me to be?

Alex Denoon: I would say that it is a natural tension and is not necessarily a problem. The alternative of saying each one has to pursue it in a silo, and has to race in a competitive fashion is challenging, but I agree with you that it is quite often a mess to try and work out in a joint-venture context who is going to have certain rights, who is going to provide follow-up funding, and so on. However, that is a necessary consequence of getting together and a natural tension that arises, rather than a reason not to collaborate.

Sean Dennehey: I agree with that. The idea that it would be better for universities or companies to work in parallel rather than together is clearly not sensible. The point is how best to mediate that collaboration. Patents provide a vehicle for assisting that in appropriate cases but, more than that, the development some years ago of model licensing agreements between universities and businesses, the so-called Lambert agreements, and the more recent development of licensing and IP ownership agreements in this particular field, have made it rather easier for potential collaborators at least to be talking the same language. The difficulty is coming to an agreement in that language, but at least people have a better understanding of what is required.

Professor Peter Andrews: In my experience, it has not been a major problem in my various collaborations with a number of companies in terms of the types of agreement that have been drawn up. It has not been a big stumbling drop in drawing up an agreement between the university and the company to share who gets what.

Lord Rees of Ludlow: If you collaborate with foreign scientists, is that a problem?

Professor Peter Andrews: We collaborate quite a lot. No, it has not been a problem and I cannot think of a good example to say where there might have been one.

Q213 Lord Dixon-Smith: I have always understood that American universities are much more commercial in their approach and tend to overcome these barriers, partly through experience, because of that. You said that they appear to understand the process rather better than we do. Is their process more straightforward and is it therefore easier for them to find their way through?

Alex Denoon: Do you mean in terms of regulation or IP?

Lord Dixon-Smith: Both.

Alex Denoon: I would say that the position on IP is fairly similar and, to an extent, the intellectual property framework is much more similar world wide. I might make a brief point about a parochial issue that I should like to address, but I would say that the regulatory pathway here is very uncertain. It has the potential for significant inconsistency between each of the regulators, from an early stage to a late stage; whereas, in the States, you speak to one FDA for your pathway. I am not saying that the FDA is soft or provides an easy pathway, but you do not have the potential for inconsistency with the FDA that you can have here. I would say that the regulatory pathway is clearer and better understood in the States. More companies have been taken to a later stage by the universities themselves and

are therefore more familiar with what needs to be done in terms of partnering. Perhaps I may get back to the point about intellectual property. By way of example, there was a lot of comment when the Brüstle decision came out, saying that this is the end for European or British embryonic stem cell research. It is a fallacy. In the event that this is a serious commercial impediment to embryonic stem cell research, it is an impediment to a researcher in Auckland as it is to a researcher in Hull or in China, because people now rarely patent in only one or two countries. In the event that your invention is valuable, you patent it as broadly as you can, subject to cost constraints and the points that make sense. The fact that you may or may not have a commercial hole in your market from Europe as a result of the unavailability of the patent does not disproportionately affect European researchers at all. This parochialism is an odd commentary and an odd reaction that I think has dissipated. The fact that things are slightly easier or harder here does not significantly impact on an IP strategy because a lot of patents will be filed through the international route, rather than through local routes. The UK IP office does a great job on patent applications.

Sean Dennehey: Briefly on the IP limb of the question, it is fair to say that the US and the European arrangements, which we are harmonised with, are very similar. There are two differences, however. One is in relation to the date from which you obtain protection. In Europe, it is the first one to the patent office who wins the race; in the US it has been the case that the first person to make the invention owns the rights. The American Government have recently legislated through the America Invents Act to change that and become closer into line with Europe. That is something that is disappearing but we would not say has had a significant effect in this area. The other difference on which I commented earlier is that there is no morality provision of the sort that we have in Europe applicable in US patent law. However, subject to the merits of others operating in this field, I am not aware that this in itself has been a significant drawback for research and development in Europe.

The Chairman: I think we have run out of time and I would like to draw the session to a close. I thank our three witnesses very much indeed. If there is anything that you feel you would have liked to have said that you have not had a chance to say, please follow up in writing. Sean, you also offered to follow up in writing with specific examples of patents; that would be helpful to us. In due course, you will receive a transcript of the session and have a chance to make any corrections. In the mean time, I thank you very much indeed.

Intercytex Ltd, Professor Anthony Hollander, University of Bristol and Azellon, and Smith & Nephew – Oral evidence (QQ 81-127)

Evidence Session No. 5

Heard in Public.

Questions 81 - 127

TUESDAY, 13 NOVEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
The Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Dr Paul Kemp, Chief Executive Officer and Chief Scientific Officer, Intercytex Ltd, **Professor Anthony Hollander**, Head of the School of Cellular and Molecular Medicine at the University of Bristol, and Chief Scientific Officer, Azellon, and **Dr Drew Burdon**, Manager, Strategic Planning, Advanced Healing Technologies, Smith & Nephew, gave evidence.

Q81 The Chairman: I would like to welcome our witness panel. Two of the three are here to start with. Dr Drew Burdon from Smith & Nephew is coming down from York on the train and he will join us as soon as possible, but his train has been delayed. I am sorry; he has just arrived. As I was saying you had been delayed, you have arrived. Welcome to our third witness.

As you know, this is part of an inquiry into the topic of regenerative medicine. We are going to focus on your experiences in setting up or working with companies that are developing the commercialisation of regenerative medicine treatments.

I would like to invite you first of all briefly to introduce yourselves for the record, starting with Dr Kemp and working along to Dr Burdon, and then we will kick off with the questioning. If there is anything you wish to say by way of brief introduction, feel free to do so, but please keep it brief.

Intercytex Ltd, Professor Anthony Hollander, University of Bristol and Azellon, and Smith & Nephew – Oral evidence (QQ 81-127)

Dr Kemp: I am Dr Paul Kemp. I am currently chief executive officer and chief scientific officer of Intercytex. I have been involved in commercial regenerative medicine now since 1987 in the US and the UK.

Professor Hollander: I am Anthony Hollander. I am head of the School of Cellular and Molecular Medicine at the University of Bristol. I am a non-clinical PhD rather than an MD, and I am chief scientific officer of a spin-out company from Bristol called Azellon.

Dr Burdon: I would first of all like to apologise to the Committee and my fellow panel members for being slightly late. That said, my name is Drew Burdon. I work for Smith & Nephew which is a FTSE-100 listed global medical devices company. At Smith & Nephew I am responsible for the development and implementation of commercial strategy relating to our advanced healing technologies business area.

Q82 The Chairman: Thank you. Perhaps I could kick off and ask each of you in turn—this is particularly relevant to the two smaller companies—what the main types of financing are that your companies have secured to develop regenerative medicine treatments and what have been the challenges in attracting finance. Do you have solutions to suggest for the future for companies seeking to finance the development of regenerative therapies? It is perhaps particularly relevant to Dr Kemp and Professor Hollander.

Dr Kemp: The funding landscape has changed tremendously. The first version of Intercytex was founded in 1999. We raised £27 million from venture capitalists in the UK, Europe, the US and Asia. We raised a further approximately £28 million on the public market. Then the funding crisis of 2008 hit, and we reduced in size from around 100 people down to seven. We are currently funded by a mix of grant funding from the MRC and the TSB and private investment from a business angel.

The challenges of funding at the moment are extremely difficult in this sector. Quite often what is happening now—I do not think it is necessarily a bad thing—is that companies are staying small, staying academic and getting a lot of the basic science sorted before they raise equity investment. Once you are on the equity investment treadmill, it is a full-time job raising funding in this environment.

Professor Hollander: I started up my company from literally nothing other than a piece of intellectual property that we had generated in the university. I spent a lot of my academic time talking to potential investors and trying to get them to have confidence in the area and in our work. I did that initially by applying for, and winning, a Wellcome university translation award grant, which, under the rules of that grant, became an investment in the company when it formed because the grant preceded the company. They took quite a bit of equity.

At the time of the first round of investment we also applied for, and won, a Technology Strategy Board grant, which was very timely. It was lucky because there was a particular call in this area of regenerative medicine at the time. If there had not been, I do not think our company would have started; so that was just accidental luck.

At that point we brought in private investment from venture capital companies, followed by a second round when that money started to dwindle from those companies plus private investors with a particular personal interest in the therapy we were developing. So it has been a tough job and one is living on a knife edge all the time of whether you can get the work done that you need to before the next round of funding can come in.

In terms of solutions to the kind of challenges—they are fairly unique in this area because it is a very young area—we are trying all the time to persuade investors that this is a fantastic and exciting area to be in. Indeed, we believe it, but none of us really know how they are going to make their money out of this over the next five to 10 years.

Some kind of partnership in funding from government would be an interesting way forward and perhaps a change in the regulations around when we can sell the product and when we can start getting reimbursements, and whether there can be an early phase low evidence-based reimbursement at a lower level to start bringing some income stream into these small companies to give them a bit of a footing early on. I think those are the kinds of things we should consider.

Q83 The Chairman: We will come back to more on that later. Dr Burdon, would you like to add anything?

Dr Burdon: As you said, the question is more relevant to my colleagues than to me. A lot of the funding we have internally for research and development and so on comes from revenue. Interestingly, though, over the past five, six or seven years we have been quite successful in receiving grant funding, particularly from the TSB but also from what used to be the regional development agencies. We were eligible for their calls, which is often not the case with the research councils. That R&D funding has been very helpful to us in developing some of these types of products because what we need to remember is that most of the large corporations today aren't regenerative medicine-focused companies. We are a medical devices company, so our R&D money and our investment money are essentially in competition with our traditional sources of income generation.

Q84 Lord Wade of Chorlton: First of all, I should declare my interest in these matters because I am a non-executive director of MAM Funds plc and we do invest into small capital companies. I am also executive chairman of RisingStars Growth Fund, which we set up some 10 years ago in the north-west to invest into new technology companies.

What I am interested in really is what you think is the most appropriate business model for developing regenerative companies. Clearly what you have suggested is that it is difficult on the traditional systems to raise money, and yet you would accept that some companies are successful. Organogenesis has been successful. I understand that Advanced BioHealing has been successful. What is the formula that makes the difference between one that is successful under the present circumstances or what is missing in those that are not able to make it?

Dr Kemp: Those are two really good examples because they were both public companies in the US and both went bankrupt. Their original business model was a classic biotech model that licensed out to big pharma: one licensed to Novartis and another one to Smith & Nephew. Both eventually went bankrupt because the business model did not fit. In their relaunch both have become fully integrated, so they manufacture and sell their own products. Therefore, they gain the whole of the revenue rather than just the royalty percentage. I think that was really the basis of the turnaround for both of them.

Q85 Lord Wade of Chorlton: Do you think that is a much better system, if you like, of a business structure in this area than it is to be merely a licensing organisation?

Dr Kemp: Yes, I think so. The market dynamics are such that the markets are not the blockbuster billion-dollar plus markets at the moment. A market of around £20 million or £30 million in revenues will be enough to start a company and become self-sufficient.

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Also, the development is reiterative. The organisation and the scientific development change with time. The regulators, to their credit, are very responsive to this. The MHRA actually coined the term “the gradual emergence of efficacy”. It is almost akin to organ transplantation. That is 50 years old now. The organs themselves have not changed but all the other processes have, and the total efficacy has improved.

I would agree with Anthony in that, if you could sort out that early reimbursement and have an early system in which you begin on a small scale and become fully integrated and grow from there, I think that is the business model for this sector.

Q86 The Chairman: Professor Holland, do you wish to add anything?

Professor Hollander: I am no expert in business models. I would not pretend to have the kind of knowledge that Paul has, but I will say that my experience of talking to potential investors is that they are very nervous about that kind of model because they do not see that they can wait the length of time it takes, especially given all the uncertainty in the field. Again, shoring up that early phase and giving confidence to investors that we can get relatively safely and quickly through those first five years and begin to generate income would really move us into a situation where we could give them confidence that we could grow as a company rather than exiting at the earliest point, which is what they are looking for at the moment.

Q87 Baroness Sharp of Guildford: There are several references in the evidence that we have had to this concept of adaptive licensing and adaptive reimbursement. This is obviously what you are also referring to in a sense. Could you tell us precisely how it would work and what you think the Government might do to facilitate this if it is a good route?

Dr Kemp: I think it is the way to go, personally, because of the reiterative development. Quite a lot of the legislation is in place. There is conditional licensing. There are exceptional circumstances in the MHRA legislation. The issue mainly is adaptive reimbursement and how those early products are paid for. You can imagine a situation whereby you are in an early clinical trial and showing early efficacy in an unmet medical need. Clinicians are able then to prescribe that treatment, and in some form—I think that is the missing key—it would be reimbursed.

There are systems in place now where individual PCTs can reimburse non-licensed treatments, but it is extremely difficult to get them to agree to do this.

Baroness Sharp of Guildford: Yes; I can imagine that.

Q88 The Chairman: Do either of the other witnesses wish to add anything to that?

Professor Hollander: It seems to me that clearly no reimbursement could take place before safety has been established and, I guess, some early evidence of efficacy, but, beyond that, a sliding scale of adaptive reimbursement would allow, if you like, a cost-sharing in the process of then gradually accumulating evidence of efficacy as these products became more widespread. It would again give confidence to the companies. I guess it would require a buy-in from the NHS and the NHS purchasing system, with all the pressures that is under. How that works I do not know. I guess that is for this Committee to figure out.

Dr Burdon: I would like to add a comment. I would like to come back to the business models question. It is such an important question because this technology space is all about the correct business model. We are lucky (in a large company) in a way that we do not necessarily have to back one technology or one type of technology. We have a portfolio of

lots of different technology types that you would call regenerative medicine under these definitions.

The challenges are so varied and vast that no single business model really fits all of them. The examples we gave at the start were both tissue-engineered products, which are a complicated product type with respect to production and supply chain cost and so on. There are other types of regenerative medicine, maybe simpler acellular or autologous-type therapies that do not necessarily have the complicatedness that those business models require. I do not think it is as simple as saying, “Is there a single business model for regenerative medicine?” Each type of technology needs to be considered on its own merits and business models developed for that specific purpose.¹⁹³

Q89 Lord Wade of Chorlton: Could I just follow that up? Do you think then that it will be only big pharma that can actually take full advantage of the development of the regenerative technologies?

Dr Burdon: Not necessarily. Again, it depends what you mean by “regenerative technologies”. If you are talking about big, cultured cellular therapies that require a massive amount of infrastructure and investment, then obviously big pharma is well placed to do that. That is not to say that someone such as Shire and Organogenesis could not do that on their own. As Paul said, they were fully integrated, so they were doing that on their own. The investment challenge in that type of regenerative medicine approach to cellular therapies is enormous, no doubt.

Q90 Lord Turnberg: Some of our earlier witnesses, particularly those who fund the basic research, say that the basic science is not there yet and there is a long way to go, except that that does not give a lot of confidence to investors at the moment, I presume. Is it that or is it the regulatory burden that people have to go through? What would encourage an investor to want to go in, when the scientists are saying they have a long way to go?

Dr Kemp: Yes, in a lot of the examples the basic science is not there yet. Quite often, there is a rush to the clinic before the basic science is in place in order to satisfy the investors. It is a gamble then as to whether that is going to show efficacy or not. Quite often, pure statistics says that it will not, and that forms this kind of spiral. There are successes out there already. There are companies making large profits in this sector but, as Drew said, they are simple regenerative medicine. The concepts you hear in the media of repairing lungs and hearts are many years away, but I still think the sector will grow as these technologies come on stream.

When I started, there was no business model and there was no way of manufacturing it. The regulatory system was very vague. All those pieces are coming into play. As soon as there is a technological breakthrough, that could be exploited rapidly because the other parts of the puzzle are in place now.

Q91 Baroness Hilton of Eggardon: I want to go back to funding again. I imagine that continuity of funding is one of the major problems. You can probably initially persuade an investment banker that you have a bright idea but, presumably, to get through stages one, two and three, which may take many years of clinical trials and so on, must be much more difficult. Are you happy that you have that long-term continuity? This is probably Dr Kemp’s

¹⁹³ Note from witness: and until we consider it in that vein the developments of these technologies will be commercially challenging.

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and Professor Hollander's problem rather than a major organisation's. Are you happy that you have that continuity of funding?

Professor Hollander: Obviously not. There is never enough money, but there are particular problems and I alluded to them earlier. For example, investors are really looking for some kind of partnership and some kind of risk-sharing. Bringing in a grant from the Technology Strategy Board is a great way to do that, but the TSB goes in peaks and troughs. It has cycles of funding. If it happens to be a period when it is not funding regenerative medicine that particular year, we are kind of stuck. It is really a question of luck. If there was a more response-mode approach to TSB funding, where you could go back particularly on a project it had already funded and get follow-on funding without waiting for another call, that might be a way for investors to have confidence that they could get some kind of partnership funding for moving forward to the next phase.

Q92 The Chairman: Does the TSB hand out money on a sufficient scale to carry you through these different stages of clinical development?

Professor Hollander: As I understand it, the scale depends on the money being invested by the private sector. There is a match-funding basis and a proportionate basis.

Q93 Lord Dixon-Smith: There is a very simple question that I want to ask. I completely understand both the investment climate being difficult and this being in a sense, as you have already said, a high-risk business. The simple question is: if that is the situation, are you running into a brick wall from time to time or are you generally able to find a way through, even if it is a lot of hard work and there is perhaps a great deal of nervous energy involved?

Dr Kemp: Yes, you can run into brick walls. I have done on numerous occasions in the time I have been in regenerative medicine. There are ways around it. You quite often have to pick yourself up and start again. Organogenesis did; Advanced BioHealing did; we have. It is almost a rite of passage to get to a certain level and then there is a problem.

I have found that the main issue with investment is not the amount of investment but the time horizon of those investors and when they want a return on their investment. It is typically three to five years, and that is way outside the cycle of developing a medicinal product. The early investors want their return by selling that idea to another round of investors. Ideally, it is passed on from one to another and the value increases in proportion to the investment.

It needs only one little hiccup for that whole system to break down. If there is one clinical trial that does not give the results that you want, the whole system collapses. Those are the cases in the examples of regenerative medicine to date. Continuity is hard but it is getting that insurance, almost. In some cases there is not a way around it. It is just a fact of life.

Q94 Lord Willis of Knaresborough: I want to ask two brief questions. First, the adaptive reimbursement model clearly involves the taxpayer putting in resource at some point. Does the taxpayer then get any say in terms of the IP, or does that remain entirely with you and your other private sector funders? That is the first question.

Secondly, on Friday of last week, the Chancellor made a very significant statement at the Royal Society about not exactly backing winners but backing winning areas of development, one of which was regenerative medicine, and will be making a statement in December about supporting regenerative medicine. What is it that you would like him to say?

Dr Kemp: In the first case I think the IP needs to stay with the company, although we have been in discussions with charities that are dealing with specific diseases in which a long-term arrangement could be organised and companies would be willing, potentially, to share IP. An example we are working on is epidermolysis bullosa. There was a patient who had a huge ulcer on her back. She had had it for 24 years. We did a series of injections with fibroblasts and it reduced the size of that ulcer. She said it changed her life. If there was a way of then getting that series of treatments reimbursed—we provided the first amount of cells for free, but we just could not keep doing that. It is not a huge amount of money that we are talking about. The advantage to the company is not necessarily in the money; it is in that system being in place and the fact that someone is willing to pay a certain amount of money for a certain treatment. That gives a level of confidence that the treatment is worth while, the cost of goods fits and the business model fits.

Professor Hollander: I have two brief answers to the question. One is that, under reimbursement, no, that is not an equity model, but presumably UK plc would benefit from companies retaining IP, staying in the UK, growing and employing more people and paying more taxes themselves. There should be a payback in the long term if we grow the industry that way.

Secondly, on the other hand, one could envisage an equity-sharing model if the Government were to partner, a bit like I said Wellcome did with my company early on. I do not know if it is feasible, but, if the Government could put more money into share equity on the same terms as private investors, then the Government could presumably own a share of those companies.

The Chairman: The other question was about your wish to the Chancellor.

Dr Kemp: It would be this progressive system. It would be bringing in place this system that can break this cycle of having to have a huge potential pot of gold at the end of the rainbow for investors and then the hope that you get to this magic moment, as you call it, of licensing and then reimbursement.

Q95 Baroness Sharp of Guildford: Bringing in revenues, yes. It fits with your integrative model, does it not?

Dr Kemp: Yes, exactly.

Professor Hollander: I agree with that. The second area, which we have not really talked about, is how you stimulate more activity at the interface where I sit between universities and companies and making that transition, which generates a lot more potential IP so that you can afford then to lose some and bring out the winners. There is a quick example. At the moment universities have a very small budget for patenting for intellectual property and yet the time taken to develop that intellectual property satisfactorily is quite long in this field. Once the patent is filed, you have a limited timespan before you get to national phase, where the costs are very high. At that point, if you haven't already got private investment, the universities will not pursue it any more. If there is a way to fund the maintenance of intellectual property within the universities for a longer period—that national phase before going out to private investors—that would allow us to do more science before we formed a company and took it forward.

Q96 Lord Cunningham of Felling: Gentlemen, in your experience what are the most effective ways to encourage partnership working between academics, clinicians, industry and

charities to try to ensure that world-class science leads to effective treatments as frequently as possible?

Professor Hollander: My chair is funded by a charity, Arthritis Research UK. I work in a university and I have a spin-out, so I work across all those fields. This interface is critical. It is about culture and, in particular, about academics feeling rewarded for working at this interface, particularly with industry, because it is often seen as being a rather non-academic activity to be doing the kind of stuff I do, frankly. Part of that would be culture change. Part of it is funding models. At the moment funding through the TSB is very milestone and goal-oriented from an industrial perspective, and that is very important. But, if you could mix that with developing science at the same time within the same broader projects, then you will have much more iterative feedback in the development of the technology.

A good model for this is the way European Union consortia are funded. They will often have a company leading a large grant, but with multiple university partners as well and with some commercial development aims but also a lot of fundamental science. I have been a member of those sorts of consortia for some time and they do work very well at this interface. That kind of model within the UK consortia could be very effective.

Q97 The Chairman: I wonder whether Smith & Nephew have experience of that.

Dr Burdon: Yes. As I say, through grant funding, we collaborate widely with academics and clinicians all over the world, frankly, not just within the UK. My answer to the question is that it is really those two things. It is about timing and the actual mechanism. We hear a lot about funding calls and advisory boards drumming home that we need this combination of clinicians, academics and industry. I agree with that, but the question is who really is responsible for doing that? Is it up to the companies to pull the technologies through or is it up to the academics and the clinicians to push it up? At the end of the day, who is responsible for that? That is my question back to the Committee.

We look at many different companies and many different technologies in this space. It is great when you meet companies, which have strong technologies and have done good groundwork; but it can be heart-breaking when you meet a company that has really nice ideas and nice technology, but something has happened in its commercial development which makes it either commercially worthless or very challenging to go back and repeat what may need to be done to make it commercially valuable.

The question really is who is responsible for bringing those groups together and does it always have to be around funding, or could it be some independent organisation or body that are incentivised to bring these groups together in a less arbitrary way than around a funding call.

Q98 Lord Wade of Chorlton: What you are saying there is that there is a certain lack of leadership at certain levels through this process. We have heard that from other people giving evidence to us. Where would that leadership come from? Is it the academic side of the business that needs more leadership? Is it the business world that needs more leadership or is it the Government that need more leadership in that area?

Dr Burdon: That is the killer question. As an industrialist, I would probably say industry should lead it, but obviously I am biased.

Q99 Lord Wade of Chorlton: How could they be encouraged to lead it?

Dr Burdon: I do not have a good answer. In some of the written evidence I was going through there was a reference to an Australian organisation, which sits outside of all these entities and provides support to start-ups and SMEs while they are going through early commercialisation. Part of that support is bringing together the right people at the right times. I don't know whether that is in a consultation capacity or incentivising some sort of investment. I had not heard of that model before but it resonated quite well that somebody outside this triangle of interested parties comes in and provides that motivation.

Q100 The Chairman: Dr Kemp, did you wish to add something?

Dr Kemp: Yes. There are three points. I agree with Drew that the leadership should come from industry. One of the issues is that we are all classed as industry but we are very different. We are small and struggling to survive versus Smith & Nephew, and yet we are both considered industry. Academia quite often considers industry as a source of funds and yet we are way poorer than any academia.

The Cell Therapy Catapult, which has just started, could be an example of leadership. It is intended to be industrially oriented but spans that interface between industry and academia. It could be regarded as more of a level playing field rather than industrialists who just want to make money.

Professor Hollander: I agree that industry should lead. It is not just money; it is project management expertise in this particular area. It is regulatory expertise that we do not have in universities. Bringing that to universities and leading forward is very important.

Q101 Lord Cunningham of Felling: Is it your opinion that, here in the UK, we have a pretty poor record of taking what is often world-leading fundamental research and getting it through the translational period and to the market?

Professor Hollander: Yes. Again, I am not an expert in world comparisons, but I sit on the Grant Review Board for the California Institute of Regenerative Medicine and look at the amounts of money being put into university/company partnerships and the energy and different incentives for galvanising those collaborations. It is on a much bigger scale, with a bigger degree of risk-taking and partnership. I really do not think we do that effectively enough here.

Dr Burdon: A lot of attention and effort has gone into the academic and clinical community in terms of what we call translational medicine. Generally what we mean by translational medicine is translating things into the clinic. More focus on genuine commercial translation right at the early stage of start-up life is certainly one of the things that need to happen more.

Q102 Lord O'Neill of Clackmannan: Dr Kemp and Professor Hollander, in your evidence to us, you have suggested that current incentives in the system encourage universities to spin out companies perhaps prematurely. Could you maybe give us some examples of that and how you would envisage there being a system that could avoid this requirement? Could you give examples and then a recommendation?

Dr Kemp: As examples, when we started Intercytex I worked with five academics, I think it was, in the UK, all of whom went on to start their own spin-outs and all of whom really just became a name on a door. It was not truly a spin-out company. One of the things I said in my evidence is that it is very frustrating that an academic can suddenly create a limited

company and then compete with us for industrial funding, and yet we can't create a university and compete with them for research council funding.

An example I have worked with was a company called Odontis. It was looking at tooth repair. I think the technology was amazing. I think it had great promise. It was funded by Wellcome but the time horizon was just too small. They asked them to do too much too soon. The funding was stopped, the company ceased to exist and the academic is now back in academia.

The way forward is really for the universities to put it together in a coherent plan. If I had a company with the research budget of a university and a scientist from my company came to me, I would not suggest that they start a spin-out. I would weave that into the company, with the university consolidating bits of technology and itself driving the start-up, rather than expecting a world-class scientist to become a world-class businessman as well.

Professor Hollander: Just to reiterate—I have said it before but it is very important—I agree with what Paul said. We need patenting budgets that allow us to go to a national stage with the expense that that involves. We need more high-quality project management within universities and we need more regulatory expertise in this area within universities. If we had that, then we could hold back from commercialising until we were a bit more mature.

Q103 Lord O'Neill of Clackmannan: You have said that, but there must be a number of different areas of research going on within universities. They have problems of funding, applying for patents and handling the regulatory authorities. These are common problems within the university sector. Is it not incumbent on universities to set up appropriate service departments within the institution to address some of these issues, rather than letting you fight, as you have to fight, with one hand tied behind your back, because you want to carry on your basic research as you are applying? Is this not something that the universities themselves should be addressing rather than us making big pleas to whomever?

Professor Hollander: Yes, absolutely, and speaking for the University of Bristol we have a very good department—research and enterprise development—that provides all of these, but, if you look at the number of staff that the budget is spread across all those different and varied projects, they simply cannot manage everything and they do not have enough expertise in any one area either to be able to do that. There is not a big enough budget for them really to support it properly at a high enough level and there is not enough depth of understanding in any one area to do that well.

Q104 Lord Rees of Ludlow: Lord O'Neill has really asked my question, but are there any features specific to this area of science which are not common to the issue of translation of physics-based research into industry? Is it a generic problem or can you point out specific issues which arise in this area?

Dr Kemp: I think it is a unique area. Regenerative medicine covers a whole span from small molecules to medical devices to cells, but the cellular one is the one that is unique. We are creating living products. It spans that interface really between organ transplantation and medicine. There are lots of issues, some of which are environmental. If you imagine the difference in opinion between someone who donates an organ and someone who sells an organ, we are in both camps. We are trying to be altruistic and help the human condition but also to create a stand-alone financial entity. So there are unique aspects from producing living products such as this.

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Lord Rees of Ludlow: You are saying it is more complicated than setting up a start-up in computer science or something like that.

Dr Kemp: Yes.

Professor Hollander: It is the regulation that is the problem; that is the main issue, I think.

Q105 Baroness Sharp of Guildford: You mentioned California and the amounts of money there. If you move from California to other states in the United States, where the huge sums of money that one sees in California are not always available, you do often see the state itself playing some part and having its own sort of TSB. Again, if you look at Europe, you have regional funds that are available. When RDAs were here, were you working with RDAs at all?

Dr Kemp: Me personally, yes.

Q106 Baroness Sharp of Guildford: Did you feel there was a lack of a self-standing regional group? If you take Germany, there are the Länder. They often co-operate with the local bank and again raise funds for this sort of thing. Might that be one possible solution here?

Professor Hollander: It is very patchy. For example, Scotland puts a lot of money into this area. As it happens, the South West RDA, when it existed, didn't, because it was much more focused on hard engineering because we had Rolls-Royce and Aerospace down there. It was too uncertain and the luck of the draw where you happened to be based.

Dr Kemp: We worked with the Northwest Development Agency and it was extremely helpful.

Q107 Baroness Perry of Southwark: I declare an interest. I was chair for 10 years of the Clinical Research Governance Committee in Cambridge University and Addenbrooke's Trust. My question is about the development and expansion of stem cell therapies in the future. Do you think there has been enough thought and care given to the infrastructure necessary for that development?

Dr Burdon: Again, that is an important question. We spend a lot of time in organisations considering value chain in these areas. What do we want to do, what activities do we want to do to add value, and what do we not want to do? The example in the question that we received was manufacturing. Yes, manufacturing is obviously hugely important for stem cell therapies. Within the UK it is an area where we have some very strong centres, but as a UK body have we actually looked at how we want to create value from these therapies? It could be to become the world leader in stem cell manufacturing, but it might not be that. It could be any single part or multiple parts of the value chain.

Before we commit to going down a certain path, my recommendation would be to take a brief step back and have a good think about exactly how we want to be successful in this space.¹⁹⁴

Dr Kemp: In terms of the physical infrastructure I think there is enough. In terms of GMP manufacturing facilities there are more than enough. There are quite a lot of them that are only partially used. In terms of the organisational infrastructure there is lots to be done.

¹⁹⁴ Note from witness: That should not be seen as a negative suggestion, but at this point in the development of the regenerative medicine field, it is critical to decide how we want to win, and I believe that some strategic thought now could save a lot of uncertainty in the future and provide a real focus for our efforts.

There are significant moves at the moment. There was recently a workshop between the MRC and the MHRA on the regulations of regenerative medicine. There are moves between the MRC and the TSB to work together in a kind of baton-passing funding model on the regenerative medicine platform. These things are coming together. I still think there is a need to involve the NHS in this system.

Q108 Earl of Selborne: Could we explore what seems to me to be a little bit of a difference of opinion between Professor Hollander and Dr Kemp in respect of the provision that the private sector can make towards this infrastructure facilitement of good manufacturing facilities? In Professor Hollander's written evidence, he said that he found that the private sector provision of cell production is "expensive to access and inflexible with respect to timing of access to facilities", from which I would deduce that Professor Hollander would prefer this facility to remain in the public sector.

Professor Hollander: I am not sure we are disagreeing because I don't think it is about the amount of infrastructure. It is the cost models on which they operate. For a small, young company like mine, trying to access a GMP facility where every mistake or unexpected result requiring a repeat run adds tens of thousands of pounds to your cost, which is a very high percentage of the money we have, is just not a sensible model. It is not one on which we can effectively survive. It may be that the private sector provision would be adequate once you have a fully developed therapy up and running, but, if you want to provide a GMP service facility for young fledgling companies such as mine, it needs a business model that can be much more responsive, flexible and effective than we found in the private sector. I believe the NHS blood and transfusion facilities could potentially provide that if they were given the freedom to operate not at full cost as a means of stimulating the area—the whole field.

Earl of Selborne: I do not know whether Dr Kemp would like to comment on it.

Dr Kemp: I agree with what Anthony says. Drew also mentioned that there is a vast difference in the technologies and the requirements. In Anthony's case, working with an autologous cell therapy, it is very expensive one at a time and of manufacturing. We are working with allogeneic cell therapy so that you can produce cells in bulk for many patients.

In terms of the physical infrastructure, I think an awful lot of money has been spent over the past 10 years in the UK on building GMP facilities, quite a lot of which are only partially utilised. There is still a need for the operational infrastructure to fully utilise those facilities, but the bricks and mortar are in place.

Q109 Earl of Selborne: Could I ask specifically Professor Hollander about the National Health Service Blood and Transplant Centre? At the moment you are relying on this facility to bulk up your product.

Professor Hollander: We have a contract with that facility and we previously had a contract with a private company.

Q110 Earl of Selborne: You say they need to expand their activities to support the manufacture of cell products. Could you elaborate on that as to what would be required?

Professor Hollander: If it is going to provide a service for a larger number of companies than ourselves, then in particular it needs more people and more expertise so that it has enough flexibility to run several different projects at the same time. It is also about the cost modelling and what it is and is not allowed, what freedom it has in terms of the contracts it

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sets up with companies such as ours, and whether it operates entirely in a commercial way or whether it is more a not-for-profit, near-to-commercial activity within the NHS.

Q111 Earl of Selborne: Which model would you prefer?

Professor Hollander: Obviously the less profit it makes, the less it needs to charge us and the more flexibility they can build in.

Earl Selborne: So the not-for-profit model.

Professor Hollander: Yes.

Q112 Baroness Perry of Southwark: I am intrigued that Dr Burdon felt that we should step back and have a pause before pressing ahead with infrastructure for the future. I wonder whether you, Dr Kemp in particular, agree with that, because you were rather pressing that the organisational infrastructure was lacking and was needed. Can we afford to take a step back while other countries—particularly the US, we have been told—are pressing ahead so far?

Dr Kemp: I think there are huge advantages in the UK. I have worked in both the US and the UK. The US model is just to throw money at it. I do not think we can compete with that on that scale. What we do have in the UK is a real strong UK plc attitude. It is national. There are various bodies around that could help, such as the MHRA, the NHS and the universities. Those need tying together a bit better in a coherent strategy so that we can go from the basic research right to the patient.

Q113 Baroness Perry of Southwark: Would you expect government to facilitate that?

Dr Kemp: It would help, not necessarily from the cost savings point of view on our side but from that idea of being a level playing field and an arbiter of an even system rather than industry or vested interests.

Q114 Lord Patel: First, I need to declare an interest. I do not have any specific interests related to today's inquiry, except that at one time I was involved with a charity that might have funded you, Dr Kemp—DEBRA—in regenerative medicine.

Dr Kemp: Yes, you did.

Lord Patel: The other interests I have are declared in the notes which you have. The question I have relates to the lessons that we could learn from other countries as UK plc, particularly the United States but not necessarily only the United States. There are other countries where regenerative medicine is progressing quite fast, if not in all areas, then certainly in small molecule regenerative medicine. What are the lessons we can learn? You mentioned, Dr Kemp, the Catapult. I would like your comment on whether that is a mechanism that is going to be effective. What I am after is to make sure that, if our science is good, we do not miss out on benefiting from converting that into commercialisation. I know Anthony has done it for his own product. I do not know if you did it for your trachea development.

Professor Hollander: That is not commercialised.

Q115 Lord Patel: There are issues about whether we are looking at only the end product of regenerative medicine or whether we actually have an opportunity that we might miss out on or the processes that develop before you get to that end point of commercialisation.

Dr Kemp: Sometimes the lessons to learn are things not to do. The US system is not necessarily the one to aspire to. They spend vast amounts of money. The California Institute of Regenerative Medicine that Anthony is involved with spent \$3 billion. From my point of view, an awful lot of that was spent building buildings. I think it has maybe two products in the clinic after \$3 billion, but it has a lot of money to spend. In terms of epidermolysis bullosa—and you have been involved with DEBRA—I was recently at its triannual meeting. There is an American company called Lotus Therapeutics, which has just raised \$31 million for the treatment of epidermolysis bullosa, and it has only animal models. That level of funding just does not happen in the UK.

In terms of the Catapult, I think it has the potential to really help the industry but there is potential to damage the industry. It could become a state-funded competitor to industry, depending on what it does. There are a lot of little industries set up to service the regenerative medicine community in order to provide manufacturing, regulatory or consultancy assistance. There is some caution in the industry towards the Catapult because it could go down a direction that puts some of us out of business. It is beholden upon us to get our voice heard with the Catapult Centre and I am very pleased with the management that is in place already. They do listen and they are very willing to help, but it is early days for them.

Q116 The Chairman: Would the other witnesses like to comment on lessons learned from other countries, including the US?

Dr Burdon: Yes. We have talked about the funding in the US. The thing that they really do seem to get right is the ability to form technology clusters. I have spent a lot of my working life in Boston. Boston is a wonderful city for biotechnology. At one point in time a decision must have been taken to try and incentivise companies to locate in Boston. There are hundreds and hundreds of biotech companies. With that, you get the service industries that are needed to support it automatically going there. The consultants that are relevant to that industry automatically go there because that is where the business is. The venture capitalists tend to flock there as well.¹⁹⁵ Some thought on how we can develop this clustering approach and how we can incentivise both national but particularly international companies to locate in the UK is a really important part of this environment for regenerative medicine.¹⁹⁶

Q117 The Chairman: Professor Hollander, do you want to add anything?

Professor Hollander: I do not have experience of the international company sector outside America, and California in particular. I have probably said what I need to, but I do hear and agree with what Drew has just said. In the UK we do not just have a potential clustering of companies, we also have a very strong academic base which can interface with those companies. That is part of the cluster as well.

Q118 Lord Patel: You used the example of the United States with California, and Boston on the east coast. As I said in my introduction to the question, there are other countries. There is Singapore, for example, and Japan and China now with a huge regenerative medicine centre that could dwarf what California has. Are they fools for investing huge sums of money that will not produce any gains at all?

¹⁹⁵ Note from witness: And all of this tends to be centred on world class research in the case of Boston with MIT.

¹⁹⁶ Note from witness: and a highly attractive model for value creation from many different sources (the services, consultant, and venture capital industries, and hopefully the eventual commercialisation of products)..

Dr Kemp: One example that you missed out is South Korea. They have more approved regenerative medicine products, I think, than anywhere else. You can waste a lot of money in medicine by throwing money at it. I do not think that is the answer. It is this coherent approach and what Drew was mentioning about clustering. If you imagine the size of the UK, we are really a cluster on the American scale ourselves rather than just thinking of the Cambridge/Oxford/London triangle as a cluster. We could involve the whole of the UK in a cluster.

Investing large amounts of money too soon is a recipe for disaster. Slow and steady is the approach. I am interested in the way that South Korea has had products approved very rapidly. That could be a lesson to be learned for this conditional approval approach.

Lord Patel: So the lessons are regulatory in form.

Dr Kemp: I think so—getting the products into the clinic quickly and therefore cheaply, rather than spending huge amounts of money on the traditional model of large clinical trials and then this approval and the magic moment of being able to sell it widely.

Q119 Lord Patel: Is the deficit on the UK regulatory side related to getting the product at a quicker, earlier phase to trials in patients?

Professor Hollander: I have just come back from Washington, where I was at a meeting with the FDA in a joint conference. It is very clear to me that they face even bigger hurdles in getting their regenerative medicine products licensed over there. They actually look across to here and see us as being a potentially easier route. If we can make it even easier still, then we may begin to get inward investment.

For example, TiGenix is a European-based company. It has its cartilage repair product on the market. It was the first ATMP to be approved in the European Union. It cannot get it through the FDA without conducting a second, very large clinical trial. One was enough in Europe, but two is required by the FDA and so it has given up on that market. If we play our cards right we could attract inwardly from America, but we are still not as straightforward as other territories such as South Korea.

Dr Burdon: There are many examples, of companies that have had products approved in Europe and have just decided not to pursue an FDA approval because of the perceived complexity and the laboriousness of the US system.

Q120 Lord Wade of Chorlton: The question that follows from that is: would you go to South Korea and make use of one of their facilities or make use of their curing solutions? Is the reason that South Korea is a bit of a problem and not everybody will automatically go there because the regulatory system is not regulated enough, and therefore the products are not quite as secure as ours would be? Is that a follow-on?

Professor Hollander: I am not qualified to answer whether their regulatory system is effective or not. I would not dream of criticising it directly. I guess it is about market size. I do not know if a Europe-based company would see the South Korean market in particular as big enough to warrant that.

Q121 Lord Patel: It seems as if, in the UK, we do not have an overarching organisation that looks at all the issues that will benefit the United Kingdom in regenerative medicine, including first early phase trials, early phase financing, early phase remuneration and identifying areas that could come to early fruition. You had some reservations that the

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Catapult may be able to do that, but none of you has commented about the Office for Life Sciences and BIS.

Dr Kemp: They are not focused specifically on regenerative medicine. They are very helpful in terms of business as a whole.

Going back to your earlier question, imagine someone next week coming up with a cure for diabetes, coming up with a way of culturing pancreatic islet cells, expanding them and implanting them. The entire remains of the system are in place now in terms of doing the manufacturing. We could scale up the manufacturing. What would the impact be on the NHS? I don't want to call it disaster planning, but it is almost like breakthrough planning. It was induced pluripotent stem cells that won the Nobel Prize. That came from nowhere. I do not think any of us who had been involved in the field expected Yamanaka, in particular, to come up with the invention he came up with. I think there are other developments lurking in the system that could happen in the next few years. It is worth while looking from a high level viewpoint at how that would impact on society, the NHS and the reimbursement systems.

Q122 Lord O'Neill of Clackmannan: Perhaps Dr Kemp could help us. I remember some time ago that, certainly in areas such as biotech, the aim was to get FDA approval because that was the gold standard. Now you are saying that it does not seem to be quite so important. Is it because you are not really about mass production? You are about smaller markets, individual almost micro-markets, with the products that you will hopefully be getting ready to sell. It does seem that the idea of people turning their back on the American market is rather strange. I wonder if you could amplify your views on that.

Dr Kemp: I think you are quite often not turning your backs on them. It is difficult to satisfy both regulators unless you start on day one with the knowledge that you are going to satisfy them. If you have a European approval and then try to go to America, you can find out you have missed something that you should have been doing years ago, and vice versa. The products in the US—Organogenesis and Advanced BioHealing—have been available there for 10 years. They are not approved in Europe. It is a similar situation going on with the other side.

A lot of regenerative medicine therapies now are centrally regulated through the EMA. The MHRA helps during the clinical trial process but the approval comes from Europe. At the moment that is a little bit of an unknown jump. TiGenix is the only company to have made that jump and had a European approval of a cell therapy product at the moment, so it is early days. On the plus side, once it is approved, it is approved for the entire European community so that is a vast market and larger than the US.

Dr Burdon: I would like to comment on that as well. You are quite right that America is today the big market and the big prize. The fact that companies are strategically deciding not to pursue regulatory approvals there just tells you how challenging they think it is. It is always the first market that you consider but the regulatory hurdles are higher. They absolutely are higher, and we have many examples of that. It is not about turning your back on America, but maybe the fact that there are examples of this happening tells you a little more about their regulatory system than ours.

Q123 Lord Cunningham of Felling: What are the regulatory mountains that have to be climbed in the People's Republic of China?

Professor Hollander: I wish I knew. Perhaps you can find out and tell us.

Q124 Lord Cunningham of Felling: The reason I asked the question is this. Many years ago there were entirely different standards in Europe and the United States of America on safety in motor manufacturing. In the event, through the transatlantic business dialogue between Europe and the United States of America, both America and Europe adopted the same standards. I realise that the area we are talking about—restorative medicine—is not like motor cars, but, if a uniform regulatory approach can be taken in some areas, why do the powers that be not explore the possibility of it being unified in other areas too?

Professor Hollander: Unification would be wonderful as long as it is not at the American level, which is an impossible hurdle to cross, virtually, which is a slightly specious argument.

Q125 Lord Cunningham of Felling: Is this protectionism on the part of the United States of America?

Professor Hollander: I am not sure what they are protecting because they are making it very difficult for their industry to thrive.

Lord Patel: In reality, the research councils in the United Kingdom are working with China to try to get some uniformity in the regulations, just to correct the record.

Dr Burdon: I can offer a little insight into China. We have a growing business in China. It is one of our strategic focus areas, as it is for a lot of multinational companies. So we do have some products in China. They tend to be the simpler products. I cannot comment at all on the complexities or simplicity of the system in China for more advanced products, but it is certainly possible to get more simple products regulated in that country.

Q126 The Chairman: Could I finally come back to the question of scale while we are talking about the comparisons between the US and the UK? You have commented a number of times that, although the sums of money spent in this area in the US and even in California, have additional noughts compared with the UK investment, do you think that the scale of the Catapult, which I understand is probably going to be able to fund two clinical studies per year, is appropriate given the amount of scientific research that is coming through from the university sector?

Dr Burdon: I do not think so. All morning we have talked about and alluded to how risky, vast and diverse these technology areas are. When you are entering a phase I clinical trial, for example you are essentially taking a technical and commercial bet on specific product or type of technology. To be able to make only two bets per year does not seem likely to give you a wonderful chance of a return. Do not get me wrong: it is better than nothing, but my instinct would be no, it is not.

Q127 The Chairman: Are there any other views on this?

Professor Hollander: I guess that is right, but, given that we are not going to be able to change that, I do see an advantage in an organisation such as the Catapult taking two reasonably good risks and really putting resource into pushing those risks in favour of a positive outcome. What we need in the field are some really good examples of successful therapies. If we can find one or two examples that become commercially successful, it will give investors encouragement in the future.

The Chairman: I would like to thank the three of you very much indeed for your answers to our questions this morning. You will in due course receive a copy of the transcript in draft for you to make any corrections that you wish to make. I should also say that, if there

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are any points that you haven't been able to make and you would like to write to us about them, they could be included in the evidence and published alongside the oral evidence.
Thank you very much indeed.

JACIE (Joint Accreditation Committee-ISCT & EBMT) – Written evidence

Author: Dr. John Snowden (JACIE Medical Director) on behalf of the Executive Committee of Joint Accreditation Committee-ISCT & EBMT (JACIE)

1. History

- 1.1. The Joint Accreditation Committee-ISCT¹⁹⁷ & EBMT¹⁹⁸ (JACIE)¹⁹⁹ is a not-for-profit body established in 1998 for the purposes of assessment and accreditation in the field of haematopoietic stem cell (HSC) transplantation and cellular therapy and promotion of excellence and harmonization. JACIE's primary aim is to promote high quality patient care and laboratory performance in therapeutic cell collection, processing and transplantation centres through an internationally recognised system of accreditation.
- 1.2. JACIE began in 1998 through professionals working in cellular therapy, specifically in blood and marrow transplantation, who adopted the model of the US-based Foundation for Accreditation of Cellular Therapy (FACT)²⁰⁰, established in 1996. This initiative was born out of the consensus that complex and high-risk treatment strategies for cancers and other serious blood, immune and metabolic disorders should be applied within a quality management framework requiring minimum levels of staff experience and training, adherence to standard operating procedures and good communication between the professionals contributing to delivering care.
- 1.3. JACIE's leaders and decision-makers are international experts in the field of cellular therapy and are fully abreast of developments in this sector.
- 1.4. JACIE continues to work very closely with FACT in developing joint international standards known as the *FACT-JACIE International Standards for Cellular Therapy Product collection, Processing, and Administration*²⁰¹.

2. Evolving situation

- 2.1. Early accreditation efforts were directed towards the administration of cellular therapy in the context of blood and marrow transplantation and this continues to our main focus. However, since 2006, more recent editions of the FACT-JACIE standards have broadened their scope to include other cellular therapies, also known as advanced therapy medicinal products (ATMPs). While in many cases new therapies continue to be delivered only as part of controlled and regulated clinical trials, in recent years these treatments are appearing more often in laboratories and transplant units visited by JACIE inspectors as part of the accreditation process. This trend has recently led to a review of how the scope of the current standards can be expanded to include these novel cellular therapies and their delivery within a quality management framework. In the US for instance, our colleagues at FACT recently announced a specific accreditation for processing cellular products requiring “more-than-minimal manipulation” in an effort to increase quality practices throughout the

¹⁹⁷ International Society for Cellular Therapy www.celltherapysociety.org

¹⁹⁸ European Group for Blood & Marrow Transplantation www.ebmt.org

¹⁹⁹ www.jacie.org

²⁰⁰ www.factwebsite.org

²⁰¹ www.jacie.org/standards

field of cellular therapy (FACT, 2012). Although not finalized, JACIE is likely to follow this line with a more comprehensive scope in the future.

3. Impact of Standards & Quality Management Systems on transplant outcome

3.1. In 2011, a retrospective study of haemopoietic transplant outcomes data in the EBMT registry showed that implementation of clinical quality management systems in line with the FACT-JACIE standards was associated with improvements in patient outcome for some diseases (Gratwohl et al., 2011). This is one of the first indications that the introduction of a clinical quality management system into a transplantation team can be associated with improved outcome of patients undergoing HSCT.

4. Accreditation process and activity

4.1. JACIE is based in Barcelona, Spain as a part of the EBMT Executive Office. The Barcelona office coordinates the accreditation process for all countries. Since 2000, JACIE has received over 250 applications for accreditation representing around 40% of transplant centres in Europe and further afield. We have performed over 270 inspections and accredited over 180 cellular therapy programmes and facilities. While the majority of centres are in Western Europe, centres from Central Europe, Turkey, the Middle East and Asia have also applied for JACIE accreditation. The United Kingdom is the country with highest number of applications and accreditations. At present, around two-thirds of UK blood and marrow transplant centres are accredited by JACIE.

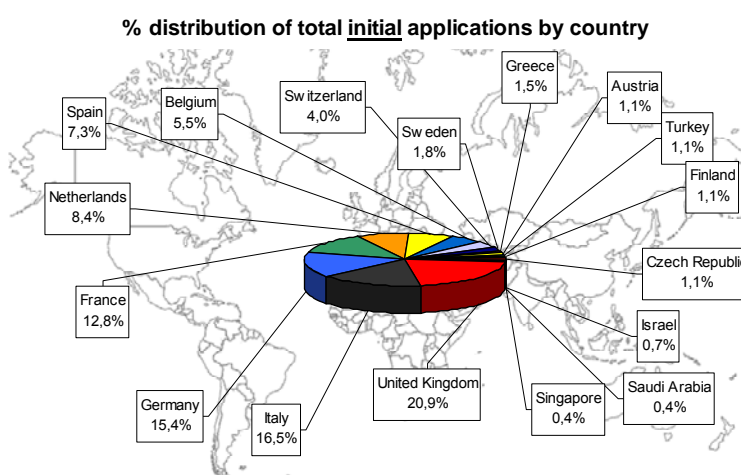


Fig 1. Geographical distribution of applications for accreditation

4.2. The accreditation process is based initially on meeting minimum requirements for transplant activity to access the process, followed by the submission of documentary evidence of a functioning quality management system, staff training, traceability and follow-up systems, product labelling and storage requirements and culminating with a site visit by volunteer inspectors - all cellular therapy professionals - and an inspection report. This report is reviewed by an Accreditation Committee who issue recommendations for corrective actions. Assuming all corrections are satisfactorily implemented, accreditation is awarded for four years.

5. Global recognition

5.1. The international character of JACIE is critical to its success. In contrast to national or regional schemes, JACIE is understood and recognised by transplantation professionals in many different countries. A centre that achieves JACIE accreditation enjoys recognition not just by their national peers but also by their colleagues

beyond their borders. The FACT-JACIE standards represent a ‘gold standard’ for many, particularly for centres in developing economies. In some countries, the possession of JACIE accreditation is a pre-requisite for re-imbursement by health commissioners and other purchasers of transplant and cellular therapy procedures, and in others, JACIE accreditation forms part of a legal and regulatory requirement for clinical quality assurance (see section 6).

- 5.2. This global recognition is important in a context where an increasing number of cellular therapy products (e.g. harvested bone marrow stem cells) now come from outside the patient’s country and JACIE accreditation provides confidence that a high level of quality assurance will continue between various countries and their health services.

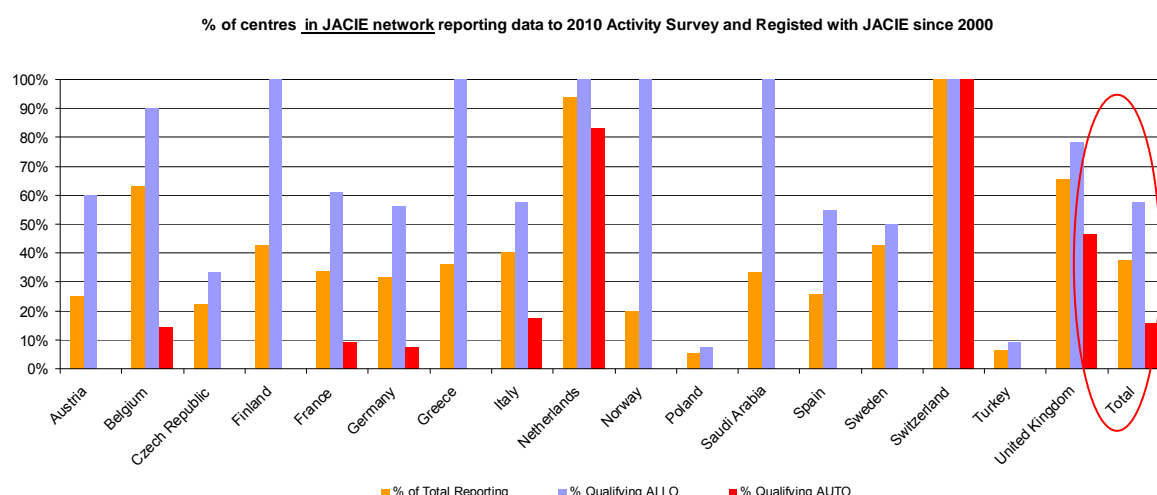


Fig. 2. International comparison of take-up of accreditation by transplanting centres. Data based on Baldomero, H. et al. The EBMT activity survey 2009: trends over the past 5 years. *Bone marrow transplantation* **46**, 485–501 (2011). UK is circled in red.

6. JACIE & Health Authorities

- 6.1. JACIE accreditation is now a requirement in a number of EU countries and also features as part of a number of national guidelines:

Regulations

- France
 - Engagement with JACIE is a requirement for allogeneic transplant centres according to *Arrêté du 3 avril 2009 relatif au contenu du document d'évaluation des activités de greffes d'organes et de greffes de cellules hématopoïétiques*
- Switzerland
 - Accreditation required to receive reimbursement for treatments from Social Insurance
- Italy
 - *Decreto Legislativo 25 gennaio 2010, n.16* implementing the European Directives on Tissues and Cells cites JACIE
- The Netherlands
 - Accreditation required to receive Ministry of Health authorisation to transplant

Guidelines

- Belgium

- Reference to JACIE standards in the Superior Health Council *Standards de qualité pour les tissus et cellules reproducteurs / Kwaliteitsnormen voor reproductieve weefsels en cellen* 5 August 2009.
- European Directorate for the Quality of Medicines & Health
 - *Care Guide to the Safety and quality assurance for the transplantation of organs, tissues and cells*, 4th edition (2010)
- Italy
 - *Piano Oncologico Nazionale 2010-2012* cites JACIE accreditation
- United Kingdom
 - JACIE cited in National Institute for Health and Clinical Excellence (NICE) guidelines *Improving Outcomes in Haematological Cancers* and *Improving Outcomes Guidance in Cancer in Children and Young People*.
 - *The Future of Unrelated Donor Stem Cell Transplantation in the UK. A Report from the UK Stem Cell Strategic Forum* (July 2010). NHSBT
 - JACIE cited in Specialised Services National Definitions Set (3rd edition) SSNDS Definition No.2, Specialised Services for Blood and Marrow Transplantation (all ages)
 - Welsh Health Specialised Services (WHSSC) Blood and Marrow Transplantation Commissioning Policy
 - UK national representative for JACIE, Dr. Kim Orchard, is a co-opted member of the executive committee of the British Society for Blood and Marrow Transplantation (BSBMT).

6.2. JACIE received EU funding in 2003-2004 and in an independent review, was praised for being an exemplary project:

The JACIE project is considered an outstanding example of how EU funding can facilitate the harmonisation, implementation and use of common standards. It is also outstanding in its continuing activities after the end of the project period and its success with regard to international collaboration and contribution to public health policies and regulation. (COWI, 2011)

7. Conclusion

7.1. The field of blood and marrow transplantation (or Haematopoietic Transplantation) is arguably the most successful form of cellular therapy and regenerative medicine to date, having been translated from pre-clinical science to procedures routinely delivered to many thousands of patients throughout the UK and the world. The complexity and high risk nature of such procedures led to the development of FACT-JACIE accreditation covering quality management systems, facilities and personnel within individual programmes. Over the last decade, JACIE accreditation has become widely accepted, and there is now published data supporting an improvement in patient survival outcomes through its implementation. In the future the remit of JACIE is increasingly likely to cover other types of cellular and regenerative therapies, including neurology and cardiology, and may therefore be a valuable resource for the House of Lords Select Committee on Regenerative Medicine.

3 October 2012

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Professor William S. James, University of Oxford – Written evidence

1. I make this submission in a personal capacity, as a scientist working with embryonic and induced pluripotent stem (iPS) cells.
2. My active research interests are in understanding the cell biology of HIV and Parkinson's Disease with a view to the development of curative interventions and early diagnosis, respectively, and in this, iPS technology is making a transformative contribution.
3. Chronic infectious diseases and diseases of old age will create an increasingly unsupportable burden of morbidity in advanced economies as they continue to push back the acute threats to life in childhood and middle age.
4. Consequently, high priority must be given to identify generic approaches by which these diseases may be cost-effectively alleviated if we are not to be the victims of our own success.
5. In my view, the most outstanding breakthrough that promises to address this comes from the development of human induced pluripotent stem cells by Shinya Yamanaka at Kyoto a mere five years ago.
6. Following further important technical improvements by many other groups, it is already possible to generate iPS lines from any living person, from which we can generate fully functional neurons, macrophages, liver cells and other essential cell types in the laboratory.
7. This technology continues to advance dramatically, and it is already embedded at many research centres such as ours around the UK.
8. Although important technical barriers remain to be overcome, it is realistic to imagine that within five years, these centres could offer a routine service of deriving iPS cells and generating a transplantable adult tissue type that will cure a chronic disease for a few thousand pounds per patient.
9. Significantly, new methods of iPS generation, such as that of Mahito Nakanishi at Tsukuba, and "footprintless gene conversion" mean that within this time frame, the new regenerative tissue will carry no exogenous genetic material other than precise genetic enhancements for direct therapeutic benefit.
10. For the full potential of this technology to be realised, many further breakthroughs will be needed, for example in efficiently expanding iPS-derived blood stem cells for transfusion, and in organizing multiple cell types to generate physiologically functioning tissues. With adequate investment over the next decade, UK science is in a good position to make these breakthroughs.
11. In addition, the technology allows us for the first time to observe and manipulate vital human tissues in the laboratory without invading the body. This approach enables us to study disease processes at a molecular and cellular level in unprecedented detail, and to evaluate the effect of candidate drugs in authentic tissues.
12. Britain provided much of the developmental biology basis on which the iPS revolution was initiated in Japan and the US, and has substantial centres of expertise and innovation at the technology's leading edge, in London, Cambridge, Oxford, Newcastle, Edinburgh and elsewhere.

13. These centres are engaged in multiple, focussed collaborations with each other and external collaborators in order to move the fields affected by the technology forward expeditiously²⁰².
14. For the UK to benefit from the medical and economic implications of these advances over the next decade, it is essential for these centres to be encouraged to push further with technology innovation, and to educate and train the next generation of scientists and medical practitioners who will deliver it.

10 August 2012

²⁰² For example, Parkinson's Disease: <http://opdc.medsci.ox.ac.uk/> ; iMi StemBANCC: <http://bit.ly/QVLEIW>

Paul Kemp PhD – Written evidence

Personal Background: I have been actively involved in commercial Regenerative Medicine for over 25 years both in the UK and US and have developed cell based and acellular Regenerative Medicine products which are now approved and marketed. Following Post-doc studies at the University of Manchester, I moved to the US in 1987 when I was recruited from the UK to be one of the first scientists at Organogenesis Inc. This company eventually became the world's first profitable Regenerative Medicine Company. While there, I was the principle inventor on the technologies and patents used to produce the world's first allogeneic, approved cell therapy (Apligraf). This product has now treated over 250,000 patients in the USA suffering from venous stasis or diabetic ulcers and has treated more patients than have been treated by all other manufactured cell therapies combined. I returned to the UK in 1997 to set up Intercytex and I am currently its CEO and CSO, although I am writing here mainly in a personal capacity.

Intercytex Background: Intercytex was founded in 1999 on initial VC funding from Avlar Bioventures and J&JDC. In a series of investment rounds the Company raised a total of £26M from VCs in the UK, US, Singapore and Japan. Intercytex Group Plc floated on AIM in 2006 and raised an additional £27M in three rounds of funding. At its peak the Company had 85 employees and 4 products in clinical trials in the US, UK, Poland and Canada. The 2008 economic situation occurred just when Intercytex needed to raise additional financing and poor clinical trial results on its lead product meant it was unable to raise additional funding and was therefore forced to sell all its assets. Four of these technologies were sold to U.S. Healthcare companies and one to a UK Angel Investor who relaunched Intercytex Ltd in 2010. Intercytex Group Plc delisted and underwent voluntary liquidation in 2010. Intercytex Ltd now has 9 employees and a single product in two Phase II clinical trials, one trial is funded in part by the TSB and DebRa (patient charity) and the other trial is funded in full by the U.S. Dept of Defence. Intercytex Ltd also has a service business, Cell2therapy, which provides contract Translation services to other Regenerative Medicine businesses in order to offset Intercytex's capital requirements. It currently has contracts with UK, European and US clients.

Summary

1. Regenerative Medicine has the potential to provide cures for many of the diseases that currently cause a huge and growing chronic health burden although the reality is behind the public expectations
2. There is a large amount of basic research needed and Universities are pushed into premature translation of a technology in order to receive funding.
3. UK is very strongly positioned to take a leading role in Regenerative Medicine if its intellectual and industrial assets are brought together in a coherent fashion
4. There is a massively duplicative and redundant regulatory burden characterised by sequential approvals and huge delays to the system without protecting patients.

5. The requirements for SMEs to match grant funding and the inability of SMEs to apply for research council funding creates a very uneven and unfair environment biased towards academia and big industry.
6. Adequate funding is very difficult to raise and a progressive licensing system that allows early patient access with appropriate reimbursement would greatly narrow the “valley of death” faced by SMEs

1) Where does the UK have strengths and weaknesses in the field?

The UK's main strengths are in the areas of cell biology, developmental biology, and immunology. I moved back to the UK in 1997 at the time of “Dolly the Sheep” to set up Intercytex as it seemed for the first time that Developmental Biology was becoming linked to Regenerative Medicine in a serious way. In the past, the field had been dominated by engineers with an “anything nature can do we can do better” mentality and very little background science was available. I had hoped that the basic understandings of organ development first exemplified with the haematopoietic system would be extended to other organ systems and lead to the development of true Regenerative Therapies. Unfortunately this linkage seems to have been lost to some degree. The best scientists have returned to their basic science roots and the applied scientists are focussed in the rush to the clinic. I am in strong agreement Prof Braben's opinion written in Science in Parliaments Report “The future of Pharma” where he says that addition of “pathways to impact” to all grant applications inhibits creativity in Universities. I applaud the creation of the strategy for UK Regenerative Medicine and the creation of an MRC UK Regenerative Medicine platform but I worry about the constant drive for Translation at the expense of advances in the huge number of unknowns in our basic understandings needed to properly exploit this field. We don't fully understand how cells change when we culture and expand them in-vitro, we don't understand what is the “minimal transplantation unit” needed to support cell growth and development in-vivo and we don't understand how the host would be required to interact with implants and immunological monitor them in order to eventually form functional, chimeric tissues and organs.

I hope the MRC's Centres for Regenerative Medicine will be focussed on a deep understanding of the basic biology involved rather than being measured on how quickly they get therapies into the clinic.

2) What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

As a commercial developer of medical therapies I am always confused by the regularly used 5-10 years time frame. 5-10 years to what? First in man studies? demonstration of efficacy? or an approved medical product? It means different things to different audiences and this confusion has led to a great deal of hype/misunderstanding and overexpectation.

There are a great number of exciting research projects being carried out at the moment in various areas and I definitely feel that **IF** the various academic, translational and commercial players in the process from lab to marketed product are encouraged to concentrate on their areas of expertise **AND** duplicative and unnecessary regulatory red tape in the regulatory process is reduced to an absolute minimum **AND** appropriate and transparent paths to fair and incentivising reimbursement are created then all the skill sets needed are already in place in the UK and in place to a level that would make the UK **THE** world

leader in translation of new therapies. Treatments for such things as coronary disease, dry AMD, strokes, nerve deafness are probably the closest “blockbusters” but a great many other therapies are in the wings.

The frustration I personally feel and have seen time and time again comes from the need for the quick win or banner headline and the various players are not being brought together in appropriate ways. Development of new Medicines is a relay race not a sprint and the rush for the middle ground of an early, small clinical trial with no comprehensive plan of what needs to come later, ultimately leads to initial promise, followed by delays and disappointments and quite often total failure for commercial reasons not related to the science. The simplistic theory is that if a Technology is simply made “Phase III ready” that big pharma will scoop it up and complete the necessary development, obtain the marketing license and health economic data as well as providing all the marketing and sales infrastructure to generate a healthy licensing revenue that can then be re-invested in new technologies. There is almost no evidence that this strategy has worked in the past 30 years for Regenerative Medicine and several high profile examples (one discussed below) where it has failed.

The ageing baby boomer generation is going to cause a huge “bulge” in the number of old people in the UK and around the world suffering from chronic diseases and placing a massive burden on the healthcare systems in the next 10-30 year time frame. Although Regenerative Medicine is FAR behind where popular opinion and some vocal academics feel it is, I strongly feel it does have the ability to provide curative treatments for many chronic diseases, but that there is a large amount of **BASIC** science still to be done.

3) What difficulties are encountered when conducting clinical trials and how could these be overcome?

I have been involved in designing and/or running clinical trials on Regenerative Therapies in the UK, US and mainland Europe for over 20 years and have worked with both autologous and allogeneic cell therapies. I would like here to voice my support to the staff at the MHRA and the overall European Regulatory system. I hear people say that “if only the regulatory system was clearer all would be well” and that they then focus this criticism on the MHRA. The regulatory System as a whole needs to be streamlined but that is not due solely to the MHRA. I have found the MHRA to be staffed by extremely well informed, pragmatic, supportive professionals and that the European system has a LOT of flexibility built in it that can help the developer which is not seen in the U.S. which tends to be very rigid with a lot of box ticking that was designed for molecular therapies and is not necessarily relevant to Regenerative Medicine. That said, there is MASSIVE duplication of paperwork between the MHRA, the ethics committees and the R+D committees, much of it, although relevant to one is not to the other but still included in the review and most of this system works in sequence rather than parallel. I can provide many examples where this system has caused Intercytex Ltd delays that are regularly in the region of 3-6 months each which have just been red tape exercises rather than providing patient safeguards. If only approvals of the various stages were given to allow a company to move forward to the next stage in the approval process based on face to face meetings and discussion between highly trained professionals and then the paperwork followed then this would save YEARS. Just one example of this was when Intercytex needed to add an additional GMP manufacturing site to its IMPD license in order to manufacture material for a clinical trial. In order to do add this site, an MHRA inspector needed to visit the facility, then he needed to write a report, then the MHRA had to issue a license, then Intercytex had to attach this license to a

CTA amendment and send this back to the MHRA. Then the MHRA had to first validate that our application was complete and only then assess it and then they needed to inform us in writing that we could produce material at the new site. The whole process took over three months during which time the clinical trial was on hold. In an improved system, the MHRA auditor could have given his verbal OK and then we could have followed the paper exercise as outlined above but while we were producing material for the trial. At the moment the entire regulatory process is a step by step paper exercise and reports/ forms need to be written and analysed and checked and approved before then next small step can be taken and it totally clogs and slows down the system.

4) What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

As many reports have highlighted, performing clinical research in the NHS is extremely frustrating. The 2005 McKinsey report “Clinical research in the UK” very clearly demonstrated the issues, and since then nothing really has changed that has had an definite impact on cost, speed to approval and patient recruitment of conducting trials within the NHS and all the data I see suggests that the situation has become worse since 2005 rather than better. There are examples of best practise however, the most notable of which in my opinion, is the Salford Lung Study that show what can be achieved in the UK. From my perspective the problem in providing a systemic cure this is related to the size of the system and I think focussed exemplars in particular area and possibly a single PCT such as occurred in Salford could provide the best way forward rather than looking to change the whole NHS

The EMA’s road map to 2015 focussing on a “staggered approval” is, I feel, absolutely critical to fixing the problems of developing new medicinal treatments and I also feel that current UK and European statutes already allow this IF the various players in the system (NHS/MHRA/developer) work together and IF a “staggered reimbursement” is also adopted so that companies would not need to raise so much speculative investment that needs to gain its return by making the few approved products VERY expensive.

I do not feel that the proposed MHRA’s early access scheme provides any benefit to this system and is not drastic enough to make an impact. By saying this, I am not suggesting relaxation of the critical role of the MHRA in ensuring safe/effective/quality treatments reach the patient.

Patient recruitment is often a HUGE issue with carrying out clinical research in the NHS and clinicians almost always give overly optimistic expectations of the rate of patient recruitment in order to attract clinical collaboration.

In the UK we have no tools to record this information as a matter of course unless the investigator is sufficiently motivated to set up his/her own research pool database. It is quite shocking that in the digital age we do not centrally capture the patient's interest in clinical trial participation. So the reality is that when we embark on a new study we have to ask the site or the appropriate Clinical Research Network to conduct feasibility by speaking in general terms with potential trial subjects and to confirm predicted subject numbers for us. We can (and do) ask for evidence of study subjects. However, the investigator will put as much or as little effort into this as they see fit, and generally will have supreme confidence in the numbers which they provide! At the best, this is so inefficient. The Clinical Research Networks that were set up with the intention of helping are under resourced and have in fact created yet more delays and inefficiencies in the system

5) What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

Regenerative Medicine therapies will, at least initially, be expensive because there are not yet cheap ways to manufacture the materials, but they should provide curative treatments and it is this aspect that presents a definite problem for the future when NHS budgets are 1-5 years. How will costly cures that replace lifelong treatments be budgeted and paid for. I think imaginative systems will need to be developed that share risk between NHS and supplier.

6) What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

As I have mentioned earlier there are several regenerative Medicine treatments approved in the US that have treated hundreds of thousands of patients and presumably they are also cost effective over the treatments that they replaced and that the first ones of these were approved by the FDA over a DECADE ago. I am shocked as to why these treatments are STILL not available in Europe and that alone should be the subject of some questioning as it could highlight specific regulatory/reimbursement/commercial barriers that could be seen by other UK based companies developing new therapies. Why are Apligraf, Dermagraft and Carticel not benefiting UK patients and the NHS when they have been commercially available in the US for well over ten years? These therapies have obviously been shown to be safe, effective, cost-effective and produced at high level of reproducibility and quality. Have they not been introduced into the UK because the EMA's regulatory barriers are higher than the FDA's (These products would have to go through central licensing) or is it because the route to reimbursement is not clear? Or is it some other reason?

As to the current commercial value of the sector to the UK economy, particularly through UK based companies, it is currently insignificant because the number of Regenerative Medicine companies in the UK is small and we are ALL massively underfunded. The future commercial value of Regenerative Medicine has the potential to be MASSIVE and to have an impact on the economy and the health system. I truly believe all of the potential of Regenerative Medicine will be realised although unless the entire system changes and becomes much more "joined-up" then maybe not for 20+ years

7) Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

I am sure much of the evidence that will be sent to this inquiry will say if only there was more funding and less regulations then the sector would thrive. I returned from Boston to set up Intercytex in the UK rather than the US as I feel there is a very strong and very real sense of UK PLC here that is lacking in the US. I think that ALL of the elements needed for commercial success are already here in the UK but there just isn't the joined up thinking in place and a massive amount of trivial red tape reduction necessary to allow these elements to flourish. Innovation and entrepreneurship is suffocated by forms and by paperwork and by the need for sequential approvals of the most minute aspects of the process.

The funding that is needed to develop a Regenerative Therapy will be mainly spent on satisfying this huge and duplicative bureaucratic system. I feel that the era of large VC investments into healthcare is past. History has shown that in aggregate there has been very poor returns on investment in this sector and there are other areas of higher, faster return

for speculative VC investment. I think therefore that Government can make a difference not only by providing more funding but by reducing the need for funding in imaginative ways that do not compromise the commercialisation of safe and efficacious products. I have heard many examples of how this can be done and a but there is a huge inertia against its implementation.

Public money funds the invention of innovative Regenerative therapies through the various Research Councils. It funds the bureaucracy that has evolved to regulate the licensing of these therapies and it funds the eventual purchase of these therapies that have to then pay the returns to the private investors who were required to take the risks to satisfy this bureaucracy. A gradual, phased approach would bring therapies to the patient faster, allow the developer to generate data on the safety, efficacy and cost-effectiveness of a treatment, reduce the amount of investment that they needed to raise and eventually result in cheaper therapies that had “evolved” and been modified during the development phase.

The term “the gradual emergence of efficacy” has been coined to describe the development of Regenerative Therapies and I feel this is a very appropriate description as much of what we do parallels the advances of organ transplantation which has reached such massive clinical success because of convergent advances in surgery, immunotherapy and post-operative rehabilitation. This will also happen with Regenerative Therapies IF the system allows and encourages it.

8) What business models are most appropriate to support the development of regenerative treatments?

Interestingly, the Companies with approved, marketed products in Regenerative Medicine are all fully integrated and develop, manufacture, market and sell their own products. These are Organogenesis Inc (OI), Advanced Biohealing (ABH) (Now Shire Regenerative Medicine), Genzyme and Tigenix. Some of these companies initially tried the licensing route to large healthcare companies such as Novartis and Smith and Nephew but the partnership didn't work and some companies went bankrupt. Interestingly, they were brought out of bankruptcy as private, fully-integrated companies and have now gone on to become profitable and successful. An example is given below:

- i) Advanced Tissue Sciences (ATS) Inc was formed in the late 80s and developed Dermagraft for skin treatment, products for cartilage and other tissue replacement technologies. The Company was VC funded, floated in the 90s on NASDAQ with all time high market cap of around \$1Bn. It formed a Joint Venture in 1996 with Smith and Nephew (S&N) in which ATS manufactured the products and S&N marketed them. The deal proved not to be economically viable for ATS which went into Chapter 11 bankruptcy in 2002 and S&N took over the further product development and manufacturing. It was not very successful in marketing Dermagraft in the US which by now was approved for the treatment of diabetic ulcers and it decided to sell the technology in 2005 for a relatively small amount to a private US equity firm who created the company Advanced Biohealing as a fully integrated company concentrating on just Dermagraft. In just 5 years, they increased sales around 20 fold over S&N's best results to over \$200M per year and they were purchased in 2011 for \$750M cash by Shire.

9) What are the barriers to securing finance to develop such treatments?

The TSB have been outstanding at supporting Regenerative Medicine and I feel that without them stepping to the plate in 2008/2009 definitely Intercytex and possibly the entire

commercial sector would have disappeared. The Cell Therapy Catapult is another strong step and has the ability to greatly aid in the translation as long as it doesn't just push treatments into the clinic in order to reach some governmental set milestone. I know there is a lot of hope in the whole Regenerative Medicine community that the Catapult will have a positive impact but also a LOT of nervousness that the catapult will either soak up all the future Government funding for this sector or at worse become "state sponsored competition" to SMEs struggling to develop their own products or services.

A major limitation of TSB and Biocatalyst funding relates to the matching element required from Industry. It appears very arbitrary what % match is required and the company match has varied from 50% to 25% in grants that Intercytex has applied for. This match in itself is often a barrier for an SME and it is frustrating to small companies to have to compete against large profitable companies for these grants when these large companies have less issue with the match and less need for the grant funding. However, the situation is MUCH more onerous if an academic partner is involved as their institutes require full cost before they will give approval to the collaboration. As it is the FULL grant that needs the match then this means that a situation can very easily be created whereby ALL of the grant ends up going to the academic partner which is a complete disincentive to the SME to be involved. If the situation was altered such that the academic partner was fully funded and only the SME partially funded (to as large a % as possible under state aid ruling) then this would greatly improve the situation.

The moves of the Government to provide funding to SMEs is very laudable but SMEs are often caught in the middle in terms of competing for these grants. As they are classified as an industry, they often have to compete as mentioned above with large, profitable industries who it could be argued are much less in need of such financial assistance. However, they also have to compete with academics who are strongly encourage to set up start-ups while within the protective environment of the University and as such are also able to apply for both TSB Research Council funding (and often NIHR funding if associated with a teaching hospital). While creating TRUE spin outs from Universities is useful, quite often I have known examples whereby the spin out was formed solely to be able to access TSB funding. It isn't possible for the reverse competition to occur and for an SME to compete for research council funding for their own science projects and these projects may have as much scientific merit as a University project. The playing field is far from level and the SME is often forced to the low point in the field.

Raising public and private equity financing in the life science sector gets increasingly difficult globally as the timeline and costs to marketing approval steadily increases, "blockbuster" treatments become rarer and alternate investment opportunities in IT and green technologies show faster returns become available and unless there are some drastic changes to this model I don't see this trend reversing. The model needs to be completely changed and I think the only way this can happen is through some form or other of progressive licensing and reimbursement.

10) Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

No, I don't think they are appropriate. Initial costs for these treatments will be high but will, like any new technology, fall dramatically as the sector becomes successful and improvements are made. Unless this is taken into account and the cost structure of

supporting an acute cure vs chronic treatment is somehow addressed then the incentives will not be there to support their development.

11)What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

The US is often shown as an example of best practise but in my experience it can be very wasteful and although good at infrastructure development is also stifled by a very rigid and litigious approval system. They have the first profitable regenerative Medicine Companies but these were all started in the late 80s and many years before the sector really began in the UK. The critical lesson to be learned from the U.S. is that supporting the re-imbursement of expensive, but cost effective, treatments is necessary to incentivise industry to take the financial risks inherent in development of medicinal products.

South Korea seems to be taking a leading position in Regenerative Medicine. (<http://stemcellassays.com/2012/07/stem-cell-industry-korea/>) and has definitely taken the lead in progressive approval

12)How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

Cell based regenerative medicines as ATMPs are all covered by the centralised procedure so eventual European Marketing Application will have to be made to the EMA rather than the MHRA. Medicinal science is a global enterprise with very few boundaries but approval of medicines is a very nationalistic enterprise. I think in the future, that for relatively small, fully integrated Regenerative Medicine companies the decision as to which “markets” to target will be defined both by market size and time to market.

18 September 2012

Sir Bruce Keogh, NHS Medical Director, Professor Richard Lilford, University of Birmingham and NHS England – Oral evidence (QQ 343-356)

Evidence Session No.16

Heard in Public

Questions 343 - 356

TUESDAY 26 FEBRUARY 2013

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Rees of Ludlow
Lord Patel
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Sir Bruce Keogh, NHS Medical Director, **Professor Richard Lilford**, Professor of Clinical Epidemiology, Vice-dean for Applied Health Research and Director of Primary Care Clinical Trials Unit, University of Birmingham, and **James Palmer**, Clinical Director Specialised Services, Medical Directorate, NHS Commissioning Board.

Q343 The Chairman: I would like to welcome the three witnesses in our first evidence session this morning. In a moment, I will invite you to introduce yourselves for the record and make any brief—I emphasise brief—opening statement that you might wish to make before we come on to the questions. For the members of the audience, the declared interests of the Members of the Select Committee are on the sheet that is being provided, as well as an outline of the inquiry. Perhaps I could kick off by inviting Sir Bruce to lead off by introducing himself.

Sir Bruce Keogh: Good morning. Thank you very much for giving us the opportunity to meet you today. There are three things in particular we would value your deliberations on. One is connections, the second is alignment of the levers for change that we have in a newly structured NHS and then the third thing is how we bring simplicity to complexity in terms of change in structures. We are in a process of transition in the health service at the moment and we have not built all of this, so we are very receptive to suggestions

Sir Bruce Keogh, NHS Medical Director, Professor Richard Lilford, University of Birmingham and NHS England – Oral evidence (QQ 343-356)

The intention, as you know, from the Health and Social Care Act is to focus our NHS primarily on clinical outcomes; secondly, to give greater clinical leadership in the system; and, thirdly, to give patients more control. But the missing ingredient, which has been consistently missing for some time in our health service, is our ability to innovate in a way that makes the health service the go-to place for the pharma, med-tech and other industries, as well as customer focus. We are here obviously to talk about the former, but one of the things that the new Health and Social Care Act has done is that it has brought a duty of innovation both on the Commissioning Board and on clinical commissioning groups. As we have moved into that arena, we have conducted some work on behalf of the NHS chief executive to try to understand the barrier to change. We would like to try to, hopefully, inform you of some of those issues and seek your advice on how we can improve our ability to innovate.

I am Bruce Keogh. I am a cardiac surgeon. I worked in the NHS for some time but have also been professor of cardiac surgery at UCL.

Professor Richard Lilford: I would make two brief points. The first is that the great potential for regenerative medicine carries with it an in-built danger of hubris. The corollary of that is the importance, as I am sure you are all fully aware, of evaluation at every stage in introduction. This in turn underlines the importance of the new mechanisms that are coming in under the Commissioning Board (such as the new mechanisms for commissioning new regenerative medicine solutions) being closely aligned to the research funding mechanisms. In this way new interventions can be put in place around an evaluative framework so that they are not kept as two separate activities, with the one following out of synchrony with the other. The NIHR and the Commissioning Board therefore need to find a way of working together. From my own experience—I was a civil servant for a brief period of my life—I know that is much easier to say than to actually accomplish.

My second point is the importance of health economics: that every new treatment has to compete and be a sufficient improvement over the next best treatment to justify its cost. My particular point around that is the importance of doing the economic evaluation not just at the end—at the demand side (if you like, when it comes to NICE)—but prospectively, at the very early stages. I suppose I have a conflict of interest here because I have had a grant now for nine years from the Engineering and Physical Sciences Research Council to develop a set of tools to assist in that process.

I am Richard Lilford, a gynaecologist who has now lapsed fully into research and administration. I am disappointed to see my colleague gynaecologist Lordships are not here today. I send them my best wishes.

James Palmer: I am James Palmer. I am a neurosurgeon half the week and now work with the Commissioning Board for half the week. My responsibility has been setting up the architecture for the clinical leadership in the direct-commissioned element of services—this is a difference between the CCG-commissioned services and services commissioned directly by the Commissioning Board—which counts for about 10% of the whole of the NHS. The majority of regenerative medicine will probably lie within those specialised services, so my remit in terms of developing services runs from renal transplantation to cardiac surgery to paediatric surgery to blood and marrow transplantation. I am here to answer questions about how the new architecture will help the translation of research into practice in clinical medicine.

Q344 The Chairman: Thank you very much indeed for those helpful introductory comments. I would like to kick off by picking up something that you alluded to in your

introduction, Sir Bruce, which is barriers to innovation. I really wanted to ask you what you think should be done to make the NHS more effective and efficient in adopting innovative treatments and technologies. We are aware that Sir David Nicholson, a couple of years ago, produced a report—*Innovation Health and Wealth*—which identified a number of barriers to adoption and diffusion of novel technologies. But we are also aware that the TSB's value report suggested that the current pathway for the adoption of innovative therapies is clear, but poorly understood by both the industry and the NHS. I would like to ask, first of all, Sir Bruce, and then maybe Professor Lilford and Mr Palmer if they wish to add anything, how we can get through these barriers. We have had guidance and analysis, but how do we move from guidance and analysis to understanding and action?

Sir Bruce Keogh: Perhaps I can tell you what we have done with respect to those barriers and then, secondly, where I think that we need further deliberation. The barriers that were outlined in *Innovation Health and Wealth* were, first, that we have still relatively poor access to evidence and data. Secondly, we have a health service that does not really celebrate innovation in the way that it could. Another barrier is effectively silo-budgeting: the “not in my budget” syndrome for innovation. We have been, I think, devoid of a toolset that enables us to promote innovation. Furthermore, I do not think innovation has been seen as a priority in the NHS and, in some areas, we have fallen behind the rest of the world; although not as far as some might like to argue.

Then there are two other points. First of all, our NHS is an increasingly disaggregated federal system of semi-autonomous, semi-competitive organisations, and the question is how we use that competition to drive innovation. Finally, fear is an inhibitor: fear of new things and fear of complexity. I know that you have addressed some of the complexity, particularly around the regulatory process, which I certainly found an inhibitory thing in clinical research in my previous career.

To try to address those very specific issues, we have done several things. First of all, we have seen the success in areas like Boston of Boston Partners, where the university—particularly Harvard—and the provider medical organisations come together in a partnership arrangement to drive change in quality. That led us to think about developing academic health science centres in a very formal way in this country. We did that. We appointed five of those, but what became clear was that we needed to have them more closely integrated into the delivery system of the NHS. So we are now in the process—or we have just been completed the process—of identifying and appointing 15 academic health science networks. The idea of a network is that it brings together, under, if you like, the umbrella of a leading university, other players in the healthcare system, such as the Commissioning Board, Health Education England, local authorities, the pharmaceutical industry, the third sector and the device industry. We see those 15 academic health service networks as being not only the incubators for innovation, because they are led by the university sector, but also the spread agents because of their relationships.

The second thing, which I learnt about three years ago from the flu epidemic, when we had to roll out extracorporeal membrane oxygenation to save the lives of young people, is that if we use specialised commissioning as a tool, we could roll out even very complex procedures very quickly. We have now appointed James to lead the specialised commissioning endeavour, and I am sure he will talk to you in some detail about how that can be used to ensure innovation. Previously, specialised commissioning had been done by ten different specialised commissioning groups under each special health authority. We have now brought them together in one place, and we have good clinical leadership in that and a good set of tools.

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In terms of our next endeavour, we have identified high-impact innovations through NICE and are using a commissioning tool, which we call CQUIN—commissioning for quality and innovation—which is a financial tool which will enable us, I think, to provoke the uptake of the most transformative ideas, products and services.

The next thing we have done is we have introduced something called the NICE implementation collaborative, which is chaired by Sir Ron Kerr, a previous director of operations for the NHS and now chief executive at St Guy's and St Thomas's. He chairs a partnership board which brings together those players in the system who can influence change, such as the Commissioning Board, the NHS Confederation, the Association of British Healthcare Industries, the Association of the British Pharmaceutical Industry and so forth. When enough people want change, it will happen. We think that they are quite an important player in this. The next thing we have done is put some money aside—about £10 million—in what is called the small business research initiative, in order to help small businesses; the very tiny players who have difficulty with the procurement problems in the NHS and with rolling stuff out. Finally, we have introduced a number of innovation challenge prizes to try to celebrate innovation in the NHS. I can go into any of those in more detail if that would be helpful.

Q345 The Chairman: Thank you. If I could just ask one question, for a very brief response: how will you assess the impact of these various measures and over what timescale?

Sir Bruce Keogh: Well, we have started. With commercial colleagues, we have developed a scorecard to measure the uptake of NICE-approved technologies. The first one of those was published last month, I think by the information centre. It is not as good as we would like and there is quite a lot more work to be done on that. But one of the big levers that we have for change, particularly in a disaggregated NHS, is transparency of data, so we are going to be using that as quite a significant tool.

The Chairman: So would you, for example, look at the performance of the NHS in international comparisons? Would you like the NHS to be a world leader in the adoption of regenerative medicine technologies and treatments?

Sir Bruce Keogh: Can I be absolutely clear? I have no ambition for mediocrity. I think we are the biggest integrated healthcare system in the world and we are not far from a tipping point where we can undoubtedly be the best healthcare system in the world. The point I tried to make in my opening remarks is that one of the big missing ingredients has been the ability to take up new ideas and to spread them widely. A lot of our IP leaves this country and is picked up abroad. I know you are seeing Lord Howe and David Willetts later, and that there are a number of tax incentives and other things that we are trying to put in place to keep things in our healthcare system.

The Chairman: In a moment, I would like to turn to Lord Cunningham but I wonder whether Professor Lilford and Mr Palmer would like to add anything brief to Sir Bruce's very helpful summary.

Professor Richard Lilford: I will be extremely brief. Based on my experience as a non-executive director of a large hospital in Birmingham, I believe that the people that work there are very innovative, imaginative and creative people, who have no cultural hostility to new technology at all. Their problem is money—finding enough nurses for the wards and making sure the system is safe is always in competition with new treatments, which is one of

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the reasons why NICE approved innovations are not always taken up. One of the most encouraging things that is happening now, and which Sir Bruce has just mentioned, is the creation of a specialist commissioning function, which will have some money through which people can be reimbursed and which is specifically ring-fenced, at least to the point where the innovation has got some broad purchase in the NHS. Of course there are great disadvantages and great difficulties in working out how much money should be held back and ring-fenced but it is very encouraging for the dissemination of new technology that a pot of money will be available; with the rider that things must be evaluated. Many new regenerative medicines will not be better than the things that they are competing with.

The Chairman: Is the scale sufficient? We visited the California Institute for Regenerative Medicine, where things seemed to us to be operating in orders of magnitude different in scale from the sort of scale that you have alluded to. Is it just a drop in the ocean, or can it really make a difference?

Professor Richard Lilford: I, too, have visited the California Institute for Regenerative Medicine, which, of course, has a much wider remit than simply the uptake of a licensed product in the health service, which I think is what we are talking about now. It has a huge remit, and is of course an important part of this whole equation, of bringing things to the point where they can even be contemplated being absorbed into the service. That said, as in my previous answer, knowing how much money to hold back for specialist commissioning is going to be a difficult judgement to make, but a very important one to get as right as possible. If you put too much money in that pot, it will be starving the service, in a constrained system, of resources. There is a need for those nurses on the wards at night.

Q346 Lord Turnberg: I just want to follow this up. One of the problems hitherto has been the lack of interest in the PCTs—which are going—and among the GPs involved in commissioning for research. I remain to be convinced that the CCGs will take a bigger interest in this area. How will these academic health science networks and centres work together? And do you think the extra funding you are talking about for commissioning—£10 million for all of this—is going to be sufficient?

Professor Richard Lilford: I am on the interim board of our academic health science network. My own opinion is that I do not think we can look to academic health science networks to solve this problem. Money, I am convinced, is the important thing. If the specialist commission has the money, then that will overcome the biggest block to uptake of treatments that are already licensed. That is not tantamount to saying that I do not think that the NHS academic health science networks have an important role—I think they do—but we cannot look to them as the critical node in unblocking the development of regenerative medicine.

Sir Bruce Keogh: May I—

The Chairman: Sir Bruce, and then I would like to ask Mr Palmer if he has got any brief comment before I turn to Lord Cunningham.

Sir Bruce Keogh: I share some of your anxieties about how we get the clinical commissioning groups, particularly in a tight fiscal environment, to engage in research and innovation. But, firstly, they will be part of the academic health science networks. Secondly, we are going through the licensing process for academic health science networks at the moment, which will enable us to determine certain areas of interest for those academic health science networks. For example, it would not be helpful to have all of them showing

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an interest in cardiovascular disease. We will want some to lead in different areas, so one of the options we have is to identify specific academic health science networks that may have an interest in regenerative medicine. I can address some of the concerns about funding, if you would like.

The Chairman: I think we should press on. Mr Palmer, did you wish to add anything?

James Palmer: Not at this stage. We may want to come back later and talk about how we might implement the service changes that are currently taking place in research but I do not think that would be appropriate now.

Q347 Lord Cunningham of Felling: Gentlemen, BUPA was able rapidly to adopt the regenerative medicine therapy ChondroCelect through its clinical decision algorithm. From what you are saying, Sir Bruce—forgive me if I am getting what you said wrong—you seemed to imply that you thought that the National Health Service had been too slow in making progress on some of these issues. Is that because the NHS is overengineered in management terms? Is it because our regulatory system is too complicated for people to deal with? If the private sector can do something rapidly, why can the National Health Service not? It has far more resource, it has far more knowledge and it has greater skills.

Sir Bruce Keogh: Thank you for the latter part. I think we have addressed that issue, and I will ask James to say a few words about that. One of the problems was that we had 151 PCTs, each of whom had their own board, their own chief executive, their own ideas and their own set of rules. We had 10 specialised commissioning groups, all working to the strategic health authority boards and each with their own agendas. All of those 161 organisations have now been replaced by one: the Commissioning Board. That brings a level of simplicity to this. The person who will be driving the thought processes behind the clinical aspects of specialised commissioning will be James, so he might wish to say a few words.

James Palmer: That step change is not a minor step change. It is a major step change. From my point of view as a clinician, this is a real opportunity for clinicians to lead the process of the most complex areas of our healthcare system. For example—if I have a moment—the key levers that we have put in place to help the clinicians develop have four main themes. One is a service specification, which is a specification of what a service to deliver a particular set of treatments might look like. The key one in relation to regenerative medicine translation is a clinical commissioning policy—what types of treatments can be accessed by which elements of the population that fill specific criteria. The third one is what is called an innovation portfolio for each of our clinical areas, as to what is in the pipeline for innovation—not just for regenerative medicine but for nanotechnology, for pharma and all parts of the aspects for each of our services. Finally, and the gel of all the previous three, is what are the quality measures each of those services is trying to change. One of our key ambitions over the next three to five years is to focus on what are the quality ambitions for each of those services and how you therefore align the ambitions for the research and the innovation, to improve those quality changes.

So the clinical structures that we have in place are forming those products. For the first time ever in the NHS, we have had 140 service specifications published out for national consultation defining a single, unified way of delivering a whole set of the most specialised services. That is how we will simplify from where we have been—in the same set of services, we had in the region of up to 50 different ways of providing the same type of service. When we are talking about the specialised commissioning elements of the service,

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from April, we will have one way of how we commission it, although it is naive to say that is how it will be delivered uniformly, as we will then have to work on how the pathways will change. That is how we are trying to get simplicity into the system.

The Chairman: Did you wish to come back?

Lord Cunningham of Felling: I thought Professor Lilford was going to say something there and was anxious to hear what he had to say.

The Chairman: Okay, and then I will come to Lord Willis.

Professor Richard Lilford: I shall be extremely brief. Behind your question is the assumption that BUPA got it right and the NHS wrong. I think we have to be a little careful there. What has happened in the NHS is that they have acted as the site for an MRC trial of chondrocytes for knee defects, to prevent the late onset of arthritis. That trial is still ongoing and will complete only in 2017. It may turn out that the NHS was right to be cautious; it might not add as much value as we hope.

Lord Cunningham of Felling: I did not think that Sir Bruce was talking about caution, I thought he was talking about the inability to grapple with these issues more quickly and more expeditiously. That is not caution, that is failure. Are there any lessons in any of this about ring-fenced budgets aimed at adopting new technologies in NHS practice?

Sir Bruce Keogh: I will ask James to comment on that in a moment. We think there is, but we are not yet sure how to do it. We are about to take to the Commissioning Board proposals for a ring-fenced budget for a thing called the specialised services commissioning innovation fund. It will not be a large fund—we think it will be just in excess of £50 million— but we see that fund serving the promotion and the uptake of innovation. When we couple that with the amount of money that we have available for the small business research initiative, we think that will help.

The Chairman: Over what period was that £50 million?

Sir Bruce Keogh: That will be annually. I should stress that has not been approved by the board yet.

The Chairman: Lord Willis wanted to come in, and then I will turn to Baroness Sharp.

Q348 Lord Willis of Knaresborough: I was intrigued by the rather disingenuous comment that the NHS is getting simpler. The one thing the NHS has never lacked is structures, and to claim that we have got rid of 151 PCTs and 10 regional boards, and replaced them with an NHS Commissioning Board, seems to ignore the fact that there are 212 clinical commissioning groups, four regional offices and another 27 local offices. That does seem to be part of the picture, and we cannot ignore all those. You mentioned, Professor Lilford, that money was the key thing. Could I suggest to you that it also people who are the key thing? One of the things that has been dramatically missing in terms of translating research through innovation into patient treatments has been the conservatism, with a small “c”, of consultants within the NHS system, who have often been the gatekeepers to treatments. Could you explain—or perhaps this is your job, Sir Bruce—why the new contracts for consultants do not contain a requirement to engage with research, despite the fact that it is now a duty of on Secretary of State, a duty on the Commissioning Board and a duty on every local commissioning group? Without clinicians being required to engage with research and what is coming out of the research pipeline, how on earth can we

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expect to get the sort of innovation which you quite passionately believe in—and I think you do believe in it?

Sir Bruce Keogh: First of all, you are worried about whether this getting rid of a whole bunch of organisations and replacing them with others is all in fact a bit of an illusion.

Lord Willis of Knaresborough: I am not normally sceptical.

Sir Bruce Keogh: It is a fair scepticism, actually. What is different is that we now have a commissioning system and a provider system. The commissioning system used to be fragmented into a load of independent organisations, particularly, with respect, I guess, to specialised commissioning. That is now done under one board, not 161 boards with 161 chairmen and 161 chief executives. So that side is simplified. You are quite right to raise the issue of the clinical commissioning groups, but the other point that I would like to make is that the regional offices that you referred to and the local area teams are not similar in any way to the regional offices of strategic health authorities or the PCTs. They are one organisation. It is like branch offices in a bank. Their job is to liaise with the clinical commissioning groups, helping them to maximise the ambition of the commissioning system, which will be driven through the board. The board will be talking at an individual level to CCGs to try to encourage them to partake in innovation. That is how we see it. As you know, we are in transition, and things have to play out, but that is how we hope it will go.

With respect to consultants, as you know, the doctors' and dentists' review body have recently reported on the remuneration for consultants. Similarly, the Secretary of State has indicated an interest in reviewing the consultant contract, and the productivity of consultants has been subject to a National Audit Office review, which itself is going to be subject to a Public Accounts Committee sometime within the next month, where I am sure that I will be expected to address your question in more detail.

The Chairman: Thank you. Very briefly, Professor Lilford; then I think we need to press on, because we have covered the questions about research, so I will press on to Lord Selborne's question.

Professor Richard Lilford: I think there is a distinction between all consultants being required to do research and all consultants being required to be research-literate. I think the second is a more realistic aspiration than the first, even though I have spent my life in research.

Q349 Earl of Selborne: I wanted to come back to the pricing of regenerative medicines and treatments, which we have touched on already. Clearly the issue here is that many regenerative treatments and cell therapies will cover unmet medical needs for which there is no cost at the moment therefore by definition, or replace an existing lower-cost therapy with a much more expensive but equally much more beneficial therapy. What really we need to establish is how we are going to have an appropriate pricing and reimbursement mechanism. Does the concept of the value treatment starting in January seem to help or hinder?

Professor Richard Lilford: I used to be on the appraisal committee of NICE, and I currently serve the needs of the MTAC—Medical Technologies Advisory Committee—of NICE, and I think your question is very well put. In order for the treatment to be a net benefit to the NHS, it must justify its opportunity costs. It must have sufficient value over and above the existing treatment so that it does not detract value overall to the NHS. In other words, it must be what we call cost-effective. It is terribly important that we do not forget that in our

enthusiasm for regenerative medicine, because lots of treatment add some value, but just might not be cost-effective. The knee cartilage method mentioned earlier may end up being such a case—who knows? The trials are still out. The treatments for heart attack by injecting regenerative medicine cells into the heart seem to show some small benefit, but we do not know whether it will justify its costs in terms of long-term outcomes.

It is terribly important that we try to always insist that new treatments are cost-effective, both for patients but also as a matter of industrial policy, because it sends the right signal to the industry that they need to come up not with small incremental gains, but should seek larger effects and direct their investment to things that are really going to make a difference. That takes me back to the point I made at the beginning about doing your health economics not when you have got your product and it is about to go to NICE and might fall, but when you are still at the design stage, when you can garner early evidence of its potential value to the NHS.

Earl of Selborne: Clearly the whole concept of determining value for money is “At what point do you stop the evaluation?” Some of these therapies will have impacts way beyond the costs which you would normally measure. Is that a valid consideration?

Professor Richard Lilford: It is an extremely valid consideration. Anybody who followed the multiple sclerosis saga back in about 2001 when NICE said no to the multiple sclerosis drugs and the Government then had to come up with a risk-sharing scheme, knows that the whole problem there was that trials all ended at two or three years, but the really important outcomes were at 10 years, when one would have hoped that the new treatments would reduce a patient’s chances of needing a wheelchair. Of course, that is exactly the problem with the cartilage repair as well. The long-term aspiration of the cartilage repair is to delay the time, or even prevent the time, when a person has to go and have a knee replacement. That is the difficult thing to measure. All you can do if you have only got short-term results is model the long-term effects, and it is not an entirely satisfactory answer, but down here on earth it is probably the best we can do.

Q350 Lord Wade of Chorlton: Professor Lilford, you are on the subject that I have been toying with for some time, really, but I would like you to take it a bit further. What I would like you to look at—does the industry look at it?—is the longer-term implications of the development of regenerative medicine in cost terms. Let us face it: the face of the reality is that the taxpayers’ of this country can hardly afford the health service we have got today. It is putting every pressure right up—social activities, old age and all these matters. It is slowly making the country bust, to put it bluntly. How do you see that unfolding? Do you see regenerative medicine as something that over a period of time will reduce the cost of the health service, or is it something that ultimately is going to lead to older age and older problems, and actually just move the cost to a different part but increase the cost over time? Has anybody looked at that?

Professor Richard Lilford: Yes. There are two dimensions to that. The first is time. If we look far enough into the future, then the world will be very, very different in all probability, and there will be some spectacular treatments down the road. We just do not know how long it is going to take to reach that point. The second point is that I do not think there is a general answer to that question. Some regenerative medicine therapies will be a great success. Lord Patel and I are both gynaecologists, and we have watched the ultimate regenerative therapy, IVF, unfold during our lifetimes. Others will be less successful. It is important to not try and have an assumption that regenerative medicine will always be the

solution. Sometimes it will succeed, and sometimes it will fail, and sometimes—this is again why research is so important—it will introduce new hazards.

There is a tendency in documents that you read for analysis to go thus: stroke costs the country so-many billions of pounds a year and that is not in dispute, so regenerative medicine is terribly important. But of course that supposes that regenerative medicine is going to solve the problem of stroke. I am not a technical expert, but my reading of the technical details is that we have got a long way to go before that comes along.

Lord Wade of Chorlton: I suppose my concern was not so much to get an answer—but is somebody looking at it? Is this an issue within the health service, because that is what has to find the costs? Are they looking at the wider implications of the impact of regenerative medicine—as it unfolds, short term, long term, longer term? Somebody needs to understand that, as you so rightly said in your very opening remarks.

Professor Richard Lilford: I was talking to James Palmer on the way here, because one of my petitions is that we should look at this on a case-by-case basis at the early stages of development, and I was very encouraged to hear James Palmer say that that is exactly what he has in mind.

The Chairman: James, do you wish to add anything?

James Palmer: Yes. A lot of these technologies will come through as being very high-cost, low-volume treatments initially to the health service, so a lot of regenerative-type procedures will come out as very high-cost, low-volume. To date, up until April this year, we had a structure called AGNSS which reported through the Department of Health, and it worked on a different paradigm of what can be decided as a value-for-money proposition for the health service. A good example this year has been a treatment for cystic fibrosis which focuses on a particular genotype of cystic fibrosis and effectively stops the lungs filling up in that small group of patients. But it is very expensive, and it is way beyond the cost per QALY threshold established by NICE. NICE have been asked to take over the process of AGNSS in terms of looking at the high-cost, low-volume treatments and building a different paradigm of how you would decide whether that is a value proposition for the NHS. They are going live and picking up their first treatments as we speak, in terms of assessment for this coming year. So that is a different set of processes to the other processes within NICE.

Q351 Lord O'Neill of Clackmannan: The new roles for Monitor and the NHS Commissioning Board would seem to have certain difficulties. There are obviously questions of overlap. Although on the organigram we have been given there is quite a space between them, the functions and the responsibilities seem to be a wee bit close, but that is something that only experience will tell us. At the moment, there seem to be concerns about the information that they currently have. There has been the PwC report on the evaluation of reimbursement of NHS care, which suggested that frankly the stats were a shambles—that not only were they perhaps not that readily available, but they seemed to vary quite significantly between different parts of the country.

Secondly, I accept that Monitor has said in *Costing Patient Care*, “We will try and do better”, but how quickly will we see this improvement given that we have an organisation assuming new responsibilities based in part at least on information that is less than perfect? We have got this statement, “We will try to do better”.

Then there is the other thing. Are you satisfied that these bodies will be sufficiently staffed with expert people who are capable of making decisions and carrying them through? Are

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you in fact satisfied that NICE has the expertise to move rapidly where they can do? We had evidence from UCB Pharma suggesting that—I think it is called—the belimumab treatment seems to be taking an incredibly long period in being properly assessed by NICE. They have attributed that, as much as anything, to the lack of staff expertise within the organisation. Are you confident that the monitoring and the Commissioning Board will be able to function, given inadequate information and suggestions of inadequate staffing?

The Chairman: Could I have a very brief response, because we are pressed for time?

Sir Bruce Keogh: You raise some really legitimate concerns. With respect to speeding up the NICE processes, they are planning now to embark on a system which is much quicker than their technology assessments, and they will produce briefings which encourage the NHS to move in a certain direction. James may wish to say something about the role of speeding things up through specialised commissioning, which I think we can do. The second thing is that, in the new world, Monitor takes on the role of pricing. If I speak to my clinical colleagues, one of the frustrations that we have is our ability to change pricings quickly enough to promote the change of innovation. I would like to see a process where we can change tariff in-year so that if new proven methodologies come along we can roll out the innovation quickly. The Commissioning Board is in discussion with Monitor on that at the moment, but it remains an issue. James may wish to say something about the speed.

James Palmer: Very briefly, Chair. The process that we are putting in place is called commissioning through evaluation, which allows us to start using a treatment and evaluate its effect and ensure that it aligns to a research protocol on the way. That will have a different way of working out its pricing and costing outside of tariff. Do not forget that 50% of all specialised commissioning is outside of tariff. Tariff only covers about 50% of everything else that we do, and we have to negotiate prices for nearly half of everything that we do. That is a £12 billion total budget, so £6 billion of that is outside of tariff.

The Chairman: Thank you. Would it be possible for you to just send us a note with a bit of detail on that point?

James Palmer: Certainly, Chair. It is an important, key point.

The Chairman: Yes. Thank you very much. I would like to turn now to Lord Broers.

Q352 Lord Broers: This question really takes us back specifically to regenerative medicine, but in some ways is a follow-on from Lord Wade's question. Taking into consideration the short lifetime and people-specific nature of regenerative medicine treatments, does the NHS have adequate delivery systems to ensure that regenerative medicines and treatments can be distributed and delivered effectively?

James Palmer: We intend to, from April. As I say, the bit that has been made simple is the bit around the direct commissioning element of the NHS. It is that 10% of the more specialised elements of NHS delivery. By having those tools that I mentioned earlier, the commissioning policy is the key tool for implementing a new treatment. So the NHS and the NHS Commissioning Board can form a unified, single policy for the whole of England, for all providers to give a single type of treatment. We have got 40 of those out for consultation now for implementation in April this year which cover a range of forefront treatments that are coming into the NHS.

A policy can be formed throughout the year, so it does not even need to wait for the next contracting round to be formed. We think that we can implement new, innovative

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treatments within about 12 weeks. This is what we achieved with the drug for cystic fibrosis, so we have tested it in a transition year. That process can function within 12 weeks of an agent being appropriately licensed for use. We are anxious to make sure we roll it out in a controlled manner—that we understand which clinicians are the ones who are leading in terms of the research, who are going to evaluate those new treatments effectively and count how it is affecting patients and how patients themselves experience having those treatments.

We have a system. We have the architecture of a real step change, and we have tested it in transition and can show that it works, so I have significant confidence that is a real change for the NHS.

Lord Broers: So you have got sufficient in-depth education for everybody?

James Palmer: The process that we have taken is a devolved leadership model. Within specialised services—we have about 140 different services—we have what are called clinical reference groups for each of those service areas. There are 75 national clinical reference groups, and on each of those clinical reference groups are around 25 individuals who include clinicians throughout the country. What we have learnt is that to bring to clinicians to the forefront of that decision-making is much more important, because they can tell us what is the right and the wrong bit to focus on in that particular area. As a neurosurgeon, I have very little knowledge of blood and marrow transplantation and I need a team of people who will help with that. Those groups are in place; they have been functioning for over a year and have a highly effective way of engaging multiple clinicians in delivering change. So, yes, I have significant confidence that we have a step change coming for April.

Q353 Baroness Hilton of Eggardon: Specifically, in relation to the distribution of some of the biopsy material that needs to be done, on the analogy of the blood transfusion system, would you support a centralised hub for collection and distribution of material in relation to regenerative medicine? I see Professor Lilford shaking his head. You do not think you need a centralised system?

James Palmer: The only bit of a centralised system that I work directly with is with NHSBT, and they have helped significantly in making sure we have organs available for transplantation. That bit has worked very well, and we work closely with NHSBT because we commission the transplantation of organs, yet NHSBT is a separate organisation that commissions the collection of organs for transplantation. So we have experience of systems that can work, but for the particular issue I am not an expert; I would seek advice.

Professor Richard Lilford: I think it is so difficult to give a generalised answer to that. Regenerative medicine is such a huge field, ranging from products that are commercially available now, which anyone can use in any hospital, to very specific therapies like the injection of foetal cells into the brain in Huntington's chorea—which happened in the university you used to run, Lord Broers—and things in between, where cells have been taken out of the body, manipulated in some way and put back in. But I think the country is in reasonably good shape here for two reasons. First of all, many large centres, including my own in Birmingham, have a clinical research facility, many of them funded initially by the Wellcome Trust. Secondly, there are a number of biomedical research centres and units which the NIHR—National Institute for Health Research—funds, scattered all over the country, which have facilities for this kind of translational research. I am sure it is not perfect, but I think the country has been put in quite good shape in that respect.

Q354 Lord Willis of Knaresborough: Could I ask Sir Bruce a small but important question? The direction of travel for the NHS is in fact to devolve services commissioned by organisations who are qualified providers, and not necessarily the traditional NHS providers. How confident are you that those organisations—I make no comment about their quality—will engage with the research translation and innovative processes that you are wanting to see happen? How can you make it happen?

Sir Bruce Keogh: That is a difficult question to answer, because we still have quite a lot of thinking to do on that, but I think it is going to be in the contractual arrangements, in the same way that we are looking at how we enforce them to take part in the training of junior doctors and nurses in the service. So, in my head, that is the route that we will need to take in terms of research.

Lord Willis of Knaresborough: You understand that the cost will fall disproportionately on what is left of the NHS—traditional NHS?

Sir Bruce Keogh: Yes, I do. Bear in mind that 17% of NHS activity happens in those organisations, so we have, as you have alluded to, a significant interest in extracting a return from those organisations.

Professor Richard Lilford: I would not be too cautious about the role that the private sector or the third sector could play. The reason I say that is one which, again, Lord Patel will recognise: in vitro fertilisation in this country started off almost entirely in the private sector. I remember when I was first a university professor I had an IVF unit in my own academic department, which I could not get funded in the NHS. Now it has been taken up widely in the NHS.

Lord Willis of Knaresborough: But charge an awful lot more than the NHS.

Professor Richard Lilford: I do not think I was. I do not think so.

Q355 Lord Rees of Ludlow: I have a question about the GMP facilities. We were told that there were eight around the country, and some of those who wrote in to us said that perhaps that was not optimal and that some should be expanded and should be closer to the research. Would you like to comment on any way in which you think the GMP facilities should change?

Professor Richard Lilford: I have got nothing to add on that particular point. It is just beyond my expertise.

Sir Bruce Keogh: I cannot answer that, I am afraid.

James Palmer: I cannot either.

Lord Rees of Ludlow: We were told that it was perhaps a disadvantage that they were all within the NHSBT network, which meant that they were perhaps not as close as they should be to the research. Is that a fair comment?

James Palmer: Yes. I do not know the direct links of NHSBT with research functions, and that is not in my particular commissioning area. But the mechanism that we have to answer both these questions is that we do have the option of specifying clearly the services that we are expecting from providers. That can influence significantly their research elements within their training elements. That is the lever that we have to change these types of situation.

The Chairman: None of you was prepared to comment on GMP facilities, yet it does seem to us from evidence that we have taken from other witnesses that, if regenerative treatments are really to be rolled out in the NHS, we will need in the country GMP facilities that can deliver products in sufficient quantity for phase 2, phase 3 and presumably beyond that for actual clinical delivery, and that that is something that we do not yet have. If one is taking a 10 to 20-year view, surely this is something that, between you, you should have a view on, so I am a bit surprised that none of you do.

Professor Richard Lilford: I am sorry we have let you down in this particular respect, but the other people you have taken evidence from are probably more expert than us. I know that there is the Catapult. I suspect you might have taken evidence already, or be about to take evidence, from them, but I guess they have a duty to do the math on that—to work out, under reasonable assumptions, what the ideal capacity is.

The Chairman: But let us say we go back to the very beginning—we were talking about barriers to innovation, and Sir Bruce gave a very articulate summary of the barriers to innovation. If indeed a practical issue like the development of sufficient GMP facilities were part of the barrier to innovation, surely that is something that you should be concerned about.

Sir Bruce Keogh: Would you like us to send you a note on that?

The Chairman: Yes, please; that would be very helpful.

Q356 Lord Patel: I was going to make exactly the same point, but now that you have made it I might go back, if I may. By the way, my apologies, Lord Chairman, and to everybody else: I got delayed by transport. Apologies for that.

I am surprised that you did not expand on the pricing mechanism. Can I suggest to you that you will need to address the issue of how regenerative medicine therapy will have to be priced, particularly for autologous cell therapy, where it will be one individual, one treatment? Also, the model that NICE currently uses of cost-effectiveness will have to be thought of in a different way, because it will be one individual, one treatment, and quality of life for that individual, not for patients with the same problem. I suggest that even if you cannot answer it now, it is something that you would agree you would have to give some thought to.

Professor Richard Lilford: I think that particular question can be answered, Lord Patel. The existing toolkit for health economics is fit for purpose for making that calibration—working out the cost-effectiveness of a treatment, irrespective of the number of people that are affected by it. Of course, the number of people may affect the cost, but that will all be taken into account with the standard toolkit. James Palmer has brought out the excellent point that when a treatment first comes in it may come in at a price that is too high because it is early in its genesis, and it can be expected that it will follow a kind of Moore's Law and will gradually decrease in price. What James has described is a mechanism to overcome that early stage market failure—in other words, to make sure that the industrial policy is taken care of as well. In defence of NICE and the profession of health economics, if you like, I think that we do have the necessary toolkit to make exactly the calibration that you identify.

The Chairman: I think I would like to draw this session to a close; we are more or less up against the time limit. In thanking you all for your very helpful comments, there were a couple of points that you agreed to send us a note on. James Palmer, I think you were going

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to send us a note on commissioning through evaluation; and Sir Bruce will send us a note on GMP facilities, particularly addressing the question of how the existing provision of GMP facilities will need to be developed in order for the wide-scale manufacture and adoption of regenerative medicine treatments into the NHS—so, as we scale up, what needs to be done in terms of investment. That will be a very helpful note for us to complement what we have already heard.

I would like to thank you all very much. If there are other points that you wish you had had a chance to make to us, please again do feel free to jot them down and send them in to us, and they will become part of the evidence that will be in the public domain. You will receive a copy of the transcript to make corrections if you wish.

Professor Peng Tee Khaw, UCL Institute of Ophthalmology, Professor Roger Barker, University of Cambridge and Professor Michael Schneider, Imperial College London – Oral evidence (QQ 21-41)

**Professor Peng Tee Khaw, UCL Institute of Ophthalmology,
Professor Roger Barker, University of Cambridge and
Professor Michael Schneider, Imperial College London – Oral
evidence (QQ 21-41)**

Evidence Session No. 2

Heard in Public

Questions 21 - 41

TUESDAY 30 OCTOBER 2012

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
The Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Professor Peng Tee Khaw, Moorfields Eye Hospital, UCL Institute of Ophthalmology, **Professor Roger Barker**, University of Cambridge, and **Professor Michael Schneider**, Imperial College London, gave evidence.

Q21 The Chairman: I would like to welcome our second witness panel and to repeat what I said at the beginning of the previous session. Members of the Select Committee are urged to declare any relevant interests before they speak for the first time in this inquiry. This is an inquiry into the topic of regenerative medicine. The focus of this session is going to be around the public understanding, in part, of what is available through regenerative medicine, so we will ask you about certain articles that have appeared in the press. We are trying to understand what actually it is in reality, as opposed to the hype there is in presenting to the public what is going on in the field.

What I would like to do is invite you to introduce yourselves for the record. If you wish to say anything in addition to introducing yourself, please feel free to do so but keep your

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comments brief because we have a limited amount of time. I would also like to remind you that in the second part of the session, say the last 20 minutes or so, we have a number of questions that were submitted by the public through Twitter and we want to put some of those questions to you, so that those who have submitted the questions—who we hope will be watching the webcast of this session—will have the chance see their question being put before top experts and hear your responses to them. We will not be able to cover all of the questions because of time, but we will cover a number of them. So without further ado, could I ask you to introduce yourselves, starting with Professor Khaw?

Professor Khaw: I am Professor Peng Tee Khaw. I am a clinician scientist, working in a disease area called glaucoma, but I have an interest in regenerative medicine and also drug therapeutics to enable that and to prevent scarring. I also direct the NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and the UCL Institute, which has the express purpose of fast-tracking translation, and the infrastructure behind that.

Professor Barker: I am Professor Roger Barker. I am a Professor of Clinical Neuroscience at Cambridge University. I am a clinician and a neurologist who sees patients. For the last 20 years I have been involved in regenerative medicine around Parkinson's and Huntington's diseases. I coordinate a European consortium on a foetal transplant trial in Parkinson's disease.

Professor Schneider: I am Michael Schneider, the British Heart Foundation Chair in Regenerative Cardiology at Imperial College London. As a member of the MRC Council I was a participant in the research council/Technology Strategy Board working group that crafted the UK's Strategy for Regenerative Medicine, which was alluded to in the earlier session.

Q22 The Chairman: Perhaps I could kick off with the first question, which relates to the press articles that were sent to you. There were three articles, one from *The Guardian*, one from the *Daily Mail* and one from the BBC. What we would like to ask you is whether you could comment on the treatments discussed in each of the articles and, particularly, when they might be available to patients on the NHS and whether the articles portray a realistic view of the efficacy of the treatments. The one from *The Guardian* talked about improved vision for a man with Stargardt's disease; the *Daily Mail* one talked about Parkinson's disease; and the BBC one talked about heart attack scars. Perhaps on the question of treating diseases of the eye I could turn to Professor Khaw and invite you to talk about the report from *The Guardian* by Sarah Boseley.

Professor Khaw: I think Sarah Boseley's article was a good one. It reflected some of the clinical issues facing us—and our patients' desires—and it shows very well how passionate our patients feel about wanting stem cell treatments. There is not a week that goes past that I do not get asked about this. It also reflected quite nicely on some of the difficulties facing the translation of stem-cell research.

On this particular issue, though, going back to the public's desire, the board of Moorfields Eye Hospital meets the public every year. This year an elderly gentleman stood up and said, "I have dry age-related macular degeneration; is there any hope for me? Will there be stem cell treatment?" I answered. I said, "Unusually, I am not going to tell you, 'Five to 10 years' time'. I am going to tell you that within 18 months we are going to have the first stem cell

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clinical trial.” I was wrong, because we actually started the first clinical trial six months after I made that statement. That is a very unusual situation for us, but it is a reflection of the rapidity at which—at least certainly in the field of regenerative medicine for the eye; in gene therapy we treated the world’s first patient a few years ago—this is moving forward. It is moving forward rapidly.

Going back to the articles, I think the public is inevitably very hopeful about this. Early reports of the first two patients for a particular stem cell retinal treatment were published in *The Lancet* which was carried out by a former alumnus of ours in Los Angeles. The ACT (Advanced Cell Technology) people came across to our NIHR biomedical centre, because obviously we are very big and have much expertise in this area, to carry out the first trial in Europe. These trials are obviously for safety; they are not for therapy. Inevitably, however, in these very front-line treatments—and I include gene therapy in that—we begin to see some very interesting results. That naturally raises the hopes of the public a lot, because in many ways a safety trial also accelerates expectation, because some of the patients have experienced quite interesting improvements in their vision. They have been very helpful in some ways because they have shown that, going back to stem cell therapy, it is possible to do it; secondarily, the stem cells have not been overtly rejected, which is always a major concern; thirdly, at the moment, there do not appear to be any tumours or other issues that we have seen so far. That is very helpful, but obviously there are still significant challenges moving forward to the future. Of course, there are issues about whether we can really get this through to full clinical use within the NHS. That will depend on the whole licensing issue and other issues of funding for both researchers and Government.

There is no question that the desire is there. That gentleman’s question reflects the desires of literally millions of people around the world for this treatment to work; therefore, I suppose, it is within our scope to try to see how we can make that a reality. I think this is not just hype. Going back to your initial question, there is real hope. We are proceeding; we are right at the front line. There is a lot more to do, and a lot of the problems have been identified here, but certainly we are moving fast and moving forward.

Q23 The Chairman: In terms of a specific answer to the question of when might the treatments be available to patients on the NHS, you have said you hope that in the future they would be, but you have not hazarded at whether that would be five, 10 or however many years off?

Professor Khaw: The trials are moving quickly. One of the interesting things about stem-cell therapy is that, unlike pharmaceuticals, because you are going for regeneration, you may need less patients. It is still very difficult to do these trials because you need very sophisticated analysis techniques to look at efficacy, but you do not need so many patients. This is important in relation to your question, Chairman, because if the safety trial goes well—these will hopefully complete in perhaps the next year or so—then companies will hopefully move forward to later-phase trials. Clearly, if they do show efficacy—and that depends on regulatory issues both here and around the world—then potentially the treatment will go through the normal licensing process. Given the speed at which you can go, given the small number of patients, it is possible that treatments like this will be available within the next five years, or at least be licensed. There are other issues, of course, governing availability of treatments such as cost etc, but there is a distinct possibility that they could be available within the next five years. That is an exciting possibility for all of us.

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Q24 The Chairman: Now I would like to move on to the second article and ask Professor Barker to comment. This is the article from the *Daily Mail* by Sadie Whitelocks: “Hope for Parkinson's treatment breakthrough as human stem cells successfully used to treat disease”.

Professor Barker: This refers to this very influential and important paper that Lorenz Studer's group published last year in *Nature*. As is often the case with newspaper articles, the headline is somewhat distorting what the article was saying. In the field of Parkinson's disease, the use of cell-based therapies to repair the damage of Parkinson's has been going on for 25 years. In Parkinson's disease (PD) there is a loss of cells that produces a specific chemical, dopamine, so any cell that can produce dopamine could, in theory, repair the PD brain. For 15 years, up to the turn of this century, foetal dopamine cells were being used with mixed efficacy for this purpose. Many people, though, have got confused with the idea that foetal tissue is the same as stem cell-based therapies. So, in the public's mind there is confusion between when you talk about foetal-based cell-based and stem-cell therapies. Are the two, one and the same? Have stem cells not been around for a long time to treat Parkinson's disease?

The big problem in considering the use of stem cells for treating Parkinson's disease has been three-fold. Firstly: do foetal dopamine cells actually work in Parkinson's disease? I would say the answer is yes but it is not consistent, and that is the reason for our trial. Secondly, are those stem cells which you are producing truly of the right character to produce the same efficacy as you might see with a foetal dopamine cell? Finally, there is a problem with stem cells to do with tumour growth and things of that nature. So, in Parkinson's disease, the critical question has been this: have you been able to make a safe dopamine cell which is of the right type to treat Parkinson's? It is not just that you have made any old dopamine cell, but an appropriate dopamine cell.

This paper by Lorenz Studer took a new strategy, which was to take a developmental-biology approach and say, “How do dopamine cells normally develop? and can we recapitulate that.” They did that successfully using human embryonic stem cells, and then transplanted them into immunodeficient rats, mice and immunosuppressed monkeys for a short period of time and showed that the transplants that survived made dopamine and restored deficits in those animal models which are a crude approximation of what you see in the clinic. This paper was important because it demonstrated that it was possible to make safe and appropriate dopamine cells from a human ES cell source. The next problem then is about when that will translate to the clinic. I think there are a couple of issues there. One is that we do not know whether dopamine-cell therapies truly work, which is the purpose of our European fetal dopamine cell trial. Secondly, the dopamine cells as produced from these stem cells still do not have all of the hallmarks of normal dopamine cells. There are still issues to do with their ability to grow proper length processes or axons.

So when will these treatments come into the clinic? It is envisaged that there will be early trials using this technology in patients at some point in the next five to 10 years, but they will be phase I trials. Lorenz Studer himself has applied for funding to do this through the New York Stem Cell Foundation. In addition we have just received a grant from the MRC with a team in Edinburgh led by Dr Tilo Kunath to take Roslin GMP-grade human embryonic stem cells, through to dopamine cells to transplant into animal models of PD. If successful, we would have a cell that is of clinical grade, that could then go to the clinic. If

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that all goes according to plan and those cells work, then the fundamental question which will face the NHS is this: is that treatment any better than any other dopamine therapy that is out there? In my mind there is clearly an issue here. You can get something to work, but is it then competitive?

In Parkinson's disease, as you may know, whilst the loss of dopamine can be remedied with these type of approaches, the disease is much more diffuse than that. For example, dementia is quite common in Parkinson's disease and that is independent of any loss of dopamine cells. All therapies for Parkinson's disease which are currently available in the clinic work on the principle of replacing dopamine. Fundamentally, will a stem cell-based therapy be any better than a Duodopa infusion or an apomorphine pump or any other dopamine based therapy?

Q25 The Chairman: Professor Schneider, would you like to comment on the BBC news article "Stem cells used to 'heal' heart attack scars"?

Professor Schneider: Yes, the trial being discussed is the CADUCEUS (CARDiosphere-Derived aUtologous Stem CELls to Reverse ventricUlar dysfunction) trial led by Eduardo Marbán at UCLA. To put its importance into perspective, I would say that over the past decade there have been more than 1,000 patients treated worldwide with stem cells of different kinds for heart repair—typically bone-marrow cells or their circulating derivatives in the blood stream. The consensus from those trials is that small benefits are seen and overall they are safe, but the benefits might be less than the enthusiasts would have wished, partly because the bone-marrow cells probably do not turn into beating cardiac muscle cells and therefore do not achieve myocyte replacement as might be necessary for the optimal restitution of heart function after a heart attack.

This particular trial was one of two reported in *The Lancet* this past year that used, instead, dormant stem cells from adult heart muscle along with other cells grown from a cardiac biopsy, which have a very well proven potential to form new beating heart muscle, both in tissue culture experiments and in experimental animals. The point to which the title of the BBC report made reference was the shrinking of the scar by advanced magnetic resonance imaging technologies. I agree very much with the caveats Professor Khaw raised. These are Phase I trials that are designed and powered chiefly to prove safety and gain the approval to go ahead from a few dozen patients to a few hundred patients in the Phase 2 study. It is really only in the Phase 3 study involving thousands—and sometimes tens of thousands—of patients that we get genuine proof of clinical effectiveness.

Piggy-backed on the safety trial, however, are studies which are designed to provide a preliminary indication of effectiveness, such as the imaging that was done in the case of this trial. The problem is partly that the media do not always make it clear to the public what a trial is and is not. A Phase I safety trial is not proof of effectiveness; it can contain a preliminary indication of effectiveness, but those are not the same thing.

Q26 Lord Winston: I have two brief questions, Lord Chairman, if I might.

The Chairman: Keep the questions brief and the answers brief, please.

Lord Winston: One is the paper by Kim published over 10 years ago in *Nature* on tyrosine hydroxylase activity in dopamine. You will remember this paper, which showed

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clear efficacy in rats for the treatment for Parkinson's disease. One of the issues is that this was over 10 years ago. It takes a hell of a long time; I wonder if you could address that.

To Michael Schneider, very briefly, one of the issues, as we have discussed in the past together, is the fact that the early trials with stem cells—whatever kind of stem cells were injected—all looked rather good. There were all sorts of parameters which showed an improvement, but actually once randomised controlled trials were done the improvements, if at all, were extremely small.

Professor Barker: Yes, there are always reports claiming that they have derived dopamine cells from stem cells. This paper was from Ron McKay's lab. The ability to turn a stem cell into a TH+ cell, which is the enzyme which makes dopamine, has been shown many times and in this paper this was shown using mouse ES cells. These cells were shown to have efficacy in animal models in PD. However, in order to reverse the simplest behaviour in an animal (drug induced rotation), you only need around 160 nigral TH+ cells. In order to have a successful transplant in a patient based on foetal material, you need 100,000 TH+ cells. Extrapolating from animal models to patients is always very difficult. It is a starting point, but the issue is the reproducibility of that technique or protocol in other people's hands. In those particular cells, what the cells looked like was not the same as what Lorenz Studer has managed to do with his human ES cells, but even then his cells still do not look like normal nigral dopamine cells.

Professor Schneider: Turning to the small effect of bone marrow in the early clinical cells for heart repair, I would agree with your point that even preliminary indications of efficacy are more convincing if randomised rather than not. However, I would say that a lot is learned even from the early trials that affect the design of later trials. For instance, although the overall effect of bone marrow was just a small improvement in the ability of the heart to eject blood each time it contracts, other kinds of improvements can be detected more readily in trials, such as protecting the heart from progressive dilatation and wall-thinning. That effect is a big one, not a small one. Those early trials also helped pinpoint those patients who might be most likely to have a big improvement. If you inject bone-marrow cells in someone who has a small, uncomplicated heart attack, whose heart is pumping well already, there is not much benefit. Those patients in turn diluted out the benefit that is seen in patients who have a big heart attack whose hearts are pumping worst, in whom the benefit was largest. In talking about the early bone-marrow trials, I think a lot was learned that affects the design of the trials we see today.

Q27 Baroness Sharp of Guildford: These sorts of articles are leading to a lot of interest, obviously, in stem-cell therapies of one sort or another. The question I want to put to you is whether there are dangers for the public travelling overseas. There are quite a number of places overseas that have been setting up clinics of one sort or another. We have seen this happening. Are there dangers to the public if they travel overseas to have regenerative treatments of this sort and, if so, to some extent, what can be done about this?

Professor Barker: I think you are absolutely right. There is a danger to patients; there is also a danger to the whole field. If something goes wrong in one of these clinics, it will impinge on all who are working on stem-cell therapies across the globe regardless of the origin of that transplant. This is a very big problem and I have been involved with it on two levels. I have been to China twice, where there are a lot of these clinics, to talk to the clinicians out there to see if I can persuade them to try and adopt a slightly different strategy—without success to date. The other way in which I have been involved with this is

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with the International Society for Stem Cell Research (ISSCR). This organisation has tried to set up guidelines to help patients decide whether a stem cell therapy advertised on the web is worth pursuing. It is though very difficult on an individual level. I, have one patient, for example, who has young-onset motor neurone disease and who came to see me and said, “I want to go and have an umbilical-cord stem-cell transplant. Would you support that?” I said, “No, there is absolutely no scientific evidence that that works at all.” The patient then said, “Is there any possibility that it could work?” I said, “Of course there is a possibility it could work.” to which they replied, “but you are offering me nothing!” So some possibility against no possibility seems quite good odds to a lot of people, even if it costs £20,000 to £25,000.

This is very difficult, because within those clinics there may be something useful coming out which we currently cannot gauge or assess. The way in which the trials are done—certainly in the clinics I have been to—have no scientific or clinical basis, the follow-up is minimal and the results have many interpretations and not that which they necessarily put on them. I think it sets up an unrealistic expectation of benefit and linked into that, with the patients in the UK, there are two other issues that are often cited as being supportive of going to these overseas clinics. One is that you do not get this type of therapy in Britain because, “The NHS does not have any money; that is why I have to go abroad to get it.” It is the cash-strapped NHS which means I have to go abroad. If we had enough money we would all have it. You have to disabuse people of that idea. Secondly, it is to do with the ethics: there are major ethical problems with using human embryonic stem-cells and foetal tissue and these adult stem cells—bone marrow or whatever (which are typically being offered in other parts of the world in these clinics) circumvent that problem and so are better to use. Therefore they must be a better source of cells to use. That is what the clinics often play on. They play on this ethical issue to get around it; they say that these are much more ethically acceptable. There is no scientific basis for their use, but given it is ethically more acceptable to use them, then they should be given to patients!

It is a big problem, this stem-cell tourism; people are travelling the globe to do it. When I was on this ISSCR Committee and the list of clinics was sent out for us to review the document ran to dozens of pages listing clinics across the globe, so this is a vast industry that is out there.

Professor Khaw: Certainly, in eye diseases—and optic nerve disease, which currently is irreversible—we do have many patients writing constantly in and saying, “Should I go? Should I go?” I will not go over the comments that Professor Barker has been through, but I would absolutely reiterate that issue. It is a difficult situation for us when you have a relatively untreatable condition and a patient is desperate. I suppose my reiteration of that would be that the way to try to go through this is the issue of information. We must provide the individual with as much information as possible about what we know about where they are going—that includes the individuals running it—and also what they know is available out there. I think that is the first thing that has been very helpful, perhaps, in informing people.

The second thing is the personal approach, actually. When they are in a very desperate state, people want to know whether you would send your mother or your child. Actually, my answer is that I look at these things and I explain to them, “Although I am not in your position, my answer is I would not, and this is why.” That actually is persuasive, to be honest. I give them information, but it is that very personal approach that is helpful. They need information; they need recourse to clinicians who are familiar with the area, familiar

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with the science and, actually, can give them a very frank, personal opinion also about the pros and cons of this.

Professor Schneider: I share the concern that Professor Barker raised that safety accidents in this field in unregulated clinics with poorly designed trials could have an adverse effect. I suppose, to an extent, we are fortunate there have not been more than have been reported to date. There is one instance that I am aware of: a young man went to the former Soviet Union for injections of foetal neural stem cells for a neurological disorder. He subsequently developed a tumour, which advanced pathological tests were capable of showing was donor cell derived. If one thinks back on the history of gene therapy and the recoiling of the investment and clinical community from gene therapy, this was based on a very small number of safety disasters. The same could happen here and so these kinds of activities do put an entire promising field in some jeopardy.

Q28 The Earl of Selborne: The article in *The Guardian* refers to a tide of suspicion to stem cell therapy and the need for practitioners to fight back. Is the tide on the ebb or the flow at the moment and what research has been done on public perceptions and attitudes to regenerative treatments? What does that tell us?

Professor Barker: I have limited experience of this. As part of our European foetal transplant trial we have an ethical work package within it and the EU has been quite keen on collecting public opinion on regenerative medicine. My colleague, Professor Gottweis, who is a Professor of Life Sciences in Vienna, pointed me in the direction of a thing called the Eurobarometer, which looks at various different aspects of this, which I am sure many people are familiar with. Certainly, within the UK the support for stem-cell research and stem-cell therapies is very prominent. It is the highest in Europe. In this Eurobarometer, 80% of people would support the use of stem cells for research and for therapies. What would be interesting is, when you actually move it to the clinic, how many people would support it on an individual basis. For example, with the foetal transplant trial, whilst we have lots of people who have joined our trial, when you actually say, “Would you like a foetal transplant because we are about to start,” people just step back a little bit from that. I think people are generally—certainly in the world of neurology and in general with stem-cell therapies—very supportive of it. When it comes down to an individual person in a trial, it changes slightly. In general, people are supportive of it but it does vary across Europe. With a lot of funding for European-wide trials, this creates a certain tension in how you move some of this work forward on an EU wide basis.

Q29 The Earl of Selborne: Would further public engagement be helpful to meet some of these issues that you are referring to when it gets to the clinical stage?

Professor Barker: I am a huge fan of public engagement, because I think there are a lot of misconceptions about things. There are a lot of things we do not think about as scientists and clinicians; the public are very good at educating us on these and thinking about it differently. Managing expectations is the most important thing for these type of therapies, because, as the papers tend to report things in a rather bold fashion. For example—when I give talks on cell transplant in Parkinson’s Disease, there is a headline from *The Guardian* which says, “... miracle cure turns into disaster catastrophe,” which refers to a foetal transplant trial in America. So often for the press, there are essentially two outcomes: it is either miraculous or disastrous. Therefore the public have this hyperbole to deal with: it is either going to cure everything or cure nothing. Trying to give them some sort of realistic

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expectation of what it could do over what period of time in what aspect of disease is important.

Professor Khaw: As part of the NIHR we have had several very large public engagement days on different diseases; inflammation and retinal disease. Obviously, these groups of patients have a particular interest because they suffer from these diseases so you might expect them to be more engaged about wanting the treatments, but there is often a very active debate about whether we should be wanting stem-cell treatment. I can tell you that at the end of the day we often have a session where we ask them to take their Post-it and stick it on the bits of the board that they are really keen on. Of course, research comes very high, even though they are all sufferers of the disease. From the few informal surveys that we have done, certainly they are all very much in favour of stem-cell therapy. In ophthalmology, we have not done a large-scale public analysis of whether the same sentiments are held. However, I can tell you personally—and certainly through our wide exposure to the public through our public patient engagement—that there is very strong support for this because they do see it as giving them some hope, particularly in many of the conditions that are essentially untreatable. There is very strong support, certainly from the patient groups.

Professor Schneider: I would share your point that there is insufficient public knowledge of the nuances of clinical research of many kinds. This is something which most of us in academic medicine are resourced to do either through our NHS trusts or the NIHR Biomedical Research Centres and Units. I think back to Lord Winston's programme of four or five years ago, *Super Doctors*, which painstakingly made the point that in a clinical trial half the patients do not get the treatment and that, indeed, would have been a surprise to many members of the public. There are many things that the public would benefit from understanding better. We as a community would benefit from improving their knowledge.

Q30 Lord Patel: Because the question was put as the public attitudes to regenerative medicine, it implied that we are talking mostly about treatment; of course, we are not. We are talking about research, too. In the context of research, what engagement do research funding bodies, including the councils, have with the public before the research starts? Are you aware of that?

Professor Barker: I do not have a specific answer to that. To be honest, I have more to do with the disease-specific charities. For Parkinson's UK, for example, I often go and give public lectures to people with Parkinson's disease and interested parties about regenerative medicine and things of that nature. I do not know so much about the MRC and the Wellcome Trust and whether they have specific public outreach symposia or days, I am afraid.

Professor Khaw: I am not so sure about the Wellcome Trust or the MRC, but certainly through the NIHR there are very proactive PPI (Patient and Public Involvement) engagement activities through web media and other things. We have priority-setting partnerships, for instance, in which the public has been engaging very strongly by emailing in what they feel really matters to them in their lives in terms of research. That priority-setting process is underway at the moment; it will identify some key priorities, many of which hopefully will be funded by the NIHR and other sources.

Professor Schneider: In a small number of areas the ethical issues loom large. That kind of consultation takes place in a proactive way. The recent Academy of Medical Sciences report on animal/human hybrids would be one example. Foetal tissue research is another example

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and, of course, human embryonic stem cells would be a third. As several speakers have pointed out, this field of work, more so than others, is very dependent on high-quality animal research, both for model organisms providing us cell types of different kinds, which one can study and then learn from, and the human model organisms like the salamander, the zebra fish and even the new-born mouse, which have a much greater regenerative capacity than middle-aged or aged humans. We learn from the model organisms mechanisms of repair that then might apply to the clinic.

In addition to those two streams of fundamental research requiring the animal models, I would point to the need for large animal studies to develop the technology for delivering cells safely, prudently and effectively to diseased sites in diseased organs. The kinds of treatments that we are talking about virtually could not exist without these three strong streams of animal-based research leading to the first-in-human innovations. That is an area where increased public awareness of these needs might help to shape public opinion in the future as more tolerant of the need for animal studies.

Q31 The Chairman: I would like, now, to move to the Twitter questions that we received and I think you received copies of. We are very pleased that we had a good response to this experimental request for input on Twitter. We probably will not get through all the questions in the remaining 20 minutes or so, but we will pick out some to start with and see how we get on. I hope you will be able to give us reasonably succinct answers. Some of them reflect points that we have covered already but it would be good to recap them in the context of these questions. I am going to turn to Lord Rees to put the first one from our list.

Lord Rees of Ludlow: Is there a regenerative medicine research programme with measurable and realistic goals? Should research be focused on one condition to concentrate efforts?

Professor Schneider: I would like to respond to the second of those first. In regenerative medicine, the mechanisms of benefit vary from cell replacement to indirect effects on the host tissue including blood vessel formation and wound healing. I would argue against picking one prototype disease allowing us to solve all the problems in the area. Turning to the questioner's first question—is there a good roadmap for working forward?—the UK Strategy for Regenerative Medicine, which includes not only injecting a naked suspension of cells, as it were, to the diseased tissue, but also cell-three therapies based on the hormone-like proteins that stem cells make and also engineered constructs, having more of the three-dimensional configuration of the tissue. That is a very comprehensive plan that incorporates many of the elements of regenerative medicine and it is a very good roadmap if adequately resourced.

Professor Barker: I would support those views entirely. Regarding concentrating on a few conditions within one area of medicine, in the world of neurology Parkinson's disease is an obvious target because it has a specific pathology. Targeting one condition is a sensible thing to do; we have a very useful way of taking it forward. However, one of the key challenges of the future in using cell implants to the brain, is how you measure whether your therapy has really worked in the time frame that we think about. If I give you a tablet for your high blood pressure, you would expect to see a result within a few weeks; if I put a cell in your brain to make it repair that bit of the brain, it may take five, 10 or 15 years before you see the real benefits. Thinking about how we can actually do trials better is a real challenge and that, I think, has been a problem in the American system, where trials have

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been ended prematurely based on how they see drugs working, which has had major consequences in regenerative medicine for trials across the planet.

Professor Khaw: Again, I would start with the second question first, like Professor Schneider. I think it is a mistake to say that just because a disease area is currently costing you a lot it is more important. I am not saying that it is not an important factor; it is very important. But the issue of rare diseases is an important one. The UK has a unique ability to bring together groups of rare diseases. I will give you an example: the world's first gene therapy in a human, done in the UK, was a very rare condition. It is only because we are able to gather, in the UK, these very rare conditions together that we are able to do these very early proofs of principle. Rare diseases are often incredibly good ways of finding a proof of principle for a new treatment because they are often very dramatic and very precise. Once you have that proof of principle, you can apply that principle to much more common diseases. Some of the things we have learned in gene therapy from these incredibly rare diseases could now be applicable in, for instance, potentially the treatment of the retinopathy of diabetes, which is a major blinding problem in young adults in this country. I would not stress that we should only treat diseases because they are very common. There are paradigms of disease, particularly in the UK—due to the way the health system is set up—that could make us be able to complete very effectively.

The second question, going back to the first one, was whether there are programmes with measurable and realistic goals. I think the answer from all of us is absolutely yes. The trials you have heard about, the London project and many of the other stem-cell projects have very clear goals for progressing and translating through to clinical use. Perhaps we will touch on that. I would like to raise one point about that. Translational research, which you have raised today in your Committee, is not an accident. It is something you do because you want to do it so much it burns in your heart and it hurts that you want it so much. I suppose the analogy of translational research is that it is a bridge of which every single rung has to be in position. That makes it different from some of the world-beating science that you have seen. Not to denigrate science—science is extraordinary—but to make things translate, if one rung of your long bridge is missing, you will fail. It has to be very deliberate; it has to be recognised; it has to be cultural. Often the people who put those rungs into place are not recognised or are not provided for. I think that to make translation research work, you have to want to do it so much that you put all of the rungs in position so that it works. That is how we have succeeded in some of the things we have been doing.

Q32 Lord Turnberg This question is to Professor Khaw. You may have covered some of it in your first remarks. It is about the FDA (Food and Drug Administration) granting orphan status for human embryonic stem cells for treatment of inherited macular degeneration in children's Stargardt's disease. Are we going to see this used in the UK on compassionate grounds?

Professor Khaw: Clearly, if you are a sufferer of Stargardt's, you are reading at least good safety reports so far—albeit reasonably small numbers—and you are thinking, “Can I have this treatment now, please?” This is what our patients are asking us. Obviously, for a drug to be made available for compassionate use, many things have to be in place; first and foremost, of course, you have to have enough data, on balance, to be sure that it is safe and that there is at least some evidence of efficacy. We are moving towards that but obviously that takes time. I suppose the answer to that question is that further analysis, completion of the current trials and perhaps one further trial are all needed before companies can provide

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this treatment for compassionate use. Obviously, however, it is a possibility once we reach the state of evidence where that might be possible.

Q33 Lord Wade of Chorlton: Can I ask what Stargardt's disease is?

Professor Khaw: Stargardt's disease is basically a form of macular degeneration that occurs in young people. It is a good model. Obviously, it is very tragic and very devastating for young people who lose their central vision, the vision we are all using now to read our papers and do everything, but it is a very specific condition and is relatively rare. It is obviously a very good condition in which to do an early-phase stem-cell trial.

Q34 The Chairman: Does the fact the FDA had granted this orphan status mean they have assessed the efficacy and safety of this?

Professor Khaw: Orphan status purely refers to a disease that is sufficiently rare. Going behind the thinking underlying both the European and the FDA definition of orphan, it is that nobody would develop any treatment for rare diseases if they did not make the pathway a little bit easier. The route, if you like, to licensing an orphan disease is a little bit easier. I think that is the main issue about orphan disease designation.

Q35 Lord Winston: I have Twitter running in front of me, which is why I am asking the question, and I see that more than one person has quoted Professor Yamanaka from Japan. I hope one day to use iPS cells, rather than human embryonic stem cells. I wonder if you would like to comment on that specifically, because it relates to this particular respondent as well.

Professor Khaw: Obviously we were very thrilled with the award of the Nobel Prize to Shinya Yamanaka for his very revolutionary work on iPS cells. Obviously, iPS cells have raised a lot of hope because of the fact that you can take adult cells and convert them into multipotent cells that can do various things. There are a lot of technical issues, some of which are probably beyond me, about iPS cells. There are a lot of technical hurdles with iPS cells at the moment. Embryonic cells are not used just because they are available. At the moment, we know a lot more about the current cells that we are using. Take, for example, those in the ACT trial in the London project, which are embryonic-derived and therefore we are able to move forward much more safely. With iPS-cell technology we are still very uncertain about where to go. There is obviously a lot of work being done on iPS cells and their potential for therapy. However, at the moment, we are not in a position to be able to move forward with iPS cells therapeutically.

Q36 Baroness Perry of Southwark: My question you touched on several times in your replies. I think, Professor Barker, you talked about the importance of managing people's expectations and so on. The question is this: is there a need for improved patient education on the whole subject of regenerative medicine? Should there be better science communication strategies designed to provide accurate and realistic messages about such technologies to the public?

Professor Barker: I think it is a very dynamic process because this field moves forward at quite a speed. Six or so years ago, no one knew what an iPS cell was. The term did not exist. Well, perhaps not in 2006 but a few years ago it did not. Peoples understanding of what these terms mean and what they bring to the field is very important. Education is very important, especially as we live in a world where there is often a lot of commercialisation. The situation which often happens with stem cells is that some of them get attached to

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companies and once they get attached to companies there is generally only one piece of news you will hear about those stem cells, which is good news. Again, it is this which heightens expectations: “There are lots of things out there, but if only I had access to it I would be much better treated and even cured.”

It is great when you have people like my colleagues on the panel who patients can talk to and say, “What do you think of that?” However, having a broader remit, whereby one can educate people and understand what they mean by stem cells, is important. An embryonic stem cell is different from an induced pluripotent stem cell, which is different from a neural stem cell, which is different from a bone marrow mesenchymal stem cell. These are all different stem cells; they all have used the same term and people group them together. It is important to educate people on the science: what is a stem cell? What can you do with it? It is important to educate people on where you are trying to take that therapy—taking that cell into the clinic—and the realistic expectation of what that would actually mean to a patient in the short term, and in the long term, and the risks that that brings with it.

Professor Schneider: I agree very much with the point. This is the kind of activity that we do with our partners in the NHS trusts. Indeed, on this exact topic we had a so-called Café Scientifique just earlier this month. It is important to get these concepts across. The one community that we actually have not spoken about in terms of the need for education is the GPs. This is highly specialised and rapidly evolving knowledge; finding the right mechanisms to educate them as well is as much of a challenge, and sometimes more of one, than knowing how to reach the patients.

Q37 Baroness Perry of Southwark: You are not getting much help from the press, are you? I think, as Professor Barker said, it is either a disaster or a triumph, so to speak. The amount that you can do as individuals is quite limited. You talk to specific audiences. Surely the GPs are the ones who see patients over time.

Professor Schneider: That is exactly the limitation I would point to in our activity of last week. If it was 40, 50 or 60 patients it is just a drop in the bucket. It is a worthwhile activity; reaching GPs would be important.

Professor Barker: The headline writer is who you really need to educate but of course their job is to sell copy—not to sell the true nature of the story. The articles themselves are often very accurate; it is the headline that is misleading. That is, of course, what the patient takes away.

Professor Khaw: If I may say so, one of the opportunities is the modern media. I think we have already explored how certain parts of media by necessity—or however you wish to define it—have to sell stories in a much more extreme way. However, with the increasing democratisation of media through the internet and Twitter and various other things, that does become an opportunity to present a more balanced view—at least to the public—that they can accept. The issue is availability. One of the great difficulties of modern life is where do you look? You get covered in an avalanche of data and the question is what makes somebody go to one source rather than another. I think we can resolve that. There is a beautiful section on neural stem cells; on stem cells for eyes on Eurostemcell.org. It is a nice, simple article that refers to all of the current technologies. The problem is how does the public get there? What leads them there? What do they trust as their source of information? If we can help with that guidance for the public—and also make them want to go there for other reasons—that could help a lot.

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Q38 Lord Patel: My question from Twitter relates to the impact that the European Court of Justice ruling in *Brüstle v Greenpeace* will have, in particular on investment in research, and particularly on the huge European funds which are available for research. Would you like to comment?

Professor Schneider: I think it is worthwhile turning back to Lord Winston's question about iPS cells versus ES (embryonic stem) cells to put this one in perspective. Although iPS cells in principle and in substance can adopt many if not all cell fates, both as a platform for regenerative medicine and as a platform for related activities like pathway dissection, drug discovery and drug safety testing, the question is not whether the cells can become a neuron or a heart-muscle cell or a blood-forming cell. The question is just how good are their functional properties once they have made that lineage decision?

One of the most important and instructive examples that I have seen recently on the need for continued work on human embryonic stem cells was shown at a drug discovery symposium in Manchester last month, where an investigator from industry, from AstraZeneca as it happens, was doing systematic comparisons of drug toxicity in a panel of human ES cells on the one hand and human IPS cells on the other hand, using cardiac muscle made from these different sources. It was found, for reasons not yet understood in a fundamental or reductionist way, that the findings in terms of predictions of toxicity were very strong using cardiac muscle made from embryonic stem cells and much weaker using the cardiac myocytes made from iPS cells. That is not to say that those kinds of problems will not be sorted out in future, but I just point to that as an example for now where the ES cells would clearly be out in front.

It seems reasonable to me that a company like AstraZeneca or others ought to be able to engineer human ES cells in different ways that make them particularly well-suited for the kinds of toxicology studies that they need, for the kinds of target discovery activities that they need to come up with new drugs. Currently, if they were to do that in the cell product that is best for the purpose, they would not be able to patent it. If they were to do the same manipulation in an iPS-derived heart-muscle cell, less fit for purpose, they would be able to patent it. That is one example at the drug discovery and big pharmaceutical level where the EU court decision is very destructive, putting aside all of the issues relating to human ES cell derived heart muscle as a potential therapeutic product. It would seem logical that the steps involved in bioprocessing, in ensuring genome stability in long-term processed cells, in purifying the cells to homogeneity and also to delivering them, all of that, would qualify for intellectual property protection, were it not for the latent religious objections to embryonic stem cells on the part of a small but vocal minority.

Q39 The Chairman: Are there any brief comments? I would like to come to one last question from Lord Wade in a moment.

Professor Khaw: I would comment that of course it is uncertain, but certainly one of the major partners our centre is working with, which is Pfizer, has been surprisingly robust in moving forward despite the ruling, which is encouraging. Given that sometimes a problem is also an opportunity, going back to what we heard just now about the engineering issue, modern stem-cell technology is often a complex interplay of some of the high-level technological manufacturing issues and delivery issues. For instance, we have had to design special instrumentation to deliver some of the stem-cells that we are doing.

I think if we are clever about it—let us put it that way—and work in a multidisciplinary way, there can still be the platform for investment with some protection for the companies who

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invest. That belies the issue of the technological investment that the UK makes into this field. It is not just the cell and all of the biology behind it. There is a whole raft of technological co-patenting that occurs that makes it a unique product. If the UK were also to invest in some of the co-investment, then actually the value would still be there. I just wanted to make that point.

Q40 Lord Wade of Chorlton: The Twitter question is would possible long-term benefits to society justify increasing tax breaks for promising research for regenerative medicine? I suppose the underlying question is what are the long-term funding implications for the development of this technology?

Professor Barker: I do not know the answer. It is such a complicated area because there are so many “ifs” and “buts” in what happens. At the moment, for example, there are issues to do with the withdrawal of one drug for one indication because they have suddenly found it to be very successful, and it coming back to the clinic at a higher price because they now know it works. This is always going to be an issue. Once you have found something that works, how do you market it and offer it in the best way to as many people as possible? I do not know the answer to that. If I speak for myself in terms of the world of neurology, I think these therapies will never become mainline therapies for the vast majority of people. I think they will always be kept for use in specialist centres for relatively select groups of patients. They will therefore get the funding they need, because it will be to a restricted group. It becomes different when you move it out of, say, the field of Parkinson’s disease and you have a treatment that could help everyone with diabetes or prevent them getting diabetes, because suddenly you have a vast market. How you can regulate and support that I do not know.

Professor Schneider: The need for more funding is there but I leave it to others wiser than myself to decide whether the financial instrument should be tax breaks versus grants and other kinds of mechanisms such as support through the Technology Strategy Board.

Professor Khaw: I feel very strongly about this. If you look at what we have been successful with in getting through to first in man and other successes, it has been reliant on a variety of things. If you look at the way the funding packages were put together for these highly successful first or second in the world-type initiatives that we do, it is very diverse. There has been a lot of leadership from the people who head up these programmes, who go all over the place to find the mixture of funding that you need to make this work, without which I would not be sitting here talking about our centre having these first in the world achievements for the UK.

There is no question that the partnership with the commercial sector is essential. The London project is advancing rapidly—a British-based project we had to put huge infrastructure in, from charities, from the MRC and NIHR, from a private US philanthropic donor. Peter Coffey makes the point that, so far, they have had to do 37,000 pages of documentation. No academic on the planet can do that. Even though they have all of the ideas and the science, they need support—probably from specialists in the field who tend to be located in industry. Industry needs to have some incentive to come in and work with us to write 37,000 pages of documentation. So whether it is tax breaks or other things, what is absolutely essential is support for intermediary funding, without which we simply cannot take these treatments through to clinical usage.

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Q41 Lord Wade of Chorlton: Is this an issue which you think we should look at in this report?

Professor Khaw: Absolutely, because I think it is essential for success. If I look back to the things we are succeeding in, without that degree of support to fill in this huge amount of regulation and administration that you need to do to get through this stage, we cannot possibly succeed in bringing treatments and technologies—particularly in the UK, for UK-born ideas—through to patients, in industry or elsewhere.

The Chairman: Thank you very much. Sorry that we have run over time, but it is partly a reflection of the very interesting answers you have given to our questions. It has been an excellent session. I would also like to thank all of those who sent in the Twitter feed questions. We did not get through all of them, but we had responses to at least some of them. Others were covered implicitly in the earlier responses. You will, in due course, receive a draft of the transcript for you to make any corrections. If there are any comments that you want to make in addition to those that you have made today, do feel free to write in and it will be included in the evidence that we publish with the report. Thank you very much indeed for your comments today.

King's College London (KCL) and King's Health Partners (KHP) – Written evidence

Introduction

This submission is made on behalf of King's College London (KCL) and King's Health Partners (KHP). KCL is one of the top 25 universities in the world and is the largest centre for healthcare education in Europe. KHP comprises KCL, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust and South London and Maudsley NHS Foundation Trust. Our NHS Foundation Trusts provide the full range of medical and healthcare services, from acute and specialist medical care through to mental healthcare and services that promote physical and psychological well-being. They serve a local population that is amongst the most ethnically, socially and economically diverse in the world. KHP is one of the UK's five Academic Health Science Centres, combining basic and translational health research, clinical care and education in order to create world-leading improvements in healthcare.

Within KCL and KHP the community of researchers with expertise in stem cells and regenerative medicine totals over 40 PIs. We cover all aspects of the field, ranging from clinical trials through generation of induced pluripotent (iPS) stem cells and clinical grade human embryonic (ES) stem cells to mechanistic studies with model organisms. KCL has invested heavily in staff and infrastructure and a new Centre for Stem Cells and Regenerative Medicine, covering over 1000 m² and costing over £6 million will open shortly under the leadership of Fiona Watt.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine? The UK leads the world in several respects. Our legislative framework governing donation of pre-implantation human embryos and adult tissue is widely admired. The NHS is seen as an ideal environment for clinical trials because it obviates the risk of procedures being performed for profit. Furthermore, NHS patient cohorts are well annotated and patients show commendable willingness to take part in research and clinical trials.

Where does the UK have strengths and weaknesses in the field? There are two major weaknesses. While we have a small number of internationally world-leading researchers in the field, there are a large number who are best described as mediocre. The UK still has a long way to go to encourage meaningful partnerships amongst the different constituents in the field, particularly involving laboratory-based researchers and clinicians, regulators and the commercial sector.

Who are the major funders of research in the field of regenerative medicine?

What funding is available to support this research? The major funders are the Research Councils (in particular the MRC), the Wellcome Trust and Charities such as the British Heart Foundation and Diabetes UK. Researchers are well supported to pursue their own programmes of work, but there is a need to fund more interdisciplinary research and proof-of-concept clinical research. The traditional academic measures of success, such as high-impact, senior author publications, are not always relevant to work in this area. For this reason, we would encourage ring fencing of funds for clinical application.

Reflecting the potential opportunities presented by induced pluripotent stem (iPS) cells, the Wellcome Trust and MRC are to fund a collaborative project involving KCL that aims to establish a human iPS cell resource from normal and patient groups, allowing the exploration of the impact of genetic variation on cell phenotype and ultimately providing new insights into disease mechanisms.

Application of the science

What are the current applications of the science of regenerative medicine for the treatment of disease in the UK? KCL stem cell researchers already have practical experience of moving cell based therapies into the clinic. Researchers include Jack Price (neural stem cells for stroke), Anil Dhawan (hepatocytes for acute liver failure) and Phil Harrison (dendritic cells for hepatocellular carcinoma). In addition, there are active programmes in developing cell-based therapies as an alternative to islet cell transplantation (Stephanie Amiel) and to treat Type 1 diabetes (Giovanna Lombardi and Tony Dorling). KCL also has expertise in gene therapy, exemplified by phase I clinical trials for graft versus host disease and Netherton syndrome (a collaboration between Adrian Thrasher at UCL and Farzin Farzaneh at KCL).

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver? We are optimistic that within this time-frame new treatments will become available. The first clinical trials involving derivatives of human embryonic stem cells are underway, and patient-derived iPS cells are already being used for drug discovery. Treatments involving autologous or allogeneic cells from adult tissues are already available (for example for skin, cartilage and bone repair), but are too costly and labour-intensive to be made widely available. In seeking headlines, the public sometimes overlooks the importance of steady, incremental progress – for example, in the field of pancreatic islet cell transplantation.

Barriers to translation

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: *Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Strategy Board's *Strategy for UK Regenerative Medicine* sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? We endorse the Government's strategy, particularly the creation of interdisciplinary research hubs, the workshop on regulatory hurdles, and engagement with the international research community.

However, the report fails to recognise that there is over-regulation in this area. The most substantial barrier to translation is the considerable regulatory load in the UK. Much is made in the report of the 'Stem Cell Toolkit', and how it will lead biotechnologists through the maze of regulatory hurdles. The report cites the number of 'hits' it has received as evidence of success, without recognizing that the Toolkit only draws attention to the number of regulatory authorities from which approval needs to be gained before progress to clinical trial can be made. The regenerative medicine community looks to the Government to take genuine steps to reduce this complexity. We note also that while an

Action from the report is to review the UK Stem Cell Toolkit on an ongoing basis, this has not happened. Now in September 2012, it cites the GTAC as a regulator even though they lost that role in July 2011. The regenerative medicine community will not see this report as an effective response to the over-bearing regulatory regime that discourages innovation in the UK.

What difficulties are encountered when conducting clinical trials and how could these be overcome?

Regenerative medicine products should not be treated as investigational medicinal products, since this makes it very difficult for researchers without pharma support to fulfill the regulatory authority requirements.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

Most of the cellular therapies that are developed have a very narrow spectrum or very specific indications for a small group of patients. Organizations like NICE or National Commissioning Groups are not sympathetic towards their wider use.

Barriers to commercialisation

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do? We are delighted to be able to host the TSB Cell Therapy Catapult on the Guy's Campus. It is still early days, but we believe that the Catapult has considerable potential to facilitate commercial development in the field.

What role does patenting play in the commercial development of regenerative treatments? Patent protection makes products more attractive to Venture Capitalists and the pharma industry. Nevertheless, we are not unduly concerned about the outcome of the case brought against Oliver Brüstle by Greenpeace. We consider that the main commercial benefits will be derived from technical know-how (how to differentiate cells, how to deliver them) rather than the starting material (cells).

21 September 2012

**King's Health Partners (KHP) and King's College London (KCL) –
Written evidence**

[Submission to be found under King's College London \(KCL\)](#)

Korea Health Industry Development Industry (KHIDI) evidence I – Written evidence

Author: Mr. Chang-Goo Kang

Regenerative Medicine

The research base

- **Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?**

In Korea, government and industrial sectors are investing in regenerative medicine R&D

1. Government sectors are the Ministry of Health and Welfare (MoHW) and the Ministry of Education, Science, and Technology (MEST) : The R&D investment, focused on stem cell research, of these two ministries in 2012 has been about 94 million USD.
2. Industrial sectors are Medipost (www.medi-post.com), Pharmicell (www.pharmicell.com), and Anterogen (www.anterogen.com) : The Korean FDA has approved 3 stem cell therapy products developed in 3 companies stated above.

Barriers to commercialisation

- **What is the current, and potential future, commercial value of the sector? What is its value to society?**

Regenerative medicine including stem cell therapy can serve as a new therapy for the incurable and rare diseases which are currently incurable with conventional therapies.

- **Does your Government, where there is market failure, provide incentives to attract investment in companies working in this high risk area?**

Korean government requires a certain percentage of industrial matching funds for R&D investment. For the R&D in Stem cell and Regenerative medicine, the requirement of the industrial matching funds is lower than standard to attract the company to invest in the high-risk R&D area.

27 December 2012

Korea Health Industry Development Industry (KHIDI) evidence 2 – Written evidence

Author: Mr. Chi-Goo Kim

Regenerative Medicine

Barriers to translation

- **What difficulties are encountered when conducting clinical trials and how could these be overcome?**

Ethical problem is the most and the first barrier to be overcome. To promote researches related to the regenerative medicine, it has to be considered to be less restrictive in legislation for stem cell researches, biomaterial resources, and ethical problem.

- **What other difficulties are encountered conducting translational research within national healthcare systems and how could these be overcome?**

In Korea, most of the researches are still in the status of basic scientific researches. Translational research cannot be conducted until the researchers focus on the mission-oriented, or purpose-oriented projects for keeping on their researches. Government or the R&D funding agencies are required to develop the strategy for conducting translational researches by pushing the purpose-oriented researches as well as researches to satisfy the unmet need from the national healthcare system.

- **What barriers are encountered when seeking approval for the use of such treatments in national healthcare systems or through private healthcare?**

Ethical issues in dealing with human biomaterials including legislation and safety issues.

Barriers to commercialisation

- **What is the current, and potential future, commercial value of the sector? What is its value to society?**

Regenerative medicine has a value in using self cells, fast and highly-adoptive therapeutic approaches compared to the traditional researches to solve health-related problems. It also opens a new possibility to cure for the previously incurable diseases which could not be effectively treated in present societal health system.

- **Does your Government, where there is market failure, provide incentives to attract investment in companies working in this high risk area?**

Governmental R&D support in the high-risk areas is increasing in Korean to promote more challenging projects. Recently adopted 'Fail although sincerely performed' projects by final evaluation make researchers possible to challenge frontier projects in high risk area.

- **What role does patenting play in the commercial development of regenerative treatments?**

Patenting is essential for the commercialization of the regenerative medicine. To generate profit, IP of the therapeutic treatment has to be secured first, and following researches have to be continuously conducted to make a positive circulation of research-commercialization-funding. Patenting would be the key factor to create this circulation.

- **What are the barriers to securing finance to develop such treatments?**

Uncertainty for the R&D success and possibility for commercialization.

International comparisons

- **Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?**

Not sufficient, but pretty much efforts to harmonize between standards and regulations. It seems that much more efforts in regulations in many countries.

27 December 2012

Lawford Davies Denoon (LDD) – Written evidence

Authors: Alex Denoon and James Lawford Davies

Lawford Davies Denoon (LDD) is a law firm specialising in life sciences. We have a particular focus in regenerative medicine and cell therapies, advising on a range of regulatory, commercial and intellectual property issues relating to research and products in this sector. We are fortunate to advise a large number of academic institutions, private companies, charities and NHS organisations active in this area. We also act for a number of companies outside the UK which either operate in the UK/EU or are thinking about doing so. The research pursued and products developed by our clients also arise in a variety of different areas, whether autologous or allogeneic, adult, fetal, embryonic or induced pluripotent cells. In this context, we believe that we have a good insight into a range of factors which both facilitate and inhibit the growth and development of regenerative medicine in the UK and we hope that our observations below are useful.

We are very pleased to have the opportunity to respond to the Call for Evidence in relation to the on-going inquiry into regenerative medicine. We have only sought to answer the questions which are firmly within our area of expertise. We are aware of other submissions which will address the scientific and translational questions in detail and we do not propose to repeat those analyses. Instead, we have focused our submissions on intellectual property and regulation in the context of commercialisation.

Barriers to commercialisation: Intellectual Property

Brüstle v Greenpeace

We wanted to write in relation to the discussion generated by the decision of the Court of Justice of the European Union in the case of *Brüstle v Greenpeace* (18 October 2012). In discussing this topic we will address a number of the specific questions raised in the Call for Evidence.

In the *Brüstle* case, the court concluded that inventions which use human embryonic stem cells as a base material are not patentable on morality grounds. Without seeking to comment on the merits of the decision or the proper interpretation of the EU Biotechnology Directive, we wanted to comment on the practical ramifications of the decision for those developing therapies based on embryonic stem cell material.

Some have contended that the unavailability of patent protection spells the death knell for embryonic stem cell research on the basis that the outputs of such research cannot be adequately exploited without patent protection. Opponents of embryonic research have extended this reasoning to seek to restrict funding for such research or therapies on the basis that this is not commercially viable.

It is axiomatic that the crucial role of a patent in respect of a medicinal product is to attempt to provide the inventor with a monopoly period within which third parties cannot sell a competing product. The societal justification for this is to ensure that developers of such products are rewarded for the enormous effort (not to mention inherent risk) required to bring a new medicinal product to market.

We do not seek to trivialise the ancillary value that a patent can deliver, but it is important to focus on the primary role of the patent, namely to prevent *generic* competition. As a result, one needs to consider the barriers that a developer of a generic version of a stem cell therapy might encounter.

We shall use the term Advanced Therapy Medicinal Product (**ATMP**) to refer to a stem cell therapy which has been granted marketing authorisation in Europe as an ATMP pursuant to Regulation 1394/2007. We will also refer to a generic version of such an ATMP by the statutory terminology, namely a **biosimilar**.

In order to obtain approval for a biosimilar version of an existing ATMP, one must establish that the biosimilar is “bioequivalent” to the original ATMP. While the clinical assessment of the biosimilar would be significantly less than the requirements of three phases of clinical trials, it would be necessary to conduct some clinical trials of the biosimilar as compared with the original ATMP.

It is instructive to note in this context that only about half of the applications for biosimilar versions of existing monoclonal antibody medicinal products have been approved to date. A monoclonal antibody is significantly less complicated than a stem-cell based ATMP. As a result, it is difficult to imagine any regulator approving a biosimilar version of an embryonic stem cell ATMP.

It is also notable that:

- a biosimilar cannot rely on the clinical data supplied in respect of the original ATMP for at least 8 years after the original ATMP was granted a marketing authorisation; and
- even if the biosimilar could satisfy the requirements mentioned above, it would not be granted a marketing authorisation for at least ten years after the original ATMP was granted a marketing authorisation.

As a result, companies developing embryonic stem cells may be liberated from the tyranny of a 20-year patent life.

While one cannot deny that this case has had an unsettling effect on the sector, we believe that it is more nuanced than some have suggested and we wanted to ensure that any response to the decision in *Brüstle* is fully informed.

We would commend the joint statement from the Association of Medical Research Charities, British Heart Foundation, European Science Foundation, European Genetic Alliance, Medical Research Council, Parkinson’s UK and the Wellcome Trust in relation to this topic.

Barriers to commercialisation: Regulatory

There are very good reasons why the UK regulates research and product development in the way that it does. We have a mature regulatory framework, largely shaped by many years of evolution and policy development in the UK, though increasingly influenced by EU law and regulation. This maturity gives our regulatory landscape its strength and depth,

based as it is on a solid foundation of policy and consultation over many years. However, the same decades of development have also resulted in a complex, multi-tiered regulatory framework which can be confusing, expensive, inconsistent and uncoordinated in its application.

There are many critics of the UK system. Most criticisms, however, focus on comparatively minor or specific issues and fail to take into account the broader framework. While we have no doubt that many of these specific issues could be very helpfully addressed, most of our clients consider that the existing regulatory framework for regenerative medicine is, on balance, adequate and proportionate. However, we are concerned that the perceived complexity of the UK framework is a significant disincentive to international researchers and companies looking at opportunities in Europe: on a number of occasions we have found that companies keen to come to the UK have been put off when they learned more about the UK's regulatory framework. In the course of developing a cell therapy product in the UK, it is possible that a company might have to apply to, engage with, seek approval from, and/or pay fees to:

- The Human Fertilisation and Embryology Authority (HFEA)
- The Human Tissue Authority (HTA)
- The Medicines and Healthcare Products Regulatory Agency (MHRA)
- The European Medicines Agency (EMA)
- Research Ethics Committee(s)
- The Gene Therapy Advisory Committee (GTAC, part of the NRES)
- NHS Research and Development Office
- Health and Safety Executive
- Home Office Animal Licensing Inspectorate

This can be a daunting, expensive prospect.

Similarly, a lack of coordination (and in some cases inconsistency) among the different regulators in relation to various issues regarding the procurement, storage, derivation, trials, manufacture, clinical use and vigilance and reimbursement of regenerative therapies have given rise to serious concerns on the part of our clients. This is amplified by the fact that some of the regulators are European while others are national authorities. Related to this, there is no mechanism for resolving conflicting advice from different regulators: there is no pre-eminent regulator at EU level.

A very simple example of this arises in the context of consent for the donation and use of human tissue. There are a large number of laws (often with conflicting objectives and requirements) that need to be taken into account. Data protection laws would require narrow, specific consent (with the possibility of re-consent), while intellectual property considerations would require a single broad unqualified consent. The EU Tissues and Cells Directive demands traceability, while data protection laws allow for the right to be forgotten. Neither of these sit well with the obligations of healthcare professionals in relation to disclosure of unexpected results. Conversely, in some cases disclosing the purpose for gathering the data may influence the results. Clients seeking to reconcile these considerations have no mechanism to seek resolution of these requirements.

In our experience, this lack of coordination is already inhibiting progress in the sector in the UK, and prevents the UK from taking a stronger role in the sector. We are aware of a number of research projects and clinical trials that have been commenced in other jurisdictions as a result of uncertainty regarding the application of the existing regulatory framework, and/or its complexity.

In order to avoid this further jeopardising the UK's standing and future opportunities in the sector, and bearing in mind the proposed reforms of some aspects of the regulatory framework, we respectfully suggest that the Select Committee recommends that:

1. the proposed new Health Research Authority be tasked with:
 - a. actively promoting novel therapies; and
 - b. chaperoning novel therapies through the regulatory framework and resolving inconsistencies;
2. the various regulators involved in all stages of regenerative medicine therapies be required to meet on a regular basis (eg quarterly or every six months) with the specific objective of resolving inconsistencies or potential inconsistencies and simplifying the path to market; and
3. patient representatives are involved in decision-making regarding future developments.

20 September 2012

Lawford Davies Denoon, Professor Peter Andrews, University of Sheffield and the Intellectual Property Office – Oral evidence (QQ 196-213)

Lawford Davies Denoon, Professor Peter Andrews, University of Sheffield and the Intellectual Property Office – Oral evidence (QQ 196-213)

[Transcript to be found under Intellectual Property Office](#)

Leukaemia & Lymphoma Research – Written evidence

1. Introduction

1.1 Leukaemia & Lymphoma Research welcome the opportunity to respond to the Lords Science and Technology Committee inquiry into Regenerative Medicine.

1.2 Leukaemia & Lymphoma Research is the UK's largest blood cancer charity with a current £65 million commitment to research. Our 260 active research projects around the UK cover areas such as improving the diagnosis of blood cancers and developing new treatments. We receive no government funding and rely entirely on voluntary support.

1.3 Our current grant portfolio includes research into production of human stem cells for transplantation, better management and reduction of side effects of Graft versus host Disease GvHD and research into individualised and less toxic blood cancer treatments.

Our response is primarily concerned with the barriers to translation of scientific research and difficulties when conducting clinical trials which are ultimately barriers to improving outcomes for blood cancer patients. In that respect we have identified three main obstacles in this area:

- complexity and cost of regulation
- lack of skills and infrastructure
- recruitment of patients

1.4 Our views and recommendations are drawn from the experience of our research grant holders and early insights from the Trail Acceleration Programme – an innovative approach to clinical trials that Leukaemia & Lymphoma Research launched with £2.3million investment earlier this year.

2. Issues affecting research into blood cancers

2.1 Every 20 minutes one person in the UK is diagnosed with a blood cancer – around 30,000 people are diagnosed in the UK each year. Each year blood cancers kill more than 12,000 people in the UK – a higher toll than from breast and prostate cancer.

2.2 90% of all stem cell transplants are for blood cancer patients. Although it may be the only hope of a cure, it is a very intensive treatment which has many risks. For instance, 40% of siblings and 60% of unrelated recipients get significant GvHD.

2.3 Clinical trials are vital for moving breakthroughs discovered in the laboratory into new treatments but only 6% of blood cancer patients take part in clinical trials in the UK, compared with up to 18% for patients with other forms of cancer.

2.4 Early phase trials (I and II) are underrepresented for blood cancer patients in the UK and this is causing a bottle neck that prevents new treatments getting to blood cancer patients, when they most need them.

2.5 Clinical trials in the UK, particularly in blood cancer, are difficult to set up and slow to deliver results. Currently it can take anything from four to ten years to complete a trial and analyse the results. This is for a number of reasons including lack of staff resources, the necessary bureaucracy around getting new protocols off the ground, and the fact that blood cancers as individual diseases are relatively rare.

2.6 There are growing concerns among research community that fewer and fewer clinical trials are being run in the UK as pharmaceutical companies choose to take these studies further afield into Europe and Asia, where trials are easier to set up. This means that patients with blood cancer are missing out on access to new drugs and treatments in the UK.

3. Barriers to translation of scientific research and setting up of clinical trials

3.1 Academically the UK is leading the world in the development of cell and gene therapies for a wide range of inherited and acquired disorders including blindness, deafness, degenerative neurological conditions and cancer. However, its inability to rapidly translate scientific findings into early phase clinical trials remains a major hurdle.

3.2 Clinical trials are currently over-regulated in the UK with disproportionate regulation designed to mitigate the risk to patients recruited to trials and the Sponsor of clinical trials. Dr Emma Morris, Co-Director of R&D for the Royal Free London NHS Foundation Trust, Advanced Therapies Theme Lead at the newly formed UCL Clinical Trials Unit and Chair the Joint UCL, UCLH, RFH Gene Therapy Safety Committee for Clinical Trials, is one of the current Leukaemia & Lymphoma Research grant holders. She commented:

“A number of recent initiatives have been designed to help, such as MRC DPFS and DCS pathways, TSB Cell Therapy Catapult Centre, NIHR support for Rare Diseases, Harmonisation of sign-off for NHS permissions and R&D approval for trials involving multiple sites. However, the reality remains that trial set-up - ethics approval, NHS permissions, including contracts, sponsorship agreements and dealing with HTA/Blood and Tissues Directive - takes as long as the steps taken to optimise clinical scale production of cells for clinical use.”

3.3 Professor Paul Moss, Head of the School of Cancer Sciences and the Birmingham CRUK Centre, University of Birmingham, is another Leukaemia & Lymphoma Research grant holder. He reported some improvements in the approval process, particularly in working with the MHRA which now have a one month turn around, though the concerns about the efficiency at the local level remain:

“NHS is generally getting better. Local R&D offices are still too slow. In many cases it appears that they are under no obligation to act with appropriate timing. Indeed, much of the difficulties relate to local institutions over-interpreting regulations. It is no exaggeration to say that for every professional that wants to drive development of a new gene/cell therapy trial, there will be 20 people working on regulation.’

3.4 The complexity of regulation inevitably increases the costs. The modest early phase 'safe' trials cost up to 0.5 - £1 million and the outcome is simple - many fewer trials are done and they take longer to get into practice.

3.5 It could be argued that high costs and complexity of regulation originate from setting the sector on the wrong path by modelling it on the pharmaceutical industry. This is inappropriate when working within a university or NHS setting, as Professor Francesco Dazzi MD PhD, Head of Stem Cell Biology at Imperial College pointed out:

“The regenerative medicine and cell therapies are massively regulated and that is inherited from big pharma where the regulation is extremely strict. That means costs are extortionate for an academic or NHS based institution.”

3.6 Professor Moss highlighted that the ethical position in society is also very confusing:

“Almost everyone seems to fall into the 'default' position that every possible attempt must be made to regulate every step. I would see it very differently: money is limited in society and we must do what we can with it to treat patients with incurable disease. It is not ethical to waste this on unnecessary regulation. “

3.7 There is a lack of infrastructure for the development and GMP grade manufacture of cells and biomaterials for clinical trials within the UK academic and NHS sectors. In the absence of sufficient facilities, many aspects of the trial are outsourced to a few commercial companies (e.g. GMP grade viral gene therapy vector production), which escalate the overall cost of carrying out the trial.

3.8 There is also a lack of investment in training specialist staff, doctors and nurses, to run such facilities and support delivery of early phase trials. Dr Emma Morris commented: “The majority of hospital based R&D staff, and indeed some staff at the UK MHRA have a poor or limited understanding of the scientific and clinical risks of Advanced Therapies and novel biomaterials.”

3.9 Finally, it is difficult for a single hospital to recruit enough patients onto a particular trial that has very specific requirements, often meaning that some trials are never completed. There is currently no incentive for NHS to help patient recruitment as the impact on the outcomes is longitudinal rather short-term.

4. Trial Acceleration Programme

4.1 To address some of the difficulties in setting up clinical trials, improve access to new treatments and increase blood cancer patients' chances of survival, Leukaemia & Lymphoma Research recently launched Trial Acceleration Programme (TAP) - an innovative network that links 13 leading hospitals in the UK²⁰³ giving patients the opportunity to take part in a national clinical trial and have access to cutting edge treatments at their local hospital, wherever they live within the UK, within shorter time scales.

4.2 The TAP is coordinated from a central hub in Birmingham by an expert team skilled at setting up clinical trials to ensure that we cut through bureaucracy and ensure that new trials open at each of the 13 treatment centres simultaneously.

²⁰³ Southampton General Hospital, Barts Hospital London, The Christie Manchester, King's College London (King's Guy's, St Thomas'), St James' University Hospital Leeds, Queen Elizabeth Hospital Birmingham, Hammersmith Hospital London, Belfast City Hospital, Gartnavel General Hospital Glasgow, Royal Liverpool University Hospital, Churchill Hospital Oxford, Cardiff University Hospital, Nottingham University Hospital

4.3 Running trials at all the 13 centres also increases the catchment area meaning that each trial meets its recruitment target more efficiently, and the results are delivered faster. Each TAP centre has a dedicated research nurse and data manager to look after patients on our trials and to get the results processed more quickly

4.4. Government representatives, including Sir Mike Richards and National Cancer Action Team, are aware of TAP and have shown interest in its concept. The pharmaceutical industry has recognised it as a potentially paradigm-shifting model of how to effectively deliver early phase clinical trials in the UK. Through TAP we plan to nurture the relationship with the pharmaceutical industry and lever potentially life-saving new blood cancer drugs that can be tested in patients, at little cost to the charity and the NHS.

4.5 Working in partnership with the pharmaceutical industry, TAP will make over £50 million of new life-saving drugs available to patients across the UK. TAP also has long-term benefits to UK industry with the potential for creating hundreds, or even thousands, of new jobs.

5. Conclusions and Recommendations

5.1 Regenerative medicine and stem cell therapies have the potential to dramatically influence for the better the health and wealth of the nation. We therefore welcome Government support for this area and commitment to develop a UK national strategy for regenerative medicine.

5.2 To bring sustainable and long-term development of the sector we recommend that:

- Patient outcomes should be at the heart of a UK national strategy for stem cell therapies and regenerative medicine.
- Regenerative medicine and stem cell therapies are fast growing area and regulation needs to keep up with current developments and be fit for purpose if it is to be a stimulus rather than a hindrance to the sector.
- We need to train doctors and nurses to understand stem cell therapies and the process of clinical trials.
- Government should do more to increase access to clinical trials and raise awareness of benefits to patients of regenerative medicine.
- The UK MAHR should broad its remit to include helping set up innovative trial protocols.
- Infrastructure for development and manufacturing of new treatments, including clinical trials, needs to be shared and jointly managed by institutions to maximise its efficiency and use. Funding bodies must be prepared to invest in infrastructure and regulatory teams to support studies. Lessons from the Leukaemia & Lymphoma Research TAP model could be shared across other cancers, even other diseases.

We would be happy to provide further information and expand on any of the issues mentioned above. We would also welcome the opportunity to invite the Committee

Members to visit one of our research centres and experience first-hand how our ground-breaking research is benefiting patients and to find out how our innovative TAP model could be rolled out to other cancers, and even other diseases.

20 September 2012

LGC Limited – Written evidence

Author: Dr. Maria Chisholm, Head of Commercial Development & Partnerships, Measurement Research, LGC

About LGC

1. LGC, previously known as the Laboratory of the Government Chemist, was privatised in 1996 and has since extended its scientific reputation through substantial internal investment, grown revenue 10-fold and created many hundreds of new jobs for the UK. LGC is now one of the leading private science facilities in the country, employing over 1600 individuals undertaking chemical and biological analytical and measurement services for industry and governments on an international scale, with operations in Europe, Asia, Africa, the Americas and the Far East.
2. Through our role as the designated National Measurement Institute for chemical and biological metrology, we have a strong reputation for the delivery of high quality measurement science, producing robust and reliable methods and standards that underpin several sectors. Our link with the Regenerative Medicine (RM) sector dates back several years to the earliest examples of commercial exploitation of RM research in the UK, and LGC was instrumental in the delivery of the first Publicly Available Specification with the British Standards Institute and other members of the RM community (BSi PAS 83), as well as more recent PAS publications (PAS84, PAS93), providing guidance to companies operating in this domain.
3. LGC chairs the BSI RGM/I standards committee, which is a national committee that acts as a forum for stakeholders to identify overlapping and common standardisation interests, with a view to agreeing priority work items for the UK. This will act, in the short to medium term, as a forum for the development of new industry guidance documents, to aid the UK regenerative medicine industry. The accurate characterisation of biological RM products is a particularly important but technically challenging requirement that will underpin the successful commercial exploitation of effective and safe RM therapies. LGC is a leading force in developing robust measurement solutions to support this industry, promote trade and protect the consumer.

Research base & application of the science

4. The UK has a broad and dynamic research base operating in various domains of RM, covering all elements of the “value chain” from product discovery through to large scale manufacturing, distribution and clinical application. We perceive the UK’s research in this domain as competitive and internationally well respected. This reflects the relatively high levels of investment that have been directed to the field both by government and industry over the past decade.
5. However, there have only been a very small number of successful product launches to date, although there are signs that an increasing number of RM products are nearing the final stages of clinical trials. There has been relatively little therapeutic delivery and hence commercial return, at least in the area of cell therapies, despite significant Research Council support since 2003, increasingly promoting a more translational R&D

funding agenda. We remain convinced that there is realistic potential for RM to bring major step-change advances in therapeutic benefit, but perhaps not quite to the extent that is being claimed by some researchers who promise a panacea of revolutionary therapies, and may be creating an environment of somewhat over-ambitious expectations (possibly reflecting the still early stage of development of this field).

Barriers to translation

6. So there continues to be a significant weakness with regards to translating this research into commercially viable products and companies. Part of the difficulty with translating a RM invention that looks promising in a particular laboratory setting to large scale production and clinical application is the lack of full understanding of critical attributes that influence therapeutic activity and consequently the lack of measurement tools and standards to accurately measure those attributes for the purpose of quality control.
7. For the last 6 years LGC has worked on this challenge with support from the National Measurement Office, the European Metrology Research Programme and the Technology Strategy Board, in collaboration with other centres of expertise in translational research. However, we think that significantly more effort and government funding is required to deliver reliable measurement solutions and quality control systems to help innovators meet regulatory requirements and bring safe and effective RM products to market.

One cannot manufacture what one cannot measure

8. Further work is required to:
 - Fully understand the mode of action of these therapeutic products
 - Determine the critical attributes of the therapeutic product and the manufacturing process that need to be controlled to assure product quality, activity and safety
 - Develop robust methods for measure those attributes to ensure high quality products, patient safety and sustainable (and economic) commercial production.

There are for instance some major challenges associated with ensuring cell quality (and genetic stability), and defining appropriate product release criteria based on robust characterisation methods.

Barriers to Commercialisation

9. A major challenge for RM innovators is in securing finance to perform the necessary and costly steps to achieve regulatory compliance (including clinical trials) and establish the infrastructure for full scale production. This finance is not easy to secure, particularly in the current risk-averse economic climate. There is a need for innovators to “de-risk” their inventions and provide strong evidence (scientific measurement data) of the robustness of their product, through extensive pre-clinical evaluation, in order to place them in a strong position to secure finance for commercialisation. LGC, through its National Measurement Institute function, has the appropriate capability and specialised skill set to help innovators “de-risk “ their products and hence facilitate access to finance for commercialisation.
10. There is still a relatively low level of investment by the larger established pharmaceutical companies in this domain, and RM represents a significant shift in the traditional pharmaceutical business model. The UK needs to identify appropriate new business models that will lead to a sustainable RM industry in the long run. We know from our work on the TSB-funded BRITS project that there are numerous obstacles that innovative (usually small) RM companies face even once finance is secured to progress

with the commercial development of their product. A particularly significant challenge is that of managing the organisational changes (people, skills and facilities) required to progress from the initial stages of pre-clinical product development to larger scale production for clinical trials and ultimately to full scale manufacturing capability. The BRITS project seeks to develop a set of management tools to support cell therapy companies with the planning and design of their business, to maximise commercial success.

11. There is a strong practical and economic case, we believe, for RM innovators embarking on commercial development to outsource the manufacture of their products to reputable contract pharmaceutical manufacturers that have established processes, skills and infrastructure to conduct this work and comply with regulatory requirements. There is a high financial risk associated with developing this capability in-house, and large contract manufacturers can achieve economies of scale that are not achievable by small bioprocessing establishments. Our view supports observations made in the BIS 2011 report “Taking Stock of Regenerative Medicine”, which mentioned that a large number of (small) UK bioprocessing centres have been established over the past 20 years, but these struggle to perform efficiently. As part of the BRITS project LGC’s Process and Operational Efficiency team is working with a leading multinational pharmaceutical contract manufacturer to develop a modelling capability to simulate manufacturing processes for cell therapies, optimise the associated resources, and maximise efficiency (thus minimising costs).
12. We believe that continued government support will be critical for the translation of UK RM science into a commercially successful industry by:
 - Helping to deliver and maintain a reasonable and practical regulatory environment for product validation and acceptance (enabled by appropriate measurement solutions)
 - Creating a favourable environment for inward investment and retention of UK expertise
 - Addressing the risk-averse funding climate
 - Supporting the NHS to adopt RM technologies (currently limited by the absence of clear care pathways and the relatively high cost of RM treatments).

20 September 2012

LGC, Genetic Alliance UK and Consulting on Advanced Biologicals (CAB) Ltd – Oral evidence (QQ 330-342)

LGC, Genetic Alliance UK and Consulting on Advanced Biologicals (CAB) Ltd – Oral evidence (QQ 330-342)

[Transcript to be found under Genetic Alliance UK](#)

LGC Limited – Supplementary written evidence

This memorandum has been prepared by Dr Julian Braybrook, Director of Strategy, Measurement Research, LGC.

In your view, does the current regulatory regime strike the appropriate balance between ensuring standards of safety and efficacy, and encouraging innovation?

Getting the right way forward on regulations is important. The regulator has to balance risk and reward; and innovation and safety. These are difficult balances. There has to be a level of public debate on the role of the regulator and the balance of innovation and safety.

It is necessary to do the right kind of science to help the regulator make the correct decisions. In particular there has to be a shared definition by key stakeholders of the problems to be addressed and the method(s) used to address them – if we don't do that no one will believe the results (e.g. 'comparability' assessment).

This links closely with the need for support through guidelines, Publicly Available Specifications (PASs)/pre-standards or common standards.

Standards are important enablers and the UK shows leadership in this area.

'You can only control what you can measure' – successive studies have demonstrated that the amount of innovation activity in business sectors increases with acquisition of measurement knowledge. Where measurements are performed incorrectly, significant costs are incurred and quality of life can be affected adversely. The regenerative medicine landscape is dominated by small and medium enterprises that can ill afford such adverse impact.

The aforementioned activities provide a valuable de-risking resource, particularly for emerging and early stage companies and researchers looking to capture and define their product development pathway and requirements for regulatory compliance.

How does the UK regulatory regime compare with other countries – both within and beyond Europe?

Having a solid regulatory regime, which other countries beyond Europe have largely based their legislation, should not be under-estimated as an important asset (complexity or not!), provided that it is articulated and demonstrated to be as much.

Working with international colleagues in the development of standards to support legislation is essential due to the international marketplace.

Effort is required now to increase UK industry understanding of the issues relating to manufacturing and supply at scale.

Complementary to this is the issue of process quality; what is required to control the manufacture of a high quality regenerative medicine product? The emergence of "Quality by

Design (QbD)" as a manufacturing best practice discipline needs to be developed and underpinned by standards. Again, the first to determine QbD and put this into action will be the ones who are successful in dominating the industry in the early stages. Furthermore, large pharma will not pick up a process that it does not think it can manufacture or control and get out of the regulatory package. This is a real gap in the system right now and requires significant investment, alongside government R&D investments, to develop:

- a strategic view on the necessary standards to underpin QbD, probably in collaboration with the Cell Therapy Catapult
- a delivery plan to produce these standards.

16 January 2013

Life Science Investment Organisation of UK Trade and Investment – Written evidence

- UK Trade and Investment (UKTI) has established a dedicated unit to support overseas investment into the UK from the earliest research collaborations through to clinical trials, commercial operations and development partnerships. The team in the UKTI Life Science Investment Organisation (LSIO) helps overseas companies navigate the UK investment environment to become established and expand in the UK. The team's objective is to enable overseas investment into the UK to improve the UK's life science ecosystem, benefiting both businesses and patients through the development and commercialisation of innovative life science and health products and services.
- The LSIO is working to attract inward investment into regenerative medicine in the UK. The UK's world-class regenerative medicine capabilities represent a timely opportunity to attract further foreign investment into the UK and the LSIO is actively engaging with such opportunities through the UK's Embassies and Consulates worldwide.
- Foreign investment would enable the commercial exploitation of the UK's science and technology research base in regenerative medicine to generate increased growth in the UK's Life Science sector.

The Commercial Opportunity

With an ever ageing population, suffering from an increasing burden of chronic degenerative diseases, there is a growing unmet medical need to discover, develop and then practically apply new disease-modifying treatments and therapies in a cost-effective way. Regenerative medicine is a technological response to this unmet medical need by using new and existing methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function. Consequently, there is an emerging commercial global market for cell therapies, tissue engineering, gene therapy and biomedical engineering techniques to complement the use of pharmaceuticals, biologics and devices, which are also needed for effective tissue regeneration. The UK is positioning its research base to facilitate the translation of its fundamental scientific knowledge into effective treatments but also needs to engage with the commercial opportunities that are required to practically apply such capabilities for the benefit of patients and the economy. Furthermore, an understanding of future reimbursement mechanisms for such new technologies is an essential component of assessing the overall long-term commercial opportunity for the UK and for businesses planning to invest, expand or set-up here. Consequently, the current inward investment opportunities are mainly focused on accessing the UK's existing research base through early stage research and development collaborations and partnerships, as well as promoting the UK's capabilities in bioprocessing and biomanufacturing.

The LSIO's Strategy for Regenerative Medicine

Working with the Office for Life Sciences (see Supplementary Evidence on the UK Capabilities from the Department for Business, Innovation & Skills and the Department for Health, dated 16th January 2013), the LSIO has assessed the UK's existing capabilities in regenerative medicine from a commercial perspective, is promoting the UK's current

capabilities and is continuing international inward investment discussions with interested companies. The LSIO launched its new UK Life Science Prospectus in December 2012 to promote the overall investment opportunities into the UK, which includes regenerative medicine. In 2013, The LSIO has also launched its new inward investment propositions for Stratified Medicine and Dementia Research and will launch similar campaigns for Medical Technologies and Experimental Medicine, all of which encompass key aspects of regenerative medicine. The LSIO is currently working to define new opportunities for the UK's projected future strengths in this rapidly evolving field and the potential to translate these capabilities into commercially tractable opportunities for the global healthcare industry to invest in and partner with the UK. Consequently, the LSIO will launch further messaging on regenerative medicine research later in 2013, capitalising on new developments from Sir John Gurdon's joint Nobel Prize last year (see the LSIO's UK Life Science Prospectus) to the projected opening of the new facilities for the Cell Therapy Catapult later on this year. This messaging will focus on the use of stem cells as research tools across the Life Sciences Sector through to the potential new opportunities in cell-based therapies now opening up in the UK, as well as longstanding strengths in tissue engineering, gene therapy and cell culture and bioprocessing. Nevertheless, it should be borne in mind that relatively few companies focus solely on the technologies of regenerative medicine and the potential UK investment opportunity must be put into the context of the commercial world, which is often focused on a particular therapeutic area using a variety of complementary approaches to manage a particular disease.

The LSIO's Business Development Process

Based on UKTI's initial work on the regenerative medicine subsector opportunity last year by its sector specialists, the LSIO, once formed in mid-2012, identified this opportunity as a key area of focus to promote the UK to overseas investors. To date, the LSIO have mostly refocused UKTI activities through the targeted business development themes described above, which will be complemented with further more detailed targeting on regenerative medicine research later on this year. Nevertheless, through the UK's Embassies and Consulates worldwide, UKTI have actively pursued regenerative medicine projects for many years. However, smaller companies focused on regenerative medicine tend not to be so well funded, so active inward investment projects can stall easily and smaller research and development collaborations are a more tractable solution for companies to invest in and partner with the UK. There is also considerable interest from international academic and public sector organisations to find partners in the UK. As examples, the Science and Innovation Network and UKTI teams in Boston brokered a significant partnership between the UK Stem Cell Bank and the University of Massachusetts Human Stem Cell Bank and Registry focused on standards, training and commercial opportunities in March 2011; and the Medical Research Council (MRC) and California Institute of Regenerative Medicine (CIRM) have partnered on a UK-California collaborative opportunity in translational stem cell research. Some specific examples of business development activities are highlighted below:

- 1) UKTI has co-ordinated a number of Inward Missions from overseas organisations (most notably from India) wishing to investigate the capabilities of the UK regenerative medicine industry with a view to establishing research and development collaborations.
- 2) UKTI has also helped a number of UK regenerative medicine companies access partners and funding opportunities overseas through trade missions and seminars focused on regenerative medicine over the last few years.

- 3) UKTI team members have made focused overseas visits (most notably in India, Korea and Japan) to meet with companies in order to generate new opportunities and enhance the UK's reputation in regenerative medicine. They have also organised round-table discussions with key stakeholders in selected overseas markets.
- 4) UKTI in the USA are involved in promoting the UK's regenerative medicine capabilities to encourage inward investment, as well as research and development collaborations. Promotion of UK leadership in stem cells and regenerative medicine has also been a key theme for the US Science and Innovation Network (SIN) team for several years. UKTI and SIN have supported visits of leading UK-based key opinion leaders and partner organisations, like the Technology Strategy Board and HealthTech & Medicines Knowledge Transfer Networks, to the USA. Examples include:
 - a. UKTI and SIN worked with the Technology Strategy Board, and the HealthTech & Medicines Knowledge Transfer Network to bring a UK regenerative medicine mission to the US in 2010 to promote the UK's capability and to identify global barriers affecting the commercialisation of stem cells and regenerative medicine.
 - b. The SIN and UKTI teams in San Francisco and Los Angeles hosted a Clinical Trials Road Show in March 2013 to promote the UK as a destination of choice for translational research and clinical trials, with a special focus on regenerative medicine. Representatives from the Cell Therapy Catapult, the NIHR Office for Clinical Research Infrastructure, UK research base, and UK regulatory experts participated.
 - c. The Cell Therapy Catapult is attending the BIO Convention in Chicago in April 2013. UKTI are using promotional materials provided by the Cell Therapy Catapult to raise the profile of the Cell Therapy Catapult and explain the offer to global businesses.
- 5) UKTI and the Cell Therapy Catapult are starting to work jointly on both the promotion and delivery of inward investment projects.
- 6) Scottish Enterprise and Scottish Development International have been promoting opportunities for international investment into Scotland in stem cells and regenerative medicine and UKTI has worked collaboratively with them to support active inward investment projects.
- 7) SIN continues to work closely with UKTI globally to promote the UK's regenerative medicine capabilities and facilitate links between researchers, research funders, regulators and businesses.

Conclusions

While the UK has underlying strengths in the technologies that will support the commercialisation of products and services for regenerative medicine, such as stem cells and tissue engineering, this is still an emerging global market. Compared with more traditional disciplines like pharmaceuticals, there are relatively few regenerative medicine or cell therapy products in active clinical development and even fewer have undergone regulatory approval or commercial launch in global markets. With evolving business models, significant regulatory risk and a general lack of commercial funding for life sciences businesses, the immediate term inward investment opportunity is through research and

development collaborations, stem cells as research tools, partnerships for clinical development, direct investment into UK companies, as well as in building manufacturing and supply chain capacity. For UK companies currently developing regenerative medicine products, international partners and investors may be key to reaching the next phase of development and to prepare for future commercial launch. As such, the LSIO is working to increase foreign investment that would enable more effective commercial exploitation of the UK's science and technology research base in regenerative medicine. Consequently, the LSIO will continue to proactively target inward investment through UKTI teams at Embassies and Consulates worldwide, as well as by working with SIN and other partner organisations to maximise our global reach.

26 March 2013

Professor Richard Lilford, University of Birmingham, NHS England and Sir Bruce Keogh, NHS Medical Director – Oral evidence (QQ 343-356)

Professor Richard Lilford, University of Birmingham, NHS England and Sir Bruce Keogh, NHS Medical Director – Oral evidence (QQ 343-356)

[Transcript to be found under Sir Bruce Keogh, NHS Medical Director](#)

Professor Michael Linden, King's College London, Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge and Professor Steven Sacks, King's College London - Oral evidence (QQ 1-20)

Professor Michael Linden, King's College London, Professor Charles Ffrench-Constant, University of Edinburgh, Dr Ludovic Vallier, University of Cambridge and Professor Steven Sacks, King's College London - Oral evidence (QQ 1-20)

[Transcript to be found under Professor Charles Ffrench-Constant, University of Edinburgh](#)

Professor Michael Linden, King's College London – Supplementary written evidence

Currently, the UK is in a unique position with its potential to translate gene therapy approaches into clinical reality. Several supportive parameters combine to create a particularly suitable environment for the development of this complex therapy concept.

- The NHS: based on the current structure of the NHS, costs of clinical studies are a fraction of those in comparable research environments, e.g. the US. As feasibility is directly linked to cost and funding, this represents a significant advantage.
- The UK enjoys one of the world's most efficient and successful research environments, which is an inseparable prerequisite for successful gene therapy discoveries, development and translation.
- Funding mechanisms for translational research are available, including the NIHR BRCs as well as MRC DPF schemes.

In part based on these supportive parameters the UK has been leading in a significant number of proof-of-principle studies for gene therapy treatments.

Gene Therapy can become Medicine. Within the context of worldwide gene therapy translation it is important to recognize that, excluding Chinese cancer drugs, there is only one example of a gene therapy treatment that has received market authorization. This drug, Glybera, which targets a very rare fat metabolism deficiency, provided the proof of concept that gene therapeutics have the potential to go from bench-side experiments to becoming available and approved medicines.

Pipeline projects in phase I and III stages. The UK research community has positioned itself ideally in order to be considered a contender for international leadership in the field of gene therapy. This phenomenon was manifested by high-profile publications of a number of phase I clinical studies (representative examples):

1. X-linked severe combined immune deficiency syndrome. This severe disease, resulting in the absence of a functional immune defense against microbes leads to death in early childhood (bubble boys). Replacement of the defect gene *ex vivo* in haematopoietic stem cells via retroviral vectors has resulted in an impressive reversal of the disease phenotype in over 20 children at UCL and Hopital Necker in Paris. In spite of some children suffering from severe side effects (leukemia) as a result of the therapy, this example demonstrates the potential for a resounding therapeutic success in an otherwise deadly disease. Follow-up studies designed to circumvent the side effects are currently ongoing.
2. Leber's congenital Amaurosis: This inherited degenerative eye disease has been treated by adeno-associated virus (AAV)-mediated gene therapy and promising results have first been published by a group from UCL and a group from Children's Hospital of Philadelphia. In addition to demonstrating the feasibility of treating an as yet untreatable condition, these studies have demonstrated that eye diseases are a prime target for gene therapy approaches. This is based on the extraordinary suitability of the AAV vector for the different cell types in the eye as well as on the

relatively privileged immune status of this organ. As a result, a number of promising approaches for various eye diseases, including more prevalent conditions as for example macular degeneration, are under development and in late-stage pre-clinical phases (i.e. toxicology evaluation).

3. Haemophilia B. This blood clotting deficiency is based on mutations in the factor IX gene and approximately 1 in 25000 males are affected. A phase I study that was coordinated by UCL has shown that in a small cohort of patients curative levels of correct factor IX can be achieved after AAV-mediated gene therapy. In addition to demonstrating an exciting opportunity for patients suffering from this disease, the study also demonstrates the potential benefit to the health services. Although the study only enrolled a handful of patients, the gene therapy intervention led to a significant decrease in the need for costly recombinant factor IX protein, usually given to these patients. Within the first year of this study approximately £1.5 million were saved as some patients did not require additional protein treatment any more, thus demonstrating the potential for a significant impact of public health cost through long-lasting gene therapy treatments.
4. T-cell receptor gene transfer. This ex-vivo gene therapy approach is in early stages of clinical development and designed to transfer “designer T-cells” with re-directed antigen specificity. This approach is developed to attack diseases such as leukemia and complications that may arise from allogenic stem cell transplants. In this case, retroviral vectors are used in order to modify the patient's T-cells that then, after expansion, can be re-infused into the patient.
5. Cystic fibrosis. A consortium of groups from Imperial College, Oxford, Edinburgh, together with NHS trusts are in the early stage of gene therapy to treat cystic fibrosis which affects around 10'000 people in the UK. In this trial, an artificial vector consisting of DNA which is wrapped in liposomes (fat molecules).

Together, these clinical studies clearly demonstrate a vibrant and focused community aiming at the development of gene therapeutics to the stage where large pharmaceutical companies can pick up projects in order to develop drugs that can reach market approval. Currently, a certain ambiguity exists with regard to defining the suitable stage at which these companies are willing/able to invest the significant funds and efforts required in this translational step. In this context, it might be relevant to consider that a number of different funding mechanisms exist by which early stage clinical projects are driven:

- A. Government funding: In the UK, various funding streams have significantly contributed to these studies. Among those are BRC-related funds and MRC funds that are designed to support translation. These funding streams are very helpful and in my view, additional support would have significant potential return opportunities with regard to public health.

General considerations: One issue that needs to be recognized is a subtle difference in culture between basic science and goal driven translation. As it stands, basic research is funded to a large part based on hypothesis-driven quests and past achievements. Translational efforts in my field, however, have at least two prerequisites that are not entirely compatible with this culture. One is the need for milestone-driven research and the second is that based on expensive infrastructure and procedures (such as for example GMP procedures) the required dedicated funding needs to be upfront and sufficient (and as such administered in a flexible manner). In that sense, a novel and dedicated funding mechanism that takes into account these prerequisites at all levels of translation might need to be evaluated.

Possible approaches: a) dedicated review panels that take into account such differences. b) dedicated funds within BRCs c) infrastructure funds for vector production.

- B. Collaborative efforts between university laboratories and biotechnology firms. This approach is less controllable and usually developed on a project-by-project basis. The advantage of this approach is that the spirit of such collaborations is goal- and milestone-driven and thus less vulnerable to unnecessary delays. In addition, usually such collaborations address disease targets that are by design clearly translational.

Possible support: In general small biotechnology firms have limited funds and universities might need to consider lower overhead charges for such collaborations compared to those for big pharmaceutical companies. Specific agreements of this kind might significantly enhance the appeal of good academic laboratories for such enterprises and thereby also help stimulate economic development. Secondly, flexible approaches to intellectual property management need to be available.

Bottlenecks in the development of gene therapy. To date the most restricting bottleneck for the development of gene therapy approaches towards cures is the availability of suitable vectors at the required quality (good manufacturing practice [GMP]) and quantity. For example, AAV vectors are currently among the most promising reagents for *in vivo* gene therapy. Yet, there is only one facility in the UK that can produce such vectors at this grade. I am heading this UCL-based facility and I am thus quite familiar with its potential and limitations. The Wolfson Gene Therapy Unit at UCL is approximately 75m² in size and thereby one of the smallest facilities known to me. Although this size does provide some flexibility, the requests far outweigh the capacity. A consequence of this is that the most promising projects requiring large amounts of viruses (such as haemophilia) are forced to work with institutions in the US and other countries, thus relinquishing some of the scientific credit and, importantly, potential commercial benefits. A similar situation is evident for retrovirus-based vectors, where the capacity for production also represents one of the most significant rate-limiting steps.

Possible action: targeted investment in facilities to be established in order to provide pre-clinical (to secure a strong pipeline of projects) and, more importantly, clinical grade vectors. Such a relatively modest investment could result in significant enhancements of UK-based gene therapy developments, and ultimately in marketable drugs.

05 December 2012

London Regenerative Medicine Network (LRMN) – Written evidence

The research base

1. A significant volume of world-class research and development in regenerative medicine takes place in the UK, including work on cell therapies, on small molecules to trigger *in vivo* responses to disease, and early developmental-stage stem cell research.²⁰⁴ There are a number of centres of excellence around the UK working in this area of research, including centres in Edinburgh, Nottingham, Bristol, Cambridge and across London, including King's College London, University College London (UCL) and Imperial College. A fierce pace of development has advanced the field rapidly but also revealed new challenges, including how best to commercialise the technology. Whilst the UK is on a level playing field with the US with regard to leading on high-class research coming out of academic institutions, it is a little way behind with regard to translating that research into viable commercial opportunities.
2. With regard to the research base, the UK has particular strengths in bioprocessing and manufacturing strategies (especially at UCL and Loughborough University), induced pluripotent stem (iPS) cell research (especially Nottingham, Cambridge and King's College London), stem cell therapies for diseases and conditions of the eye (especially retinal pigment epithelial [RPE] technology and limbal stem cell therapies at UCL) and neuronal cell work (especially in Edinburgh), to name but a few focus areas. The challenge to routine translation of therapies remains, however, there is a strong research base within the UK.
3. Major funders of research for the field include the Medical Research Council (MRC), the Wellcome Trust, the UK Stem Cell Foundation, the Engineering and Physical Sciences Research Council (EPSRC) and the Technology Strategy Board (TSB), though the latter tend towards funding translation-focused research and development projects, with industrial collaborations as an integral part. In March 2012, a new £25 million cross-research council UK Regenerative Medicine Platform fund was announced by the MRC²⁰⁵, which acts as another strong source of funding for research, and the £650m interdisciplinary medical research initiative, the Francis Crick Institute (due to open in 2015) is likely to include regenerative medicine-focused projects within its remit. The TSB has further money available for the sector, both through the Cell Therapy Catapult as well as together with the MRC, through the Biomedical Catalyst Fund (though both of these funding strategies are again not intended for research and instead will be for industrial-driven, translation-focused projects – see paragraph 14, below).

Application of the science

4. There are an increasing number of cell therapies available internationally, containing either somatic or stem-derived cells, with a large number of therapies in clinical development. There are more than eight FDA/European Medicines Agency (EMA)-

²⁰⁴ Culme-Seymour E.: The House of Lords inquiry into regenerative medicine: mapping the UK route for the commercialisation of cell therapies. BioNews Comment. 20 August 2012

http://www.bionews.org.uk/page_169246.asp?dinfo=PpFHghccO2vIcmY8mfxjzdmR&PPID=169107

²⁰⁵ <http://www.mrc.ac.uk/Fundingopportunities/Calls/UKRMP/MRC008535>

approved cell therapies on the market, including therapies for wound repair, knee injury and a prostate cancer vaccine, Provenge (manufactured by Dendreon, Seattle, USA).^{206,207} These therapies are not currently available on the NHS, however, European approval is being sought by a number of the companies. In addition, there is a range of therapies available to patients on individual or unique terms, for example, Osiris' (Columbia, MD, USA) stem cell therapy Prochymal, which gained approval in May 2012 to be able to be marketed in Canada for the treatment of graft-vs-host disease in children.

5. With regards to therapies in clinical development, over 2700 cell therapy clinical trials were enrolled on clinicaltrials.gov between 2000 and 2010, with substantial numbers within the later stages of clinical development (i.e., 40% in Phase II and 10% in Phase III).²⁰⁸ Please see Appendix I for a list detailing some of the clinical trials taking place in the UK. It is worth noting that this list of therapies does not include the huge number of bone marrow transplants that have been performed for over 40 years, as well as the recently rapidly emerging practice of cord blood transplants – both good examples of using cells as therapies.
6. Regarding treatments containing human embryonic stem cells (hESCs), in the US, Geron (Menlo Park, CA, USA) led the first Phase I clinical trial using cells differentiated from hESCs with their spinal cord injury trial that initiated enrolment in 2010. However, the company have now ceased further enrolment to the trial and further development of the therapy. Clinical development of hESC-derived therapies is certainly still underway though, with Advanced Cell Technology (Santa Monica, CA, USA) pursuing two Phase I/II trials for diseases of the eye using hESC-derived cells, which directly impacts directly upon the UK field since the procedure is being performed by surgeons at Moorfields Eye Hospital (London, UK).
7. The potential for cell therapies to treat many more patients in the future is ever growing with every new therapy that comes onto the market. However, media hype has led to repeated questions about the timeframe for treatments becoming available, as with every report of a successful cohort of patients treated within a Phase I safety trial comes the associated media coverage describing the therapy as a cure, soon to be available on the market. Cell therapies are similar in this respect to every other forerunning medicine; there is a 10-15 year life cycle from discovery to market, therefore time has to be permitted for clinical development to properly ensue. Patients desiring immediate cures rather than incremental changes can be misled by the media hype and thus may suffer from frustration or disappointment. In addition, the nature of regulatory approvals for cell therapy clinical trials has led to caution in preferring to treat patients with later stage disease (see paragraph 9) or indeed treating with a lower dose number than deduced from pre-clinical studies for the therapy in question: this can in turn lead to unnecessary disappointment with the time required to take a new therapy to market. Undoubtedly, some applications are further ahead than others and there are a number of indications for which there are treatments already available (see paragraph 4), albeit offered through private

²⁰⁶ Mason C, Manzotti E: Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010. *Regen. Med.* 5(3), 307–313 (2010).

²⁰⁷ <http://www.dendreon.com/products/provenge/>

²⁰⁸ Culme-Seymour EJ, Davie NL, Brindley DA, Edwards-Parton S, Mason C: A decade of cell therapy clinical trials (2000-2010). *Regen. Med.* 7(4), 455–462 (2012).

healthcare or through a clinical trial. Widespread NHS adoption is a little way off yet and the implementation has its own challenges with regards to the completion of the value-based pricing strategy (see paragraph 15). It is certainly true, however, that cell therapies will deliver a step change in the type of treatments available, purely due to the activity and specificity of cells.

Barriers to translation

8. Whilst the above demonstrates that there are indeed a number of therapies already in the clinic, it could be said that UK science is being translated at a slower pace than is possible. The later stages of the process from lab bench to patient bedside, therefore, remain particularly important to focus on. Gaining regulatory approval, negotiating reimbursement with healthcare providers, improving access to patients, and establishing long-term clinical uptake all pose challenges.²⁰⁹ Clinical trials that require large numbers of identical batches of cells to be produced present challenges in relation to proven, reproducible manufacturing. There are financial challenges in getting high numbers of identical batches of cells to be used in treating more than 200 patients in Phase II or Phase III trials, without significant funding available from a big pharma partner. More incentives for discussions with experienced manufacturers or clinical trials operators would help developers reach the necessary stages to engage investment and achieve financial support.
9. Another issue is that the regulatory approval for a trial will often be such that it allows treatment of patients only in the late phase of their condition. This often results in the trial therapy being tested on the target condition but with associated complex multisystem pathology and thus little real opportunity to demonstrate significant patient benefit.²¹⁰ One suggestion to improve on this could be to encourage more discussions with those approving the clinical trials (the Medicines and Health Regulatory Authority, MHRA) and involve more clinician input with the design of the trial. This type of engagement could also be encouraged in designing cell therapy trials where an immune response is needed, since one challenge with this particular application involves the fact that the immune activity of certain cells for some individuals will not be identical to the response seen in others, hence the patient recruitment and placebo or 'new entity' assigned-arms need careful planning. Indeed, the use of biomarkers in the initial patient enrolment stage could help to select patients for which the therapy would be of benefit, in order for the new product to then proceed through proper trials against the best available treatment.

Barriers to commercialisation

10. The societal value and impact of cell therapies is huge, with the potential they have to treat life-threatening and debilitating conditions, and to offer improvements where there are none currently available. The cost to the NHS of long-term, debilitating diseases are set to increase; for example, the predicted annual cost of diabetes for the NHS it is set to reach £16.9 billion by 2035²¹¹. With enough investment and

²⁰⁹ Culme-Seymour E.: The House of Lords inquiry into regenerative medicine: mapping the UK route for the commercialisation of cell therapies. BioNews Comment. 20 August 2012
http://www.bionews.org.uk/page_169246.asp?dinfo=PpFHghccO2vlcmY8mfxjzdmR&PPID=169107

²¹⁰ *Ibid.*

²¹¹ Hex N., Bartlett C., Wright D., Taylor M., Varley D.: Estimating the current and future costs of Type 1 and Type 2 diabetes in the United Kingdom, including direct health costs and indirect societal and productivity costs. *Diabet. Med.* 29(7), 855–62 (2012).

support, a cell therapy industry could become firmly embedded in the UK and would be capable of generating valuable health benefits to the NHS population suffering from such diseases. The global cell-based therapy industry was estimated to be worth \$140M in 2008, £2.3M in 2012 and projected to be worth \$4.7M in 2014.²¹² If you include the cord blood banking industry, these figures increase to \$410M and \$5110M respectively.

11. The patenting of cell therapies is different to the patenting of standard pharmaceuticals in some notable ways. In 2011, there was a great deal of negative media coverage of the decision of the Court of Justice of the European Union in the *Brüstle v Greenpeace* case in which the court ruled that a process that involves removal of a stem cell from a human embryo at the blastocyst stage, entailing the destruction of that embryo, cannot be patented.²¹³ At the time, some scientists and politicians were concerned about the implications of this judgment for commercial development. However, cell therapies and regenerative medicines are somewhat more nuanced than standard medicines, and many products require key knowledge of cell culture techniques or specific automated approaches. Hence, in order to reach commercial goals, it is sometimes more worthwhile to concentrate on patenting these types of developments rather than focusing on the cells themselves.²¹⁴
12. There is much on-going discussion and research around suitable business models for the regenerative medicine sector. For example, the LRMN is a project partner on the TSB-funded British Regen Industry Tool Set (BRITS) project. The aim within this project is that using this tool set, experts will be able to make recommendations to academics, developers and investors with new products about how to take those products through development. One solution for a new product emerging from a university, for example, would be to keep the process at a small scale within an academic setting for as long as possible, with the toolset ideally demonstrating these benefits, through the production of both cost and manufacturing estimations. Ideally, this would continue through Phase I and also Phase II trials, so that big pharma are then only required to fund the development of the Phase III trial, before moving the product through approval and onto the market. This keeps the costs of setting up a new entity as low as possible, in turn improving the chance of reaching the critical Phase II stage without the company having to seek huge amounts of additional investment.
13. In work that our group has published looking at cell therapy clinical trials²¹⁵, there is a higher number of 'transient' cell therapies (where the implanted cells and/or their progeny have a limited lifespan/'half-life' in vivo i.e., typically days/weeks) in development compared to 'permanent' cell therapies (where the implanted cells and/or their progeny remain in vivo for an extended period i.e., typically years). This could act to help to facilitate more big pharma involvement for certain product

²¹² Evers P.: *Advances in the Stem Cell Industry*. Global Business Insights (2009).

²¹³ Court of Justice of the European Union. (2011). *Oliver Brüstle v Greenpeace eV*. Judgment of the Court (Grand Chamber) of 18 October 2011. Case C-34/10.

²¹⁴ Lawford Davies J., Denoon A.: *Brüstle Decision Is Unhelpful, but Not Catastrophic*. *Cell Stem Cell*, 9(6) 500–501 (2011).

²¹⁵ Culme-Seymour EJ, Davie NL, Brindley DA, Edwards-Parton S, Mason C: A decade of cell therapy clinical trials (2000–2010). *Regen. Med.* 7(4), 455–462 (2012).

types, as these ‘temporary’ therapies could be developed following more similar business models to those used for previous blockbuster medicines that have gone through successful development, since the transient cell therapies may involve numerous doses of an ‘off-the-shelf’ product for a longer period of time, compared to a single implantation of a ‘permanent’ cellular construct. In addition, the work also showed that 33% of cell therapies in development are related to ‘conventional’ grafts (tissue/organ grafts and bone marrow, cord blood or mobilized blood progenitor cells to replace bone marrow with healthy bone marrow stem cell post-chemo-/radio-therapy) which, if commercialised, will benefit from over 40 years of historical data on bone marrow transplants for new product application and development.

14. Significant developments in the UK over the past few years have improved the funding environment for those working in the sector. The recent establishment of the Technology Strategy Board (TSB)-backed Cell Therapy Catapult at Guy's Hospital in London should enable investment in cell therapy applications to reach those within the community seeking such funds. In addition, the £180 million TSB/Medical Research Council Biomedical Catalyst Fund launched earlier this year is also likely to include cell therapy and regenerative medicine-focused translation projects within its remit. However, for those seeking venture capital or seed funding investment for growing companies and new products, the environment is still widely understood to be risk-averse, mostly due to the tough economic climate. Many investors look for positive clinical results before promising funds, which is difficult to achieve for a developer without sufficient investment from an alternative source from the start. Education for investors on the scientific issues, including demonstrations of positive returns from cell therapy and regenerative medicine products, together with more guidance on the products and processes likely to succeed, would be likely to help to encourage further investment in the sector.
15. All therapies need to remain cost-effective in order to be recommended for use on the NHS by the National Institute for Health and Clinical Excellence (NICE). Making highly personalised medicines (for example autologous cell therapies) available on the NHS is essential in order for them to reach large numbers of patients, but it must also be at a price sufficient to ensure commercial viability for the developer.²¹⁶ Depending on its final form, value-based pricing²¹⁷ looks likely to work as beneficially for cell therapies and regenerative medicines as for other new medicines arriving on the market as a result of its ability to take account of additional value gains and wider health benefits that the standard QALY approach may have missed.²¹⁸
16. There are a number of facilities across the UK suitably equipped to manufacture advanced therapy medicinal products (ATMPs i.e., cell therapies, gene therapies or tissue engineered products). The LRMN has been involved with setting up a working group for the ATMP manufacturing community, “the AMC”, which has in turn gathered information on UK good manufacturing practice (GMP) clean room capacity in order to create a database that may be accessed by potential overseas

²¹⁶ Culme-Seymour E.: The House of Lords inquiry into regenerative medicine: mapping the UK route for the commercialisation of cell therapies. BioNews Comment. 20 August 2012

http://www.bionews.org.uk/page_169246.asp?dinfo=PpFHghccO2vIcmY8mfxjzdmR&PPID=169107

²¹⁷ http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122760

²¹⁸ Culme-Seymour EJ, Lawford Davies J, Cowell W, Mason C: Value-based pricing for the cell therapy industry: the sensible way to price a cure? *In preparation* (2012).

investors seeking to develop products in the UK.²¹⁹ The database currently holds information regarding twelve MHRA-licensed facilities suitable for ATMP manufacture and a further eight planned, showing that there is adequate capacity for manufacturing to take place in the UK. For large-scale commercial development, experienced contract manufacturers do have some existing capability within the UK, for example, Lonza (Basel, Switzerland) have UK facilities including within Slough and in Cambridge, but encouraging the increase of this offering would be of certain benefit for long-term UK manufacturing capacity.

International comparisons

17. Internationally, there is a wealth of regenerative medicine and cell therapy development underway, and there are numerous lessons for the UK to learn from abroad. Translation centres, such as the Wake Forest Institute for Regenerative Medicine (Winston-Salem, NC, USA) and the Centre for Commercialisation of Regenerative Medicine (Toronto, Canada) have been in existence for a few years, and they have helped to support the development of both products and industrial processing approaches. The UK has already made movements to follow this lead by making the first steps towards establishing the TSB-led Cell Therapy Catapult; however, it is vital to continue to learn lessons from established centres around the world regarding project selection, focus and delivery to ensure we catch up in translating our research into products. This may entail focusing on specific areas of therapeutic development or those indications that are further down the developmental pathway, for example, or might require more robust efforts to concentrate funding in specific areas or locations within the UK.
18. The LRMN is often approached by people seeking information about treatments that are offered abroad and asking for advice on whether they should proceed with these procedures. We advise them to investigate whether the therapy is based on peer-reviewed work and available in a regulated healthcare system, if there is strong evidence of safety data, whether it is clear what the claims are based on, and to be aware of all risks before proceeding with the treatment. We also suggest to search the clinicaltrials.gov website and the UK Clinical Trials Gateway²²⁰ in order to investigate whether they may be a better option closer to home. It is fortunate that as well as having a strong science research base and a good number of therapies in development, the UK has strict regulatory hurdles to adhere to before treatments can be offered here, hence there are stronger safeguards in place to protect patients here rather than overseas.

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Appendix I

A number of cell therapy and regenerative medicine clinical trials are currently taking place in the UK, including the following:

²¹⁹ Foley L., Callens S., Osborne A.: The ATMP Manufacturing Community (amc). *Regen. Med.* 7(3), 285–289 (2012).

²²⁰ <http://www.ukctg.nihr.ac.uk/>

- ReNeuron (Guildford, UK) have progressed the field with their PISCES Phase I clinical trial using neural stem cells to treat disabled stroke patients, in which 7 out of 12 patients have been treated to date, with no adverse events or safety issues reported.
- Azellon Cell Therapeutics (Bristol, UK) received regulatory approval in 2011 for a 10 patient Phase I/IIa clinical trial for their stem cell therapy for the repair of meniscal tears in the knee and are due to begin the trial in late 2012 at Southmead Hospital in Bristol (UK).
- Cell Medica (London, UK) are involved in two later stage trials addressing the use of adoptive cellular immunotherapies for treating cytomegalovirus (CMV) infections.
- Intercytex (Manchester, UK) are also involved in two later stage trials investigating the use of a cell therapy for wound repair.
- Gene and cell therapy combination therapies have been used for a number of rare genetic disorders by doctors at Great Ormond Street Hospital and the UCL Institute of Child Health (both London, UK), with clear clinical benefit evident from the procedures.
- Around 25 patients have been treated to date by Julie Daniels at the Institute of Ophthalmology (UCL, London, UK) and Moorfields Eye Hospital (London, UK) on the Cells for Sight Transplantation programme, where both autologous (from the patient) and allogeneic (from a separate donor) limbal stem cell therapies are constructed for patients.

Professor Graham Lord, King's College London, Sir John Tooke, University College London (UCL) and Professor Robin Ali, UCL – Oral evidence (QQ 64-80)

Professor Graham Lord, King's College London, Sir John Tooke, University College London (UCL) and Professor Robin Ali, UCL – Oral evidence (QQ 64-80)

[Transcript to be found under Professor Robin Ali, University College London](#)

Professor Sheila MacNeil, Professor John Haycock and Professor Stephen Rimmer,
University of Sheffield – Written evidence

**Professor Sheila MacNeil, Professor John Haycock and Professor
Stephen Rimmer, University of Sheffield – Written evidence**

[Submission to be found under Professor Stephen Rimmer, University of Sheffield](#)

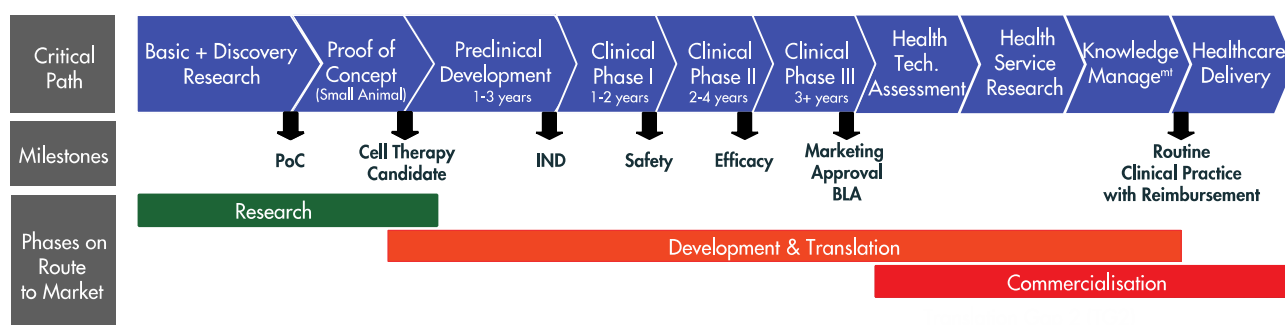
Professor Chris Mason, University College London – Written evidence

Introduction – Cell Therapy

1. Regenerative medicine is all about regeneration of cells, tissues and organs by whatever means including small molecule drugs, biologics, gene therapy, medical devices and/or cells. Thus regenerative medicine is not a specific platform technology but the medical specialty of regeneration. Whereas, cell therapy is a platform technology – administering living cells as therapies regardless of the clinical indication. My evidence will specifically focus on cell therapy (includes tissue-engineering) and the cell therapy industry since the paradigm shift is to living cells as therapies which has its own unique challenges that are very distinct to the those of the established therapeutic platforms – small molecules, biologics and medical devices.

The challenge to establish and grow an internationally competitive and sustainable cell therapy industry (CTI) in the UK

2. Chancellor George Osborne in his 2011 Budget speech finished with a call for action, “We want the words: ‘Made in Britain’, ‘Created in Britain’, ‘Designed in Britain’, ‘Invented in Britain’ to drive our nation forward. A Britain carried aloft by the march of the makers. That is how we will create jobs and support families.” Unfortunately with respect to cell therapy, at present the future looks more like ‘Discovered in Britain’, ‘Translated in Britain’ and ‘Manufactured and Commercialised Elsewhere’. This does not have to be the case. The flag of convenience by which the phrase ‘regenerative medicine’ is used instead of ‘cell therapy’²²¹ in order to avoid any association with human embryonic stem cells is a similar flag of convenience whereby ‘translation’ has replaced the word ‘development’ in order to appeal to the scientific community and their funding agencies. Likewise the words ‘manufacturing’ and ‘commercialisation’ are lost (or possibly buried in the term ‘translation’). For a cell therapy candidate to progress from initial discovery, it requires to go through the steps research-development (translation)-commercialisation (please see figure below).



3. The UK is a world-leader in stem cell research, however, for a multitude of reasons, we are currently in great danger of failing to exploit this scientific advantage. We are starting to make good progress towards translation. For example, recently there have been significant moves to establish an integrated post-research funding route including the £25M UK Regenerative Medicine Platform fund, the establishment of the Technology Strategy Board (TSB) Cell Therapy Catapult, and the £180M TSB/Medical Research Council Biomedical

²²¹ Cell Therapy Industry: billion dollar global business with unlimited potential. Mason C., Brindley D.A., Culme-Seymour E.J. and Davie N.L. Regenerative Medicine, 2011, Vol. 6(3), 265-272

Catalyst. But what about the final crucial step – Commercialisation? We live in hope that candidate cell therapies that successfully transition through the academic-clinical pathway (funded mainly by UK tax payers) to the end of clinical trials will be snapped up by venture capital funded start ups, pharma, biotech or medical device companies. Maybe this will be the outcome, but how much of the value created will be retained in the UK?

Cell therapy industry (CTI) and sector metrics

4. Currently there are approximately 300 cell therapy companies globally^{222,223}. The majority are in North America with approximately 20-30 in the UK²²⁴. A few of the healthcare multinational companies are starting to move from a protracted exploration period to exploitation, the leading players being Sanofi (after the acquisition of Genzyme) and Shire (after the acquisition of Advanced BioHealing). Big pharma in the UK is actively engaged in cell therapy including Pfizer in collaboration with the UCL Institute of Ophthalmology and Athersys (USA), and GSK in collaboration with Fondazione Telethon/Fondazione San Raffaele (Italy). There are approximately 30 public companies solely in cell-based therapy, the remainder are privately owned²²⁵.

5. As of 27th June 2010 there were approximately 1,000 cell therapy clinical trials underway²²⁶ (excluding bone marrow/cord blood/mobilized blood progenitor cell trials for oncology replacement therapy post radio/chemo therapy). Of these 1,000 trials, just over 41% were autologous (patient specific) and just over 46% were allogeneic (universal therapies). Approximately 500 were in Phase 1, 400 in Phase 2, 100 in Phase 3. This reduction in numbers with advancing clinical trial does not reflect the attrition rate but rather the overall age of the sector, coupled to far few cell therapy clinical trials started in the early 2000s due to mainly to a global technology funding shortage following the bursting of the internet bubble. The above metrics are for both commercial and clinician/hospital-sponsored trials. Today, globally there are just over 300 clinical trials being undertaken by commercial companies^{227,228}. As of September 2012 there are 10 cell-based therapies with either FDA or EMA regulatory approval²²⁹. It is estimated that in 2010, the combined annual revenues for FDA regulatory approved product was in the order of £300M. In 2011 these revenues increased to £450-600M with Advanced BioHealing, Dendreon and Organogenesis making up the vast majority of this total^{230,231}. The CTI had global sales of £260 million in 2008, and is predicted to grow to £1.7 billion by 2012 and £3.3 billion by 2014, with even greater growth expected to follow²³². Whilst the majority of the commercial activity to date

²²² Proteus Venture Partners (Palo Alto, CA, USA) database

²²³ Cell Therapy Group (Vancouver, Canada) database

²²⁴ Based on actual cell therapy companies who are members of the BIA Cell Therapy and Regenerative Medicine Industry Group

²²⁵ Promising growth and investment in the Cell Therapy Industry during the first quarter of 2012. Brindley D.A., Davie N.L., Sahlman W.A., Bonfiglio G.A., Culme-Seymour E.J., Reeve B.C. & Mason C. Cell Stem Cell, 2012, Vol. 10(5), 492-496

²²⁶ Estimated from data presented in A decade of cell therapy clinical trials (2000–2010). Culme-Seymour E.J., Davie N.L., Brindley D.A., Edwards-Parton S. & Mason C. Regenerative Medicine, 2012, Vol. 7(4), 455-462

²²⁷ Cell Therapy Group (Vancouver, Canada) data (September 2012)

²²⁸ If the cell therapy clinical trial attrition rate is no worse than for biologics (presently on a very small sample size, it looks far better), then applying the biotech industry average for going from the start of Phase 1 to the successful conclusion of Phase 3 (9%)²²⁸ to only the commercially sponsored clinical trials then approx. 25-30 cell therapy products could be predicted to receive marketing authorisation over the next 10 years.

²²⁹ Apligraf, Organogenesis; Carticel, Genzyme (Sanofi); ChondroCelect, Tigenix; Dermagraft, AdvancedBioHealing (Shire); Epicel, Genzyme (Sanofi); Gintuit, Organogenesis; HPC Cord Blood, Clinimmune Labs, Univ. of Colorado Cord Blood Bank; Laviv, Fibrocell; Hemacord, New York Blood Center; Provence, Dendreon

²³⁰ Alliance for Regenerative Medicine data <http://www.alliancerm.org/>

²³¹ Mason C., Brindley D.A., Culme-Seymour E.J. and Davie N.L. Cell Therapy Industry: billion dollar global business with unlimited potential. Regenerative Medicine, 2011, Vol. 6(3), 265-272

²³² Mason C., Brindley D.A., Culme-Seymour E.J. and Davie N.L. Cell Therapy Industry: billion dollar global business with unlimited potential. Regenerative Medicine, 2011, Vol. 6(3), 265-272

has been in the USA, Asia is fast appearing on the scene. For example, over the last few years, there have been least 7 commercial cell therapies gaining regulatory approval including products from South Korea and Japan. The total number of patients treated to date in the US with cell therapies (excluding bone marrow transplants) is in excess of a million.

6. The above metrics are very predominantly US dominated with the UK having only a few per cent of the total. UK companies such as Altrika (previously CellTran), Cell Medica, Intercytex, ReNeuron and StemCells (previously Stem Cell Sciences now part of the US company StemCells) are undoubtedly world class, but overall the UK currently lags behind the USA with respect to the commercialisation of cell therapies. Part of the problem is the highly fragmented geographical locations of the industry's stakeholders and the resultant lack of globally-competitive critical mass in any one UK location. The UK therefore urgently needs a logistically well-positioned commercial cell therapy industry cluster if the nation is to benefit from its sizeable investment in the research and translation of cell therapies is to be realized. Otherwise this substantial investment (hundreds of millions of tax-payer pounds) will be lost to other nations with more commercial orientated environments e.g., Boston, the Bay Area and San Diego. This need not be our future, however, this will require the setting up, promotion, patient support and commitment to a single location. This location will need to have all the elements needed to make it the must-go-to-centre for aspiring cell therapy entrepreneurs, start-up companies and divisions of established pharma, biotech and medical device companies. The unique selling point would be the UK as the gateway to the European and Middle East and North Africa (MENA) markets for cell therapy products.

Responses to the Select Committee's Direct Questions

Barriers to translation

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this interdisciplinary field? If not, what more action is required? In particular: What difficulties are encountered when conducting clinical trials and how could these be overcome?

7. Early cell therapy clinical trials (Proof of Concept/Phase I) are usually led and performed by an enthusiastic clinician-scientist(s). However, there is currently a general lack of clinician-scientists in the UK to champion, instigate and promote the trialling of potential new therapies. More needs to be done to promote and support the training and retention of clinician-scientists. This needs to be at every level from the training and career advice to medical students, Royal College continuing professional development (CPD), funding agencies and the NHS.

8. The later stage clinical trials (Phase 2/3) require more clinicians to be involved (the original clinician-scientist alone is unlikely to be able to complete a larger study single-handed within a reasonable period of time). In general, there is a paucity of clinician time (pressing service commitments to be met) and a lack of incentives to pursue clinical trial activity especially when it involves a new technology with its own unique requirements and steep learning curve.

9. Presently clinical trials for potential new cell therapies have been largely performed on patients who have exhausted other therapeutic options. This is mainly to reduce the impact of unforeseen safety risks by regulators (i.e. a general perception that new technology platform will have unknowns). This results in clinical trials, which even if successful, can only at best demonstrate limited efficacy, since the patient's medical condition will probably have already reached a terminal phase. More needs to be done to enable clinical trials to proceed with patients at an earlier stage in the target medical condition where cure or a life-changing therapeutic effect could be seen. (Dendreon's Provenge is an excellent example of the above.)

10. There needs to be a smooth and predictable funding stream that enables the transition through the research-pre-clinical development-clinical trials pathway (and beyond) that ensures that promising therapies are not lost due to a lack of funding or suffer staccato funding which disrupts teams, may lose the competitive edge for the product, and saps patent life. The escalating cost of each stage of a clinical trial is significant. There is therefore a risk that early trials (relatively low cost) will be funded, however, even if successful, there will have no follow-on funding route forward. There needs to be a greater emphasis on the need to demonstrate the business case for a potential cell therapy before it starts the translation process including predicting the cost of the entire process of translation and who the likely commercialisation partners will be (ideally with an early dialogue with the potential commercial partners). There is little point in travelling hopefully with a potential new therapy if the benefits cannot be realised. Better to fund other project with a better chance of delivering.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

11. There remains the potential for significant differences in opinion between UK regulators (MHRA) and EMA over important clinical trials issues such as the design of a specific trial. This needs urgent resolution.

12. The cost of cell-based therapies is likely to exceed the cost of other drugs (mainly due to cost of manufacturing), therefore successful products will need to demonstrate adequate cost:benefit ratios to justify their place in the clinic. NHS drug budgets will need to factor in the cost of purchasing cell therapies especially as they go from their presently miniscule level to main stream routine clinical practice. Many cell therapies will cover unmet medical needs (therefore existing drug budget will be zero/minimal) or replace an existing lower cost therapy with a more expensive but far more beneficial new therapy. For example, venous ulcer bandages and tissue-engineered skin are orders of magnitude different in cost to purchase, however, tissue-engineered skin has repeatedly demonstrated an overall financial benefit when every aspect of the patient's treatment is taken into account²³³.

13. It is highly encouragingly that BUPA is in principle highly supportive of cell-based therapies²³⁴.

Barriers to commercialisation

²³³ An economic assessment of Apligraf (Graftskin) for the treatment of hard-to-heal venous leg ulcers. Schonfeld WH, Villa KF, Fastenau JM, Mazonson PD, Falanga V. Wound Repair Regen. 2000 8(4):251-257

²³⁴ Gin Warren (BUPA), TSB-funded VALUE Program – Dissemination Event 2012:
https://connect.innovateuk.org/c/document_library/get_file?p_l_id=136145&folderId=6237186&name=DLFE-68621.pdf

What is the current, and potential future, commercial value of the sector to the UK economy?

14. Cell therapy represents the last major therapeutic platform opportunity. All the indicators are that it will grow as big as the existing three therapeutic pillars of healthcare – small molecules (pharma), biologics (biotech) and medical devices (medical device industry). Estimates for the size of the cell therapy market are typically in the order of £3-5B over the next decade with even greater growth expected thereafter²³⁵. The success of the UK will primarily depend upon two key factors:

1. Whether a sustainable and international competitive CTI can be established in the UK through mixture of start-ups, big pharma/biotech/medical device companies choosing the UK to build their cell therapy businesses and inward investment e.g. attracting American and Asian SMEs to establish bases to not only access the UK market but also act as the gateway to the EU and MENA cell therapy markets.
2. How much of the value chain can be retained in the UK especially the manufacturing component.

15. Secondary drivers will include promoting the UK as the best environment to facilitates the close alignment of future cell therapies with:

1. Stratified/personalized medicine. This is to be encouraged since stratified therapies have both translational and commercial benefits. For example, reduced clinical trials costs by targeting specific subsets of patients. This linkage to stratified/personalized medicine would enable the UK to leverage its highly successful medical device sector to engage in companion diagnostics.
2. Gene therapy. The UK is a world leader in gene therapy. Over the last few years, gene therapy technology has matured and moved into becoming a real therapeutic contender. The first regulatory approved gene therapy product is expected to be announced within a few weeks by the European Commission (Glybera, UniQure). There is also a growing convergence between cell and gene therapy e.g. the *in vitro* genetic modification of cells to either produce a particular therapeutic outcome or as part of the manufacturing process (e.g. ReNeuron's ReN001 is controllably immortalised by genetic modification of the cell line).

16. The commercial value to the UK is best divided into direct (CTI companies) and indirect (infrastructure and support organisations). Both these components will be important to the UK and will result in major synergies. Both will create jobs, wealth, inward investment, exports (and thus reduce imports). The scale is hard to predict, but it is very likely that for the UK to succeed in the space will require a true (i.e. not virtual) CTI cluster with the necessary critical mass to act ideally as a global hub or at the very least as the European and MENA gateway. At present, there are no established CTI clusters anywhere in the world. Manufacturing capability and capacity would play a mission-critical role in such a cluster and would be pivotal for the success of the cluster.

17. There are also other commercial opportunities. For example medical travel ("ethical stem cell tourism") – encouraging patients from the rest of the world to come to the UK for private cell therapy treatment. This would benefit a number of UK industries including the medical, travel and hospitality sectors.

What is its value to society?

²³⁵ Mason C., Brindley D.A., Culme-Seymour E.J. and Davie N.L. Cell Therapy Industry: billion dollar global business with unlimited potential. *Regenerative Medicine*, 2011, Vol. 6(3), 265-272

18. Cell therapies, because of their broad range of clinical indications and potential for cures and life-changing therapies, will impact everyone. However, in order to be commercially successful, cell therapies (due to their higher cost of goods) will need to demonstrate clear cost:benefit advantages – ideally cure or life-changing (transformative) results. Thus the returns to patients, their carers and society will be far greater than for a pharmaceutical or biological drug, the majority of which are administered on a regular basis to control symptoms or manage a specific medical condition. Patient benefits will therefore include an overall shorter period of contact with the medical services, increased quality and quantity of life, greater employment prospects (including not giving up work due to ill health, shorter time off work and returning to work), and reduced risk of premature death. Carers and relatives will likewise benefit from the improved healthcare outcomes for patients produced by successful cell therapies.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

19. The UK is undoubtedly a world-leader in stem cell research, however, for a multitude of reasons, we are currently in great danger of failing to exploit this scientific advantage. Due to fierce global competition, this will be the UK's only chance to realise its substantial investment (hundreds of millions of tax-payers' pounds) in research and to create sustainable companies, new jobs and generate wealth. However, this is likely to be an all or nothing position. Either the UK seizes the present opportunity, by absolutely committing everything necessary for outright success, or accepts that cell therapies are yet another product that we import into the UK. Critical mass is everything in the establishment, development and sustainability of new technology sectors. This can only be achieved by the UK facilitating and actively promote a single CTI cluster. To be globally competitive the cluster would need to be located very close to a number of must-have world-class resources including: capital, clinical trials centres with diverse patient populations, regulatory and reimbursement agencies, global/EU/MENA/national distribution and logistic capability, and support infrastructure e.g. patent lawyers. The unique selling point would be the UK as the gateway to the European and Middle East and North Africa (MENA) markets for cell therapy products.

What role does patenting play in the commercial development of regenerative treatments?

20. To date, the role of patenting, with respect to cell therapies, has been overstated principally by the academic community. Whilst patents are important, their value in therapies that are not principally composition of matter is limited. This is compounded by the long product development times that leave little time before the patent expires. Of greater value is company know-how and trade secrets, which will far outlive the life of a patent. Patents are traditionally used as a barrier to entry for the competition. For cell therapy products, even greater barriers are intrinsically present. These include: the cell source (especially if allogeneic), bioprocessing materials and methods, Good Manufacturing Practice (GMP) including standard operating procedures, and the clinical trial process. Today, even the venture capital community who have traditionally felt comforted by the presence of a patent portfolio are putting much less emphasis on master patents as a requirement for investment – freedom to operate is far more important.

21. There is presently a potential patent thicket for certain cell types especially with respect to adult stem cells derived from bone marrow and induced pluripotent stem (iPS) cells. This

situation is not expected to be resolved until actual products (i.e. revenue generation) are on the market. However, these perceived thickets do not appear to be stifling innovation and growth for these cell types.

What business models are most appropriate to support the development of regenerative treatments?

22. Successful business models for cell therapies are not yet established. The challenges revolve around two key issues: the high cost of manufacture and their impact on healthcare, for example, the ‘one treatment and cured’ aspect. Presently the main commercial themes for potential business models are: autologous (patient specific) which lends itself to a service model, allogeneic (universal therapies) which are more similar to biologics, and point of care bioprocessing devices (minimal manipulation) which are a combination of healthcare provider service and a medical device industry ‘razor/razorblade’ business model.

23. Reimbursement schemes are a particular topic of discussion for the CTI (and gene therapy community²³⁶) and include the two extremes of the spectrum:

1. One off payment – if so at what level since a single dose may replace a high cost lifetime treatment regimen or may treat a previously unmet medical need.
2. Annualized payment stream for the period of success for the therapy to a pre-agreed maximum level.

24. There is also the opportunity for deploying cells for non-medical treatments e.g. bioaesthetic treatments. The potential business models will still likely revolve around, service, universal products and point of care bioprocessing approaches, however, reimbursement is entirely from the private sector. The first products in this space are LaViv (Fibrocell) and Gintuit (Organogenesis).

What are the barriers to securing finance to develop such treatments?

25. Over the past year, the opportunity to secure venture capital has been improving slightly, but still life science let alone cell therapy is not the number one target on VC's hit lists. The constant challenge for the cell therapy entrepreneur is having to compete with other sectors offering with shorter timescales and often less financial commitment e.g. social media enterprises. However, a few VCs are entering the space in part due to the increased maturation of the science and the large bolus of cell therapies now reaching late stage clinical trials.

26. Venture capitalists fluctuate between backing platform technologies and therapies or both. Currently therapies are the order of the day. However, most small companies, due to their level of resources are single product companies. Therefore one hiccup with a clinical trial or a major delay for uncontrollable reasons (e.g. regulatory hold) and the whole company is at great risk of collapse.

27. Unlike the USA, the UK lacks experienced commercial managers and other key people. Because the USA has had several earlier waves of cell-based (including tissue-engineering) companies, many of which grew to a substantial size (200-300+ people) before failing (e.g. Advanced Tissue Sciences, the original Organogenesis and Systemics), there are many highly experienced veterans available for hire, advice or to start new companies.

²³⁶ First gene therapy nears landmark European market authorization. Nuala Moran. Nature Biotechnology. 2012, Vol 30(9), 807–809.

28. Investors intensely dislike uncertainty, therefore unchartered/unproven infrastructural issues such as regulation and reimbursement, which lie outside of their control are viewed highly unfavourably. Hence UK solutions which reduce uncertainty greater than elsewhere in the world are likely to be rewarded.

29. Lack of UK market pull. The NHS is not seen as an early adopter of new technology and since the NHS is the market in the UK this is a significant barrier to the UK being the first market for the intended product.

30. There is a global lack of liquidity/exit opportunities with very few IPOs even in the USA. Strategic partnering or acquisition are seen currently as the only exit routes. The UK's cell therapy sector has overall had poor results from listings on AIM principally due to poor liquidity and few analysts with knowledge of the cell therapy sector.

31. The convergence of cell and gene therapy, whilst scientifically and clinically a step forward, still awaits the VC community to overcome their decade-old fear of gene therapy following early failures and high profile negative publicity e.g. the death of Jesse Gelsinger. This fear may possibly now just be starting to be reverse with the pending regulatory approval of Glybera (UniQure).

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

32. Entrepreneurs, cell therapy companies and investors all want to see long-term market pull (cf. the current technology push which has traditionally driven the sector). For the UK to succeed in developing a sustainable and internationally competitive sector, the NHS will need to demonstrate real willingness to develop and cell therapies and then to robustly perform by buying the therapies at a realistic reimbursement rate and volume that justifies the initial commercial investment.

33. To help remove uncertainty, if NICE could enter into very early dialogue with potential cell therapy companies to provide potential pricing ranges and expected healthcare benefits this would greatly help business angels and VC to decide whether or not to invest and then whether or not to continue to invest in a specific project. The predicted reimbursement range would enable far better business plans to be developed and executed including the maximum cost of goods to make critical 'go'/'no go' decisions.

34. The impact of successful cell therapies goes far wider than the Department of Health. Other UK government departments will also benefit e.g. the Department of Work and Pensions (if patients are cured then greater employment opportunities result for both the patient and their carers). There is therefore a good argument to be made that cell therapies should receive funding from both the DH budget and other government departments that benefit, this would enable cell therapy companies to receive a higher level of reimbursement, one that better equates with the overall benefit (and saving) to UK plc. Since cell therapies will play a major role in 21st century medicine, it will be desirable to develop costing models that take into account all the economic benefits (both positive and negative) of cell therapies to UK plc.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

35. For the near future, most early CTI companies will be virtual, also many multinationals do not manufacture all their therapies), there is therefore the requirement for adequately resourced contract manufacturing operations in the UK especially to meet later stage clinical trials and routine clinical practice demands.

36. Since many of the current therapies that have been commercialised or are in late stage clinical trials have short shelf lives (hours/days) or are autologous requiring the safe collection and reliable transportation of patient biopsy material, there is the real requirement in the UK for a distribution and logistics hub. This would need to be part of/close to the UK's CTI cluster.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

37. The UK has limited financial resources compared to many of the larger global players such as the US and China. Whilst the UK has many world-class assets that it can potentially leverage, perhaps it is now time to reconsider the position of 'backing races rather than individual competitors' especially with respect to helping facilitate the commercialisation of cell therapies. The later stages of development e.g. Phase 3 clinical trials are costly and there will likely be inadequate funds available to try to back all. There is therefore the pragmatic need to make hard decisions and show real leadership.

38. Several of our European competitors are benefiting from receiving *de minimis* awards (€200,000 over a 3 year fiscal period to a single recipient). In addition a number of EU member states have applied and received 'exemptions from state aid rules' to fund at even higher levels without requiring a degree of matched funding. The Technology Strategy Board has run one round of *de minimis* funding which was very well received by the CTI community but this has not been repeated.

39. The US military has had substantial impact upon market pull including purchasing commitments to emerging technology platforms such as cell-based therapies. For example, the Defense Advanced Research Projects Agency (DARPA) and Armed Forces Institute of Regenerative Medicine (AFIRM)²³⁷ are funding multimillion-dollar collaborative R&D and translation cell therapy programmes involving academia and CTI companies.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

40. The major regulatory issue in Europe is the 'Hospital Exemption' clause that is currently stifling the European CTI. The Alliance for Advanced Therapies is leading on the reform of this clause²³⁸, "...the inconsistent implementation of the Hospital Exemption in the Member States and routine preparations of treatments under an exemption impede the development of new safe and effective treatments. Therefore, the Alliance believes that a harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients... Furthermore, Hospital Exemptions should no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal Product (ATMP) is available."²³⁹

²³⁷ AFIRM: <http://www.afirm.mil>

²³⁸ Alliance for Advanced Therapies (AAT): <http://www.allianceat.org>

²³⁹ Full AAT submission to the European Commission to be printed in the November 2012 or January 2013 issue of *Regenerative Medicine*: <http://www.futuremedicine.com/loi/rme>

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

41. The US remains the prime market for healthcare products and services. UK companies and their investors thus target this important market first. This is further compounded by the lack of market pull by the NHS in the UK and the fragmented nature of the European market despite the Advanced Therapy Medicinal Product regulation – namely 27 member states each having their own infrastructure including healthcare providers, reimbursement approaches and language/packaging requirements. The US remains an attractive market due principally to the one regulator (FDA) and a few dominant healthcare providers including CMS (responsible for Medicare and Medicaid) and VA Healthcare (US Department of Veterans Affairs). In addition CMS already has over a decade of experience of evaluating, price structures and reimbursing cell-based therapies.

20 September 2012

Professor Chris Mason, University College London, ReNeuron and Pfizer – Oral evidence (QQ 128-169)

Professor Chris Mason, University College London, ReNeuron and Pfizer – Oral evidence (QQ 128-169)

[Transcript to be found under Pfizer](#)

Medical Research Council (MRC), Wellcome Trust, British Heart Foundation (BHF) and Government–Department of Health (DH) – Oral evidence (QQ 42-63)

Medical Research Council (MRC), Wellcome Trust, British Heart Foundation (BHF) and Government–Department of Health (DH) – Oral evidence (QQ 42-63)

[Transcript to be found under Government - Department of Health](#)

[Written evidence to be found under Research Councils UK \(RCUK\)](#)

Medical Technologies Innovation Knowledge Centre – Written evidence

Introduction

1. This response to the House of Lords Science and Technology Committee call for evidence is provided by the Medical Technologies Innovation Knowledge Centre based at the University of Leeds. The Medical Technologies IKC, is an EPSRC, TSB and BBSRC funded centre for the translation and acceleration of innovation in medical technologies. The Medical Technologies IKC is founded around Europe's largest integrated multi-disciplinary medical engineering centre, the Institute of Medical & Biological Engineering (iMBE), which is home to more than 250 researchers working across 10 departments. The IKC is unique in delivering innovation right across the medical technology spectrum from implantable devices through to regenerative therapies including functional acellular scaffolds and autologous stem cells. The centre focuses on technologies that have viable and feasible routes to commercialisation and supports these through an approach that reduces late failure and cost. Unlike other regenerative medicine therapeutic approaches which describe clinical marketing and economic benefits beyond 2020, acellular therapies and minimally manipulated autologous cells are beginning to deliver growth and economic benefits now (£50m investment by the private sector into the private sector in new product development in technologies translated from the IKC in last 3 years).

The research base

Q1: How does the UK rank internationally in the scientific field of regenerative medicine?

2. The UK ranks highly in the regenerative medicine research but lags behind the US in terms of scale of funding dedicated to the field. The UK is strong in underpinning basic science research and translational research with the aim of replacing, repairing or regenerating human cells, tissue or organs, to restore or establish normal function. The UK has a significant global position in acellular regenerative medicine (referred to as regen med from hereon) -technologies which include both biological and synthetic scaffolds. The scaffold market is projected to be worth £20B per annum and is predicted to grow due to the increasing demands of the ageing population, obesity and chronic diseases.
3. The University of Leeds is in a leading position with its research into functional acellular biological scaffolds and translation. The University has established a successful track record of commercialising this capability and has established a successful new start-up company Tissue Regenix Group PLC which has been floated on AIM and has a market cap of around £75m. Tissue Regenix was founded upon IP created solely by the University which protects the processes to decellularise natural tissues in order to reduce the immunological response when transplanted into patients. Tissue Regenix has developed a vascular patch using porcine pericardium which is now sold as a commercial product for vascular surgery. The University's IP for decellularisation has also been exploited in partnership with the NHS Blood & Transplant Tissue Services to enable allogeneic donor tissues to be decellularised and implanted into patients.

Q2: Where does the UK have strengths and weaknesses in the field?

4. Strengths

- a. Strong in basic research base in the UK
- b. Functional acellular biological scaffolds and matrices- e.g. decellularised biological scaffold technology for musculoskeletal and cardiovascular applications developed at the University of Leeds. These technologies deliver the potential for regenerative therapies at lower cost development and shorter time to market compared to cellular therapies. The scaffolds technologies are regulated as class III medical devices rather than advanced therapy medicinal products (ATMP) and thus the regulatory requirements are better understood and allow a more rapid translation and commercial development pathway.
- c. Proven track record of commercial development of acellular biological scaffolds within Leeds University. Scaffold technologies have been successfully transferred to commercial and clinical organisations. Xenogenic decellularised scaffold technologies have been licensed to Leeds spin out company Tissue Regenix for commercialisation and allogeneic scaffold technologies have been licensed to the NHS Blood & Transplant Tissue Services for use within the NHS
- d. Leeds also has strength in biomimetic scaffolds based on self assembling peptide technology with unique biological functionality. This technology has been licensed and commercialised through Credentis, a Swiss SME with a UK office, for the regenerative treatment of early dental caries (Filling without Drilling). The product received its CE marking in January 2012 and is marketed as Curodont in Europe.
- e. Leeds is developing the unique capability to simulate and test natural hip and knee joints which will accelerate development and reduce risk earlier for new regenerative treatments for osteoarthritis and other joint injuries.

5. Weaknesses

- a. Commercialisation of inventions/technologies.
- b. There is a lack of appropriate and representative animal models of disease to facilitate development and testing of new therapies. (global weakness)
- c. Securing funding to enable new technologies to progress into clinical trials
- d. Regulatory uncertainty and long regulatory routes

Q3: Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

6.

- EPSRC, BBSRC, MRC and in collaborative projects with industry, Technology Strategy Board Biomedical Catalyst scheme, NIHR i4i
- The Wellcome Trust
- NIHR, NHS BT R&D
- The new Cell Therapy Catapult offers a significant funding route for regen med technologies that utilise cell therapy approaches, however to fully realise the commercial and clinical potential of regen med higher levels of funding are likely to be required to take technologies through to the market.

- There is a major funding gap at technology readiness levels 3 and 4, with the need to develop and prove the technology and make it ready for commercial /private sector investment in commercial product development.

Application of the science

Q4: Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

7. In general stem cell therapies are still in development and not close to the market, with many technologies currently in clinical trials – eg Osiris and Mesoblast., but with limited clinical or commercial scope to deliver therapies on a global scale in next 10 years. However, tissue engineering approaches, such as scaffolds and matrices, are used clinically as exemplified by Actifuse (Baxter) and Chondromimetic (Tigenix), which were both developed within the UK.
8. Leeds University and the Medical Technologies Innovation and Knowledge Centre (IKC), an EPSRC, TSB and BBSRC funded centre for the translation of medical technologies has to date supported the progression of 35 products to market. It should be noted that these are not all based upon regen med technologies as the IKC supports medical device development as well as biological scaffolds and minimally manipulated autologous stem cells.
9. Within the University of Leeds challenge-led research has been successfully translated into regenerative therapies as demonstrated by the successful spinning-out of Tissue Regenix Group PLC and translation of its patent protected decellularisation technologies for commercial use, and also through clinical translation in a not-for-profit route through the NHS Blood & Transplant Tissue Services (NHS BT TS)and commercialisation of self assembling peptide technologies for regenerative dental application through the Swiss company Credentis.

Q5: What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

10. Allogeneic cell therapies for chronic diseases such as heart disease, osteoarthritis, cancer and diabetes are probably still 10 years away from reality. There are also concerns related to immunological incompatibility issues when used clinically for allogeneic cell therapies. However in the short-term there will be alternative interventions that will significantly improve patient outcome, and financial burden on the health service. In Leeds, we believe that this is where the acellular scaffolds and matrices will make an impact on clinical practice. These scaffold technologies will deliver physical and biological functionality in musculoskeletal, cardiovascular and systems applications in a cost effective manner.
11. Another key strategy supported by the IKC in Leeds is the development of autologous minimally manipulated stem cell therapies. These therapies involve the isolation, processing and application of the patient's own stem cells to the site of disease or injury within the timeframe of a surgical procedure and will remove the need for complex and expensive large scale manufacturing which is required for allogeneic or autologous expanded therapies. This will lead to the development of

regenerative medicine therapies which can be delivered to the clinic in shorter timescales and at lower developmental cost and risk.

Barriers to translation

Q6: Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

Q6.1: What difficulties are encountered when conducting clinical trials and how could these be overcome?

12.

- Funding for clinical trials
- Ethical approval to undertake clinical trials
- Engaging the NHS and supporting healthcare providers in terms of how to conduct trials in the NHS

Q6.2: What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

13.

- Funding
- Ethical approval for use of human cells/ tissues
- Research time for clinical staff/ engagement of clinicians / current disincentives for young medics to undertake research

Q6.3: What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

14.

- Complex and time consuming ethical approval system (IRAS)
- Cost implications and the resulting slow return on investment creates a cash flow issue for companies.

Barriers to commercialisation

Q7: What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

No comments

Q8: Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

15. The economic climate has created risk aversion in potential investors and we have seen that companies are seeking technologies that offer lower risk and a higher return on investment. This has created a translation gap that is preventing the outcomes of research and the development of new regen med technologies successfully progressing to market. In addition the close of regional development agencies and other funding mechanisms has created a lack of proof of concept

investment that is available for technology translation. Government could invest in a national proof of concept scheme that would help progress new technologies close to market. In Leeds we recognise that in order to successfully progress new technologies, dedicated and professionally experienced technology and innovation managers are needed to work alongside proof of concept projects to ensure the right opportunities are identified and that the project work plan will address key issues that will give confidence to potential investors. These innovation managers can also play a role in terms of supporting protection of the IP and identifying the right commercial partners whether they are those companies who may licence the technology or venture capital partners who may wish to create and invest in a new start up company.

16. Across all markets there is a demand for increased reliability and assurance of throughout lifetime performance of medical devices and regenerative medicine therapies. The environment is becoming more stringently regulated with the classifications being raised. A further driver is the global harmonisation of the Medical Devices Directive (93/42/EEC, plus amendment 2007/47/EC) that will see the essential requirements for regulatory approval increasing from 13 to 19, increasing the cost of compliance for manufacturing companies. The balance between compliance, performance, and life-cycle cost in medical devices has never been more difficult to maintain, and there is a driving need for more innovative and safer regenerative therapies that will deliver long term performance in vivo.

Q8.1: What role does patenting play in the commercial development of regenerative treatments?

17. Patenting and protecting intellectual property is critical to the commercial development of regenerative therapies and capturing the value for the company, its shareholders and UKplc. Without patenting new invention and knowledge generated in the UK is likely to be capitalised outside the UK by larger players in the US and Far East. Without IPR organisations would protect their investment by confidentiality and trade secrets. This would stifle further innovation and lead to developments in the regenerative medicine field slowing and in turn have negative impact on health services and patients.

Q8.2: What business models are most appropriate to support the development of regenerative treatments?

No comments

Q8.3: What are the barriers to securing finance to develop such treatments?

18. Increasing tendency to invest in lower risk with shorter term investment
19. See question 8.

Q8.4: Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

No comments

Q8.5: What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

No comments

International comparisons

Q9: What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

No comment

Q10: How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

No comments

Q11: Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

No comments

Q12: What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

No comments

18 September 2012

**Medical and Healthcare products Regulatory Agency (MHRA),
European Medicine Agency and Health Research Authority – Oral
evidence (QQ 295-316)**

Evidence Session No. 13

Heard in Public

Questions 295 - 316

TUESDAY 8 JANUARY 2013

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Professor Sir Kent Woods, Chief Executive, Medical and Healthcare products Regulatory Agency, **Dr Hans-Georg Eichler**, Senior Medical Officer, European Medicine Agency, and **Dr Janet Wisely**, Chief Executive, Health Research Authority.

Q295 The Chairman: I welcome our first witness panel this afternoon. In a moment, I will invite you to introduce yourselves and, if you wish to, to make any very brief opening statement. Please feel free to do so, but keep it brief. The session is being webcast, so sotto voce comments will be picked up by the microphones and broadcast to the wider public.

The aim of this session is for us to gain a better understanding of the regulatory environment in relation to regenerative medicine. We are very grateful to you for coming along to offer your comments as witnesses. I invite the panel, starting with Dr Janet Wisely, to introduce themselves.

Dr Janet Wisely: I have a few opening remarks. The Health Research Authority is a relatively new organisation. It is a special health authority and was established on 1

December 2011. Unlike the other organisations that you will hear from this afternoon, we do not license or inspect. Our National Research Ethics Service reviews and approves research. As the Health Research Authority we have set out an ambition to make it easier to do good quality, ethical research in the UK building on a lot of the improvements that we recognise were delivered through the National Research Ethics Service. Of particular interest to the Committee may be the new arrangements we have put in place since we were given responsibility for the Gene Therapy Advisory Committee last May. That is the ethics committee that reviews gene therapy applications. We have already shown considerable improvement in the operation of that committee, and I would be happy to share further information if there is interest.

Professor Sir Kent Woods: I am the chief executive of the Medicines and Healthcare products Regulatory Agency. I am also currently the chairman of the management board of the European Medicines Agency and, as you will hear, the national competent authority role and the European regulatory role are relevant to the products we are talking about.

Dr Hans-Georg Eichler: I am the senior medical officer of the European Medicines Agency. As Sir Kent just said, it is involved in the licensing of ATMPs—advanced therapy medicinal products. We work in a network model in Europe with the national competent authorities, of which your organisation is one, and probably one of the leading ones.

Q296 The Chairman: We have heard from quite a few witnesses about the complexity of the regulatory process for regenerative medicine in the UK. Some have told us that too many regulators are involved; some have told us that the process is bureaucratic and duplicative. Just to give you a quote, we were told: “there is significant duplication and redundant regulatory burden with sequential approvals and major delays to the system”. We have also been told that although fine words have been spoken and written in policy documents, no progress has actually been made in reducing the regulatory burden for setting up clinical trials. How do you respond to these quite strong criticisms from a number of witnesses?

Professor Sir Kent Woods: I would take issue with that assessment in several respects. There is no doubt that the regulatory system is complex but, as one of your witnesses has already said, so is the science and the technology. Therefore the organisational structures around that are far less significant than, first, whether the functions of each regulator are absolutely clear to those being regulated, which touches on the question of the way in which the regulatory authorities communicate, and, secondly, the extent and quality of the interactions between the regulatory bodies themselves. I feel very confident that, first, the MHRA is very accessible to those seeking to do research in this area. We work very actively with investigators in responsive regulatory and scientific advice and also proactively in workshops and seminars. As regards the relationship between us and other bodies, such as the Human Tissue Authority, there are operationally excellent relationships between the two and innovations, such as, for instance, joint inspections to make sure there is not duplication of function, are something we have worked to achieve and, in fact, already deliver.

We are very conscious of the potential harms of overregulation. We take the support of innovation as being one of our public health responsibilities, but if you break down the components of regulation, what they are there for and what protections they are intended to provide within the constraints of the very new science and technology, the regulatory system functions efficiently.

The Chairman: Would the other witnesses like to add comments?

Dr Janet Wisely: I fully support Kent's views. We should recognise the considerable improvements that have been made. We work very closely with the MHRA and the HTA. However, there is room for improvement, and I think we have set out a good agenda to tackle that. In terms of facts and figures, we have halved the timelines for the first three studies that have gone through the new GTAC arrangements by recognising that we can rely on the expertise of the MHRA in looking at the scientific aspects rather than duplicating them ourselves. There are areas where, as well as the longer term improvements, we can demonstrate recent improvements.

Dr Hans-Georg Eichler: Very much like my colleagues, I do not think it is fair to say there is duplication. I understand that the entire framework and edifice of regulation must look daunting to those players who are new in this field. We know very well that when we are looking at these new advanced therapies, we are not dealing with big pharma, which is very well versed in that. We are dealing with very small companies or academic groups that have no experience in the field and are overwhelmed by the entire complex regulatory system. The emphasis should be not so much on changing regulations. I fully agree with my colleagues that the overlap in regulation, duplication, is not the issue. The issue is the different cultures and the lack of familiarity. The room for improvement is probably how we can better bridge that cultural divide. How can we interact better and earlier with those new players where both of us are on a steep learning curve?

Q297 The Chairman: We will pick that point up in a minute. Before I turn to Lord O'Neill, I am a bit puzzled, because on the one hand I have witnesses—not just the odd one or two, but quite a few of them and witnesses with substantial authority—saying that there is a real problem of complexity, duplication, delay and so on, and I am being told by the regulator that there is not a problem. I wonder how I should respond to that. Do I think that these witnesses are overegging it, or do I think that you are being a bit too complacent about it? How do I respond?

Professor Sir Kent Woods: I have looked carefully at the oral evidence. Clearly, we listen very hard to the community we regulate to see whether there are areas in which we could do better. Clearly it would be a concern to have those remarks made about areas for which we have responsibility. This goes back to the work that the Academy of Medical Sciences did about the regulation of clinical trials. It is very important to be absolutely clear in diagnosing what the problems are that are being complained about. There are many practical, operational difficulties in running clinical trials within the UK healthcare system, but when you drill into them, they may not be regulatory issues. They may be concerned with local NHS R&D approvals, or they may be concerned with reimbursement challenges. There is a raft of things that can get badged as regulatory obstacles, but if we dissect what specifically is the sticking point and where the delays and duplications are, I have not seen anything in my reading of the transcripts of the oral evidence that you have heard that suggested that there was some systemic problem here that we are all looking straight through.

The Chairman: What is your target time from an application to an approval, assuming the application is fully valid and up to speed?

Professor Sir Kent Woods: If it is an application for a clinical trial authorisation, which would be the agency's responsibility as a national authority, our target time is 30 days, which is extendable to 60 days if there are special factors that have to be debated at greater

length. Particularly when we are talking about advanced therapies, it may well be necessary to involve our clinical trials expert advisory group, but that is the order of timeline that we are working to. For phase I trials of pharmaceuticals, not specifically advanced therapies, we would look to get a turnaround time of 15 days. We publish those, and we stick very rigidly to them.

The Chairman: Those are your targets and your performance is within them.

Professor Sir Kent Woods: We deliver them 100%.

The Chairman: I am going to come to Lord O'Neill in a moment, but I think Lord Winston may be raising his eyebrows in a meaningful way.

Q298 Lord Winston: When you are treating human patients, you can understand the need to be absolutely strict, but we are talking about regulation on a much broader front than merely clinical trials. If you want to do stem cell research, for example, in my laboratory, you have to have an animal licence, which is becoming increasingly difficult with the European directive, and you also need to have a licence from the HFEA, which is often quite pointless and does not add in any way to the work. Why can this not be centrally regulated by one body? We are losing a number of students at PhD level. I can give you many examples of people who have been turned away from this science, particularly in the stem cell area, and also, to some extent, where animals are used, because of the difficulty of getting registered in time to do a PhD, which is the backbone of British and European science.

Professor Sir Kent Woods: I shall respond to those two specific points. First, I carefully qualified what I said by describing the areas of regulation that we are responsible for. The regulation of animal studies is not our responsibility. I cannot speak for the Home Office or comment on the criteria, timelines and likewise in relation to the HFEA. I think you will have an opportunity to ask questions of the HFEA directly, but this is not within the remit of the MHRA.

Lord Winston: Why should they be involved at all? What expertise do they bring to the subject that is necessary for regenerative medicine?

Professor Sir Kent Woods: I think you will probably have to ask other witnesses to answer that question. We take on the oversight responsibility for a product when it is moving towards the market as a medicinal product. In the case of a stem cell therapy, that would be the point at which a master cell bank has been established. You are describing processes and obstacles to research which are significantly upstream from where we would become involved.

Why should we take on responsibilities for pharmaceutical trials at that stage? There is an obvious read across to the authorisation of a product for the market, the accumulated knowledge and understanding of the product that is necessary for that step and the processes by which that knowledge is gained in pharmaceutical clinical trials. Quite frequently, the fact that we authorise clinical trials of pharmaceuticals means that we can use knowledge and experience that we have gained from the market authorisation of that or a similar product to understand fully what we should be looking for. However, the obstacles that you are describing are considerably upstream of the stage at which we would become involved.

Q299 Lord O'Neill of Clackmannan: Dr Eichler, you quoted some of the evidence we have received to the effect that the regulatory edifice was “daunting”. The other words used were “and expensive”. It would appear from the evidence that we have received that the daunting and expensive character of the regulatory process has a deterrent effect on potential investors coming into the country and taking advantage of our system. Do you as regulators step back from the understandable health and safety considerations that are paramount and try to assess whether what you are doing is counterproductive in a financial and economic sense? To follow on from the point Lord Winston made, people are leaving but, equally importantly, people are not coming. If we want to make a success of this, we want to make it a commercial success as well as a medical one. To what extent is that a factor in your approach or is it purely scientific and health and safety and the financial and economic aspects are far down your hierarchy of priority? I quoted Dr Eichler, but really the question is to Professor Woods or Dr Wisely.

Professor Sir Kent Woods: I will gladly start responding. We see ourselves as a public health organisation. We are there to represent the public interest in this. We do not have a primarily economic remit but, having said that, in public health terms, it is clearly in the public interest that innovation should happen and that new treatments should come forward for currently unmet medical needs. The perspective we have on it is very much the perspective of the public interest, which includes not simply the safety, efficacy and quality questions that are at the core of all the judgments we make but the broader responsibility to ensure that in any possible way innovation is supported because that contributes to public health. I hope that answers your question.

Lord O'Neill of Clackmannan: Do you have within your organisation people whose sole responsibility is that rather than the medical issues? I understand that you correctly have a hierarchy of priorities in which the financial and economic ones are fairly far down, but without an economic benefit at the end, there will not be a strong case that can be made to government for continued public funding for the operations of your clients. I realise that they pay you by way of fees.

Professor Sir Kent Woods: The strictly economic issues are not things we analyse. We do not have information about the market and we do not have information about or responsibility for pricing or reimbursement. All that comes in at a stage beyond the point where a product has received a marketing authorisation. We cannot begin to assess those considerations. In terms of the level of our fees, which was your starting point, they are set and reviewed annually. They go to Parliament annually. They are statutory fees. They are set, they are consulted on and they go to the Treasury. Our objective in setting fees is that we recover the costs of what we do, but that is precisely what our fees are set for.

Q300 Lord Patel: I want to come back to the original question that the Lord Chairman asked. You, Sir Kent, did not dismiss it but tried to answer it by suggesting that the witnesses who we have heard—and there are several of them, who commented on the complexity, the lack of co-ordination and the difficult-to-understand regulatory burden—have that perception but that that perception is wrong. If that is true, how are you going to deal with this evidence because it is addressed directly to you?

Professor Sir Kent Woods: As one of your witnesses said, the regulation is complex, but the science and the technology are complex. I do not dispute—

Lord Winston: That is not an answer.

Professor Sir Kent Woods: If you take regenerative medicine, it operates on a broad front—cells, gene therapy, tissue-engineered products—and touches on pharmaceutical and medical devices issues. In each of those areas, we are dealing in very rapidly growing areas of science. Our responsibility is not to make life complicated for innovators but to try to ensure, first, that the safety of participants is protected—

Lord Patel: The regulatory authorities are an important part of the Government's strategy to deliver on life sciences. If the regulators do not understand or accept that there are concerns from a variety of different groups, and I accept your comment that their perception is wrong, but if that is the case, how would you handle this criticism?

Professor Sir Kent Woods: Can I give you some specific details of what we do to communicate with the research community because this is the core of it? I fully accept the perception that this is complex and, as has already been said by Dr Eichler—

Lord Patel: Does it need to be made simpler?

Professor Sir Kent Woods: The first thing is to make it clearly understood. We have extensive guidance on our website. We have a regulatory helpline that takes 20,000 calls a year. We host seminars and workshops and go out to visit research groups. This week, two of my senior staff are out visiting research groups in this area. We are on the point of bringing this all together by setting up an innovation office. In the first quarter of this year, we will have an innovation office within MHRA as a single point of contact for those who are at an early stage of product development. Indeed, there is a meeting with the main industry associations on Friday this week to flesh out the details of how that will work. We are not indifferent to the comment that this is complicated and at times can be confusing for those who seek to apply for authorisation, but rather than saying that there are bits of the regulation we can do without, our first task is to make sure that the regulation is fully understood and that we work with other agencies to make sure that we lighten as much as possible that regulatory burden. We do not require information that goes to one regulator to go to another. Indeed, the work with the Health Research Authority on a single research application form is a classic example of that. We do not replicate inspections of facilities. The work that we do with the Human Tissue Authority on joint inspections is a precise example of that. So we have to get down to the fine detail of what specifically we can do to make this system more user friendly, but I do not think that there are major elements of the system that are redundant. The worst thing that that could happen to this field would be serious clinical adverse events occurring in a research setting. That would be seriously damaging. We also have the responsibility to make sure that volunteer patients are as fully protected as we can arrange and that the quality of the data that comes out of these studies is as robust and reliable as possible.

Q301 The Chairman: Dr Eichler, do you want to add something?

Dr Hans-Georg Eichler: I fully support what Kent has just said, but we have to be clear what we are talking about. Are we talking about the implementation, the bureaucratic superstructure, and whether it is unnecessary, redundant, slow et cetera, or are we talking about the evidence standards that are required? As Kent said, if someone is aware that there is a requirement for evidence of efficacy or safety that is not scientifically sound or is superfluous, that should be debated in the open. What we have not done so far, which could happen in future, is to look at the opportunity cost of studies that are being done. To give you a concrete example: someone has calculated the cost of doing a so-called thorough QT/QTc trial, which is now required on a global level for pretty much every new drug.

They calculated that it cost X-hundred thousand dollars or pounds for a quality of life year saved. They argue that it is not cost-effective. This is a matter for scientific debate. On the other hand, it would be very difficult from now on to say that we will do away with that because there would be a public outcry if we did and if patients died as a result of arrhythmia from one of those drugs, and the effect on the regulatory system would not be too favourable. This is a very complex discussion. To say that we will fiddle with the evidence standards is not an easy route to go down.

Apart from the evidence standards, with regard to the implementation, the bureaucratic processes et cetera, we can try to simplify them and to take these companies by their hands and lead them through. Some of them avail themselves of these opportunities; others do not, which also has to be said. We offer two types of advice to them. One is very informal and we call them briefing meetings. You do not have to pay a fee. You just come in, and we tell you that you may want to look at this form and that form. The other is very formal. You pay a fee and investors or the outside community can then see what regulators think of your development programme. Both these opportunities are available to make life easier. They are partly an underutilised resource, and I would invite you to take that also into account.

Q302 Lord Willis of Knaresborough: I was horrified by your first comment that because the science is complicated, the assumption is that the regulation must therefore be complicated. I do not buy that. The job of a regulator is to make that process as simple as possible, not as complicated as possible. Perhaps you will reflect on that.

You can gather that the committee is incredibly enthusiastic about these technologies, which is why we are interested, but what has hugely disappointed me today is that if you go back to two years ago, there was huge enthusiasm for the Academy of Medical Sciences's report which was born out of an overregulated space. The idea was to bring things together and streamline them. You have talked about different cultures within different regulators. It is a huge barrier if there are different cultures, and therefore having as few regulators as possible seems to be a desirable objective. Would you agree on that? Yes or no?

Professor Sir Kent Woods: No, if I have to give a one-word answer.

Lord Willis of Knaresborough: Is that no? I want to move on because the whole point of setting up the HRA was to streamline and bring some of these organisations together. We now have the HTA fighting a rearguard battle against the department, saying "We don't want to change". The HFEA is saying, "We do not want to change at all". You have the HRA, which is basically a glorified ethics approval service—that is all it seems to be—and we have gone absolutely no further forward than where we started. I would like to ask all three of you but, in particular, Sir Kent and Dr Wisely: what is your personal position from your organisation's point of view about streamlining the HTA and the HFEA and getting those components into their rightful place with the research elements in HRA and the other premises things through CQC or wherever? What is your personal view?

Dr Janet Wisely: The HRA has listened very carefully about what it should tackle and should be addressing. Going back to the evidence of the Academy of Medical Sciences, we recognise that the relationships we have with the MHRA and the HTA work well. The evidence we have gathered is in line with the Academy of Medical Sciences': what we should be tackling is the huge duplication in the activities of organisations—the National Research Ethics Service and the local trusts—in giving local trust approval. That was the main focus

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of the Academy of Medical Sciences' review. The HRA has put forward proposals to the Department of Health to ask that we are able to tackle that area.

Lord Willis of Knaresborough: What is your view? I know what their view is because I have read their evidence.

Dr Janet Wisely: My view is that the HRA should not be distracted by looking at the links between the MHRA and the HTA and, potentially, the HFEA, because it works well, and should focus all its efforts on tackling the—

Lord Willis of Knaresborough: It is business as normal—they just carry on. The HTA carries on and the HFEA carries on.

Dr Janet Wisely: No. The links between the HTA, the HFEA, MHRA and the Health Research Authority work relatively well. The big area and opportunity for improvement is to look at all that against the duplication of the activities of the local trusts. That is what I would like to tackle first.

Lord Willis of Knaresborough: So leave the regulators as they are, and it is now the problem with the trusts?

Dr Janet Wisely: No. It is for the HRA to help the trusts operate better.

Lord Willis of Knaresborough: I do not see what the point of the HRA is.

Dr Janet Wisely: We want to do an HRA assessment for the approval of research in the NHS so we take out all that duplication and free up the approval processes in the UK so that they are much more competitive.

Lord Willis of Knaresborough: So why not take on the bits of research from the HTA and the HFEA so that you have the whole of that within your one organisation?

Dr Janet Wisely: I think that is a possibility.

Lord Willis of Knaresborough: Is that what you would like?

Dr Janet Wisely: I would like to tackle—

Lord Willis of Knaresborough: Would you like that or not?

Dr Janet Wisely: Not at the moment because I think it would distract us. I think the priority is to look at R&D approvals first, but it is a question that should stay on the table.

Q303 The Chairman: Sir Kent, perhaps you could answer as succinctly as possible.

Professor Sir Kent Woods: I answered no to the question of cultural difference because I interpreted the comment that was made about cultural differences much more in relation to the nature of the research community. An academic unit, a spin-out company and a big pharma company come at regulation from very different places. I do not think for a moment that there is a deep cultural diversity within the regulatory authorities. For instance, one of my senior managers in the inspection area is currently on a two-day-a-week secondment in the Health Research Authority. There is a great deal of interchange.

In terms of the European Medicines Agency's role in this at the product market approval stage, my staff are scientifically engaged in the assessment of advanced therapies, both on the Committee for Advanced Therapies and the Committee for Medicinal Products for

Human Use. There is a great deal of interchange and exchange. I emphasise the point that Dr Wisely has made that for clinicians trying to do research in the NHS, the obstacles that they face have dominantly and historically been around the local approvals for that research to be done in individual trusts. That is a different matter from the authorisation of the trial by the MHRA. We can work to tight timelines for the approval of clinical trials, but we cannot tell an NHS trust that this study must go forward and that it must not sit on it for three months. When people complain about regulation delaying things, I go back to what I said earlier: we must be very clear that that is not what I call regulation.

The Chairman: I did not quite get your answer to Lord Willis's question. Is your view in relation to the HTA and the HFEA that it should be business as usual?

Professor Sir Kent Woods: We considered those options when the future of the HTA and the HFEA were under discussion. It would be technically feasible to incorporate the inspection function of the HTA, or a proportion of it, into our work, but we could see no functional gain by doing so. We looked very carefully at this. We estimate that of the 200 or so sites that the HTA has authorised, about 20 are also subject to inspection by the MHRA. It seems far more appropriate that we simply do joint inspections on those 20 sites than that we take over the responsibility for a whole raft of other things that the HTA does that are not related to pharmaceutical authorisation.

Q304 Lord Patel: I have a question that I will come to in a minute, but to go back to what you said, as I understand it, cell therapy, which is what we are talking about, is not in the domain of the tissue authority.

Professor Sir Kent Woods: No, when it becomes a medicinal product, it becomes—

Lord Patel: It becomes your responsibility. So in that respect the HTA is not involved in the regulation of cell therapy issues.

Professor Sir Kent Woods: It is simply the initial derivation and testing of the cell product before it gets to the stage where it starts on the pathway of medicines development.

Lord Patel: The risk about some of the answers that you gave and that Janet gave—I know Janet well because we used to work together—is that there is a complacency about different regulators. The criticism from others has been that we have too many regulators. What you say is, “We all get on well with each other, so there is no need to remove any one of us because we work together, we get on, we are good buddies”.

Lord Willis of Knaresborough: We go to dinner together.

Lord Patel: To continue to my question, which Dr Eichler answered to a degree but which you may like to develop more: what are you doing to facilitate early dialogue with companies, big pharma, SMEs and researchers in developing regenerative medical therapies in the UK and the EU?

Professor Sir Kent Woods: For example, on 30 October, the MHRA hosted a workshop between academics, regulators and the industry specifically on the subject of regenerative medicine. It was a very productive exchange, and it is representative of the type of efforts that we make to communicate well and frequently with the very wide range of interests in this area.

Lord Patel: Is there a report with outcomes?

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Professor Sir Kent Woods: The report is not yet finalised. I asked for it myself only yesterday, but it will be forthcoming and it will be published.

The Chairman: Will you send us a copy?

Professor Sir Kent Woods: Certainly.

Q305 The Chairman: Dr Eichler, I think you have answered this already, but is there anything else you would like to add?

Dr Hans-Georg Eichler: In addition to what I said, we have the offer of both formal and informal avenues to early dialogue. It means a young company or in some cases a spin-off group from academia, could come and see us and say, “We have this product, we like to think that big hopes are attached to it, how should we set out to develop it so that you will accept it at a later stage?”. That does happen, and we publish the numbers and we know how many ATMPs are part of this. It is happening, and I repeat that it is probably underutilised by the research community.

The Chairman: Is it underutilised because they do not know about it or because they are shy? It seems slightly odd.

Dr Hans-Georg Eichler: I suspect it is a combination of the two.

The Chairman: Just to quote one witness, “it is very difficult for them”—start-up companies—“to find someone to give them the guidance to take them through the regime”. The witness who said that was somehow unaware that they could come to you and have their hand held through the process without being charged.

Dr Hans-Georg Eichler: I would assume that this was someone from either a very small company or from academia. I do not think this would be someone from Pfizer or GSK.

The Chairman: We are interested in small companies and academics.

Dr Hans-Georg Eichler: I understand that fully. We have a one-stop shop at the agency for SMEs. Registered SMEs in the European Union can come and receive free of charge or at significantly reduced fees all this technical and scientific advice. Particularly for ATMPs, the regulation has made provision for certification. We are prepared to look only at the pharmaceutical quality dossier part—and perhaps the non-clinical dossier—and would give them a green light because we understand that this will help those young companies to get into a new round of financing or to be bought by someone else. Things like this are foreseen but, again, they are underutilised. To my knowledge, we have so far had one or two cases of this certification procedure. Those in the European environment who wrote the legislation thought that it would be a very useful tool. The past years have proved that it is not. Is it just because we are still on that learning curve and it is premature to see whether it is useful or is a fault built into it? I do not know, but I would like to think that it is a combination of the two causes that you have just suspected.

The Chairman: Dr Wisely, would you like to add anything, briefly?

Dr Janet Wisely: Yes, I would. We are organising an event on 29 April and we have already, through individual conversations with people in this area, been asked to look specifically at access to advice, because at the moment there is a genuine question mark in our mind whether or not there is a gap in getting access to it. We have been specifically asked to look at that at our event on 29 April.

Q306 Lord Cunningham of Felling: It is widely argued in industry, commerce, employment, the police and the social services that excessive regulatory burdens block initiative, delay progress and improvement of the services and deter enterprise. Why do those arguments not apply to the area that you ladies and gentlemen work in?

Dr Janet Wisely: I think they do. I think we are identifying at the Health Research Authority, not only where some activities would fall into that, but actually where they give a false assurance. For instance, we are looking at the whole area of reporting. Ethics committees get a progress report every year; and the fact that they do provides an assurance to others, we have found in the NHS and wider, but they are not particularly looked at so there is no real value and potentially a false assurance, as well as all of the waste. To echo what Kent has said, a lot of that activity is not really born in regulation; it is born in people's interpretation of it and where they have generated roles at a local level—I include the ethics committee system in that—

Lord Cunningham of Felling: Whatever the reason might be, there is a problem?

Dr Janet Wisely: It needs tackling. I echo what Kent said: it is about identifying the heart of the problem. In my understanding, it is not necessarily in the regulation, although I am sure that it could be simpler. Actually, it is in the interpretation of it, within the National Research Ethics Service, and particularly in the local trusts.

Lord Cunningham of Felling: Forgive me for intervening. The problem—if there is a problem; we believe there is a problem and so do many other witnesses—lies not with the regulatory system and not with the regulators, but with the people who are trying to fight their way through it? They are the problem?

Dr Janet Wisely: No, I am talking about people who are approving research, who see themselves as part of the wider regulation and are doing activity that is not actually set out in the regulations, which is slightly different. For instance, there is the fact that ethics committees ask for progress reports every year—why?—and the fact that that is a different progress report to what an NHS trust might ask for. There are lots of opportunities and areas for improvement, but a lot of that does not lie at the heart of the regulations; it lies at the heart of how people are regulating it.

Q307 Lord Cunningham of Felling: I shall ask Professor Woods whether he thinks that the ATMP regulations and the proposed clinical trial regulations are flexible enough to cope with the new demands that are going to be placed on them with, for example, clinical trial design, adaptive licensing and reimbursement. Are they going to be able to be flexible enough to allow those processes to work effectively?

Professor Sir Kent Woods: That is a really important question. In answer to the comment “Are things simply standing still?”, I should point to the huge amount of work that has been done in the last year or two to get back to the fundamentals of the clinical trials directive, which was introduced in 2004, and which undoubtedly did contain elements that could be improved on. That was European legislation that was transposed into UK law and in its operation in subsequent years, it has been clear that there are ways in which those regulations could be made more adaptable, more flexible and lighter.

It is also important to say—I make this point repeatedly when I speak to the research community—that there are already in the existing legislation quite a number of flexibilities that are not being utilised. For instance, there is the option for accelerated approval and the option for conditional approval. This is something that Dr Eichler may be better able to

talk on than I can, but we put out a communications effort several months ago through the Bioindustry Association and the other trade associations just to remind researchers, particularly in SMEs, that there are facilities within the existing legislation to hopefully find a shorter track to the market. But there is more that can be done, and I am encouraged that the proposals coming out of the Commission now in relation to the clinical trials directive are deregulatory in their tone. They offer considerable simplification. Much of that does not relate to ATMP—much of it relates to large-scale multinational trials—but in every way we need to make sure that the regulations are constantly reviewed and if necessary improved. For instance, the ATMP regulation is out for consultation. The consultation went out from Brussels in December, and that will be reviewed in March. So there is a constant review process in which our agency is a very active participant.

Lord Cunningham of Felling: Since it is absolutely essential that potential regenerative therapies can find a way through this—I almost said “maze of regulations”, but I do not want to be too unkind—complexity of regulation, surely there should be a real focus on making it clearer and simpler, particularly for small and developing businesses. Many of the people who make these observations about the regulatory burden are small, start-up businesses. They do not have the resources of Pfizer or the multinational big pharmas; they do not have those resources at all. They cannot afford to buy in the advice either. It is at that level that there seems to be a major deterrent, let us say, to people getting going.

Professor Sir Kent Woods: I spent 20 years doing clinical trials before I came into this job, so I am very much in support of researchers in every possible way. But you have to be specific. What precisely is it that you would wish to do away with in the current regulatory process? What safeguards are there that are being overegged? This is what it comes down to—the specifics.

Q308 Lord Turnberg: I wonder if I can be a bit helpful to the witnesses. The responsibilities of each of your organisations—the MHRA, the EMA and the HRA—are clearly defined. You defined them pretty well, and you obviously go about your business pretty well. But you spoke about upstream and downstream, and there are all sorts of other things going on in the area—other regulators. I am sure you are doing your job beautifully. It is just how we get all these together so that someone coming to it fresh actually understands where to go in, how to come out and how to deal with it. It is not your organisations specifically that seem to be the problem; it is that there are lots of others around that also have to be negotiated.

Professor Sir Kent Woods: I think you are absolutely right. We tend to focus on the bits of territory that we are responsible for, and adjacent to us there are—for instance—data protection requirements and animal licensing requirements, which we do not have responsibility for but if you are approaching it as a researcher those may very much impinge. There will be local requirements in NHS organisations. Again, they are outside our gift, but it is a tapestry of things and we must make absolutely certain that there is nothing in there that is unnecessary, and that those things which are necessary are actually handled in the most efficient administrative way possible. That is very much the priority for the agency.

Q309 The Chairman: Dr Eichler, and then I want to turn to Lord Willis and then to Baroness Perry.

Dr Hans-Georg Eichler: To go back to the question asked by Lord Willis about whether the regulation is flexible enough, my response is yes. In addition to what Kent said, there is an opportunity for conditional licences and exceptional licences. Even the ATMP regulation

has an extra flexibility step when it says that you can do this and that after the initial licence. So the regulation is not the issue. The bone of contention is always the implementation. A young company comes to us and says, “We have done 10 patients, and we have assessed the effect on a surrogate end point”, and that is where the debate starts. Is that surrogate end point sufficient to say that we can let that drug loose on the population? That is not regulated anywhere, and it can never be because you cannot legislate that the surrogate end point is or is not valid. The point of contention is always in the detail of the application. The real question is: should we lower the evidence standards? If we did, I am not sure it would sit well with the community outside or with advocates of public health.

The last remaining question is: could we stagger the evidence generation in such a way that we can square that circle? On the one hand, we want to support this industry and to keep the innovation engine humming. We want to have timely access for patients, but on the other hand, we have an obligation to get a full set of information on safety and efficacy. Could we better structure that and stagger it? The answer is, perhaps, yes. We are working on that. These therapies, with their high unmet medical need, may be a very good opportunity, but this is something that will take place in the wider public context and in the wider debate, and not everybody is convinced that it is a good idea to cut corners and allow drugs earlier. We are in the midst of this debate.

The Chairman: How is that debate being conducted?

Dr Hans-Georg Eichler: In the newspapers. If something happens, you will read about it. Why did the regulator authorise this drug when there was insufficient information? That is the downside we are faced with every day.

The Chairman: That is not really a debate. That is journalism. I would have thought the regulator would be trying to structure something, perhaps involving public opinion surveys, focus groups or experts of different kinds. Are you doing that, or are you simply responding to what the *Daily Mail* and other newspapers write when something goes wrong?

Dr Hans-Georg Eichler: No, we are not simply responding to what newspapers write, but we are keenly aware that there are two sides to this debate. This is not new.

Q310 The Chairman: I have said that we are aware that there are two sides to the debate. Do you relax things and allow the possible risk that something goes wrong? It is about a proportionate level of regulation. My question is: what steps are you practically taking to navigate towards a proportionate level of regulation for these therapies that may be applicable to a small number of individuals and may be very expensive to develop and therefore the traditional model does not work? You accept that the traditional model may not work, so how are you trying to navigate towards another model?

Dr Hans-Georg Eichler: As you mentioned, the other model is called adaptive licensing. Can we allow a drug with a higher degree of uncertainty on the market with more restrictions and more observations? This is currently under discussion.

The Chairman: You are repeating that, but I want to know what “under discussion” means. How is the discussion taking place, who is doing it and when can we expect to see an outcome?

Professor Sir Kent Woods: The concept that Dr Eichler has just referred to—adaptive licensing—is gaining a great deal of attention among regulators and others worldwide. There are initiatives in the United States, Europe and other countries to see what could be

done to shorten the time it takes to get truly innovative medicines into clinical use. In terms of specifics, there are two things I can mention to you. These relate not directly to ATMPs, but to pharmaceuticals more widely. One that we have been discussing, which went to public consultation a few months ago, is an early access scheme. Is it possible to make innovative products available before they have completed the licensing process on the responsibility of the prescriber and with some form of agency assessment of what we know about risk and benefit? The early access scheme went out to public consultation, the consultation closed in October, and we are working through the responses we had to it. That is one line. The other is within the authorisation process—early access is a step outside the approvals process. The adaptive licensing concept is one that I have been chairing an expert group on in the MHRA, with representatives from industry, academia, other regulators and other parts of government, to see whether there is a way we could offer a pathway to full market authorisation which is more hospitable to small companies and specialised products. A large part of this goes back to the European approval process which has to happen. In other words, these are all centrally authorised. A workshop is due to take place in March this year at the EMA to discuss this question of adaptive licensing. We think we are getting clearer about what might be possible, but we have not yet seen the candidate products: molecules that the industry would like to see taken through the adaptive licensing process. We are actively seeking candidates because once we see candidates and understand their therapeutic activity we can decide whether they could be fitted into an adaptive licensing model.

The Chairman: Thank you. Lord Willis and Baroness Perry have questions, and then I will turn to Lord Selborne.

Q311 Lord Willis of Knaresborough: I want to be very brief. Professor Woods, you have said on three occasions what you want to do away with. I do not think that is the question that we are asking. Clearly, a committee of non-experts would be rather unwise to be telling you what you should be doing away with. What we are trying to get at is: given the plethora of different regulatory bodies, how can we streamline that process so there is not just a single point of entry to each one? Quite frankly, that is pretty useless if you are a very small company or a small research group at UCL wanting to begin work—sorry, at Imperial, I must get this right. Are you in any way working together with the other regulators to try to find a streamlined, single point of entry right through the process, or are you depending on the catapult to be able to help that?

My second point is specifically to Dr Wisely. You talked about ethical approvals at site level somehow not being part of the regulatory process. They are part of the regulatory process. You simply say, “Well, it’s their problem at site level”. Given the fact that we are going to have very small populations of people in these clinical trials, what are you doing to ensure that at site level we are going to have a different approach? The point that the chairman was making is: is there a plan ahead to have a different approach to clinical trials so that people working at the research level know that they can get stuff very quickly through the process?

The Chairman: Please be very brief because we are running short of time.

Professor Sir Kent Woods: I will be brief and make just two points. First, is there a single way in through these various regulatory bodies? We must look at the functions and not the structures. To talk about the structures through which regulation should be delivered is not the question. The key thing is the functions that need to be delivered and whether they

are being delivered in a joined-up way. The second thing is whether there is a way into all this. The regulators and the Department of Health put together a regulatory route map for cell products. It is widely available on the website. It was issued in 2009 and revised last year and is there to help people through.

The Chairman: Dr Wisely, answering the question about local approval.

Dr Janet Wisely: I am sorry if you misunderstood, but there is no local approval now. It is a national system with one approval for the whole of the UK. The site I was referring to is the local trust approval, which was not originally within the remit of the Health Research Authority, but we submitted proposals to the department late last year to suggest that we should look at and bring into our remit how we streamline that into the HRA remit. There is a proposal for a feasibility study with a pilot in March where the HRA would do an assessment and we would then ask the NHS to take its assurance from that assessment so that it is not duplicated. You should not underestimate the amount of duplication there is at the moment across all those local site approvals and, potentially, across to the one ethics approval. There is a huge amount of work to do there. We are very firmly taking that into the grasp of the Health Research Authority, and we have set up a collaboration and development steering group where we hope we have all the right people around the table so that we do not simply shift the problem from one place to another but actually solve some of these issues.

Q312 Baroness Perry of Southwark: I think Dr Wisely has already in part answered my question because it is about the trust level of approval. I spent 10 years chairing the Addenbrooke's trust. During those 10 years, until the beginning of 2012, the department laid more and more responsibility on trusts, and we as a trust obviously had first-line responsibility for the patients in our hospital. I am delighted to hear that you have now initiated a thought that that might be the core of the approval because part of the regulation that we had to apply included assuring ourselves on whether the other regulatory authorities had already given their blessing. The trusts have patient representatives and patients' relatives representatives all laid down in regulation by the Department of Health. How would you streamline that bit of it so that somebody in a clinical school or in the NHS starting on a research project starts there and relies on others to feed in the outside regulation that comes from elsewhere?

Dr Janet Wisely: I would see that the information is not only created in one place, which it is at the moment through the Integrated Research Application System, but is submitted to one place—the Health Research Authority, working closely with the MHRA, in terms of an initial evaluation—so that we ensure first off that there is one person validating that data set. What we are looking at is how many of the things that are looked at across all the different sites at the moment could be looked at once by the Health Research Authority, and then the local trust could take assurance from that.

We are not saying to the trust, “You won't be able to ask those questions”. We are saying, “When we have finished our assessment, ask us if you still have questions about the information sheet, the data protection issues and all that”, so that for researchers, it is significantly more streamlined. That has potential to make a huge difference in the UK and that is where the HRA must put and is putting its energies—as well as maintaining the ethics service and other work.

Q313 Baroness Hilton of Eggardon: I would love to ask you how you think it will work where much research is now done across several trusts, but I do not think there is time.

Dr Janet Wisely: Just to add one thing, I think the key is the perception of risk and who people think is taking the responsibility for that risk. I think that research is not a high-risk activity. If you have got the disease, you have the risk of the disease, whether you are in research or not. I would be quite happy for the HRA, with its assessment, to take some of what is seen as the liability of research so that not only are we asking the trusts to take our assessment, we are taking some of their perception of risk away as well.

Baroness Hilton of Eggardon: There would have to be a lot of legislation on that. The trust's responsibility for the safety of its patients is paramount.

Dr Janet Wisely: It is interesting that there is no legislation to unpick on the advice from the department to give us the remit to do that assessment. All the local trust activity and additional activity around research, which it puts on top of its responsibility to the patient, is not based on legislation.

Q314 Earl of Selborne: I would like to move to the European and international dimensions. You will have seen that a number of people who have given written and oral evidence have drawn attention to the lack of consistency in member states and national regulators in the interpretation of the regulations and therefore in the implementation. Dr Eichler, what efforts are being made to harmonise the interpretation of regulation across Europe and to harmonise regulation internationally for that matter?

Dr Hans-Georg Eichler: Let us stay within Europe. Clinical trials are not our responsibility. The new clinical trial regulation is a direct response to the problem that you have outlined, and there is hope that there will in future be more harmonisation across Europe when it comes to the running and authorisation of clinical trials. With regard to ATMPs, very clearly there is room for different interpretations. For example, we all know that the hospital exemption clause is handled very differently across Europe. That is the letter of the law. What is being done is that people meet and try to set up guidelines to mitigate, but it would be naive to say to eliminate, the variation across Europe.

When you come to international, what do we mean by the harmonisation of regulation? There is the outcome of regulation, which in the domain that we are responsible for would be the licensing. Do we want to harmonise that? I not sure we do. With regard to the evidence standard, I fully agree that every effort should be made to enable a global development, particularly in those innovative fields where we have small players. It is not affordable that Europe says, "You shall do this trial" and the US FDA says "No, you shall do a different trial". Efforts are being made to harmonise that. If you asked me whether these efforts are 100% successful, I would freely concede no. We discuss with each other, particularly with the FDA, what are the evidential requirements. In nine out of 10 cases, we can agree, and in case number 10, we agree to disagree because there is serious scientific disagreement.

The Chairman: Some of it seems to be definitional. Regenerative therapy may be defined as a device in one country and not a device in another country. That is not to do with evidence, but to do with categories.

Dr Hans-Georg Eichler: I agree that it is to do with categorisation. There is certainly room for improvement, but I was looking at the definition that you provided. That is again very different because you say erythropoietin would also be part of that, so we would not see that as an ATMP. I accept your point that there are different interpretations and definitions.

Earl of Selborne: Clearly some member states are faster than others in producing national frameworks. Whose job is it to try to ensure that everyone goes at the same speed on this or that the slow countries catch up?

Dr Hans-Georg Eichler: First, please be aware that I am not speaking for the Commission. We are just a decentralised body. The European Commission sets out a framework, and within that framework, individual member states have liberty to implement it the way they wish. Usually there are certain time limits, but within them, they are free. That is the whole idea of the deferred way of regulation.

Q315 Earl of Selborne: There is clearly going to be a lack of confidence in investors if there is inconsistent interpretation and implementation of these regulations. It is therefore clearly desirable that while one has to accept that member states have a certain degree of autonomy in this, it is important for the science to be implemented universally.

Professor Sir Kent Woods: I would like to respond on that. You have raised some important and interesting topics. First, let us take Europe in terms of harmonisation. We work to a single legal base. Virtually everything we have discussed so far comes out of European directives and European regulations. When you talk about the implementation of those regulations, there are two ways in which diversity can occur. One is if individual member states start creating additional, gold-plated requirements, which really should not happen. In fact, the answer to that is not to have a directive that is transposed into national law, but to have a regulation which applies across the whole of Europe. That is the direction of travel in the revision of the clinical trials directive. The revision will be a clinical trials regulation, so the law will be the same across Europe. The implementation of that law has two elements. First, can we make the administrative processes as simple and streamlined as possible, even if the study is being done in multiple member states? The UK was instrumental in setting up across the EU a clinical trials facilitation group in 2004 to achieve exactly that. We have developed a voluntary harmonisation process which means that if you wish to do a clinical trial in five countries, instead of going to one, two, three, four and five, those five countries collectively will do a single assessment. You will put in a single application, and you will get a single answer. That was a member state initiative to make the process smoother.

A distinction has to be made between clinical trials authorisation—the harmonisation process I have described is about clinical trials authorisation—and the market authorisation for the product when it has completed its development path. That is, under European law, a single centralised licence. If you get a market authorisation for your ATMP, that will be valid throughout Europe, so to that extent there is a very considerable degree of harmonisation. The science that underpins that judgment as to whether the product is fit to be let loose in public is collectively arrived at through the scientific contributions of the member states at the EMA. It is a single decision, so much work has been done on consistency and harmonisation within Europe. Between Europe and the United States, Canada and other jurisdictions, we work to different legislation and, fundamentally, if the legislation tells us to do something in a different way, we have no remit to change that.

Earl of Selborne: Dr Eichler mentioned the problems that are being faced at the moment on hospital exemptions to the ATMP regulation. I think you admitted that there is an inconsistent approach on this which is causing issues. Would you at least agree that where there is a fully validated, centrally approved ATMP there is no case for hospital exemption?

Dr Hans-Georg Eichler: I am not sure I fully get the question. Are you alluding to products where you have one centrally authorised?

Earl of Selborne: Yes, if you have one centrally authorised one, why should there be an exemption?

Dr Hans-Georg Eichler: In parallel, we have others that are run in different countries. That is a fact. We know that. Whether that is desirable is a matter of taste. We would say that if you still have the opportunity of going local, you are undermining the centralised procedure. So a case could be made against it. On the other hand, there are people who will say that it gives us a little degree of freedom, so it depends on where you stand.

Professor Sir Kent Woods: This is an important question because concern has been expressed that the hospital exemption in some way would undermine the commercialisation of products that have gone through the whole process and have their market authorisation. I think the hospital exemption was put in the legislation to allow for the fact that products develop iteratively and that you need this local flexibility to enable products to go through the early states of translation. The risk of this undermining the economic viability of a marketed product is more theoretical than real. Use of the hospital exemption is actually very scanty. We have authorised one site in this country to develop a product under the hospital exemption rules. At this stage, it is difficult to see how that could jeopardise the economic growth of the sector.

There is another exemption, which is the specials process. It means that despite the legislation it is possible for an individual clinician to prescribe a medicine to meet the specific needs of an individual named patient where there is no product licensed that will meet that need. If there was a licensed product, the specials regime would not apply. It would not be acceptable. We have about 15 laboratories that have been approved under the specials regime, but once there is a product on the market that has been authorised, one cannot claim a specials dispensation for a product that has not been authorised.

Q316 The Chairman: I think we have run out of time. I would like to thank our three witnesses very much indeed for their responses to our questions. You will receive a transcript in draft form for you to make minor amendments and corrections if you wish. I think that Sir Kent offered to send us a report of your workshop when it becomes available. If there are any other items that any of you would like to submit in writing as follow up where we have not given you enough time to clarify points, please feel free to do so and they will become part of the evidence. Thank you very much indeed.

Dr Hans-Georg Eichler: This is a paper that was written by colleagues: *Clinical Development of Advanced Therapeutic Medicinal Products in Europe*. I am happy to leave it here because it might be of interest.

The Chairman: Thank you very much; that would be helpful to us.

Medicines and Healthcare products Regulatory Agency (MHRA) – Supplementary written evidence

MHRA response to the question:

"How many regenerative medicine clinical trial applications have you received in each of the past 5 years and how long did it take to reach a decision on authorisation for each trial"

Application	1st assessment	Time for response	2nd assessment	Final decision	Comments
2008/9					
1	120 days			Day 120	This included repeat EAG/CHM ²⁴⁰ review and a clarification meeting
2	28 days	40 days	1 day	Day 69	
2009/10					
1	23 days	22 days	6 days	Day 59	
2	29 days			Day 29	
3	28 days	16 days	9 days	Day 53	
2010/11					
1	21 days			Day 21	
2	23 days	22 days	6 days	Day 59	
3	25 days			Day 25	
4	24 days	23 days	1 day	Day 48	
5	23 days	27 days	23 days	Day 74	
2011/12					
1	30 days	31 days	On day of receipt	Day 61	
2	30 days	26 days	1 day	Day 58	
3	21 days	30 days	9 days	Day 60	
4	30 days	25 days	3 days	Day 61	
5	29 days				Rejected – no response received to additional questions
6	85 days	31 days	30 days	Day 172	This included repeat EAG/CHM review and a clarification meeting
2012/13					
1	157 days			Day 157	This included repeat EAG/CHM review and a clarification meeting but only one formal

²⁴⁰ EAG/CHM = Expert Advisory Group/Commission on Human Medicines

Medicines and Healthcare products Regulatory Agency (MHRA) – Supplementary written evidence

					assessment performed
2	30 days	29 days	6 days	Day 65	
3	27 days	29 days	4 days	Day 60	
4	28 days			Day 28	
5	29 days			Day 29	
6	178 days			Day 178	This included repeat EAG/CHM review and a clarification meeting but only one formal assessment performed - rejected
7	Pending				
8	Pending				Received in the last two days

15 March 2013

Medical and Healthcare products Regulation Agency (MHRA), NHS Health Research Authority, Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) – Supplementary written evidence

1. We all want to see research continue to thrive in the UK. To ensure this, as regulators we must facilitate high quality research, manufacture and clinical use. Effective regulation provides essential safeguards for ensuring quality and safety, and supports good practice and high quality science – which in turn leads to improved healthcare. There is no doubt that some of the regulation in this area is demanding, reflecting the nature of the technologies and their risks, but this should not mean that the regulatory demands are unnecessary, excessively complex or burdensome. A key role of regulators is to provide clarity and support to organisations working to the regulations.
2. We are fully supportive of close scrutiny of regulation to ensure that any unnecessary obstacles are removed. As regulators we should be vigilant to ensure that we are supporting innovation. Our track record of collaboration and working with the sector demonstrates how we are committed to this; we work in partnership to maximise clarity and minimise burdens on the sector.
3. This document sets out the roles of the regulators in regenerative medicine, how our legislation aligns, and how we work to reduce the regulatory burden on researchers through collaboration and other initiatives.

Our roles in regenerative medicine

4. We each have a clear remit and regulate distinct areas of the regenerative medicine process. However, there is adjoining legislation and we work closely together to provide effective advice and guidance to support establishments through these regulations. Each regulator has a core set of standards that apply depending on where you are in the process. We are focused on ensuring that the standards that are applied at one stage of the process do not act as a barrier at another. The role of each of the regulators in regenerative medicine is set out below:
 - a. *Human Fertilisation and Embryology Authority (HFEA)* – The HFEA regulates treatment in hospitals and clinics using eggs and sperm. It licenses 4 establishments in the regenerative medicine sector out of a total of 132 licensed Clinics. In the context of regenerative medicine, it regulates the use of human embryos or human admixed (human-animal) embryos to derive stem cells for use in the treatment of patients.
 - b. *Health Research Authority (HRA)* – The HRA protects and promotes the interests of patients and the public in health research, to ensure the UK is seen as a place to do high quality research. Specifically it has a remit to approve the ethical aspects of clinical trials involving stem cells and other regenerative medicines through the Gene Therapy Advisory Committee

Medical and Healthcare products Regulation Agency (MHRA), NHS Health Research Authority, Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) – Supplementary written evidence

(GTAC). It also provides a system (IRAS) through which applications and approvals from GTAC and MHRA for clinical trials involving regenerative medicines can be made.

- c. *Human Tissue Authority (HTA)* – The HTA works to ensure that human tissue and organs are used safely and ethically, with proper consent. It licenses 800 establishments, 15 of which are in the regenerative medicine sector. In the area of regenerative medicine, its remit relates to the use of human tissue or cells as starting materials for advanced therapy medicinal products (ATMPs). Under the European Union Tissues and Cells Directives, it licenses establishments that remove, test, process, store, and distribute tissues or cells that will (or may) be used to treat patients.
- d. *Medicines and Healthcare products Regulatory Agency (MHRA)* – The MHRA's mission is to protect and improve public health through the effective regulation of medicines and medical devices, underpinned by science and research. In the area of regenerative medicine, its remit includes responsibility for granting the appropriate authorisation ATMPs which are prepared and used under the hospital exemption, and for ATMPs made and supplied under the specials scheme under the relevant provisions in medicines legislation. In the area of clinical trials, MHRA's remit includes assessment of applications for clinical trial authorisation and the associated manufacturer's licence for investigational ATMPs. By way of comparison of scale, MHRA's wider responsibilities include responsibility for inspection and supervision of 830 medicinal product manufacturing and import sites and 3500 medicines wholesale distribution sites. On 1 April 2013 the National Institute for Biological Standards and Control (NIBSC), which houses the UK National Stem Cell bank, will officially become a new part of the MHRA.

Simplified regulatory route from embryos to medicines

- 5. Because of the stepwise process of developing regenerative medicines, only a small number of establishments (less than 12) will hold a licence from two regulators at any one time. When this does occur, each regulator is responsible for different aspects of the development of regenerative medicines, under different pieces of legislation.
- 6. For example, in the case of the derivation of stem cell lines from embryos, the HFEA will regulate the early stage of procurement. Once the embryo is dissociated, the HTA regulates the derivation process in preparation for banking for later manufacturing. MHRA will grant a licence at this stage for an Investigational Medicinal Product (IMP) which may be used in a clinical trial.

Diagram 1.

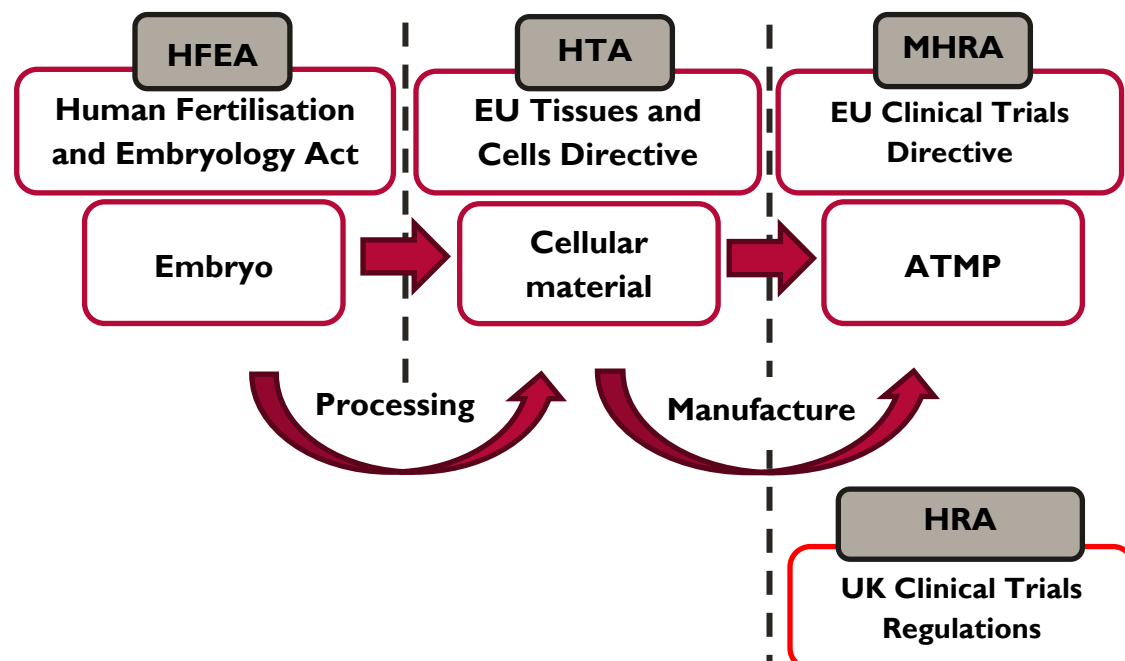


Table 1.

The role of regulators in regenerative medicine

	Licensed establishments in regenerative medicine	Approve clinical trials	Approve research projects involving stem cells
HFEA	Yes – 4 in regenerative medicine out of a total of 132 licensed clinics [under Human Fertilisation and Embryology Act 1990 (as amended)]	No	Yes – only those involving human embryos or human admixed embryos. [under Human Fertilisation and Embryology Act 1990 (as amended)]
HRA	No	Yes – ethical review through the GTAC [under the UK Clinical Trials Regulations 2004]	Yes – ethical review through Research Ethics Committees (RECs) [under the UK Clinical Trials Regulations 2004]
HTA	Yes – 12 in regenerative medicine out of 260 establishments [regulated under the European Union Tissues and Cells Directives]	No	No
MHRA	Yes – approx 20 sites across three sectors (gene therapy, somatic cell therapy and tissue engineered products) of ATMPs. Not all of these sites hold HTA or HFEA authorisations.	Yes – responsible for authorising all clinical trials of IMPs [under the Clinical Trials Directive (2001/20/EC)]	Yes – authorising all clinical trials of IMPs including investigational ATMPs [under the Clinical Trials Directive (2001/20/EC)]

Key areas of collaborative working in regenerative medicine

Joint inspections

- Over the last two years, collaborative regulatory work that aims to reduce the burden on establishments has expanded significantly. For example, the HTA and MHRA both license 12 establishments involved in the manufacture of ATMPs, and have been conducting joint inspections of these since 2010. In particular, establishments have appreciated the consistent and joined-up advice provided during joint HTA / MHRA inspections to ensure the pathway from one regulatory remit to another is seamless. In practice, this means that all of these establishments are offered a joint MHRA / HTA inspection, and four to five joint inspections take place every year. The HTA and HFEA both license four establishments involved in

Medical and Healthcare products Regulation Agency (MHRA), NHS Health Research Authority, Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) – Supplementary written evidence
embryonic stem cell research and are committed to information sharing about licensed establishments.

UK stem cell tool kit

8. The regulators in this area have worked closely together to provide clarity about regulatory requirements to guide establishments through the advice and guidance. For example, the [UK Stem Cell Tool Kit](#) has been jointly developed to provide clear guidance on the regulatory pathways that must be followed in developing a regenerative product derived from stem cells.

New arrangements for GTAC

9. In November 2012, the HRA as the Appointing Authority for the GTAC made a number of changes in the review of applications to GTAC. These changes, which clarified the respective roles for the MHRA and RECs, are already improving the service offered to researchers who wish to carry out clinical trials involving stem cells, ATMPs, and gene therapies. The approval times for ethical review have been significantly reduced, with all studies reviewed within the legal requirement of 90 days. The most recent study was approved in 38 days, surpassing the new HRA 60 day target, and approaching the average approval time for RECs in general. Options for meeting dates and locations have also improved for researchers.

Key work to reduce regulatory burden in regenerative medicine

MHRA Innovation Office

10. To help organisations developing innovative medicines, medical devices or using novel manufacturing processes to navigate the regulatory processes, the MHRA launched an Innovation Office in 2013. The Innovation Office aims to promote early dialogue between organisations and the MHRA to support their understanding of the regulatory requirements. This is built on many years of engagement with such organisations where the MHRA typically have approximately 25 such (Regulatory Advice) meetings per year.

IRAS

11. The Integrated Research Application System (IRAS) hosted by the HRA on behalf of a number of bodies, streamlines the research application process and allows researchers to provide the information needed to gain approvals – from MHRA, RECs including GTAC, and others as required – for research projects, including multicentre clinical trials. For regenerative therapies, the approvals come from the MHRA and GTAC. The HRA is leading a fundamental review of IRAS to streamline the information requirements. In future IRAS will become an application and approvals system.

HRA assessment pilot

12. The HRA is currently conducting a feasibility study of the potential benefits of a streamlined HRA assessment for all research in the NHS which would combine and replace aspects of the current review by NHS Research and Development (R&D) and RECs. Scoping work suggests that it could potentially improve both study set-up times and the quality and consistency of review for all research projects, including multicentre trials of regenerative medicines.

Summary

13. The HFEA, HRA, HTA and MHRA are committed to working together to streamline regulation and reduce burden on establishments. Our aim is to provide effective advice and guidance to support establishments through the regulations.
14. Our collaboration is demonstrated by a number of initiatives – including joint working agreements and Memorandums of Understanding – that have a positive impact on reducing the burden of regulation. We are always looking for suggestions about how we can work together even more effectively, from those we regulate, and the research community more broadly.
15. Whilst we believe the regenerative medicine community is largely aware of all this information, this summary document might still be useful, and we plan to share the document with them. Feedback on this document is welcome.

28 March 2013

Miltenyi Biotec Ltd – Written evidence

I. The Research Base

- a. As in so many fields in science and technology, the UK punch well above their weight within the associated academic fields to cell therapy and regenerative medicine, ranking well, with respected key opinion leaders and notable publications and many focal seminars and congresses reporting on advances and investigations. In addition, certain academic institutions have seized the initiative to reorganise and merge the complimentary academic and clinical aspects of their medical and life science schools to not only pay lip service to translational aspirations but to put scientists and clinicians together to realistically work towards better therapies (eg. King's Health Partners, Imperial College Healthcare NHS Trust, Bart's Health NHS Trust).
- b. This combined academic and clinical pedigree is indeed a key asset to the UK, giving a firm foundation of knowledge, development and discovery in the context of patient care and treatment that needs to be better utilised, optimised and evolved to therapy and/or commercialisation, whether that be by service or product.

The sheer numerical resource of the NHS as a whole and the cross-talk and cross-fertilisation of ideas and potential therapies between Trusts and Universities facilitates a national approach to such medical research and development, whereas many other countries have more isolated institutions with their own concerns and agendas. Such a combined approach within the NHS and between Trusts provides greater expertise, experience and a larger number of relevant patients to potentially more refined and quicker clinical trials and investigations.

In addition, the regulatory authorities in the UK have developed well within this new field and provide a reasonable stage on which such advances can be made.

The British interpretation of the ATMP guidelines is also beneficial to regenerative medicine in the UK. As each facility must be licenced by the MHRA and cell products released under this licence (rather than a licence required for each and every cell product), these regulations are easily managed and realistically applied and ATMP's can be produced for trials. This is not necessarily the case in other EU countries, as in Germany for example, where the hospitals exemption is not applied and full approval is needed for each and every ATMP product, rather than just a facilities licence, Qualified Person sign off and MHRA trial approval.

- c. The governmental, academic and charitable funding landscape is maturing well within the UK to focus on truly translational research and investigation and does guide and provide for research to evolve to therapy within initial trials. Such charities include the Medical Research Council, The Wellcome Trust, Cancer Research UK, British Heart Foundation, The Lymphoma and Leukaemia Research Fund, to name only a few, along with each hospitals' own charitable trusts.

The notable impact that the National Institute of Health Research (NIHR) has had on the cell therapy landscape must also be underlined, funding translational centres of excellence by establishing the Biomedical Research Centres, Biomedical Research

Units and cofounding the new UK Clinical Research Collaboration (in partnership with some of the above charities). This foresight and framework has already spawned a number of important early phase trials in regenerative medicine in which we have assisted, with many more to make an imminent impact within the next year. The BRU in Birmingham and the BRC of Guy's and St Thomas' and King's College are two such excellent examples, investigating liver repair and regeneration, and immune regulation in organ transplantation respectively.

In reflection of the way the above institutions and the Department of Health fund regenerative medicine from the bottom up, we must also acknowledge the efforts of the Department and Trade and Industry in facilitating and funding such medical innovation from the top down with their Technology Strategy Board and the Knowledge Transfer Networks. Funding opportunities for commercial innovation or development or commercial and academic collaboration also seed promising opportunities and the new Catapult centre for cell therapy could yield further provision and guidance for the elevation of innovation through and past clinical trials and into the market place.

2. Application of the Science

- a. We believe that medical science is slowly but surely being translated into promising regenerative medicine therapies, although only by particularly motivated individuals and institutions. To give some outline of current clinical applications within our own experience of regenerative medicine in the UK, we can list the following focuses:
 - Autologous, bone marrow stem cells in cardiac repair.
 - Autologous, mobilised peripheral blood stem cells in liver cirrhosis treatment and repair.
 - Mesenchymal Stem Cells in the repair of non-union bone fractures.
 - Angiogenic progenitors in vascular repair for critical limb ischaemia.
 - Dendritic Cell vaccines in hepatoma.
 - Dendritic Cell vaccines in High Grade glioma.
 - Tolerogenic Dendritic Cell therapy in Rheumatoid Arthritis.
 - Regulatory T Cell therapy in renal transplant tolerance.
 - Regulatory T Cell therapy in liver transplant tolerance.
 - Regulatory T Cell therapy in autoimmune disease.
 - Regulatory T Cell therapy in Graft versus Host Disease.
 - Transfected T Cell therapy in head, neck and throat cancer.
 - Transfected T Cell therapy in acute myeloid leukaemia.
 - Viral-specific T Cell therapy in post-transplant viral reactivation (CMV, AdV, etc.)
 - Fungal-specific T Cell therapy for post-transplant immune-compromised patients.
 - Natural Killer Cell and Gamma/Delta T Cell therapy in solid tumours.
 - Graft manipulation in haematopoietic transplantation to include different cell populations.

Similar and additional applications are also in use internationally.

To date, none of these approaches in the UK are further than Phase II clinical trials, although some are nearing the next phase. However, as the National Institute of

Clinical Excellence requires Phase III trial data then none are available generally on the NHS, only within institutions running such trials.

- b. Regenerative medicine holds a huge potential to treat disease in the next 5-10 years and even more so in the next 10-20 years, as techniques and cell products are refined and developed. Current Phase II trials show some exciting possibilities to treat disease but they take time for the proper investigation to be undertaken and there is an uncertain pathway beyond Phase II trials to enable Phase III in regenerative medicine that doesn't translate from the pharmaceutical industry.

This, unfortunately, is the reality versus the headlines. Timelines for proper development of cell therapy and regenerative medicine are always underestimated in the press, as is the need for refining and optimising possible treatments to get the best results, which often need subsequent follow up trials. Further to that, there is a public naiveté to the requirement of sufficient patient numbers within these trials (so many media reports are on one or two patients). This all adds up to a misguided expectation of such therapies being ready now, whereas, unless the pace of funding, set up and running of trials is accelerated, they are still years away.

3. Barriers to Translation

Many barriers to advancing regenerative medicine into Phase I and Phase II trials are now surmountable given that the right funding is in place and the trial has been designed correctly. This is the case for non-advanced (?) medicinal products (non-ATMP's) but also, as more licenced facilities in the UK come online, for Advanced Therapeutic Medicinal Products as well.

However, the Hospitals Exemption and MHRA facilities licence system utilised in the production of ATMP's are not cemented within the ATMP Guidelines, which leads to some uncertainty as to the future regulatory environment that the products must adhere to. We believe that the formalisation of these terms would benefit such regenerative medicine development and lend confidence for the future.

However, the biggest barrier to any progression of regenerative medicine is presently the no-man's land between Phase II trials and market authorisation and NICE approval. NICE stress that a Phase III trial needs to be conducted prior to any cell therapy becoming a routine treatment within the NHS. Private healthcare would, we presume, follow the NHS in this manner, at least here in the UK.

Unfortunately, there is no obvious route to the funding of such trials such that there is within the Pharmaceutical Industry. The aforementioned funding bodies have yet to show enthusiasm for such progression and may not be able to commit so many resources to just a handful of projects, with the inherent risks involved. In addition, there is no large commercial backing available, as there is pharmaceutical development. Innovation mechanisms and venture funding may be utilised but only if there is any kind of Intellectual Property (IP) involved. Without any kind of patentable 'product' there is no obvious business model beyond an 'Expert service'. The very nature of medical science then, in which results are published, shared publicly and developed further, means that there is no protectable, and thus no marketable, element to the therapy. Venture capital and commercial finance is thus difficult to acquire unless there is a proprietary element to the cell acquisition,

isolation, modulation, expansion, preparation or application, so providing the biggest hurdle to the progress of regenerative medicine to therapy.

It is difficult to see a way around the Phase III trial funding problem, unless a new regulatory level is implemented, post-Phase I/II trials but pre-Phase III. We might suggest that if safety has been sufficiently demonstrated in a Phase I and II trial and a positive trend to efficacy is clear then some kind of bridging period be established wherein these safe therapies are allowed to be utilised in a very tightly monitored and regulated fashion within that Trust and its partners. This might be time limited and very closely monitored but would allow the continuation of the momentum of the approach towards the clinic and would provide more data within this period with which to demonstrate efficacy and its worthiness for investment, which may have to be in the context of the value to the NHS and its patients, as well as any potential market value. Further thought would also have to be given to therapies that only have value to the NHS and are not fully marketable.

Other than this progression after Phase II trials, the landscape for regenerative medicine in the UK is fairly conducive to progression. It would seem from our position that some landmark cell therapy trials will commence in the next year and path ahead forged clearer, whether that be pre-empted or through trial and error.

4. Barriers to Commercialisation

- a. It is difficult to foresee the potential future commercial value of regenerative medicine without the progression of such aforementioned trials. Presently the value must be minimal but the future prospects will depend on whether the therapy is commercial in nature and can be sold to the NHS or private patients or whether the processing and procedure are merely ‘services’. The UK benefits from an established network of competent hospital and university facilities progressing towards full MHRA licencing that could easily provide many such regenerative medicine services and already do, within trials. However, such therapy would have to be paid for by the NHS, for the NHS, and so commercial value may have to be examined in terms of health economics, although supply to these services of consumables and equipment would certainly prove of worth to the economy.

If such NHS facilities were to develop and become proficient in such ‘expert services’ to provide regenerative medicine therapies, there may be some scope for contracting out to institutions in other countries in which facilities are not as complete or competent or whose progression is not as advanced. That may require the shipment of regenerative medicine products to that centre or the travel of their patients to the UK, so providing financial income from that sector.

Expertise in the procedure and processing might not be the only marketable ‘expert service’. Any regenerative medicine products that require expansion, banking and storage would also require professional systems and facilities that could easily follow a contract manufacturing model.

The clearest model, however, is if a regenerative medicine product has any patentable or proprietary constituent or element in its production. In this case, development and approval can be gained by a more traditionally commercial entity the products ‘sold’ and supplied under contract.

The value to society is possibly easier to see. Any cellular agent that prolongs life or even cures certain carcinomas or leukaemias is obvious, although benefits need to be weighed against costs. Any cell therapy product that enhances or corrects other treatments, such as transplantation, will not only benefit the patient but save that primary treatment. Other benefits of regenerative medicine may impact heavily on the standard of living for patients. For example, a certain increase in cardiac function after stem cell transplant or the saving of a limb by the transplant of vascular progenitors could save the patient from illness but also avert huge life changes, recovery and social changes, for them and their families, not to mention the impact on the economy of keeping individuals in work as well as happiness.

- b. It may be that the government, or the government funded bodies in this arena, need to better outline and assist development pathways for commercial and service approaches and appreciate the differences between them.
- c. It is unclear what role patenting plays in the commercial development of regenerative medicine. It may prove to be protective and to stimulate investment at lower risk but it can also muddy and confuse the field as the nature of the regenerative medicine product is then often hidden from the patients and the field in general.
- d. Business models have been discussed as above but will differ depending on the product, whether the operating institution establishes a product and a market place to sell it or contracts a service.
- e. Pricing and infrastructure barriers within the NHS are unclear at this early stage. Benefit to cost analysis will clearly be important and costs cannot be prohibitive but it will be seen clearer as the field progresses to routine therapies.

5. International Comparisons

- a. The UK itself is a unique healthcare market and so it is difficult to draw parallels and comparisons from other countries.
- b. The EU Cell and Tissue Directive, the EU Medical Device Directive and the ATMP and GMP Guidelines and CE certifications do provide a clear and uniform platform for European institutions to develop regenerative medicine, although local interpretations can cause problems. Again, the UK interpretations so far seem conducive and sensible. The ATMP approval system may require an interphase, as discussed before.
- c. The UK is not only sensibly and reasonably regulated in terms of regenerative medicine but also adheres to those regulations. These are purely for the safety of the populations and the individuals within the health system requiring treatment but also demonstrate the efficacy of such treatments in relation to risk. Without this strong safety net, patients are open to therapies that have neither proven safe in larger trials or effective.

17 September 2012

**National Institute for Health and Clinical Excellence (NICE),
TiGenix NV and Bupa Health and Wellbeing UK – Oral evidence
(QQ 214-243)**

Evidence Session No. 9

Heard in Public

Questions 214 - 243

TUESDAY 11 DECEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Crickhowell
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Professor Carole Longson, Director, Centre for Health Technology Evaluation, NICE,
Dr Guido Schopen, Vice-President Commercial Operations, TiGenix NV, and
Dr Natalie-Jane MacDonald, Managing Director, Bupa Health and Wellbeing UK.

Q214 The Chairman: I would like to welcome our three witnesses for this first evidence session this morning. Thank you very much for coming to join us. The session is being webcast. Members of the Committee have declared relevant interests, but if they have not declared them they should do so, please, when they speak during the session this morning. I would like to invite the witnesses, in a moment to introduce themselves for the record. If you wish to say anything by way of an opening statement, please feel free to do so but please keep it brief because we are fairly short of time. We have many questions to put to you. Perhaps I could start on the left as I face the panel, with Professor Longson.

Professor Longson: Good morning. My name is Professor Carole Longson. I am Director of the Centre for Health Technology Evaluation at the National Institute for Health and Clinical Excellence. I have no opening remarks to make.

The Chairman: When you speak, I would like you to speak up a bit.

Professor Longson: I will try my best. Is that a little bit better?

The Chairman: Because the room is quite large. I would like now to ask Dr Schopen to introduce himself.

Dr Schopen: Yes, good morning. My name is Guido Schopen. I am Vice-President, Global Commercial Operations at TiGenix. TiGenix is a company that focuses on cell therapies here in Europe and globally, and I have no further opening remarks to make.

Dr MacDonald: I am Dr Natalie-Jane MacDonald. I lead Bupa on health insurance and funding business here in the UK. In the context of your inquiry, I am also speaking with relevance to our other companies in different parts of the world, such as Australia and Spain.

The Chairman: Again, I would like to ask you to speak up when you answer the questions, because the room is large.

Dr MacDonald: Okay.

Q215 The Chairman: Thank you very much for those words of introduction. I would like to kick off by asking a general question, which sets the stage for this session. We are interested in the financial models for implementation of regenerative medicine and therapy, and we are interested in your views on what are effective reimbursement models and, in particular, what would need to change to develop a suitable system for reimbursement for regenerative medicines in the National Health Service. Perhaps I could start with you, Carole.

Professor Longson: Thank you. As you know, NICE, and particularly the Centre for Health Technology Evaluation, is concerned with assessing both the clinical effectiveness and the cost-effectiveness of new technologies. That aspect of cost-effectiveness now runs into a number of evaluation approaches. The longest running of those is our technology appraisal process. That has been going since 1999, but in 2009 we introduced two other evaluation programmes, specifically concerned with the evaluation of new medical technologies. That is our medical technologies programme and our diagnostics assessment programme. The reason for introducing those two programmes, as opposed to just expanding, perhaps, the technology appraisal programme, is to recognise the special nature of new medical technologies and the way that evidence is generated in the medical technology field that is different from the way that pharmaceutical evidence is generated, and to try to develop a set of evaluation processes and methodologies that are much more tailored to new medical technologies. So the way that we did that was to work quite closely, to be honest, with industry, in trying to understand how evidence is generated, how they think about demonstrating the value of their products, and then developing specific processes.

We take a view that if a new medical technology is, in a sense, ready for adoption, then a company should be able to come and talk to us and signal that to us. We would then go through a process of seeing whether it fits into our programme. Primarily, that is to do with whether it is designated as a medical device according to the European legislation, which of course I know we will probably have a discussion about in relation to the new procedures for regenerative medicine. If it is designated as a medical device or a diagnostic, then the way that we look at that is to take quite a holistic view about value, to look at system benefit, patient benefit, the fit within the healthcare system and what sort of things might need to change within the healthcare system in order to enable this technology to be adopted. So we are taking much more of a cost-consequence approach, looking at the

benefits and reviewing them in relation to the costs that are incurred. This is not just about the technology, it is about the costs and offsets to the healthcare system as well.

That has been running since 2009. We have had quite a number of medical devices through there. We have not had a regenerative technology yet, but we are in discussion with quite a few companies about whether their product is ready to be notified and go through that system. I will stop there, maybe as an introduction to the session.

Q216 The Chairman: We want to come back and pick up some of those things, but perhaps, Dr Schopen, you could tell us particularly about the problems that you have experienced when you tried to develop a suitable reimbursement model in Europe, and tell us about what you have done in Belgium.

Dr Schopen: Yes, indeed, TiGenix has a commercial product, the first ATMP approved cell therapy product here in Europe, and it was approved in 2009. Our position right now is very pragmatic and hands-on. We are a biotech company that has invested a lot of money—I think it is fair to say so—and we are offering a new level of evidence compared to what evidence was provided before. Right now, our efforts in Belgium, the Netherlands, and in other markets, is to gain an appropriate reimbursement. We have generated unprecedented evidence and now we are reaching out to the national reimbursement agencies to get into a dialogue with us. Sometimes we are successful with that and sometimes we are not so successful with that.

Overall, from a top-line perspective and regarding the opening question about the challenges for a company that has generated evidence for a product with the first ATMP approval? Certainly we struggle sometimes with not harmonised frameworks. What we also struggle with is lack of responsiveness of our counterparts in some markets. Last but not least, legal certainty is a big unknown for us in some markets, and these are the overall challenges that we have from a very pragmatic implementation perspective at this stage.

Q217 The Chairman: Can you tell us a bit about the reimbursement model that has been developed in Belgium, and why that model may or may not be suitable in the UK?

Dr Schopen: Yes, I am happy to do that. Besides Belgium, we are also reimbursed in the Netherlands in the mean time. As we heard before, we are entering a new field here. There are a lot of uncertainties in this field right now. We have provided a certain body of evidence that was sufficient to grant an ATMP approval, but the big problem and challenge right now is certainly on the reimbursement level. You have to compare reimbursement versus another standard, but what is the other standard? There are no benchmarks. You have already difficulties in comparing an ATMP product against another ATMP if no other ATMP is available. It is furthermore difficult to compare against a standard of care, if it is not clearly defined what the standard of care is. So we are there with a stand-alone body of evidence that this product works and it is safe; otherwise we would not have achieved an approval.

Now there are different approaches, and in Belgium a dynamic efficiency approach, as we call it, was applied. We know nothing is 100% perfect but there is the option to wait and see until we have more evidence—while patients are waiting, who urgently need this kind of therapy—or we apply this dynamic efficiency approach, which is controlled market access. Very concretely speaking, what we were able to do in Belgium, as we were invited to have a dialogue that we are seeking for in other markets as well, was to help defining the profile of the right patient. In our case, because we have the body of evidence, we were in a very good position to tailor it down to a very defined patient population, where we could show

post-hoc superiority against what you might want to call standard therapy. Within this context we also wanted to make sure that we always go only to those medical centres that can do this therapy in the best possible way, so we have expert centres that are well trained. So we are taking care that we go to the right centre; we are taking care that we find the right patients. We agreed with the Government about a target number of patients for a first step, and we also offered a risk-share programme. As we all intend to learn in the future, and we do not see it as a one-step process, we also committed to a registry kind of approach. So, besides, scientific efficacy, which we have provided in an unprecedented way, we are now seeking effectiveness on the day-to-day level to complement the controlled evidence. So far we have what I perceive as very good collaboration between the Government in Belgium and us, as a manufacturer: we work together based on the evidence that we have, and use this evidence to guide a step-wise introduction into the market.

The Chairman: Lord Cunningham wants to follow that up.

Q218 Lord Cunningham of Felling: I would like to ask Dr Schopen: how long did it take to get agreement on this process?

Dr Schopen: In Belgium it was certainly the first case that we had, and took around six to eight months.

Lord Cunningham of Felling: No, sorry, I meant to develop the effective reimbursement system that you are using. How long did it take you to work that out and get agreement to it?

Dr Schopen: We had a process discussing that with the authorities in Belgium, and it took around about six to eight months effective working time. If I may add, it was certainly a particularly challenging situation when we started to do that because it was a learning experience as well because, in parallel, we were digging deep into the data that we had to find the right sub-population to work out models that make sense to the Government, and that made sense to us as well as a commercial company, but that was around the time. In the Netherlands it was roughly the same order of magnitude—a little faster—but the circumstances were a little different, in all fairness.

Q219 The Chairman: Dr MacDonald, would you like to give us your response to the opening question?

Dr MacDonald: Yes, which is obviously slightly different since our decisions are made to fund treatment for our members, rather than from the wider population that the NHS funds, but there may be some points of relevance. Our approach is that, although regenerative technology is new, we apply the same requirements in terms of safety, efficacy and effectiveness as we would to any other treatment or intervention that we would approve to fund on behalf of our members. We take a structured, consensually based decision that seeks to ensure that the scientific evidence is of the highest standard and that it represents an improvement on other treatments. We have developed over the past 10 to 15 years a method using algorithms, starting with drug interventions and more recently in relation to cell-based therapies, that allows us to evaluate new treatments, whether they are to be funded on an unnamed patient basis, in the context of a randomised controlled clinical trial, or for routine use. Our aim in respect of any individual member who comes to us, or their physician who comes to us, is to make a decision on funding within 48 hours. Therefore, although there are similarities in the processes that we go through and in the evaluation of evidence to that which NICE might take, there are obviously differences in

terms of the cost-effectiveness approach that NICE will take, looking at it on a population base.

We are interested in two other elements, both of which have I think been mentioned. First of all, we are interested in how the new treatment or intervention will be applied in the context of the management of the particular condition that the patient has, whether the treatment will be additive and will come on top of existing regimented treatment or whether it will be replacement. That is obviously really important, looking at both the effect but also the cost-effectiveness of any intervention. Obviously, also, in terms of all our members, whose subscriptions fund all treatments—those who have other pathologies and those who are not unwell—we have to make sure that the benefits are proportionate to the costs of the particular intervention.

Q220 Lord Turnberg: I want to follow up with Dr Schopen. You have described your experience in Belgium and the Netherlands; what sort of experience have you had in the UK? Have you approached UK regulators? How far have you got?

Dr Schopen: Yes. We certainly have approached the public sector and the private sector. The private sector was certainly a different experience from the public sector. You (pointing to Dr MacDonald) can probably better explain it all from your perspective, but I think we found it a very pragmatic, a very transparent forward-looking approach. I think it was, to a certain extent, similar to the experience that we had in Belgium and the Netherlands. In its core it aimed to define who the right patient is. We had discussions about that. That was a similar approach. We have approached the public sector as well, and we were seeking to submit our materials, our data, and our dossiers for NICE review. I think you can report on that from your perspective (pointing to Professor Longson). I think overall the position was that, after we had submitted our request for guidance, it took quite some time to get an answer, and we were told that NICE is waiting for more evidence to come. So far, we are sitting there with our evidence and we would love to submit it but we cannot do so.

Q221 The Chairman: Dr Longson, would you like to comment on that?

Professor Longson: Yes. I think that is for me to respond to. Everything that you have heard from the other speakers here pretty much applies to our evaluation processes. We are aiming to find the best place for new technologies, in terms of the NHS. We do that very much in the ways that you have heard about here. We have already issued guidance on similar technologies—not exactly the same technology as the one referred to here. That guidance now is about eight years old. I think it was in 2004 that we issued it. The type of recommendation we issued for these technologies, back in 2004 when we took a look at them, was that they looked promising but more evidence was needed. We have a specific category of recommendation through our technology evaluation processes, whereby we can recommend that the NHS uses them in the context of collecting data. We use that type of recommendation, probably in about 5% to 10% of the pharmaceuticals, but what is coming through our medical technologies and diagnostics programme, is that that category of recommendation seems to apply much more. About 30% of the recommendations that are coming through the medical technologies programme are, in a sense, NICE saying to the NHS, “These are promising new technologies but they need to be used in a way that allows the generation of robust evidence about effectiveness”—that translation from the safety and efficacy environment into the real world. How is that best used and what is the patient population that will derive the most benefit? That was the category that we issued in 2004, and we have been regularly reviewing the need to update that guidance every two or three years. What you have heard about is that conversation that we are having with

manufacturers: is it time to update that guidance? We need a specific type of evidence in order to trigger that review. During that time there was a change in the regulatory environment for these types of technologies, where the medicines regulators decided that they were going to introduce more regulatory process around the safety and efficacy, and at that time we were just about to think through a review but we decided to wait for that regulatory process to emerge. It has done. Again, we are in pretty regular contact with manufacturers about the timing of our updates, and we are just about to go through a review proposal, which basically goes through the steps of saying, “Is it time for NICE to take a more general look at these new technologies?” If we do so, all of the factors that you have heard being described today will be very much part of the appraisal.

Q222 Lord Patel: Can I explore further by asking you to do a little horizon thinking? You reiterated to us what the procedure is now with NICE. What you have not said is what your thinking is for the future, as more cell therapy is developed. It might be autologous cell therapies. It might not apply to large populations. It might apply to individuals. Considering that the reforms of the NHS will rely on your advice in terms of setting the tariff, which the commissioners will then use, what horizon thinking have you done in terms of that?

Professor Longson: That is a very important question, and again when we were thinking of the development of our medical technologies programme, the way that that programme is configured is that we have four academic units in the UK which provide us with the evaluation capacity, so we liaise very closely with those academic units. Back in 2011 we commissioned one of them to develop a report for us on where regenerative medicine and regenerative technologies are going to be in the next few years. That report was delivered to us a few months ago, and I could share the report with you if that would be of interest?

The Chairman: Thank you. Yes, we would like to have that.

Professor Longson: Essentially, the summary of that report was that it is a very developing field. There are lots of technologies that are coming through to research. There are not necessarily that many that are emerging through into consideration for, in a sense, mainstream adoption into the NHS, but there are a few. They were detailed in the report, and we are looking through all of those to see whether we can make contact with the manufacturers to encourage them to engage with us. So a very important issue and we have commissioned a report to do so.

Q223 Lord Willis of Knaresborough: I will just pick up on Lord Patel’s point, because the treatment from your company—autologous therapies that you are using right now—is in some ways the most difficult area because you are not going to have mass populations, 130,000 worldwide is not exactly a large database, but clearly those therapies can be moved out and developed for treating other patients. What worries me about NICE is that you are not part of the solution. The fact that this is one of the most exciting areas of new technologies, and you have here a company that has produced a product which, in fact, gives a permanent treatment or the indication of a permanent treatment, and yet we are not interested. The private sector clearly is interested, and the private sector does not fund anything unless it will get a cost benefit for it. Why are you so out of sync?

Professor Longson: So I do—

Lord Willis of Knaresborough: You see, nothing will happen if you have this sort of old-fashioned view of life.

Professor Longson: I do not think we are out of sync but we are careful.

Q224 The Chairman: Does that mean that the private sector is less careful?

Professor Longson: We are careful because the—

The Chairman: Sorry, does it mean that the private sector is less careful?

Professor Longson: I am not really giving you a view on whether or not the private sector is more careful. I am saying, in terms of our evaluation processes, the one thing that would not be useful is for us to take on the evaluation of a technology in terms of mainstream adoption in the NHS, because that is what we are talking about. It is not reimbursement. NICE is not really a reimbursement agency. All technologies that come to market are available, but we—

The Chairman: Pause for a moment. Lord Patel wants to come back in.

Q225 Lord Winston: We might be being a bit too careful. Take your record, for example, on first-round drugs. Only about 12% or 13% are actually taken up by NICE. Does that not seem a very stringent and extremely careful record, perhaps too careful?

Professor Longson: So talking about pharmaceutical technologies?

Lord Winston: It is the same approach, is it not?

Professor Longson: I will just address that issue and come back to the care. We also have to be careful that we recognise developments in our field and we are picking up on them as soon as we can. So it is a very, very difficult balance. With pharmaceutical technologies that primarily go through evaluation through our technology appraisal programme, we are now able to look at pretty much all the significant new pharmaceuticals that come through the regulatory process, so that is about 40 or 50 new pharmaceuticals per year. Our technology appraisal programme pretty much looks at all of those. Some of those technologies that are for very, very small populations—we are looking at perhaps 10s to 100—do not go through the technology appraisal programme. They go through primarily the specialised commissioning programme, which we are now going to be responsible for from April. So I think, in terms of new pharmaceutical technologies, all the major developments in pharmaceutical medicine will come through the technology appraisal programme, and we have worked really hard on making sure that our recommendations are as timely as possible. So I come back to the careful approach that we are taking. It is a real balance.

Q226 Lord Willis of Knaresborough: May I just intervene, because I think we get the point that you are making. The question we are asking is—both Lord Patel and I; indeed, Dr Schopen also made the point—there is nothing to compare these particular technologies with. You cannot use traditional methodology. What you have not said to us so far—perhaps I have not given you the chance—is: what is your thinking about how you achieve those comparisons, in order that these therapies have a possible chance of getting to the patient?

The Chairman: Could you answer briefly? I would like the other two witnesses to come in.

Professor Longson: That gets to the heart of methodology of health technology assessment. To be very brief, we take the NHS as it is and then compare it with the introduction of the new technology to see what the new technology might bring. That could mean anything

from comparing it to an active intervention, to comparing it to no active interventions if currently the NHS is not using a health technology for those patients. So a very, very broad overview of the comparator is about understanding exactly what the NHS does. Of course, that comes down to thinking very carefully about the patient population. So you have to get that identified as early as possible in the assessment process to know what to compare it to. If I recall, going back to the original 2004 guidance, which was an autologous knee transplant, we did not compare it to anything.²⁴¹

The Chairman: Could you keep it short, please, because I want to give the other witnesses a chance to speak?

Professor Longson: It was nothing to add.

The Chairman: Thank you. Could I ask Dr Schopen and Dr MacDonald to come in?

Dr Schopen: Please allow me to respond directly to your explanations. I think what unifies us, NICE and here one manufacturer, a small company that is trying to build up something, is, yes, we are careful as well. “Careful” is the headline of our company because otherwise we as a company are “dead” and our patients will not be able take advantage from what comes out of our development. So it is a no-brainer that we are careful; it is just the way we approach it. That is where we as a company ask for open-minded discussion. We can sit there and wait for more evidence or we can be there and try what I explained, as a managed introduction and as a close collaboration. It is the call for all parties to a step-wise approach—the right patients, in a very controlled manner. The challenge for us as a company is, that we need to consider that the regulatory framework has also dramatically changed. I understand from the NICE perspective that there was little evidence a while ago, and while they are still seeking for more, the regulatory situation is changing. As of 1 January next year only ATMP-approved products should be available and made available. Looking at the body of evidence that NICE is looking at right now, historically, they have looked at five products. To the best of my knowledge these will have no ATMP approval, so that platform is gone. Looking to the future, they are waiting for more evidence. I am not privileged to have any insight into what evidence they are waiting for, but at least I know something. We heard something about a trial in France and one in the US, probably not ATMP products. In the mean time there is at least one company, at a European level, which has provided the evidence needed and we have regulatory approval for an indication. So I think there is a way forward right now, because the framework has changed—so we would really appreciate it if we could talk how we could manage that all together in the best possible way for the patients, and of course for a small company that is trying to survive.

Dr MacDonald: We are careful as well. There is no lower standard of evidence that we would use than NICE would use. We have done comparative analysis of our decisions against the interventional procedures programme and published that, and found very high concordance within that.

The sorts of things that we can do perhaps to make decision-making quicker are to be very active in terms of horizon-scanning and understanding what is in development and to use the research method and trials as a mechanism of starting to fund patients’ care on an in-patient basis, usually in the context of a clinical trial. We will indeed facilitate our members who might benefit from a particular intervention, a cell-based therapy or otherwise, being included in clinical trials that are recruiting and can help link together clinicians with

²⁴¹ Note from witness: On reviewing the NICE Guidance on Autologous Chondrocyte Implantation we can confirm that we did, in fact, compare it with other interventions.

clinicians in different centres. Then on that basis, once the treatment is at a point at which it may become available for routine funding, we already have quite a lot of experience under our belt.

There is the opportunity, too, through taking careful decisions on a named-patient basis to fund treatments early to be able to improve the quality of the evidence and the speed with which it develops, particularly when it comes to, say, phase 3 research. So we also use a common methodology for the appraisal of drug interventions and cell-based therapy, so we do not use different approaches for different types of interventions.

Professor Longson: Very briefly, just to make sure that the Committee have in their minds that currently, with the technologies that we have been talking about here, we are undertaking a review that will lead to a decision about updating that guidance. So, in a sense, we have tracked the development of the research and we are now in a position—with both that research and the new regulatory environment—to go through another review of that guidance. The question will be whether to do it in the round or, as has been described, whether to ensure that it is solely those that have gone through the new regulatory process that we should look at. That is the decision at hand for us.

The Chairman: Lord O'Neill would like to just follow up on Dr MacDonald's comments.

Q227 Lord O'Neill of Clackmannan: Yes. You have answered one of the questions we were going to put to you on the question of funding. Apparently you are forecasting that insurance premiums will go up by about 10% by 2020. Could you tell us how you arrive at that? Perhaps we can get some indication of what the impact would be if the treatments that you have identified as the cost-increasing factor would apply to the funding of the NHS, if regenerative medicine eventually gets the green light from NICE and we start having it as a treatment in the National Health Service on a broader basis than we have now.

Dr MacDonald: Healthcare cost inflation is a challenge in all developed countries, in the UK and elsewhere. We estimate that traditionally healthcare costs increase by around 8% or 9%. In addition, in our evidence we submitted that we thought, given the knowledge we have now, that cell-based therapies may add up to 10% on top of that. That is the fine line then that we have to tread, and it is why we are so interested not just in whether something is safe and effective but also in how it would play into the system—whether, for example, it will replace existing treatments that can be withdrawn, so that it is not simply adding more costs into the system. We see, here and elsewhere, huge challenges, not just in cell-based therapies. If you look at oncology, we did some work last year that suggested the cost to the NHS and inflation would be of the order of 65% over the decade to 2021, and we see exactly the same inflation on the private side.

I guess the challenge that we have is that we are funded only by member subscriptions, whereas obviously the NHS is funded via the Treasury. But the challenge is exactly the same: to make sure that people get all the healthcare they might need that will benefit them within the bounds of affordability. The extra challenge that we have is of course that all our members already pay for the NHS, and they have an expectation. So for example, historically, we may fund a drug such as herceptin before it is licensed because the evidence base is sufficient for it to be applied for particular women, particular stages of breast cancer, and our members have an expectation that, having already paid to the NHS, if the evidence is there we should fund that. It gives us exactly the same challenge, though, as is faced within the NHS, and as Carole was alluding to on the cost side, of squaring that circle. I think there is no easy answer to it. Some of it comes from the decommissioning of services, the removal of outdated drugs and treatment, improving the process of care and its efficiency

and removing waste, of which there is a tremendous amount both in the private and public sectors in most systems of the world.

The Chairman: There are a number of Members of the Committee who would like to come in: Lord Dixon-Smith, Lord Turnberg and Lord Broers.

Q228 Lord Dixon-Smith: I speak as a lay man who—dare I say it, in this examination?—keeps as far away from the medical profession as I possibly can. What I am reading into what I see here is that we seem to have a situation where the Government is doing a great deal of work to develop this particular science, and is giving it quite a lot of support, which is great. At the same time, we seem to have—if you will forgive me—the biggest potential customer for it in the country being conservative, with a small “c”, in its approach to the question, so that the biggest beneficiary potentially from this technology is the first organisation adopting it, which you might think showed a lack of government co-ordination. It has nothing to do with that at all. I wonder how we climb over this particular hump. It seems to me it is a hump, because the health service ought to have a huge amount to gain from these developments. I accept all the risks that there are involved; it is new and developing technology, but there is this paradox that Bupa now—I have to admit to being a Bupa customer—apparently are quicker on their feet, if I can put it this way. I am uneasy about that.

The Chairman: Does Professor Longson want to give a very brief response because we have other questions to come to? Can you keep it to a few sentences?

Professor Longson: As I am sure you are aware, technology development is absolutely a cyclical process. The translation from research into mainstream use absolutely requires that cycle of evidence-generation. NICE absolutely wants to encourage that cycle of evidence-generation, and as we come to the point where that evidence is at the point where we can look at it for, in a sense, mainstream adoption, that is the concept perhaps of the medical technology programme. As you have heard today, we will step in and evaluate that technology. That is the stage that we are at with these particular products. From 2004 to now it has been in an evidence-generation mode.

Q229 The Chairman: So you are saying you are not small “c” conservative?

Professor Longson: Yes, I am. But we have to think about that space in terms of NICE and what it can do to enable things. It is not just about adoption, it is about research as well.

Q230 The Chairman: What I do not get—and I guess this is what Lord Dixon-Smith is puzzled by—is why it is taking NICE longer than it has taken Bupa or the Belgian authorities. What is the difference? Why is it tougher for you than these other organisations?

Professor Longson: Sure. The model that the Belgian authorities are using is exactly the model that we can use at NICE, so I would not want to discourage you from thinking that we cannot take that model. We do it right now in our processes, but of course I think—²⁴²

Q231 The Chairman: I heard it took six months or so for Dr Schopen’s company to get approval from the Belgian authorities, and it is all up and happening there. Did I understand that correctly, Dr Schopen?

²⁴² Note from witness: In fact NICE is able to do it so I am sure I articulated this appropriately.

Dr Schopen: Yes, that is right. Forgive me, I am a commercial guy, I am very pragmatic at this point. It is just about some basic processes, which are difficult and easy at the same time, but I would avoid the impression that this is a polarising thing between Belgiums here and the UK here. Quite honestly, what we experience—in part I think I cannot disclose it because we are in the middle of the process with other European Governments and authorities as well—are established processes. If I knock at the door in France it is the “Commission Transparence” process, and if I satisfy the needs of the dossier from a formal perspective, and I have the evidence, then I can submit and I can count on a review within a certain period of time. Sometimes it takes a few weeks longer, yes, but then I have a formal answer. I have that in other countries as well. In answer to your question—what can be done?—it would help already if the evidence, in our case certainly, that is available just would get reviewed.

Q232 Lord Turnberg: I wonder if I could offer a word in defence of NICE, because I think NICE has done a marvellous job over the time it has been in operation. I think there is also an awful lot to NICE for what it does, and I think it would be wrong to get hung up on one product produced by one company to judge NICE. I would like us to hear about the review that it is undertaking, and I think the document that you spoke about earlier would be very helpful. But my question relates to the agreement to use herceptin by Bupa, which was a very impressive thing to do when it costs—I do not know—£20,000 a year for a course of treatment. Bupa agreed to fund this in advance of its licensing, and I would be interested to know how it did that and what processes it went through to ensure that that happened.

Dr MacDonald: As is often the case with that drug, and indeed with some of the therapies that you are investigating, the pressure often comes from the clinicians who want to use the application, the drug or the cell-based treatment with their patients. In that case, we reviewed the evidence that supported the use of herceptin for its clinical indication for breast cancer and felt the evidence was strong enough for the treatment to be funded. Therefore we agreed to fund it and then we negotiated the pricing through the network of hospitals and doctors that would be administering it.

Q233 Lord Broers: I have a simple question for Dr MacDonald. You are saying that regenerative medicine is going to increase the costs at roughly 1% a year. The background cost is 10 times that. Would you like to comment on what some of the components of that 10 times the cost of regenerative medicine are?

Dr MacDonald: This is an estimate. This is a forecast based on the information that we have at the moment that takes into account the general trend in medical costs inflation here. It adds what we are seeing so far, from the introduction of such cell-based therapies that are available commercially—the cost of those in terms of their administration—and takes into account, for example, that in areas such as some of the complex or common cancers, such as prostate cancer for example, that it is unlikely that the cell-based therapies that will be introduced will replace those regimes that are already there, but will likely be used as additional stages of management for patients who then need them. On that basis, what we are suggesting is that there will be additional cost to the system that we participate in of up to 10%, which is a substantial cost. Therefore, if it is to be afforded, there need to be corresponding savings made elsewhere in other parts of the system or the process for reimbursement and payment needs to help temper that inflation.

For example, I think you have mentioned opportunities around partnership models and risk-sharing and so on with manufacturers, looking at more imaginative ways to ensure—

Q234 Lord Broers: Do you predict you will have a fall-off in the number of people who can afford your premiums? They have already almost trebled in the past 10 years, have they not?

Dr MacDonald: Yes. Of course, we see this as one of the great areas of pressure in this or in other countries. Where there is a mix between public and private, and people choose to pay on top, their expectations are often of having access to things they might not otherwise get through the state healthcare system. But that can be the case only if it is affordable. Great healthcare that is not affordable does not really count, so that is one of the things that we are seeking to manage. What we do not wish to do is compromise the evidence-based approach that we take to the introduction of new drugs and treatments, and wherever possible not to deprive patients or a group of patients of an intervention that would give them either a sustainable advantage in length of life or significant improvements in aspects of quality of life. We think that would be fundamentally letting people down on the very reason they would choose to come to us in the first place, but it is not an easy equation to balance. Equally, it is not an easy equation to balance with the NHS, and I think the Professor is alluding to some of the challenges that NICE has in trying to balance that equation for the much wider UK population.

Q235 Baroness Sharp of Guildford: I think we have covered a great deal of this whole issue of how NICE is developing its framework for reimbursement and so forth, but there are a number of questions that are still outstanding. One is the new PPRS framework, the change to value-based pricing that recognises the wider value. How far is this going to be embraced within the development of your framework for reimbursement?

Professor Longson: NICE is not responsible for the PPRS. That responsibility lies with the Department of Health, and I am also not sure whether or not the proposed value-based pricing framework would apply to these types of technologies. Again, that would be in the domain of the Department of Health. What we do know from the consultation is that when a new value-based pricing framework may come into existence, NICE will be at the heart of that, in terms of the pharmacoeconomic evaluation. If and when that happens, we will then need to take a look at the components of that value framework and embed it into our methodology. That is anticipated in 2014, but unfortunately I cannot give you any more information because it is not in my domain; it is the Department of Health's.

Q236 Baroness Sharp of Guildford: As I understand it, you are basically preparing for the potential introduction of the staggered reimbursement framework in the future.

Professor Longson: What we have been doing for the past 12 months is taking a look at our current methodologies of, particularly, pharmaceutical appraisal—pharmaceutical evaluation, where the PPRS will apply as far as I understand. It is not my area of expertise. We are also taking a look at the emerging methodologies that are coming out of the PPRS development, and evaluating whether or not some of them can be applied already to our technology appraisal programme. That discussion is going to our board in January, so we have been again looking at the emerging methodological research developments, to see what we can adopt now, in a sense outwith the PPRS arrangements because those methodologies are the methodologies of economic evaluation.

Q237 Baroness Sharp of Guildford: Yes. In terms of timing, what sort of timing do you envisage in developing this? When are we likely to see a reimbursement procedure in place within the NHS?

Professor Longson: The PPRS itself is anticipated to be introduced in 2014, so any formal update of our methodologies to recognise the new pricing arrangements in the UK—which again as I stress is not the domain of NICE but that of the Department of Health—would have to happen alongside that 2014 introduction and, therefore, new pharmaceutical technologies that will come for technology appraisal from 2014 would have to adopt that framework. What I am not sure—it is just not in my remit—is whether these types of technologies would come under that banner of the PPRS. That would be something you would have to ask colleagues at the Department of Health.

Q238 The Chairman: Thank you. Can you just tell us, do you give guidance to PCTs to commission cell therapies that are appropriate for use, even if they have not had NICE approval?

Professor Longson: All of our guidance comes out from our guidance-producing programmes, and in a sense that is the signal to PCTs, as they were, and clinical commissioning groups in the future. Outside that guidance, the other things that we are doing—again, it started with pharmaceuticals but we are now introducing a similar type of output for medical technologies—are again about interesting up-and-coming new innovative technologies, to give the NHS a signal of what is coming up. We are calling them medical technology innovation briefings. We have just been in discussions with the Department of Health about the funding for those medical innovation briefings, and again a proposal to start those from April 2013 is going to our board in January. So this sits outside our formal guidance processes. It is about giving the signal to the NHS of what is coming up, what is promising, what it needs to prepare for, and hopefully some of those innovations that go through our innovation briefing document will then go into our formal guidance-production process—those really promising ones that are going to make a difference.

Q239 The Chairman: Thank you. Dr Schopen, you want to come in and then I will turn to Lord Selborne.

Dr Schopen: As a quick insight into our day-to-day experience with PCTs, yes, the PCTs know well the NICE guidance against this kind of therapy (autologous chondrocyte implantation). That then, on a day-to-day level, when there are patients in need, will be held against us despite the fact that we (ChondroCelect) were not part of the review in 2005 and later. That is what I mentioned in the introduction about framework issues. If these different constituencies do not talk to each other, it is the patient who in the end does not get the treatment.

Q240 Earl of Selborne: We have been discussing the most appropriate mechanisms for encouraging evidence-generation, with the hope that therapies and technologies will ultimately, where appropriate, be available for mainstream adoption by the National Health Service and, indeed, by other providers. We have heard also that at least for one product there seems to be a rather more pragmatic—I think was the word that was used—but certainly a faster procedure in Belgium, and an even faster one in the Netherlands, as I understand it. From all this, I think we recognise that it is an extremely complicated exercise to generate this evidence base with very often such small data. Nevertheless, are there lessons from other countries, not just Belgium and Holland, which we could draw on helpfully, particularly bearing in mind the review of guidance coming up?

The Chairman: Perhaps Dr Schopen, who has worked in other countries, could offer a view.

Dr Schopen: Yes. The guidance or the feedback I can give—I do not think I can add much more to it—is that we have an opportunity in other countries to apply much more directly, and get reviewed faster. It is acknowledged that there is not little information available. There is a lot of information now available, at least for one product and probably there will be more to come. What one can learn is a dynamic efficiency approach that other constituencies apply and in the end it is an open dialogue. We are well aware and we are all working on the same level of uncertainty and generating more evidence. This open dialogue works relatively well in other markets, and that gives us an opportunity to bring this product into the market. I cannot comment here on more countries, but there are more countries where we are pretty advanced in the meantime along this avenue. There is no Government that we are dealing with right now in our approach—this is not a kind of select case here; After all, this is the first cell therapy approved in Europe. Keep in mind that we are approved in the end. Within this framework they all approach it the same way. They just say, “What is the right patient?” and we have the evidence to show that. Through analysis in our randomised controlled trials, we have found superiority data in defined patient populations, so from health, economics and a cost perspective, we can point to the right patient. That is in our best interests as well, because we want to be successful in our offering to the market. In addition with our data on hand we are confident to offering risk-share programs (for cases where the therapy does not work) and finally, another important learning from other countries is to go to the right centres. You cannot give this new therapy just to any centre. It needs to be a trained centre. It needs to be an educated centre, and so we are approaching it step-by-step right now, but it is based on level I controlled evidence, as approved by ATMP.

Dr MacDonald: One point that might be relevant is that obviously different countries vary, both in the regulated environment and in their funding systems, as we are hearing. One of the things that we do, though, is to centralise the review of the evidence in relation to a drug or an intervention or a new treatment, on the basis that medicine and science are international disciplines and the evidential base, if it is robust enough from a scientific perspective to suggest that a treatment is as good as or better than existing treatments, that is as applicable in Australia, Spain or India as it is in the UK. So that evidential analysis we do once, and then the decision about the funding will obviously be made differently, depending on the regulatory regime in the country in question. So the way in which drugs are introduced, for example, in Australia is very different from the UK, but the evidence that we would use will be the same wherever in the world we have members.

Q241 The Chairman: Professor Longson, do you wish to answer with a brief comment about lessons that might be learnt from other countries?

Professor Longson: Yes. The models that have been described today, which you have heard about in the Netherlands and in Belgium, are models that are used and can be used in the UK, and NICE is doing that. We have a series of what we term patient access schemes or patient access arrangements, which are exactly designed to try to tailor the use of the technology to the appropriate set of individual patients in the NHS, so they are patient access scheme arrangements. Again, they primarily relate to pharmaceuticals, but the model of working through the data to be able to ensure that you get the best value for money—the right effectiveness at the best cost—is exactly the model that we would be using when we come to take a look at these new technologies.

National Institute for Health and Clinical Excellence (NICE), TiGenix NV and Bupa Health and Wellbeing UK – Oral evidence (QQ 214-243)

Q242 Lord Willis of Knaresborough: May I just ask Dr Schopen a general question? Are you owned by a large conglomerate or are you an independent company? How have you managed to get your finance together to get your product to market?

Dr Schopen: We are venture capital funded.

Lord Willis of Knaresborough: Venture capital funded?

Dr Schopen: Yes.

Q243 Lord Willis of Knaresborough: So why have you not sold out to the big Americans?

Dr Schopen: We like to be European.

The Chairman: We have run out of time. I thank the three witnesses very much for their helpful evidence this morning. You will in due course receive a transcript of the session and have an opportunity to make any corrections you wish to make. Also, if there are any points you wish to follow up with in writing, please do not hesitate to do so. We did have a promise from NICE that it would send us a document, to which Professor Longson referred, and we would be very pleased to see that. Thank you very much indeed.

National Institute for Health and Clinical Excellence (NICE) – Supplementary written evidence

This memorandum has been prepared by Professor Carole Longson, Director, Centre for Health Technology Evaluation, NICE.

Further to the evidence session on 10 December 2012, I am writing as requested to provide the committee with the report on regenerative medicine commissioned by NICE in March 2012 from the Birmingham and Brunel External Assessment Centre.

I would also like to take the opportunity to expand on the oral evidence I gave to the committee and am attaching a briefing on some aspects of NICE's medical technologies evaluation work that relates more broadly to the committee's interests. The briefing describes some of NICE's routine work to increase engagement between NICE and companies that are developing novel technologies for potential use in the NHS; and our commitment to the research agenda that is essential in enabling the more widespread use of technologies, including regenerative medicine products.

Medical technology evaluation at NICE

NICE is the independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health. Our guidance supports healthcare professionals and others to make sure that the care they provide is of the highest attainable quality, and offers the NHS the best value for money.

In 2009 NICE established an innovative system for identifying and encouraging early adoption of new or novel medical devices and diagnostic technologies that, following evaluation, demonstrate the potential to improve the experience and outcomes of patients and/or to drive efficiencies in the use of NHS resources.

This system was established to ensure that NICE is as flexible as possible in its approach to the evaluation of new technologies, and reflects of our desire to tailor our processes to the distinct characteristics and differing value propositions for medical technology products. Medical technologies submitted to NICE for evaluation through a single access point may follow one of a number of evaluation pathways, each producing different types of guidance for the NHS. The pathways are described in Appendix I.

The NICE Medical Technologies Evaluation Programme (MTEP) was constructed through a series of discussions with many interested parties – industry, clinicians, commissioners, health-service managers, academics, scientists and patients. The programme is run according to the following principles:

- All forms of evidence (published and unpublished and with no design or quality threshold) are considered, reflecting the often sparse evidence base for medical technologies.

- The evaluation timeline is as short as possible to reflect the often rapid pace of development of technologies.
- The initial assessment of a technology is based on the claims made for a single product: to simulate the decision making in health systems and ensure that guidance is as relevant as possible. During evaluation, and depending on the type of guidance being produced, the evaluation may be based on a sponsor's submission, including cost modelling. Clear and explicit value propositions about all aspects of introducing new technologies in place of 'current management' are central to evaluations.
- In medical technologies guidance development, system benefits are given equal prominence to patient benefits, and sustainability benefits are identified and actively considered.
- Technologies are notified to NICE by innovators (usually a commercial sponsor, i.e. manufacturer or distributor) so that the full range of medical technology products can be considered.
- Products which are novel but not new can be notified and may be evaluated if there is evidence that they have plausible claimed benefits and are not being routinely adopted as they should be in the NHS.
- Medical technologies guidance specifically examines products which are plausibly resource-releasing for the NHS. The economic method used is cost-consequences analysis.

The programme has a dual function: to identify and select promising technologies from those notified, and route them to the most appropriate NICE programme. This ensures flexibility in enabling a wide range of products, with different value propositions, to be handled.

One output of the programme is NICE medical technologies guidance, which indicates whether the available evidence supports the case for adopting a technology as an alternative to current management. It describes the advantages of doing so for patients and for the service; and outlines changes to care pathways that introducing the technology would require. It presents the cost consequences, calculated over an appropriate length of time. This kind of recommendation and explicit description of likely outcomes is specifically intended to influence commissioners and providers by providing the information they need to make decisions about the value of introducing new technologies. It will assist clinicians who want to introduce technologies and can influence those who are uncertain; and we hope it also provides a useful tool for patients who are keen to gain access to new technologies which will help them.

One important feature of the programme is the capacity that NICE has put in place for facilitating the development of further independent evidence through research and audit, stemming from recommendations that we make. We have appointed independent external assessment centres to support guidance production, and a key part of their remit is to facilitate the development of further relevant independent evidence when NICE

National Institute for Health and Clinical Excellence (NICE) – Supplementary written evidence

recommends further research, working with technology manufacturers as part of this process.

Case Study: Further research into a novel device to promote wound healing

In July 2011 NICE produced medical technology guidance on the MIST Therapy system, a device which claims to promote wound healing in chronic, 'hard to heal' and acute wounds by delivering low-energy, low-intensity ultrasound to the base of the wound through a continuous saline mist. It is claimed by the device manufacturer that it can improve healing rates, thus reducing treatment time and associated costs, and so offers advantages to both patients and the NHS, compared with standard NHS methods of wound management.

The Medical Technologies Advisory Committee's view was that the device shows real promise, but there was not yet enough evidence of sufficient quality to enable a recommendation for routine adoption of its use. In its recommendations it provided a detailed outline of the type of research that would be needed in order for the committee to recommend the use of the technology in the NHS.

Following this, the external assessment centre contracted by NICE has facilitated the setting up of a clinical trial²⁴³ which will recruit patients with chronic venous leg ulcers, and will be undertaken independently by Cardiff University and Cardiff and Vale University Health Board.

The trial objective is to determine if there is a difference in the mean change in wound area after 8 weeks of treatment, between patients treated with MIST plus standard care, and those receiving standard care alone.

In addition to the research recommendation, the NICE committee also advised that current users of the MIST Therapy system who are unable to join research studies should use NICE's audit criteria to collect further information on healing rates, duration of treatment and quality of life and publish their results.

NICE will review the 2011 guidance when new evidence becomes available.

Encouraging interaction between NICE and medical technology developers

In addition to consulting with industry when setting up the NICE Medical Technologies Evaluation Programme, NICE has developed a productive ongoing dialogue with both individual manufacturers and industry groups including the Association of British Healthcare Industries (ABHI), the British In Vitro Diagnostics Association (BIVDA) and the Association of Healthcare Technology Providers for Imaging (AXrEM). This is an essential part of our ongoing work with medical technologies, and allows us a better understanding of the industry's issues and requirements, as well as ensuring that our programmes continue to be fit for purpose. Systems are in place to hold discussions with developers of regenerative medicine technologies. The MTEP team has personnel dedicated to external engagement and currently about 100 meetings with individual companies are held each year. In addition,

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<http://www.nice.org.uk/newsroom/pressreleases/NICERecommendedClinicalTrialDueToStartOnPromisingWoundHealingDevice.jsp>

National Institute for Health and Clinical Excellence (NICE) – Supplementary written evidence

the Programme works closely with networks, such as MediLink UK and the Technology Strategy Board, whose function is to support technology developers.

Case Study: Developing a value proposition for medical technologies

Following the action set out for NICE in the Strategy for UK Life Sciences report²⁴⁴, and interest from medical technology developers, insurers and the investor community to better understand how NICE assesses value, the NICE Scientific Advice team developed a training seminar programme on developing a value proposition for device and diagnostic technologies. Seminars were run on five occasions between September and November 2012.

Seminars were opened by an introductory talk delivered by a member of the senior management team at NICE. Each seminar included a presentation in lecture format and practical exercises. Each seminar also included a guest speaker whose product underwent evaluation at NICE. At the end of the seminar there was an interactive question and answer session with the Medical Technologies and Diagnostic Assessment programme teams. Over 80 people registered to attend, and we aim to re-run this seminar series in 2013.

We are now exploring the potential for partnering with other organisations such as the Technology Strategy Board and UK Trade and Investment in order to reach a wider network of contacts than those currently known to NICE. We are adapting the medical technology seminar format to develop a course specifically for the pharmaceutical industry.

Appendix I: Types of evaluation carried out at NICE

The NICE Medical Technologies Evaluation Programme is the single point of access for evaluation by NICE of medical devices or diagnostic tests that offer advantages to patients and to the NHS. Technologies are usually notified by manufacturers and, if selected for guidance development, are routed to the most appropriate guidance programme.

Medical technologies submitted to NICE for evaluation may follow one of the following pathways, each producing different types of guidance for the NHS:

NICE interventional procedures guidance focuses on the safety and efficacy of interventional procedures²⁴⁵. Many of the procedures are new, but established procedures are also considered if there is uncertainty about their safety or how well they work. Unlike other types of NICE guidance, interventional procedures guidance does not provide advice on whether procedures are cost effective. Instead it provides advice on whether such procedures are safe and efficacious enough to be used in clinical practice, the circumstances in which procedures should be used, and whether special arrangements are needed for patient consent before the procedures are carried out.

A clinician intending to undertake a new interventional procedure in the NHS for the first time is required to check the NICE website and to notify the procedure to NICE if it has

²⁴⁴ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf p28

²⁴⁵ NICE defines an 'interventional procedure' as a procedure used for diagnosis or for treatment that involves making a cut or a hole to gain access to the inside of a patient's body (eg a cannula), gaining access to a body cavity without cutting into the body (eg endoscopy), or using electromagnetic radiation such as x-rays.

not already been notified. In addition, anyone may notify a procedure for consideration, and both device manufacturers and hospitals regularly do so. Interventional procedures guidance frequently refers to the need for additional evidence from data collection or other further research.

Medical technologies guidance is designed to evaluate technologies that are cost neutral or reduce costs for the NHS, so that they offer better value than current practice, and improve the efficiency of services. The technology sponsor submits clinical and cost evidence which supports the claims for the product. If the evidence supports the case for adoption, then NICE publishes guidance specifying what those advantages are, and using cost-modelling, describes the likely resource benefits to the NHS. .

There may be evidence to suggest that a device is effective but there is uncertainty about whether it would produce the claimed benefits in normal NHS practice. Under those circumstances NICE can recommend and facilitate research to answer the relevant questions and to provide information to subsequently update its guidance to the NHS.

NICE diagnostics guidance promotes the rapid and consistent adoption of innovative clinically and cost-effective diagnostic technologies in the NHS. It aims to improve treatment choice or the length and quality of life by evaluating diagnostic technologies that have the potential to improve key clinical decisions, and to improve the efficient use of NHS resources.

NICE technology appraisal guidance is probably the most well-known of NICE's guidance outputs. In technology appraisal guidance, whether on drugs or medical technologies, the focus is on clinical and cost effectiveness – essentially whether the increased patient benefits provided over and above existing NHS practice are worth the additional costs the NHS must pay for the drug or technology. If a technology is recommended by NICE for use in certain patients then there is a mandate on the NHS to provide those patients with access to its use.

Technologies are selected for the technology appraisal process following detailed consideration and are referred to NICE by the Ministers of State: this type of guidance tends to be restricted to technologies that are likely to have a major financial impact on the NHS.

NICE clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They usually include recommendations about the use of particular medical technologies.

18 January 2013

National Institute for Social Care and Health Research (NISCHR) and the Welsh Government – Written evidence

**National Institute for Social Care and Health Research (NISCHR)
and the Welsh Government – Written evidence**

[Submission to be found under Welsh Government](#)

NHS Blood & Transplant (NHSBT) – Written evidence

I Overview of NHS Blood & Transplant (NHSBT) in Relation to Regenerative Medicine

- 1 NHSBT provides blood, tissues and stem cells to the NHS in England and North Wales, and organs to the whole of the UK. Through its Stem Cell Services and Tissue Services functions, NHSBT routinely undertakes the procurement, testing, processing, storage and distribution of cells and tissues for human application via seven geographically dispersed, HTA & MHRA licensed and JACIE accredited facilities. In addition, its Specialist Therapeutic Services run six collection and processing clinical facilities within geographically overlapping areas for the national provision of 2000 haemopoietic stem cells and immunotherapies annually. Ethically procured, safe, high quality and regulatory compliant cells and tissues are the essential starting materials for Regenerative Medicine (RM).
- 2 In addition, NHSBT has obtained, MHRA Manufacturing authorisation to produce Investigational Medicinal Products (IMP) for clinical trials, and Unlicensed Medicinal Products for named patients, within dedicated and well resourced Advanced Therapy Units (ATU). These units operate under the two general business models of: -
 - Scale Up (“bulk” manufacture in a single centre for (inter)national supply)
 - Scale Out (multiple centres operating under a unified quality system and processes to deliver “close to patient” therapies)
- 3 This national network of licensed and accredited cell and tissue processing facilities is supported by integrated infectious disease, bacteriology, red cell immunology, cell culture and tissue typing testing departments, national logistics support and cold chain supply. Uniquely these are all covered under the umbrella of a single overarching national Quality Assurance and regulatory compliance structure.
- 4 The network also includes the Clinical Biotechnology Centre (CBC) in Bristol, whose expertise lies in the development and manufacture of clinical grade biologics and gene therapy products.
- 5 The management of all of the above sits within a single NHSBT Directorate. Direction is set through a national strategy group, which includes research activity.
- 6 It is NHSBT’s view that:
 - a) Our infrastructure is pivotal to the effective manufacture and delivery of Regenerative Medicine
 - b) Future strategies should focus on using existing GMP facilities rather than creating further capacity in the UK

2 The research base

2.1 How does the UK rank internationally in the scientific field of regenerative medicine?

- 7 The UK is a leader in regenerative medicine (RM) translational research, delivering 23% of the clinical trials currently recruiting throughout Europe²⁴⁶. Germany and France are also investing heavily in this area, and are seen by commercial companies as having the advantage of being geographically central within Europe. However the primary investment, globally, is in the USA and importantly this is where products are being translated into commercial therapies (e.g. Organogenesis)²⁴⁷.

²⁴⁶ Clinicaltrials.gov search for “stem cell” and filtered by “recruiting”, 15/8/12.

²⁴⁷ SCI Market Analysis, Review of New Product Opportunities and Investment Plan, February 2012.

- 8 Looking forward, a key factor to the UK's international competitiveness in RM will be its logistical infrastructure. The UK has a significant advantage in this area as it can utilise the stem cell, tissue, blood and organ supply chains managed by NHSBT (and its links to other UK Blood Services) to provide organisations with validated delivery systems.
- 9 Commercial organisations will prefer to work with a single robust supply chain. This resource is not available in countries that have federal business models for delivering blood (e.g. Germany), giving the UK an early commercial advantage. For example the American Red Cross covers 40% of the USA and is already in commercial partnerships with RM companies. Finland is also partnering TiGenix to facilitate the delivery of ChondroSelect (autologous cartilage defect treatment).

2.2 Where does the UK have strengths and weaknesses in the field?

- 10 The strengths, in addition to the established supply chain described above, are the UK's multiple academic centres of excellence; research councils and Technology Strategy Board (TSB) early translational funding; as well as the NHS as a single healthcare provider who, once a therapy is approved, can deliver RM treatments nationally;
- 11 The weaknesses are, primarily, the manufacturing skill sets of clinicians and academics who do not understand the product development rigour required to launch viable therapies; and the capability of GMP units to manufacture to the required regulatory level and manufacturing scale.
- 12 These weaknesses however represent an opportunity for the UK government to lever the UK's established infrastructure to speed clinical translation. NHSBT manages half the GMP capacity²⁴⁸ in the UK under a single quality system, and has a strong track record of working with academics, regulatory authorities and clinicians to translate research into viable therapies.
- 13 NHSBT has an extensive research programme in RM which is lead by internationally recognised experts. The RM research programme includes work in the fields of tissue engineering, gene therapy and stem cell immunology. NHSBT's Tissue Development Laboratory has developed and patented processes for sterilisation and decellularisation of tissues including bone and dermis. Decellularised human dermis has been shown to improve the treatment of chronic non-healing leg ulcers. We have recently begun to develop third generation grafts where the recipient cells are encouraged to recolonise and differentiate *in vitro* prior to implantation. Further studies have evaluated whether limbal stem cells can be combined with decellularised matrices to provide a mechanism to replace missing cornea and hence restore sight.
- 14 Working together with academics and commercial sponsors, NHSBT's researchers in Birmingham have developed adoptive T-cell therapy (ACT) for viral infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV). The success of this 'first-in-man' phase I trial lead to a multi-centre phase II randomised controlled trial (ACE~ASPECT) in unrelated transplant patients at high risk of CMV reactivation.
- 15 NHSBT also holds two Programme grants from the NIHR, total value £1.4m per annum, that are in the field of regenerative medicine. One of these Programme Grants aims to improve haematological engraftment into and reconstitution from transplanted haematopoietic stem cells (HSC) in the bone marrow after HSC transplant. The objectives are:
 - a. to understand stem cell fate decisions and improve haematological homing and engraftment following HSC transplantation to reduce graft failure and graft delays;

²⁴⁸ ATMP Manufacturing Community Review, due for publishing in summer 2012.

- b. to characterise and target acute leukaemia stem-like cells and hence residual malignant disease; and
 - c. to reduce or eradicate specific complications of HSCT that may contribute to graft failure, specifically Graft v Host Disease (GvHD) and infections.
- 16 The second Programme Grant is focused on the development of new and improved treatment opportunities for disorders with unmet medical needs using advances in gene transfer and tissue engineering technologies. This Programme has four aims:
- a. To develop novel, safe and potentially curative treatments using novel gene transfer strategies. This work builds upon the demonstration that a single peripheral vein administration of an Adeno Associated Virus vector system in a related condition, haemophilia B (HB), resulted in sustained increases in plasma FIX;
 - b. To engineer T cells for effective, targeted and durable eradication of chronic lymphocytic leukaemia by generating bi-specific gene modified T cells which recognise CMV infected cells through their native T-cell receptor (TCR) and leukaemia cells via a tumour specific receptor.
 - c. To derive iPS cells under GMP compliant conditions, for cellular replacement therapy.
 - d. To foster tissue repair through the generation of new blood vessels and supportive cellular matrix.
- 17 The success and strengths of these research programmes has been recognised by continued funding from NIHR through to 2015.

2.3 Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

- 18 The major funders are the Technology Strategy Board (TSB) and Medical Research Council (MRC) although the UK Stem Cell foundation, National Institute for health Research (NIHR) and Engineering & Physical Sciences Research Council (EPSRC) are also active. In addition European funding is available.
- 19 The challenge is not the availability of money, especially with the recent creation of the BioMedical Catalyst, Cell Therapy Catapult and Regen Med Platform, but confusion as to which fund/scheme/organisation researchers should approach. A key action for Government could be to create a road map that enables organisations to map their position in the development process against the most relevant funding resource.

3 Application of the science

3.1 Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

- 20 Translation is limited in the UK with only a handful of companies (e.g. ReNeuron) operating on a commercial footing and none providing a fully marketable product, although Cell Medica does deliver a compassionate use programme. This is due to the therapeutic cost (c£20,000 per treatment²⁴⁹) and the fact that non-medicinal therapies must be approved by Primary Care Trusts (PCTs) on an individual patient basis. In addition RM is closer to a transplant than a drug in that costs are realised immediately (surgery, etc) whilst savings are accrued over time (reduced chronic care, etc), meaning that hospitals are being asked to carry the cost of savings realised within the wider NHS.

²⁴⁹ Based on cost of TiGenix Chondroselect and Cell Medica Cytovir.

21 The RM clinical focus is on developing therapies within orthopaedics and wound healing²⁵⁰. Indeed therapies, such as autologous chondrocyte implantation, are provided on a regular basis within hospitals under the Hospital Exemption (HE) scheme provisions of the ATMP regulations.

3.2 What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

22 From a commercial view point, until the commissioning issues (cost and assessment), described above, are addressed the impact of RM in the UK will be limited. However, due to the accelerated regulatory processes and current unmet medical need, orphan indications²⁵¹ are likely to be the first to market. This will have a high impact within niche patient populations and provide exemplars of how to commission RM therapies more widely.

23 The reality of RM is that translational development is increasing²⁵² and, globally, therapies are reaching patients with an estimated market value of \$7.3bn by 2014²⁵³. Further insight can be gained if RM is categorised into structural (e.g. tissue scaffolds) and functional (e.g. cardiac treatments) therapies. It is likely that structural therapies will appear within 5-10 years and functional systems outside this window.

4 Barriers to translation

4.1 Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

24 The stock take actions, in summary, were to coordinate funding, create an integrated strategy and work with NHSBT to develop its supply and delivery chains for application within RM.

25 The creation of the BioMedical Catalyst, UK Regen Med Platform and the Cell Therapy Catapult has moved a long way to meeting these goals. However more clarity could be given around how these interventions work together and interact with more established funding streams.

26 The next action, therefore, could be to build on NHSBTs current RM operations (App I) to aid in the creation of an integrated delivery system that encompasses the consent, collection, manufacture and delivery of RM therapies.

4.2 What difficulties are encountered when conducting clinical trials and how could these be overcome?

27 The primary challenge is to improve the connectivity between academics and clinicians developing RM, and those with GMP know-how. As discussed earlier (2.2) this leads to

²⁵⁰ Progress in the Tissue Engineering and Stem Cell Industry; "Are we there yet?", Jaklenec et al; Tissue engineering: Part B, volume 18, Number 3, 2012.

²⁵¹ Orphan designation is applied to "medicines intended for the treatment, prevention or diagnosis of rare diseases (defined as those that affect fewer than five in 10,000 persons in the EU", EMEA List of orphan designated authorised medicines, 6 Nov 2008.

²⁵² Clinical Development of ATMPs in Europe: Evidence that regulators must be proactive, Molecular Therapy Vol 20 No 3, March 2012.

²⁵³ Alliance for Regenerative Medicine Annual Industry Report, may 2012.

translational delays as academically developed manufacturing processes are often not ready for the regulatory rigour required for commercial manufacture. NHSBT is in an optimal position to facilitate translation through our connections with academia.

28 To overcome this either a GMP training programme could be built into academic institutions or collaborations should be encouraged with organisations who understand how to manufacture viable RM at scale.

29 NHSBT has begun to address this by building a relationship with the MRC and the UK Stem Cell Foundation where grant applicants are encouraged to discuss their process with NHSBT before submission. Although in its early stages this will ensure that only projects capable of completing the translational process are funded.

4.3 What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

30 The rapid development of early phase clinical trials is constrained by challenges in patient recruitment and made worse by multiple trials with similar therapies. It would therefore be helpful to develop a national network for coordination of cell therapy clinical trials. This could be a role for the Cell Therapy Catapult that would also enable it to develop a strong relationship with clinical developers and researchers.

4.4 What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

31 Commissioning and cost are the initial barriers, as discussed in 3.1, with manufacturing and supply chain becoming issues as patient numbers increase (as discussed in “Where does the UK have strengths and weaknesses in the field?”)

5 Barriers to commercialisation

5.1 What is the current and potential future, commercial value of the sector to the UK economy? What is its value to society?

32 The value will be two fold. Initially with business locating in the UK due to the established infrastructure leading to increased employment (primary aim of the Cell Therapy Catapult). Secondary value will be gained through the reduction in lost working days due to chronic illness. Positive cost utility savings have been demonstrated by TiGenix (first registered ATMP)²⁵⁴

5.2 Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

33 Funding and NHS adoption are the key market failures. In terms of funding, post the recent introduction of the BioMedical Catalyst, Cell Therapy Catapult and Regen Med Platform, there is little extra that Government can provide. Indeed it is over to RM developers to accept that they are being generously funded and that there is limited venture capital available within this market. This paradigm is likely to continue for the foreseeable future so organisations need to develop more innovative business models to fund development.

34 Where Government can play a part is in developing the NHS to be an early adopter of RM. This can be facilitated, initially, by using the skills of established organisations, such as NHSBT, to deliver RM from “within the NHS”. However in the longer term the

²⁵⁴ The Cost Utility of Autologous Chondrocytes Implantation Using ChondroCelect – in Symptomatic Knee Cartilage Lesions in Belgium, Pharmacoeconomics 2010; 28 (12):

requirement is for the NHS to become a clinical trials resource that has the flexibility and culture to deliver innovative programmes.

5.3 What role does patenting play in the commercial development of regenerative treatments?

- 35 Patents are the “hardest currency” for investment and commercialisation. Know how (trade secrets) including materials and cell-lines have a value but rarely the same as patented products. Therefore being the first to patent and having one’s own patents to trade is critical to successful commercialisation.
- 36 One of the barriers is the comparatively high cost of the patent system during the early years of “product” life, especially when there is still a high risk of product or process failure. Therefore assistance for patent protection and competitor patent evaluation through grants or tax credits could significantly improve the chances of commercialisation of RM.

5.4 What business models are most appropriate to support the development of regenerative treatments?

- 37 Organisations need to move away from a reliance on grant and investment funding. A total reliance on external funding results in unrealistic investor expectations and is not feasible in the current economic climate. Companies need to be encouraged to develop a portfolio of funding sources based around core internal investment. This “bootstrapping” model of developing products and services, outside the primary therapy, to generate income has been shown to be successful in the UK by both ReNeuron²⁵⁵ and Intercytex²⁵⁶.

5.5 What are the barriers to securing finance to develop such treatments?

- 38 Big pharma are only cautiously investing²⁵⁷ because there is no clear route to market and the returns on investment are closer to lower-profit medical devices rather than high-profit pharmaceuticals²⁵⁸. Corporate investors, based on previous investment histories, perceive a higher risk in RM and are likely to wait for the “first winner” to emerge before investing heavily.

5.6 Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

- 39 Currently pricing structures are not appropriate. As described in 3.1 the challenge is that cost is realised within a hospital setting, whilst the savings are over the longer term and accrued within the community.

5.7 What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

- 40 Within the NHS the appraisal process for innovative therapies can theoretically accommodate RM. However to realise this potential more thought needs to be given to cost consequences and comparators.
- 41 Externally, the barriers are in creating robust delivery and manufacture strategy for each RM. The challenge is that manufacture is often completed in hospitals by a few highly skilled academic clinicians within facilities operating under a variety of quality systems. This adds

²⁵⁵ ReNcell is a non clinical cell line developed by ReNeuron and marketed by Millipore (www.millipore.com/catalogue/item/SCC007)

²⁵⁶ Cell2Therapy is a manufacturing consultancy service utilising the Intercytex Directors unique experience (www.cell2therapy.com)

²⁵⁷ McKernan et al, *Pharmas Developing interest in Stem Cells*, Stem Cell 2010 6(6) 517-520.

²⁵⁸ BiA, *Cell Therapy and RM Advisory Committee*, 2011.

capacity and geographic limits, therefore to move forward the industry could benefit from utilising the inherent skills, infrastructure and capabilities of NHSBT as part of its national quality systems.

6 International comparisons

6.1 What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

42 Most developed countries are investing in RM translational centres. The most recent in Canada while Germany has an established multicentre infrastructure. The Cell Therapy Catapult needs to liaise with these centres to learn from their experiences.

43 The overarching lesson from other translational centres is that long-term Government support for RM science and translational research is attractive to business partners and industry. Therefore continued support is essential if the UK is to remain a world leader.

6.2 How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

44 In the UK the procurement and production of tissues and cells is regulated under three different systems (Human Tissue Authority (HTA), Medicines & Healthcare Regulatory Agency (MHRA) for blood and separately for ATMPs)²⁵⁹. Many organisations involved in RM therefore require multiple licences. Most EU countries have a single regulator which reduces the licensing and inspection cost burden in comparison to UK organisations.

6.3 Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

45 As described above there is a lack of harmonisation in the UK. This is exacerbated by having additional regulators throughout the EU (i.e. Individual countries competent authority). The European Medicines Agency (EMA) and Committee for Advanced Therapies (CAT) are helping to speed the process but the USA, with a single regulator (FDA), has an advantage.

46 The emerging issue is that of Hospital Exemption (HE) which is an essential tool to aid the development of specific treatments, cannot be used as a strategy to avoid regulatory oversight in delivering products for routine treatment. For example TiGenix incurred the cost (through regulatory burden) of developing a cartilage treatment, whilst HE is being used to treat patients with similar indications. The issue being that if HE is allowed to be used in this way it will stop organisations commercialising their RM products.

6.4 What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

47 The UK probably has the most robust safeguards with thorough and rigorous regulations. It appears easier to get access to experimental RM in other countries where responsibility for managing risk lies with individual clinicians. This access may result in UK citizens receiving unnecessary exposure to un-proven treatments and practices.

20 September 2012

²⁵⁹ HTA for products produced under the EUTCD; HFEA for procurement of gametes and reproductive tissue and derivation of embryos; MHRA for blood for transfusion under the EU Blood Directive and for cell-based ATMP under the EU Medicinal Products Directives.

Appendix I – Current NHSBT business partnerships in RM

Consent	UCL Trachea Transplants – Collaboration with Prof Martin Birchall to consent and collect trachea for continuing research and clinical application
Collection - Tissue	Projenteq – SME who partnered with NHSBT to consent and collect chondrocytes for manufacture within Phase I, cartilage replacement, clinical trial
Collection - Cells	UK Cord Blood & Bone Marrow Registry – NHSBT Manage the NHS Cord Blood Bank and British Bone Marrow Registry to deliver c2000 ²⁶⁰ transplants annually
Collection – Blood	Cell Medica – NHSBT Specialist Therapeutic Services collect cells for multicentre adoptive immunotherapy clinical trials
GMP Development	Azellon – Contract delivery of process development into Phase I meniscal cartilage trial with Prof Anthony Hollander/Bristol University spin out
GMP Scale up (Single site “large” scale manufacture)	ReNeuron – Technical transfer of SME developed process into Liverpool facility for potential Phase II, multicentre, stroke clinical trial
GMP Scale Out (Multi site close to patient national manufacture)	CMV Specific T Cells – Collaboration, in negotiation, to deliver manufacturing services for Phase II immunotherapy trial.
GMP Closed Production (Closed system cell processing)	Example – Origin/Quest - Joint development of the Cryodoc closed cell processing system for the cryopreservation of cells for human application
Storage	Bristol Cardiac Centre – Grant funded collaboration to process and store 50% of patient sample for Multiple Sclerosis Phase I trial.
Delivery	Birmingham University – Partnership contract in place to manage a range of projects. Likely first therapy will involve the shipment of cells from Birmingham to Liverpool.
Quality Management	UCL Wolfson Gene Therapy Unit operates under NHSBTs IMP license and quality system. First product entering clinical trials in 2012.

²⁶⁰ SCI Market Analysis, Review of New Opportunities and Investment Plan, BioLauncher, June 2011

NHS England, Sir Bruce Keogh, NHS Medical Director and Professor Richard Lilford,
University of Birmingham – Oral evidence (QQ 343-356)

**NHS England, Sir Bruce Keogh, NHS Medical Director and Professor
Richard Lilford, University of Birmingham – Oral evidence (QQ 343-
356)**

[Transcript to be found under Sir Bruce Keogh, NHS Medical Director](#)

NHS England – Supplementary written evidence

Supplementary evidence following Professor Sir Bruce Keogh oral evidence on 26 February 2013

Thank you for the recent opportunity to provide evidence to the House of Lords Select Committee on Science and Technology in response to their Inquiry into Regenerative Medicine. There were several follow-up actions arising from the evidence session, which we seek to address through this submission.

Firstly, the Committee raised a question about GMP facilities – specifically, whether we would like to comment on any way in which we think the GMP facilities should change.

There are many different GMP Facilities throughout the UK, some involving tissue-processing of different sorts, and others involved with pharmaceutical production. Depending on the exact activity of the GMP Facility, all those involved with human use will be registered either with the Medicines and Healthcare Products Regulatory Authority (MHRA) or the Human Tissue Authority (HTA). We agree with the view that, subject to available resources, and within the regulatory frameworks provided by the MHRA and HTA, it might be beneficial to allow some expansion of GMP facilities to permit a closer relationship with clinical teams providing NHS specialised services.

Secondly, the Committee requested further information on the “Commissioning for Evaluation” proposal. A short briefing paper on this proposal is attached at **annex A** for the Committee’s information.

As I hope we conveyed in the evidence session, there is much we are doing to facilitate and deliver efficient and effective regenerative medicines, technologies and treatments in the NHS:

- We will have available, from April 2013, a step change in the ability of the NHS to deliver new treatments effectively. The national commissioning of specialised services allows a single national clinical policy to be formed and implemented. The timeframe can be as short as 12 weeks for the whole process. The consequence of this is that the use of a new technology becomes a contractual and ‘mandated’ obligation of provider organisations.
- To date, commissioners have had limited ability to deliver a controlled implementation of innovative practice. The aim for the direct commissioning of specialised services by NHS England is to implement the process of ‘Commissioning through Evaluation’ where new treatments are delivered by a limited number of centres in order that expertise can be developed and the clinical benefits and risks of the new practice to be evaluated in a controlled way. This will be coupled to a process of allowing equitable access to these new services regardless of where patients live.
- There are occasions when new drugs and devices show promise, but where a NICE process will take time. For specialised services (where you would normally see low volume / high cost drugs), NHS England will establish a policy position by reviewing

all the available evidence on clinical and cost-effectiveness, and by engaging patients, clinicians and industry. By sending a clear signal that NHS England is actively reviewing new innovations, as soon as NICE starts an evaluation process, it means that patients and industry can be reassured promising drugs and devices will not just sit on the laboratory shelf. That should further drive adoption and uptake.

- These Clinical Reference Groups bring together – on a voluntary basis – groups of clinicians, commissioners, Public Health experts, patients and carers, all of whom have a shared interest/expertise in a particular specialised service area. The members of each CRG work together to provide NHS England with clinical advice about each of the specialised services it will be responsible for commissioning.
- The CRG members will regularly identify new treatments including those from regenerative medicine on a regular basis, their Innovation Portfolio. NHS England will encourage acceleration through to adoption and diffusion once early promise has reached a level of effectiveness evaluation sufficient to make a commissioning policy. Once a commissioning policy has been formed all services in England can rapidly implement a change in practice within a timeframe counted in weeks.
- Ensuring that CRGs remain patient focused, each CRG will have 4 patient representatives whose views will be taken into account during discussions.
- Innovation and spread of innovation is a very clear and core priority for NHS England. Both the NHS England and CCGs have a legal duty to promote innovation, and delivery of Innovation Health and Wealth is a key commitment in the NHS Planning Framework. Delivery of high impact innovations are also linked to CQUIN payments – the first time that we have directly linked financial incentives to innovation.
- From April we will invest £75m in the establishment of 15 new Academic Health Sciences Networks. They will bring together the research and academic communities, with industry, the 3rd sector, CCGs and hospitals. Their main role will be to identify and then spread innovation at pace and scale in the NHS.
- In addition, we will also launch the Specialised Services Commissioning Innovation Fund. This new £50m fund will finance the rapid evaluation and collection of evidence for innovations in specialised services, including regenerative medicines.
- The NHS has a long track record of commercial activity – organisations like Great Ormond Street, Imperial, and Moorfields Eye Hospital, work commercially both nationally and internationally. However, it's not the norm, we need many more organisations to understand and exploit the commercial value of their knowledge, IP and products, including regenerative medicine. That's why, with UKTI, we've established Healthcare UK, and have made international and commercial activity a priority for the NHS and AHSNs.
- NHS England is committed to ensuring there are no barriers in the NHS that prevent patients receiving the most innovative treatments, including regenerative medicines. Innovation Health & Wealth, the NHS CE's review of innovation,

published in December 2011, made a series of recommendations aimed at removing those barriers, and committed the NHS to accelerate the spread and adoption of innovation. We have made good progress, but there is more to do.

18 April 2013

Annex A

COMMISSIONING THROUGH EVALUATION

This paper provides a brief summary of proposals being developed to enable some prescribed* specialised services to be commissioned on an evaluation basis.

What is Commissioning through Evaluation?

Commissioning through Evaluation (CtE) is an approach that, subject to NHS England approval, will enable some services that are otherwise not currently routinely commissioned by the NHS, to be commissioned on an initially limited basis so that further evaluation data can be collected to inform the development of a future substantive commissioning policy for that service.

Where Would This Approach Be Relevant?

Services relevant to the CtE approach are likely to be those where initial safety and efficacy has been demonstrated (perhaps supported by NICE Interventional Procedure Guidance), but where there is currently insufficient evidence of relative clinical and cost effectiveness to support a routine commissioning / funding position.

CtE is likely to be particularly relevant to specialised services where patient numbers may be too small to support more traditional research or evaluation approaches.

What Information Would You Collect During the Evaluation Period?

Evaluation measures are likely to include data on clinical effectiveness, treatment costs compared to alternatives where these are available, comparisons of the outcomes of different treatment approaches, and patient experience. Evaluation measures, the length of the proposed evaluation period, and the suggested number of funded cases / centres would be developed in advance with patient representatives, clinicians, research advisors, industry representatives and other key stakeholders. The service would continue to not be routinely funded by the NHS for patients falling outside of the scope of the evaluation.

What Services Is CtE Being Considered For?

NHS England is currently considering recommendations to adopt the Commissioning Through Evaluation approach, funding patients solely via a formal evaluation programme, in the following areas:

Deep Brain Stimulation (for some specified conditions)
Hyperbaric Oxygen Therapy
Left Atrial Appendage Occlusion (LAAO)
Mitraclip
Patent Foramen Ovale (PFO) Closure

Renal Denervation

Selective Dorsal Rhizotomy for Spasticity

** Prescribed specialised services are those to be directly commissioned by the NHS Commissioning Board from 1st April under its formal mandate.*

Ann Jarvis
Acute Portfolio Director (Specialised Services)
March 2013

NHS Health Research Authority, Human Tissue Authority (HTA), Human Fertilisation and Embryology Authority (HFEA) and Medical and Healthcare products Regulation Agency (MHRA) – Supplementary written evidence

NHS Health Research Authority, Human Tissue Authority (HTA), Human Fertilisation and Embryology Authority (HFEA) and Medical and Healthcare products Regulation Agency (MHRA) – Supplementary written evidence

[Evidence to be found under Medical and Healthcare products Regulation Agency \(MHRA\)](#)

Nutech Mediworld – Written evidence

1. Summary

1. Nutech Mediworld (NTMW) is a GLP, GMP, GCP²⁶¹ certified medical facility specializing in human embryonic stem cell (hESC) therapy. The specialization originates from our expertise in the development of embryonic stem cell lines from a single, spare, pre-implantation stage embryo from a natural IVF cycle.
2. The cell lines are processed to create hESC for clinical use. Further, the hESC can be stored under controlled conditions and used when required.
3. The ready-to-use injectable “product” has a shelf life in excess of six months, can be used universally without cross-matching and has the potential to be made available as a “therapeutic product” for use by patients across the globe, like insulin.
4. Since 2002, NTMW has used hESC therapy to treat 1120 patients (as on 8th September, 2012), all suffering from conditions presently labeled incurable or terminal, and has successfully demonstrated and documented the safety and efficacy of the therapy.
5. Progress of all patients has been documented by means of relevant medical investigations, assessment of clinical condition and videos. The data has been compiled, analyzed, and disease-wise clinical study reports have been released.
6. NTMW’s novel technology provides safe and effective treatments for many of mankind’s worst afflictions. It can play a significant role in bringing regenerative medicine to the pharmacies and address medical needs which are largely unmet at present.
7. Since the work already done is well documented, with data to establish safety and efficacy in place, the gestation period to enter the world market would be fairly short. This implies considerable savings in Research and Development (R&D) as well as a longer patent protection once the product reaches market.
8. Human Embryonic Stem Cell (hESC) therapy can play a significant role in reducing the recurring economic burden of chronic diseases.

2. Technology Highlights

NTMW has developed the technology to isolate embryonic stem cells, culture them, prepare them for clinical application, and store them in ready-to-use form with a shelf-life of six months. The technology is being used clinically to treat patients suffering from various conditions like spinal cord injury, diabetes, multiple sclerosis, Parkinson’s disease, cardiac conditions and many others that are currently

²⁶¹ GLP-Good Laboratory Practices; GMP-Good Manufacturing Practices; GCP-Good Clinical Practices

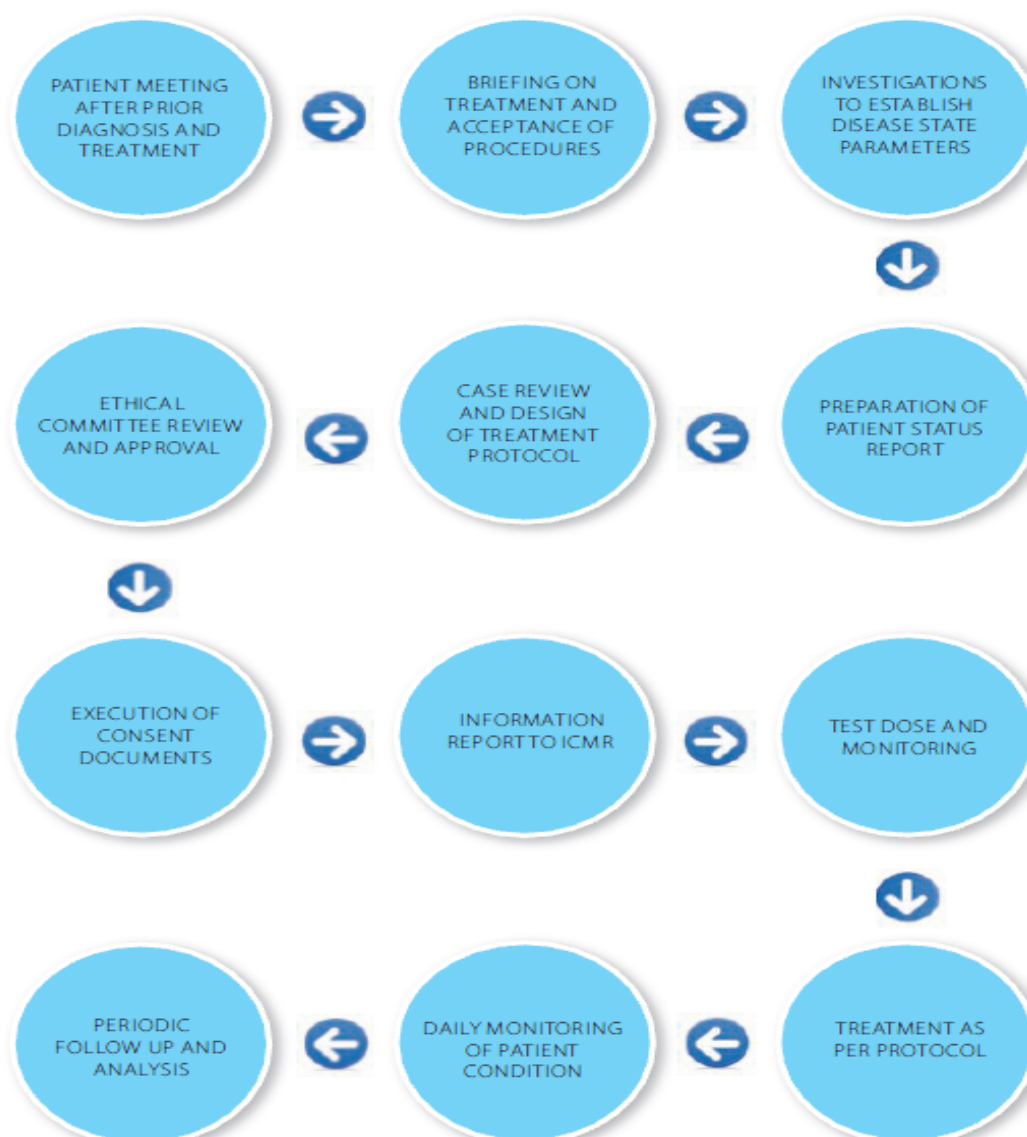
categorized as incurable diseases. In more than ten years of clinical application in over 1100 patients, the results are positive – with clinical study reports establishing safety and efficacy of the therapy.

- The technology involves the use of only one embryo. Once the cells are isolated, they can be cultured indefinitely. We have created the cell lines from a single, spare, throwaway, pre-implantation stage embryo from a natural IVF cycle, with full consent, and in compliance with the Indian regulatory guidelines in the year 2000. The cell lines are capable of infinite controlled expansion, and can, theoretically, be used to treat the entire human population, without the use of even one more embryo.
 - The cell lines are chromosomally stable.
 - The unique culture methodology allows for the stem cells to be cultured without the use of any animal products
 - The cells are universally acceptable without the need for any cross matching. Once transplanted, these cells do not invite any antigen-antibody or host vs. graft reaction. Therefore, no immune-suppressants are needed.
 - These key characteristics have allowed for the development of a product which is totally human and safe for clinical use.
 - The therapeutic product can be stored and transported in ready-to-use form with a shelf life of six months
 - The treatment protocol has been established which includes the cell type, route, dosage, frequency, period and schedule of cell transplantation.
 - Disease-wise quality and safety parameters for clinical application of hESC have been established.
 - Schedule of administration has been defined along with the routes of administration and a "therapeutically effective dosage".
 - Existing patient base of 1100+ from across the world-documentation to establish the safety, efficacy and reproducibility of the therapy.
 - No therapy related serious adverse effects observed in over 10 years of clinical use.
 - Patents have been applied for the entire technology platform, including therapeutic applications. Patent application published online.
 - Reputed external agencies have verified and validated the (i) laboratory and clinical processes, (ii) data and (iii) results of analysis.
3. An independent Institutional Ethics Committee oversees all significant aspects of our operations. Our standard operating procedure includes obtaining informed consent from the patients or their caregivers. NTMW complies with the regulatory requirements as laid down in the guidelines that the Government of India issues from time to time. A fair, transparent and progressive legislative framework is essential for the growth of the discipline.
4. **Therapeutic platform and patient distribution**

NTMW's therapeutic platform includes only incurable or terminal conditions.

5. From 2002 to 2005, in a phased manner, we assessed the safety and efficacy of our hESC therapy on patients suffering from incurable and terminal conditions with full consent and compliance. No serious adverse effects were observed. On the other hand, all patients reported feeling better, and this was further ratified through clinical tests which confirmed distinct improvement in their condition.
6. From 2005 onwards, NTMW established a quality and safety protocol to treat patients with hESC transplantation. The protocol specified the cell type, route, dosage, frequency, period and schedule of transplantation. hESC are administered via various routes depending on the requirement of the case. The routes are intramuscular, intravenous, intrathecal, epidural, caudal, eye drops, eardrops, intranasal, through nebulizer, locally, grown on meshes etc. There is a fixed dose, schedule and protocol for each disease group with scope for individualization.
7. The injections are packed in the central laboratory and dispensed as and when required. Thus, the ready to use hESC injection can easily be made available as a commercial therapeutic product (much like insulin or any vaccine). The potential scope of application, as well as the commercial value, that hESC as a product offers is huge; and a precise valuation is difficult. It suffices to say that hESC can, potentially, be made available in every pharmacy in the world to treat currently incurable and terminal conditions. It can also be used as revitalizing and non-ageing agent, and play an important role as a preventive therapy.

The Procedure At Nutech Mediworld An Overview



8. NTMW practices evidence based medicine wherein the relevant investigations- pathological, radiological, ultrasonic etc., clinical assessments, and videos, document the safety and efficacy of the therapy. After the initial work up, a test dose is given, which is followed by treatment as per the designed protocol. The patient's condition and progress is monitored on a daily basis. Thereafter, periodic follow up is maintained. Disease-state parameters are recorded before the start of the treatment, and are constantly updated during the treatment period. All clinical investigations are carried out at external specialist facilities.
9. Early on in our journey, as regeneration was being observed for first time and needed to be documented, we realized that the conventional assessment scales for most chronic/incurable conditions are more suited to gross classification of patients by type and extent of impairment, than to measure subtle improvements. This

limitation led us to develop disease-specific Nutech Functional Scores (NFS)-that define parameters for a more thorough assessment of the patient's condition and progress. The NFS provide a holistic, sensitive and workable score for tracking treatment-related improvements. However, the status of the patient is also recorded with conventional international parameters, where such parameters are available for the purpose. For example, we assess the clinical condition of spinal cord injury patients using the internationally accepted ASIA Impairment Scale, as well as the NFS for spinal cord injury.

10. The therapy works in different ways on static and progressive conditions. Static conditions are those which are stable with no deterioration over time. In such cases, cell transplantation causes regeneration which leads to lasting improvements. In contrast, progressive conditions are marked by deterioration over time. Here, cell transplantation leads to regeneration which slows down the disease progression. Continued hESC therapy is required to keep the disease progression in check and stabilize the patient's condition. This is a slow process and does not sometimes cope with the disease that has either progressed too far or is progressing too fast. In short, hESC is not a miracle cure; however, it is a safe and effective treatment option for conditions where currently no treatments, other than those providing symptomatic relief, are available.
11. The treatment and progress data of the 1100+ cases treated at NTMW is an impressive resource which provides a re-assuring insight into the results of hESC therapy. The data has been compiled, analyzed, and published from the year 2005 to 2012. These papers result from scientifically laid down clinical studies demonstrating the safety & efficacy of hESC therapy, namely:
 - Human Embryonic Stem Cells – A Revolution in Therapeutics
 - Clinical study report on hESC therapy in Chronic Spinal Cord Injury
 - Clinical study report on hESC therapy in Cerebral Palsy
 - Clinical study report on hESC therapy in Chronic Lyme Disease
 - Human Embryonic Stem Cell Therapy – Safety and Efficacy
 - Clinical study report on hESC therapy in Cerebrovascular Accident (Stroke)
 - Clinical study report on hESC therapy in Amyotrophic Lateral Sclerosis
 - SPECT Scans – Quantitative and Qualitative Reports
 - Clinical study report on hESC therapy in Multiple Sclerosis
12. These clinical studies indicate that:
 - The therapy is effective regardless of age, sex or race of the patient.
 - The therapy is effective irrespective of the disease stage when treatment is started.
 - However, the later the treatment is started, the less is its effectiveness, especially in progressive disorders.
 - The earlier a patient starts the therapy the better are the chances for recovery towards normalcy.
 - The therapy is safe with no serious adverse effects.

13. The following sample images are presented to exhibit the regenerative and repairing capabilities of hESC therapy.

- I. Case of non-healing ulcer on right foot for 3 years. Skin graft rejected. Colour Doppler showed no blood flow. Amputation was being planned. hESC treatment duration-4 months.



2.



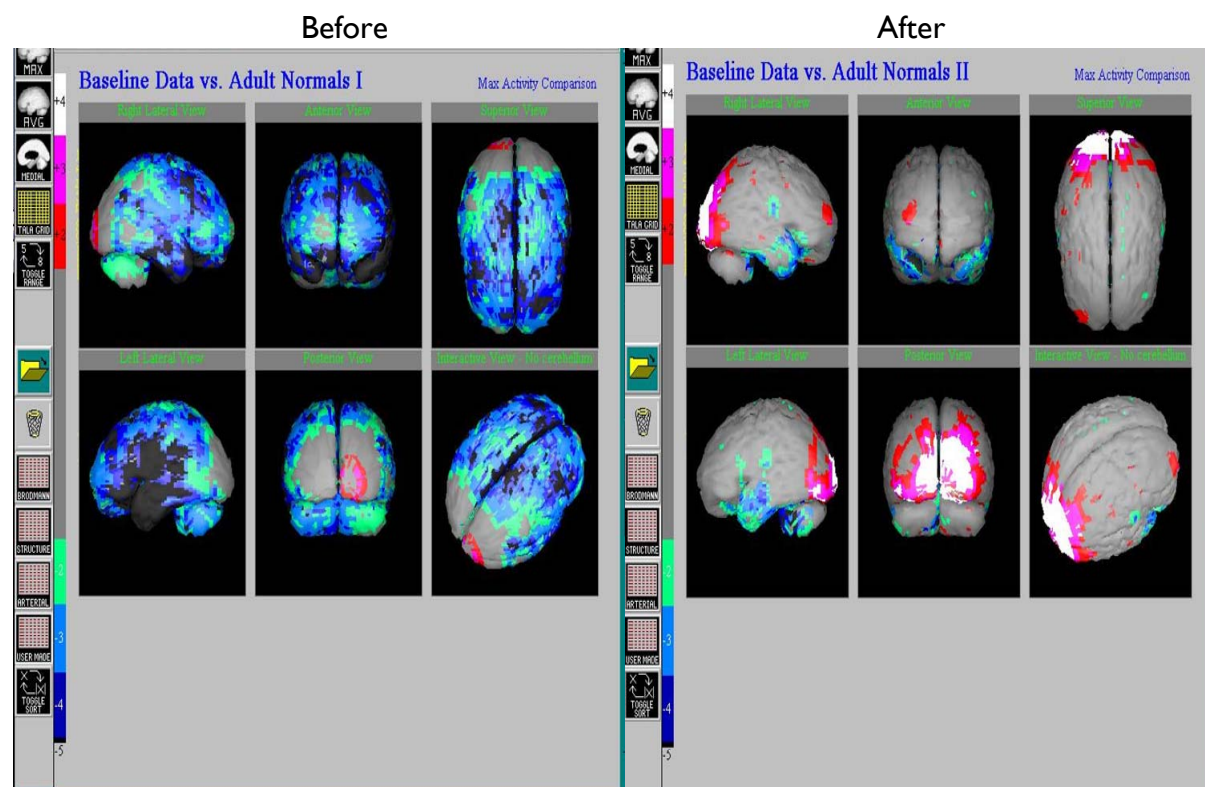
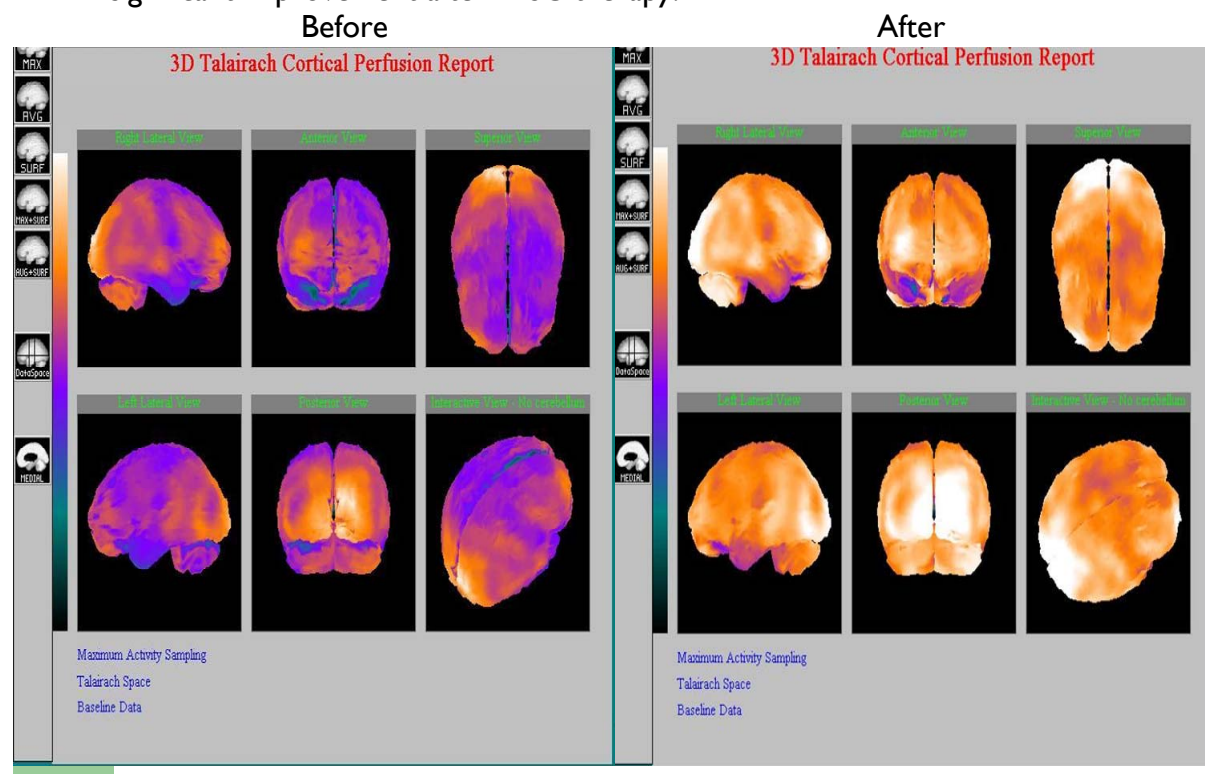
3. Tractography images of a chronic spinal cord injury patient, before and after hESC treatment. Clinical improvements seen and regenerative changes seen on images. Treatment ongoing.



4. MRI images of a chronic spinal cord injury patient showing regenerative changes after 1 year of hESC therapy. Patient's clinical condition much improved. Treatment ongoing.



- Brain SPECT scans of a patient with progressive neurological disorder show significant improvement after hESC therapy.



6. Images before and after hESC treatment of the knees of a patient suffering from osteoarthritis showing marked improvement.



14. General comments & observations

1. All due care and precautions have been taken, and it is only after a thorough evaluation of the various safety aspects that clinical work with embryonic stem cells was started. However, the commonly followed drug evaluation trails of animal models & toxicology studies are quite irrelevant with respect to human embryonic stem cells, as this is an extension of tissue & organ transplant, and has to be viewed in that perspective.
2. When treating terminally ill patients, controlled, double-blind studies, are also not practical. On the other hand, we believe that the incurability of the disease itself converts it into a control group.
3. Our technology provides a marketable stem cell therapy product in contrast to other available therapies which are clinic based and patient specific.
4. The therapeutic product can be stored and transported in a ready-to-use form with a shelf-life of more than 6 months, making it amenable to global marketing and usage.
5. Our unique cell culture methodology allows scalability of cell expansion and production. The product is already in use with a high degree of success over a sizeable patient base, and over a significant length of time. This makes it a low-risk proposition for any investor/funding agency, government body, or pharmaceutical company.

6. Since the work already done is well documented, with data to establish safety and efficacy in place, the gestation period to enter the market will be fairly short. This also implies considerable savings in R&D as well as a longer patent protection once the product reaches market.
7. Having come this far, the support of a larger entity , governmental or private, that understands its commercial & humanitarian potential is required to take this technology forward so that in a short time it becomes the first line of treatment for many of mankind's worst afflictions.
8. The therapy addresses unmet medical needs, providing treatment for conditions which presently are not offered effective treatment options. Further development & availability of the technology will thus not cannibalize existing products. On the contrary, it will provide fresh commercial opportunities to the healthcare/pharmaceutical sector.
9. The therapy can play a significant role in reducing the recurring economic burden of chronic diseases.
10. The therapy can be used as "preventive medicine" to delay the onset of age-related problems.
11. Even in end stage cases, the therapy led to significant improvements in the "quality of life" of the patients.
12. hESC therapy can be the first line of treatment for several medical conditions, many of them being without any effective treatment options at present.

18 September, 2012

Oxford Stem Cell Institute (OSCI) – Written evidence

1. Background

- 1.1 The Oxford Stem Cell Institute (OSCI) was established in 2008 to serve the stem cell community in Oxford with the vision of facilitating an interdisciplinary approach to regenerative medicine, born of the conviction that no one discipline, working in isolation, would be able to realise the therapeutic potential of stem cell biology. The OSCI now comprises 43 laboratories distributed throughout 17 Departments of the University and is associated with various SMEs and a broad network of collaborators worldwide. The Institute has particular strengths in fields as diverse as hematopoiesis, neuroscience, medicinal chemistry and immunology and has strong representation in both the basic and clinical sciences. As such, the OSCI is one of the most interdisciplinary centres of regenerative medicine worldwide and actively seeks to foster the translation of promising stem cell-based therapies to the clinic. In response to the Select Committee's call for evidence, opinions were canvassed from all group leaders associated with the OSCI: the following evidence is compiled from the various submissions received.

2. The Research Base

- 2.1 The UK scores well in all metrics of academic output in the stem cell field, having particular strengths in disciplines such as induced pluripotency, bioengineering and scaffold design, transplantation immunology and medicinal chemistry. Many groups are of international standing and produce publications that are both influential and highly-cited. Furthermore, the UK boasts an exceptional R&D base from which to launch novel strategies for regenerative medicine. Indeed, the UK's pharmaceutical and biotechnology industries, which are especially well positioned to exploit small molecules for guiding cell fate determination, have an established and unrivalled track record in discovering and developing novel treatments, having brought many ground-breaking new therapeutics to market over the past 70 years, from the first commercial applications of the β -lactam antibiotics, such as penicillin, through the discovery and development of beta-blockers, anti-ulcer drugs, treatments for erectile dysfunction and anti-virals. This experience, combined with the discovery potential of interdisciplinary collaborations between academia and the biotechnology sector will be pivotal in reducing to practise the promise of regenerative medicine.
- 2.2 Currently, funding for regenerative medicine is made available through the Research Councils UK (RCUK) and the Wellcome Trust, as well as mechanisms such as the Innovative Medicines Initiative (IMI). Disease-focussed charities have also invested heavily in the promise of stem cell biology including Parkinson's UK and the British Heart Foundation through its recent *Mending Broken Hearts* campaign. Although government spending on regenerative medicine has been preserved during the spending reviews of recent years, there is a growing perception that traditional funding streams are beginning to falter: increasingly, philanthropy is being sought to fill this void. The uncertainty surrounding future funding is inherently antagonistic to the development of a long-term vision for regenerative medicine and is consuming an ever-increasing proportion of Principal Investigators' time and resources, inevitably detracting from productivity in the field. Furthermore, any threat to funding streams at such a critical juncture in the history of regenerative medicine, risks losing the skills base accrued over many years as people

move to other disciplines or careers: the need to regain such expertise would set the UK back many years, causing it to lose its competitive edge.

- 2.3 The majority of funding available for regenerative medicine is focused on the development of cell-based therapeutics, often to the detriment of promising new approaches, such as the exploitation of small molecule-based strategies to stimulate and augment endogenous repair processes. Based on the ease of administration and control of dosing regimes, such strategies offer significant advantages over cell-based approaches for revolutionising medicine in the future.

3. Application of the Science

- 3.1 The advent of induced pluripotency has already begun to revolutionise medicine by enabling the derivation of disease-specific induced pluripotent stem cells (iPSC), thereby capturing a disease-associated genotype in a stem cell line, capable of indefinite self-renewal. This technology has begun to facilitate the study of numerous intractable diseases for which appropriate animal models have traditionally been unavailable. The same technology has begun to permit high throughput drug screening programmes and toxicology studies for promising new drugs using human tissues, differentiated from iPSC. Although under these circumstances, stem cells *per se* may not constitute the treatment regime, their use is likely to prove instrumental in uncovering the mechanisms of pathogenesis involved and identifying more conventional treatment options.
- 3.2 In recent years we have begun to see specific applications enter early clinical trials for conditions such as stroke, age-related macular degeneration of the eye and the treatment of myocardial infarction through administration of autologous bone marrow progenitors direct to the lesion, a treatment regime which has so far shown modest sustained benefit and no adverse effects. Furthermore, there are potential treatments in the pipeline for hearing loss and Parkinson's disease to name but a few, which may be realised within the next 10 years. Although much still needs to be done to make such treatments routinely available, such disease states represent the 'low-hanging fruit' since most require the replacement of no more than a single cell type: the timelines for implementation of therapies based on the replacement of entire functioning tissues is likely to be significantly longer.
- 3.3 In contrast, mechanisms to translate small molecules from initial discovery through to a commercial product are well established and provide an accelerated pipeline to the clinic. Notable examples are Eltrombopag, an oral thrombopoietin receptor agonist which increases platelet numbers, approved by the FDA in 2008 and Plerixafor, currently in Phase III clinical trials for haematopoietic stem cell (HSC) mobilisation from the bone marrow.
- 3.4 Stem cell-based technologies that make use of small molecules to guide cell fate determination have the potential to fundamentally change drug treatment from a symptomatic to a curative outcome. Multiple therapeutic applications can be envisaged, starting initially from 'topical' applications like retinal repair and wound healing, whereby the small molecule is introduced directly at the intended site of action, through to systemic applications for conditions such as the neurodegenerative diseases, where it is anticipated that orally-delivered treatments might be applied.

4. Barriers to Translation

- 4.1 There remain numerous barriers to the translation of promising new therapies to the clinic, some of which are scientific challenges, other emanating from government strategy in the field. At the level of the basic science involved, there is still much to be learned from a study of the stem cell niche *in vivo*, the switch stem cells make between dormancy

and activity and the way in which pathways of differentiation are ultimately controlled. Furthermore, there are fundamental issues of a translational nature that will need to be addressed, such as how to promote the functional integration of administered cell types into the target tissue, the inherent risk of their subsequent transformation *in situ*, and the intractable threat of their rejection by the immune system of the recipient.

- 4.2 Importantly, not all approaches to regenerative medicine are subject to such barriers: the development of small molecule therapeutics to stimulate endogenous repair of tissues is, for instance, a particularly attractive approach that circumvents many such limitations. Furthermore, the technology involved is well-practised, and its application to emerging targets involved in cell proliferation and differentiation is likely to lead to potential curative disease treatments that may be developed using established industrial paradigms. Such a strategy may rejuvenate the industry model from current ‘target-centric’, symptomatic treatments, where success rates are falling, to a wholly new regenerative approach. The clinical evaluation of such therapeutics may be facilitated by the use of suitable biomarkers, enabling patient selection and clinical trial stratification to be approached with a greater chance of a successful outcome than has historically been the case.
- 4.3 The public’s perception of stem cell biology and the insatiable demand for novel treatments is being driven by irresponsible media coverage of the field. Although some reports of breakthroughs acknowledge the obstacles that still need to be overcome, many fail to do so, creating unrealistic expectations. The resulting disappointment that promised treatments are not available is responsible for fuelling so-called ‘stem cell tourism’ in which members of the public seek treatments in unregulated clinics in other parts of the world, where scant attention may be given to issues of health and safety. The lack of efficacy from such treatments and the adverse events described in several recent cases, risks discrediting the entire field of regenerative medicine, while exposing members of the public to unacceptable levels of risk.
- 4.4 Government funding in the field strongly favours translational research. While such funding is to be welcomed, it should not be provided to the detriment of research into the basic science that underpins the field: such a strategy risks forcing the premature application of stem cells to the clinic, leading to the otherwise avoidable failure of clinical trials. The way in which funding is made available frequently requires the establishment of elaborate consortia: while these may, on occasions, prove successful, all too often they represent ‘marriages of convenience’ between groups for the sake of meeting eligibility criteria. The results of similar top-down, network-driven funding provided by the EU suggests that it is frequently inefficient, rewarding managerial acumen rather than the best science. Furthermore, funding frequently suffers from a focus on short-term outputs and is withdrawn if early milestones cannot be met, a strategy that is inherently antagonistic to the long-term vision required for regenerative medicine. An example is the funding set aside to establish the UK National Stem Cell Network which served to unite the stem cell community across the UK and provide valuable networking activities and resources: withdrawal of funding within four years of its establishment, has however led to loss of all the time, effort and resources invested and dismantling of the network it created.

5. Barriers to Commercialisation

- 5.1 In order to attract significant investment for projects either from industry or the venture capital sector, it is essential to have demonstrated proof of concept in Phase IIA clinical trials: proven mechanisms for funding research up to and including this point are, therefore, required. This is the well-known, and widening, ‘funding gap’ in biomedical

research and it is critical that this is addressed, not only for regenerative medicine, but more widely in drug discovery.

- 5.2 The current economic crisis has resulted in a pharmaceutical and biotechnology sector that is far more risk-averse than in previous years. Given that regenerative medicine remains a largely unproven approach to the treatment of human disease and is likely to be extremely costly to implement, the risks involved are immense, resulting in significant 'risk stacking'. This has been exacerbated by uncertainty surrounding intellectual property (IP) rights in the field of pluripotent stem cells, following recent directives from the European Patent Office (EPO). Furthermore, a so-called 'patent thicket' appears to be developing in the field which is inherently detrimental to commercialisation, since no individual company is likely to own all the necessary IP to bring a product to market.
- 5.3 Regulatory uncertainty in the approval of cell-based therapeutics has added substantially to the perceived risks involved in commercialisation. Cell therapies represent largely uncharted territory for regulatory bodies and may take significant time and experience to navigate, which may not fit comfortably with the expected timelines for return on commercial investments.
- 5.4 Importantly, not all approaches to regenerative medicine are subject to such risk stacking, of which the use of small molecule therapeutics is a prime example. The UK pharmaceutical industry provides massive economic benefit, ABPI figures showing that it brings to the UK greater economic benefit than any other technology-based industry. The potential impact that small molecule stem cell therapeutics could have on UK plc could potentially multiply these benefits many times over. Furthermore, it would enable the whole UK pharmaceutical and biotechnologies industries, which have undergone significant downsizing in recent years, to be rejuvenated, providing much-needed, highly-skilled jobs in the sector, as well as obvious healthcare benefits to society.
- 5.5 Current pricing structures are largely irrelevant, since regenerative medicine will adopt a curative approach to currently unmet medical needs, rather than merely alleviating symptoms. As the technology develops, and more diseases can be treated through regenerative medicine, visits to primary health care centres and hospitals will decrease, while waiting lists will shorten, leading to better health within the population and a lower healthcare burden to Government. We envisage the end truly justifying the means, as the (relatively) short-term investment in bringing the technology to fruition will pay off with the longer term benefits.

6. International Comparisons

- 6.1 Protracted issues surrounding the ethics of stem cell biology in the US have resulted in high profile legal cases that have greatly limited the field, creating significant uncertainty for academics and commercial organisations working in this space. This has afforded the UK a strategic advantage which it has exploited by providing good infrastructure and a rigorous, yet broadly permissive regulatory system, making the UK an attractive location for basic research and investment in regenerative medicine.
- 6.2 Clear and decisive action needs to be taken to secure the UK's leading position in this highly competitive field. Given the enthusiasm industry has for developing regenerative medicine-based therapeutics, and the right level of financial and legislative support from central Government, the UK is now uniquely positioned to capitalise on its ongoing investment in the field and maintain its leading position.

19 September 2012

Parkinson's UK – Written evidence

Overview of Parkinson's UK

1. Parkinson's is a progressive neurological disorder for which there is currently no cure. It results from the loss of the chemical messenger dopamine within the brain and affects learned voluntary movements such as walking, talking, writing and swallowing. As the condition progresses it impacts on all aspects of the person's life and the lives of those around them.
2. As well as the symptoms that affect movement, people with Parkinson's can find that other issues, such as tiredness, pain, depression and constipation, can have an impact on their day-to-day lives.
3. Every hour, someone in the UK is told they have Parkinson's. One in 20 is under the age of 40. There are approximately 127,000 people with Parkinson's in the UK.
4. We bring people with Parkinson's, their carers and families together via our network of local groups, our website and free confidential helpline. Specialist nurses, our supporters and staff provide information and training on every aspect of Parkinson's.
5. As the UK's Parkinson's support and research charity we're leading the work to find a cure, and we're closer than ever. We also campaign to change attitudes and demand better services.
6. Our work is totally dependent on donations.

The research base

7. The UK has a high international standing in the area of regenerative medicine and particularly in stem cell research. There is a significant level of investment from the charity sector (including Parkinson's UK), public funding agencies (such as the MRC) and the biotechnology industry. This was highlighted in Office for Life Sciences (OLS) 2011 report "Taking Stock of Regenerative Medicine in the UK"
8. The establishment of the UK Stem Cell Funders Forum, coordinated by the MRC, underlines the need for a combined approach in the area of stem cell research and this allows for a regular dialogue between the different funding bodies.
9. The majority of regenerative tissue research is carried out within the University sector. Due to budgetary restrictions, there is the potential for a decrease in real time funding to develop and maintain an appropriate infrastructure that is vital to provide the appropriate facilities for high quality research to take place.
10. If dedicated state of the art facilities are not available in which research can take place, there is a significant possibility that research funding could be redirected to other countries which have invested heavily in the development of the local research infrastructure.

11. The charity sector invests significantly into this area of research – members of the Association of Medical Research Charities invest over £1.1 billion annually in UK medical research. Charities don't fund University overhead costs and this is underwritten by the Charities' Research Support Fund. It is imperative that such a funding mechanism remains in place in order to encourage charitable funding of research within the UK.

Application of science

12. Stem cell research has made great progress over the past five years. For example, the development of induced pluripotent stem cells has revolutionised the research field and this is likely to bring the clinical use of stem cells closer.
13. The UK has had a reputation for early stage research, particularly in the stem cell field. Most of the current clinical research and therapy is in the area of bone/cartilage repair and wound healing. However, the initiation of clinical trials in the treatment of macular degeneration (London) and stroke (Glasgow) demonstrates that the use of stem cell-derived neural cells may be a therapeutic possibility. Ultimately, this could be used in conditions such as Parkinson's.
14. A research project studying the potential of a regenerative medicine to treat Parkinson's is currently underway in Cambridge. Based on the analysis of data from previous studies, an EU grant of €13.2million was awarded to investigate the use of foetal brain tissue to replace the cells that have died in Parkinson's. This will provide a platform for future studies in which stem cell-derived neuronal cells can be used in the treatment. This is an example of how progress may be made in the coming years.
15. A phase II gene therapy trial to treat Parkinson's is currently being carried out by a UK company, Oxford Biomedica. This study aims to increase the levels of specific enzymes associated with the production of dopamine (which decreases in Parkinson's) in the midbrain. However, positive results will provide a proof of concept that a gene therapy approach may be suitable for the treatment of Parkinson's. This could potentially be adapted to express factors that could stimulate nerve cell regeneration.
16. A clinical trial involving the direct infusion of a neuro-restorative growth factor into the brains of people with Parkinson's is currently being planned in Bristol. This is an area in which the UK is considered as a centre of excellence.

Barriers to translation

17. The UK has invested heavily in regenerative medicine research. We have now reached the stage that this can now begin to be translated into the clinic. In general the basic infrastructure is in place to achieve this. The establishment of the Cell Therapy Technology and Innovation Centre will play a key role in the translation of research.
18. The Parkinson's Clinical Studies Group is a component of the Neurodegenerative Disease Clinical Research Network (DeNDRoN). This group coordinates clinical trials for Parkinson's. One hurdle in the past has been the administrative barriers

which prevent the initiation of clinical trials. This may be overcome by the establishment of a “one stop” National Research Ethics Service (NRES) which will be part of the Health Research Authority (HRA). However, a consultation on the exact function and remit of the HRA is currently underway and we will need to wait until the HRA is firmly established to determine whether this is a success.

19. A key barrier has been a difficulty in patient recruitment for clinical trials. Organisations such as Parkinson's UK are helping to increase awareness of clinical trials in which people can partake. However, information about such trials is inconsistent throughout the country. The Health and Social Care Act included the vision that the NHS should have research at its core. However, we must ensure that all people with specific conditions are made aware of appropriate clinical trials that are underway in which they could potentially take part. This includes both basic drug trials to more complex studies in the area of regenerative medicine.
20. Once therapies have been approved for clinical use by the appropriate regulatory agencies, the main barrier will be financial, especially taking into account the limited NHS budget. There has been a very high level of investment in the study of regenerative medicine which is likely to continue. It is important that the NHS (and NICE) considers the longer term benefits for patients and are not discouraged from implementing the therapy due to the potential initial high cost. Appropriate commissioning mechanisms should be put into place to ensure that the technology can actually be put into routine clinical use.

International comparisons

21. While the UK has invested significant funds into regenerative medicine research in the past, the OLS 2011 report highlights how other countries plan to increase significantly their investment in this area. However, while the report refers in the UK to the development of “creative funding mechanisms”, there is no indication that additional funding in this area will be made available.
22. The European Medicines Agency (EMA) has established a specific Committee on Advanced Therapies which has responsibility for assessing novel therapeutic areas such as regenerative medicine. This committee understands that these novel therapies cannot be assessed in the same way as mainstream medicines. This is an example of how therapies such as regenerative medicine are being supported at a European level and this will be supported within the UK by the MHRA.
23. The European Commission is currently considering the budget for the Horizon 2020 research funding programme. While this will fund the full spectrum of scientific research, it is important that research into regenerative medicine (and particularly stem cells) is specifically highlighted as a key investment area.
24. In the past, legislative gaps have allowed for false hope for people with degenerative conditions such as Parkinson's. Up to 2011, a German company offered stem cell therapy for people with Parkinson's and other conditions. There was no evidence that this was clinically effective. However, because the therapy involved the use of stem cells derived from the patient's bone marrow, this was not considered as a

“medicine” but as an autologous transplant which is not covered under the existing EMA legislation. This loophole has now been closed.

25. People with conditions such as Parkinson's are anxious to obtain treatments that will in effect provide a “cure” for their condition – abolish the symptom of the condition. Stem cell therapy is an example that is often used as a potential cure, usually in the popular media. Companies and researchers, primarily based in Asia, have taken advantage of this and have offered stem cell therapy to “cure” Parkinson's. There is no evidence that this is effective and it is carried out in an environment that is not appropriately regulated. There have been reports of significant side effects – an Israeli boy who underwent stem cell therapy in Russia to treat a spinal cord injury ended up with multiple tumors in the spine.
26. In 2011, the European Court of Justice ruled that embryonic stem cells cannot be patented. This could have significant implications for the future development of stem cell research in Europe, although the full implications of the ruling and the limitations that it could impose remain unclear.

19 September 2012

Pfizer – Written evidence

Overview of Pfizer Regenerative Medicine

Regenerative medicine covers a range of different types of therapeutic intervention. Small synthetic molecules or biologic entities that can alter the body's natural processes of regenerating tissue are the most familiar type, with a number of current examples in regular clinical use (e.g., erythropoietin or EPO). Cell-based therapies are the other element of regenerative medicine research. Stem cells derived from a variety of sources are being studied as means of generating new tissue or restoring function to failing organs. Some examples of cell therapies are familiar in clinical practice, such as bone marrow transplant.

The two defining features of stem cells – their potential for differentiating into various specialised cells and their capacity for self-renewal – make them the logical focus of research into tissue regeneration. In terms of research, there are three main types of stem cells that are of interest: embryonic, adult and induced pluripotent stem cells. Pfizer makes use of each of these different types of cells in research and clinical programmes.

Pfizer's regenerative medicine work is led out of our Neusentis research site located at Granta Park, Cambridge. The focus of these activities is largely on age related and degenerative disorders, including our collaboration with University College London and Moorfields Eye Hospital to develop a cell replacement therapy for Age Related Macular Degeneration. There is also a programme investigating the use of an adult stem cell therapy to treat Ulcerative Colitis, currently in a phase II clinical trial.

Neusentis' work on regenerative medicine encompasses a full set of drug discovery capabilities, from stem cell biology through to medicinal chemistry. These functions are complemented by the other R&D capabilities and resources that Pfizer has to offer, as well as by an extensive network of alliances and collaborations.

Key Points on the Regenerative Medicine Policy Environment

- **Financing, scientific and regulatory uncertainties and uptake problems all represent barriers to translational research.**
- **There needs to be a stronger NHS component for clinical adoption of successful therapies.**
- **Pfizer would suggest that a funding mechanism could be made available for smaller companies to develop their Phase II trial programmes, perhaps via a matched funding scheme.**
- **There is predicted to be a significant imbalance in the UK in funding sources at Technology Readiness Levels (TRL) 6-8, with the majority of investment coming from the private sector. As the UK company developer sector is relatively small, there could be a role for Government to play in investing more substantially at this stage of development.**

Answers to the Committee's Questions

The Research Base

How does the UK rank internationally in the scientific field of regenerative medicine?

The UK has had a strong start in the field of regenerative medicine. This is partly down to the strong science base in this country, but also, as is well understood, a well-established and positive regulatory environment that contrasted with the restrictions that have been in place in other countries. Over time some of that leadership has shifted outside of the UK as investment funds, and Government support, have been more readily available for start up research enterprise elsewhere. The shift has mainly been to the United States due to state sponsored efforts such as in California and Massachusetts, but countries like Israel, Japan and South Korea are making major progress too.

The UK's Intellectual Property Office confirmed in 2011, 'the US leads the way in absolute numbers of inventions in Regenerative Medicine specifically, and in the life sciences more generally. Other leading countries respectively are Japan, Germany, and China, with the UK in sixth position.' The UK in particular 'falls close to, but just below, the expected level of performance [in regenerative medicine] compared to general performance [in life sciences], which translates into a shortfall of four or five inventions per year.'

Where does the UK have strengths and weaknesses in the field?

Strengths include excellent individual expertise, long-standing activity in the field, robust and positive regulation on human tissue and embryonic cells, and positive interactions with medicines regulators as stem cell projects plan to progress into clinical studies.

Weaknesses mainly relate to a lack of critical mass of activity in the UK, and the lack of a strategic impetus for clinical translation. A clear demand for these therapies within the NHS would improve matters.

Recent work by the MRC and BBSRC, and the publication of the publication of *Taking Stock of Regenerative Medicine in the United Kingdom* have given welcome direction to UK policy in this field.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

Currently there is public sector investment of circa £70m per year in the UK. Around 95% of this is spent on early stage discovery to late stage preclinical development. Only 5% is currently spent on mid-late stage clinical development and adoption. There will be further investment over the next 5 years of £95m into a 'Regenerative Medicine Platform' (MRC/BBSRC/EPSRC), TSB and new MRC-Wellcome Trust partnerships.

Substantial funding also comes from the Research Councils and charitable sector (such as the Wellcome Trust, AMRC, UK Stem Cell Foundation). The bulk of funds from these sources is in underpinning research, through preclinical and early clinical stages (TRL 1-6). In 2009-2010, the AMRC spent £13m on regenerative medicine research and an average of £10m per year for the 4 years preceding that. The British Heart Foundation's 'Mending Broken Hearts' regenerative medicine campaign aims to raise £50m. In Scotland there is an endowment from JK Rowling for a new Centre (which is state of the art and spans basic to translational medicine).

The Technology Strategy Board also funds business led technology development (TRL3-7) from preclinical through to First in Human studies, including prototype testing and platforms to underpin the safety and efficacy testing of new therapeutics.

The NIHR contributes around 1% of the current public sector investment and into late stage clinical testing (TRL 8). The bulk of user adoption (TRL 9) is funded by the ESRC in UK (around 2%).

Funding is also provided by the devolved administrations' development agencies (e.g. Scottish Enterprise) and the NHS (Blood & Transplant, stem cell banking). In addition, not-for-profit cord blood banks contribute a fraction of the overall investment.

There is predicted to be a significant imbalance in the UK in funding sources at TRL 6-8, with the majority of investment coming from the private sector. As the UK company developer sector is relatively small, there could be a role for the Government to play in investing more substantially at this stage of development.

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

In the UK, Neusentis currently has three regenerative medicine programmes in its pipeline:

- a small molecule programme in stroke recovery, now in Phase II.
- a collaborative programme in ulcerative colitis with Athersys Inc – uses a cell based product known as MultiStem®, an adult stem cell therapy that is derived from human bone marrow in Phase II.
- A cell replacement therapy to treat disease of the retina, primarily age related macular degeneration. This is a collaboration with University College London and Moorfields Eye Hospital. The basis of this therapy is differentiation of human embryonic stem cells into retinal pigmented epithelial cells which are then placed on a polyester membrane. This patch is then surgically delivered into the back of the eye against the area that is degenerating – replace the dying layer with fresh and young cells. This programme will hopefully be in the clinic next year.

Translation of the science in the UK is on the increase. This is most noticeable in certain applications such as the use of induced pluripotent stem cells for disease modelling and the understanding of the genetic basis of disease. Stem cells are used as research tools in the academic and biopharmaceutical industry sector on a routine basis to provide scientific knowledge of tissue regeneration processes and mechanistic understanding for regenerative medicines in development.

The main application for the science of regenerative medicine is in the development of cell and tissue therapies. In this context, the science of embryonic stem cells took more than a decade to reach a stage of maturation for the first patients to be treated with cell products from stem cells and now those being tested in the clinic include retinal diseases. A number of clinical centres are involved in these studies, including the Moorfields Hospital in London and the Princess Alexandra Eye Pavilion in Edinburgh.

Another intense areas of clinical research are in the cardiovascular and musculoskeletal space. In the last two years in the US alone there have been more than 160 new clinical

studies using stem cell products registered for cardiovascular disease. A Phase III, autologous cell therapy trial for acute myocardial infarction with several thousand patients and co-ordinated from the UK is ongoing in the EU with multiple clinical partners.

One cell-based EMA approved advanced therapy medicinal product (ATMP) is used and reimbursed in the UK – ChondroCelect, an autologous cell therapy for cartilage repair. This has been paid for privately in a small number of individual cases. It is expected that soon additional, newly approved ATMPs will be available for chronic wound care and immune-therapies. Products containing a combination of living cells and scaffolds (materials) or just living cells alone are being tested in late clinical stage trials for a number of indications in the UK including, chronic wounds, cartilage and bone repair.

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

In R&D terms this is a marathon and not a sprint. The reality is that breakthrough innovation to make regenerative therapies based on stem cells a routine option for many different conditions will take some time as this area of medicine is so completely new. There may be initial therapies for some indications approved in 3-5 years (wound healing, critical limb ischemia, cardiovascular indications), but it may well be 10 years or more before stem cell therapies and regenerative medicine being to make a significant contributions to the healthcare of the population and then possibly only in certain intractable, significantly unmet medical areas. Developing a therapy to regenerate the pancreas (diabetes) or the liver (cirrhosis) may also become a real prospect within 10 years.

That said, regenerative medicine could potentially offer a complete paradigm shift in the way we look at treatment of illness and long term conditions. There is long term potential as we move from symptomatic treatment to curative. Healthcare costs could be positively impacted as a curative effect could be secured for a long term disease, instead of treating the symptoms.

In 25 years time the potential of regenerative medicine is that many current therapeutic approaches may become redundant. As organs become diseased or fail, they could be replaced with brand new tissue, much as in the way one changes a worn out tire on a car.

Barriers to translation

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

Financing, scientific and regulatory uncertainties and uptake problems all represent barriers to translational research. The recently announced £180m Biomedical Catalyst fund we believe will be helpful for enterprise seeking to fund projects and Pfizer was encouraged to see that regenerative medicine was specifically identified as a potential area for funding.

With respect to the Cell Therapy Catapult Centre, Pfizer remains very interested. Pfizer wants to see it succeed and will help where it can.

Many of the uncertainties surrounding translation of cell-based therapies into the clinic relate to gaps in our understanding of the science of stem cells and how they operate in the human body, particularly in the context a disease setting, which is almost impossible to recapitulate in animal models. The more examples we have of potential therapies moving into clinical trials, the more knowledge we will build up in the field. This will also help bring greater clarity on how medicines regulation will address new cell based therapies.

However, up until relatively recently there has been no clear UK regenerative medicine strategy that pulls all the disparate pieces together into a coherent linked strategy. We believe that the MRC–TSB led strategy being implemented now, if successful, will go some way towards plugging this gap.

Importantly, there is no major role for the NHS in overcoming innovation barriers. Increased clinical adoption of successful therapies would be helpful for the science.

One of the initial difficulties before even getting to the patient is the so-called “valley of death”. A basic researcher/clinician needs to be able to do the preclinical toxicology, the regulatory discussions and filing, the scale up, and Good Manufacturing Practice (GMP) production. The path to do this is much less certain than for a small molecule, and the know-how is much less available. In principle, the Cell Therapy Catapult should bridge this “valley”.

A big barrier to the development of regenerative cell & tissue therapies by smaller companies and start ups is the significant investment needed to develop a sufficiently robust Phase II clinical trial programme to show proof of concept. Without robust data comparable to that which we would generate for in-house programmes, larger companies will not invest in potential therapies developed by external groups or academic institutions. Pfizer would suggest that a funding mechanism could be made available for smaller companies to develop their Phase II trial programmes, perhaps via a matched funding scheme. Funds could be awarded on the back of a successful case for support which demonstrates a solid case of clinical and commercial feasibility. A matched funding scheme is in place in California and the UK could learn a lot from the Californian experience of match funding there (for further information see <http://www.cirm.ca.gov/>).

What difficulties are encountered when conducting clinical trials and how could these be overcome?

Access to patients is important and the UK’s recent policy efforts to improve patient recruitment to trials are welcome. It is also worth noting that EU regulation on clinical trials has not helped recruitment onto international studies.

For certain orphan indications it is possible to more readily obtain registerable clinical data sets. Patient groups and charities are the strongest advocates for many orphan indications and provide funds for development of clinical trials. This provides an opportunity for specialist biopharmaceutical companies to partner and share the costs of early stage development. The Government could support the AMRC by providing infrastructure support dedicated to database set up, maintenance and a portal to identify potential interesting collaborators for industry who have development programmes which have a strong prospect of clinical and commercial feasibility.

What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

Access to quality clinical metadata for trial design considerations has been forecast for recent improvement with the set up of the Clinical Practice Research Datalink. It will be important to monitor how well this is supporting the development of clinical translation for these technologies.

A further difficulty is that it is not easy to identify within the NHS the physician advocates for this type of medicine.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

It is generally recognised that adoption is the main problem within the NHS. Pfizer has been pleased with the recent progress made with the *Innovation Health and Wealth* review which aims to improve dissemination of innovation in the NHS, and in particular looks to improve adoption of NICE approved therapies in the NHS.

Historically there have also been delays in trial approval caused as a result of the Gene Therapy Advisory Committee (GTAC) review being needed in addition to MHRA negotiations. We welcome the consolidation of GTAC into the MHRA and that the focus has now moved to patient safety rather than scientific re-review of the merits of a project seeking approval.

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

It would be difficult to quantify this exactly, although we would estimate that the current global value of regenerative medicine across the industry is in the region of \$1bn (i.e. c.0.1% of the global pharmaceutical market).

If the UK is successful in creating a positive commercial and regulatory environment for regenerative medicines it naturally follows that high value jobs will be created and a resultant positive impact on economic activity, in addition to the chance to transform the lives of patients currently suffering from untreatable conditions and injury. Therapies to reduce the burden of degenerative diseases in an aging population would be of huge value to both society and the economy, with a potentially transformative effect in the future.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

The key factors limiting investment and commercialisation are the lack of scientific knowledge in key areas (such as the fate of stem cells in the body, dosing, long-term impacts) and uncertainty about the probabilities of regulatory success. There is not so much evidence of market failure as such.

Lack of investment is mainly due to lack of clinical evidence that regenerative medicine therapies work, and low confidence that the business models will provide a sufficient return on investment.

If the UK set itself an achievable goal within 5 years to be the world's leader in the generation of Phase III data for regenerative medicine products then this would go some

way to raising prospects. Most critically, if the UK set a goal that within (say) 7 years it could deliver the leading platform for the most cost effective set up, implementation of Clinical Trials and fastest route to registerable dataset generation then this would also be a substantial benefit.

The challenges to investment remain lack of evidence and concerns on ROI, but insofar as government support for private sector research can play a role, what is on offer in the UK is welcome. However, UK industry, especially small companies, would benefit from more sustained support. Further tax savings and incentives, and R&D tax reductions would all be helpful.

What role does patenting play in the commercial development of regenerative treatments?

To a large extent this depends on the type of regenerative medicine in question. Small molecule programmes will critically depend on composition of matter patents. Cell-based therapies will have more complex IP positioning; data exclusivity and know-how will also be important, not just patents.

On 18 October 2011 the Court of Justice of the European Union handed down a judgment in the *Oliver Brüstle v Greenpeace* on the patentability of inventions relating to stem cells.

There has been a great deal of comment about the impact that this will have on the future of development of regenerative medicines in Europe. The situation remains unclear. In general Pfizer is concerned that the ruling may act as a deterrent to new filing and the importance placed by investors on an intellectual property (IP) position.

It is also worth noting what is currently happening with IP and regenerative medicine companies who have therapies on the market. Where patents have expired, or are close to expiring, it has been the case that it can be difficult for potential competitors to manufacture a company's product. As so much 'know how' is involved, it may not always be an attractive commercial proposition owing to the levels of investment and amount of time needed to replicate a company's product.

It is also worth noting that a lot of core Intellectual Property on methods of generating human embryonic stem cell lines may well have lapsed by the time any therapy is launched commercially.

What business models are most appropriate to support the development of regenerative treatments?

For pharmaceutical companies in this technology area, a great deal of thinking is going into how stem cell therapies can be commercialised when the commercial model for them is more similar to a medical device model as opposed to the small molecule model.

Instead of making many thousand identical treatments, a stem cell therapy manufacturing model could consist of a run of a single therapy unique to a certain patient. Pfizer is seeking to understand what that may mean for a reimbursement position, and a learning and development process with respect to commercialisation is underway.

The flow of an autologous stem cell therapy treatment (for example where tissue would be collected from a patient, then sent to a manufacturing facility, developed into a therapeutic

mechanism, and then sent it back to clinicians for implantation) is a very different model from the centralised manufacturing and wholesale distribution model of small molecules or even the cold chain distribution of biologics and vaccines. Allogenic cell therapies would be closer to existing approaches, but would still require different logistics and processes from what we are used to in the traditional pharmaceutical space.

What are the barriers to securing finance to develop such treatments?

Technical and regulatory uncertainties, and general poor performance of investments in biotech over past 20 years are key barriers. In addition key uncertainties remain in the sector as to exactly how products will be made.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

As noted Pfizer is considering pricing options for future therapies. As a general observation Pfizer would note that the UK's processes for health technology assessment could be improved to reflect better the full value of medicines. NICE represents a 'high hurdle' for access to medicines in the UK.

Given that regenerative medicine has the ability to transform patient care into the curative realm, it is important that NICE has a framework for dealing with these types of therapies.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

Barriers will be different for different regenerative medicine types. The most significant challenges are likely to be from autologous stem cell therapies. There is a need to leverage the experience and infrastructure of the NHS Blood and Transplant resource and the UK BioBank for expertise – this could really enable some trials and commercialization of products as they already deal with logistics and cell/tissue.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

Competition for bioscience investment across the globe is intense. Pfizer has observed that countries (and US states) that have invested in industry support have seen a concomitant increase in regenerative medicine research taking place in those locations. As 'critical mass' is often important in research (such as we see today in biotech hubs and clusters such as Boston in the US and Cambridge in the UK) it could be argued that bold and high profile measures and programmes to support and sustain investment in regenerative medicine in the UK now could pay future dividends.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

Not significantly as yet. The CJEU ruling is concerning; the uncertain support for stem cell research in Horizon 2020 is another potentially adverse signal for the sector. Actions in other member states are not impactful on the UK apart from via EU institutions. The switch in US federal funding policy has opened up more competition for the UK sector, too.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

The possibility of adverse events from unregulated cell therapies administered anywhere around the world could have an adverse impact on the sector via increased safety fears and consequent regulatory barriers/demands.

21 September 2012

Pfizer, Professor Chris Mason, University College London and ReNeuron – Oral evidence (QQ 128-169)

Evidence Session No. 6

Heard in Public

Questions 128 - 169

TUESDAY 20 NOVEMBER 2012

Members present

Lord Krebs (The Chairman)
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Baroness Perry of Southwark
Lord Rees of Ludlow
The Earl of Selborne
Baroness Sharp of Guildford
Lord Wade of Chorlton
Lord Willis of Knaresborough

Examination of Witnesses

Dr Ruth McKernan, Chief Scientific Officer of the Neusentis Unit, Pfizer, **Professor Chris Mason**, Professor of Regenerative Medicine Bioprocessing, University College London, and **Michael Hunt**, Chief Executive Officer, ReNeuron, gave evidence.

Q128 The Chairman: I should like to welcome our first witness panel and in a moment invite you to introduce yourselves for the record. The session is, as usual, being webcast and if you wish to say anything by way of introduction to you or the organisation for which you work, please feel free to do so, but please keep the comments brief as we have a lot to get through in the next hour. Please will Michael Hunt kick off?

Michael Hunt: I am Michael Hunt, chief executive of ReNeuron Group plc. We are a publicly quoted stem cell development business based in Guildford, Surrey.

Dr Ruth McKernan: I am Ruth McKernan, a senior vice-president at Pfizer. I am also head of Neusentis, which is our research unit based in Cambridge, where all our cell therapy work is focused.

Professor Chris Mason: I am Chris Mason, Professor of Regenerative Medicine Bioprocessing in the Department of Biochemical Engineering at the University College London. I am also senior editor of the journal *Regenerative Medicine* and chair the BIA Cell Therapy and Regenerative Medicine Industry Group. I have a background in academia, commerce and clinical work.

Q129 The Chairman: Thank you very much. I should like to start by asking you about financing the development of regenerative medicine treatments and what challenges you face

in financing. I would like particularly to ask Michael Hunt about the types of financing that your company has secured and what challenges you faced in attracting finance.

Michael Hunt: ReNeuron is perhaps a slightly odd example to give because we are one of the very few, if not the only, pure stem cell therapy businesses that chose to go public in the UK, so that set us on a rather distinct path. Right back in the early days we gained venture capital funding, but we publicly listed quite early even for a biotech company, purely because that was the only place where at that stage we could see financing being available. We have stayed on the public markets for about a decade or so. The business itself has changed quite markedly over that time and we have refocused. That is a function of how we have had to adapt to maintain our place in the public markets and keep investor confidence in us as a public stock. As regards the way we source funding now, we are a pre-revenue company, which means we use the money that is available to us to develop our treatments, take them through the clinic and then ultimately, we hope, into the hands of commercial development partners. That means that we have to raise money fairly continually, from public markets predominantly, so our own investor base is a mix even though we are a very small business. We are worth no more than about £20 million on the AIM market. Our investor base is a mix of institutional investors, the like of which you would perhaps have in your own portfolio, as well as the odd sovereign wealth fund here and there, and direct retail investors—men and women in the street who choose to invest directly in stocks like ours because they are interested in the story either from an investment perspective or perhaps from a broader perspective because they have been touched by some of the disease areas we are focused on, so we have a very disparate range of investors and that makes us somewhat unique. If you move beyond businesses like us, you will find businesses that are privately funded in Europe and perhaps in the States which have managed to gain early money from research foundations perhaps and have stayed private. You will also see some publicly quoted companies in the US which we regard as our closest peer group, if you like. There are no other quoted stem cell therapy businesses in the UK right now, so we are somewhat unique. But to get to the question, funding up to this stage has come from a variety of sources. You go where you have to go. The good news more recently for us as a business is that we are taking more advantage of the money that the Government have made available now through things like the Biomedical Catalyst Scheme, which is open to a much broader biotech range but includes regenerative medicine, of course, and we have made applications there, and more recently, the Cell Therapy Catapult, which is just about getting off the ground now. Again, I see this as a very positive step to helping bridge that classic valley of death in terms of funding and promotion of regenerative medicine in this country.

Q130 The Chairman: I wonder if the other two panellists would like to join in and say what solutions more generally they would suggest for companies seeking to develop the regenerative therapies—what financial solutions might be available?

Professor Chris Mason: The challenge is that we think about research and then translation and job done, and I think that is not the case. We should be looking at research, translation, commercialisation and going round the circle to return the money to do more research. When we think of that, it is a very long pathway, longer than just doing the clinical trials but actually getting clinicians trained up, getting the reimbursement in place and getting into routine clinical practice, so when we think about funding it has to bridge all those three separate parts. The other thing is that we start with a lot of horses running in the basic research and that narrows down quite quickly because some fail, some may not have safety, some may not have efficacy or may not be a business proposition. We narrow it down to a

few potential therapies. At that point we have another funnel forming the opposite way which is the funding funnel. We need a funding funnel that opens out to encompass the entire research, translation, commercialisation pathway. I think that is where we slip up. We do not have that funnelling out and we end up with a very staccato arrangement of funding where it comes and goes, it is not good for companies and it does not create an environment which is robust for investors to come into. They do not want uncertainty. We have to provide certainty and speed to deliver a product.

Q131 The Chairman: So what are the solutions?

Professor Chris Mason: The solutions are that we now need to move on. We have done a great job in the research space in the UK. We are doing a much better job in the translation space with things like the Biomedical Catalyst and the Catapult Centre, but now we need to address commercialisation, first by acknowledging that translation and commercialisation are not one and the same. That is very important. There are more steps that we have to go through. We need to shorten that process so that once things have got through the final bit of phase 3 they can get through to the clinic quickly. I am sure we will come back to regulation later in this session. Increasing the certainty is the answer.

Q132 The Chairman: Who will provide the funding?

Professor Chris Mason: I think Government have to step up to some of this funding. It will not be possible for the pharma companies to do everything. We may make things so-called investment ready—I guess that is probably the end of phase 2, where we have safety and efficacy data—but that in itself is not enough. The pharma companies will not be able to pick up everything. We have to have a joined-up plan from the beginning of the research through to the end.

Dr Ruth McKernan: I sit more on the other side of the fence in that we are a pharma company and we finance stem cell research and regenerative medicine. I would like to talk about two of our projects: one where, in partnership with University College London, we are developing a cell therapy for macular degeneration, and another partnership we have with a biotech company in the United States, where we run the clinical trial for an inflammatory bowel disease. The challenges for us are, first, that we will invest where there is really good-quality science and robust, high-quality efficacy data from clinical trials. We have to compete within the company for resources for the research that we do, so in order to work in regenerative medicine we had to make a proposal to the company to start a unit and to identify some key programmes where we would invest and, based on the outcome of those programmes, the company may decide to invest more or less, if the cell therapies work. It is also important to think about commercialisation, whether we can consider approval on licence or adaptive licensing for cell therapies which would get them to the market sooner and would allow us, or whoever is developing that product, to get revenue back while still understanding the efficacy. Obviously, it is really important to monitor safety of patients all the way through but many cell therapies are given once and expected to last for a long period of time, so one does not want to wait until the end of several very long clinical trials before you can start to commercialise the product. That is probably where you are going, Chris, in terms of the commercialisation.

Professor Chris Mason: Absolutely.

Dr Ruth McKernan: The other thing I would say is, as regards partnership in the UK, the quality of the science is fantastic. It is expensive to do clinical partnerships here. The full economic costing model is expensive for us. Other countries are more adaptable and

flexible in putting in constructs that allow really close collaborations. But I would say the UK has a lot of opportunity in this space.

Q133 The Chairman: Thank you. May I just ask you about this adaptive licensing you referred to? Is that something that you feel could and should work more generally?

Dr Ruth McKernan: It is not going to work for everything but cell therapy is an area where we have to look at it very closely because regenerative medicine is very different from historical models that pharma companies have been used to. We are looking at products that are given once or irregularly. We expect the effect to last a long time. It is a very complex product with multiple IP and multiple pieces of know-how involved in generating them. We need to be prepared to look at the value of the product, what it means to patients, how it is reimbursed, how NICE sees that, and think about that ahead of time so that we can get high-quality products and medicines into patients sooner and then monitor them as they get rolled out to other populations.

Q134 The Chairman: I can see Chris Mason nodding in agreement.

Professor Chris Mason: That is an extremely pragmatic way forward. We have this very long development pathway and then suddenly we get to a point where it is commercialisable. We need to break that up and make it more of a spectrum. I agree with Ruth that you have to have a safety profile that is acceptable to the patients, but I think at that point there is no reason at all why it could not go out to certain groups in certain very specialist centres so we would start to gain knowledge, but more importantly the company would start to get reimbursement.

Q135 Earl of Selborne: I should like to follow up Dr McKernan's observation on the role of big pharma. You described how you had partnerships with academia and I think you mentioned a company in America, which is presumably a small company—an SME perhaps? Could you describe how you see this partnership working? What is it you expect from the other parts? What should they expect from big pharma?

Dr Ruth McKernan: I think the ecosystem of life sciences is really changing and pharma companies are doing much more work in partnership. That is not just the case with Pfizer; I think it is probably true of many pharma companies, so we expect to work very closely with academics or with SMEs with biotech companies. I would say that our collaboration with University College London has been exemplary in that we set up that partnership when Peter Coffey and Lyndon da Cruz had done a lot of work, understood the science and that work was funded by the London project. They were at a stage where they needed a pharma mindset to understand what the product should look like, how to take it through the regulatory process, how to make it in a GMP way and all the checks and balances that pharma experience has in putting molecules or products into patients for the first time. That said, the team has been very close, so when it came to the MHRA conversation, the team went together. I think there has been a lot of shared learning about how to do things well. We always have a lot of science to learn and a lot to learn as regards the flexibility, adaptability and creativity of our academic and biotech partners. They can see the value of a lot of our regulatory knowledge, our understanding of what makes a product and of how to go through very carefully the safety issues that might be necessary before we consider putting a product into patients. The clinical programme is being funded by Pfizer but most of the early stage research had already been done by the academics. Our partnership with the biotech company in the United States is very much along the same lines. We designed the clinical trial between us. They had a lot of experience in producing the cells. We run and

manage the clinical trial but we have colleagues from the biotech company as part of the team and we work on it together. That is the only way I think it can work. If you get into a very strict transactional arrangement, it is never as effective as having a very open communications style.

Q136 Earl of Selborne: Could I pick you up on something, or ask you to elaborate on something, you put in your written evidence? You said in that evidence, “There is predicted to be a significant imbalance in the UK in funding sources at Technology Readiness Levels (TRL) 6-8, with the majority of investment coming from the private sector”. You are asking that the Government step up to the plate. Could you elaborate on that?

Dr Ruth McKernan: I think this goes to Chris’s point in that the UK is really strong in the early stages of the science. The MRC, the BBSRC and the TSB are well connected and their *Taking Stock of Regenerative Medicine in the United Kingdom* was very informative. The challenge is getting through the clinical trials and into commercialisation—the later technology readiness stages, as you point out. While we have quite a few GMP manufacturing facilities in the UK, running robust clinical trials and thinking through how we will then roll out the new therapies to patients has not been well thought through. Do we need specialist centres, for example, with a GMP facility and cardiologists, if a heart therapy is involved? On our RPE (Retinal Pigmented Epithelial) programme we have been working very closely with Moorfields, but in order to commercialise that product, should it work—the studies will start only next year—we have to think about how we make the RPE patches and send them out to different centres. Then they have to be implanted. There is a lot of expertise involved in using cell therapies. They are not pills or injections, by and large. How to commercialise a product and get it out to a lot of patients is the bit that we have not really worked through because we have not had that many case examples. To think of it ahead of time would be really good. You might consider that in some instances our fertilisation clinics would be a model that might be adaptable to such a process. Is that what you were looking for?

Q137 Earl of Selborne: Thank you. Just one last point to Mr Hunt. In your submission, you advocated mechanisms such as citizens’ innovation funds. Frankly, I understand that they are not very reliable at the moment. Is this just a hope and a prayer or is it a sensible proposal for the funding sums, which are quite enormous?

Michael Hunt: Within context, that is just one example of mechanisms that do not necessarily call on government to provide funding but rather to stimulate funding mechanisms through advantageous tax systems. That is one example which I know the biotech trade body—the BIA—is strongly promoting and, of course, we would endorse that. But to go back to the original question on financing, what you are hearing about here is increasing confidence. From the perspective of a small SME that has to work in this space, which is inherently high risk, and perceived to be so, you have to provide a level of confidence to investors which means that they are not expected to do all the heavy lifting in terms of funding. That is where schemes like the Biomedical Catalyst can add real value because we know that investors love to see that someone else is taking some of the burden of the funding. They believe that those guys know what they are talking about and perhaps know more than some of the generalist investors do. Therefore, those generalist investors will rely on the due diligence that is done by these grant-awarding bodies. That gives them confidence to match funds so it becomes self-fulfilling. If you can crack that one, some of the mechanisms that Ruth and Chris have described then come into play whereby you can demonstrate to an investor that there is a route forward to market and there are sensible

mechanisms that perhaps allow early access if you can generate great phase 2 data, or maybe phase 3, depending on how, in the case of the MHRA, the early access consultation moves. Again, that would play very well into the regenerative medicine scene, as would providing some mechanism or confidence to investors that there is a route to market and adoption. In this country we have the National Health Service, which is an amazingly valuable resource that our competitors do not have that we should make more use of, most especially when it comes to regenerative medicine. If you can get endorsement at an early stage, as we have done in our own trial on stroke, and have a clinical trial process adopted by the NIHR, that provides a level of confidence to investors that someone is looking at what we are doing and taking it seriously. That will ultimately lead to further investment and will help us to get the job done, so it is a case of providing a pathway and a series of mechanisms which help to move the field forward, and perhaps more importantly for us as an SME, provide a level of confidence to those we expect to back us to get there.

Q138 Lord Cunningham of Felling: The committee has regularly heard that the United Kingdom is very strong in basic research in these areas but not so good at taking it through the translational phase and into commercialisation. I should like to ask each of you what you think should be done to encourage more effective working between academics, clinicians, industry and charities to try to ensure that world-class science in the UK leads to more effective treatments and the commercialisation of therapies. What do we need to do to unlock this?

Professor Chris Mason: There are a number of ways of doing this but one is particularly important and has been touched on in previous sessions; that is, we do not really have a cluster in the UK. There is no global cluster for cell therapies—period. These therapies are very different from biologics or small molecules in that a lot of them cannot be stored. They go out as fresh products. Therefore, there is a demand for very good logistics and the ability to get from manufacturer to clinical centre, ideally within 24 hours or possibly less. For example, with ReNeuron products it is less than that. Therefore, there is a unique opportunity for the UK to build an embedded sector. By that I mean a cluster which would have manufacturing at its heart and would be able to distribute not just to the UK but to Europe and possibly even the Middle East and North African markets. That way, we would get round the glitch of the NHS at the moment not being a technology puller, or market puller, I should say, and not necessarily having early adoption. We would therefore be able to access a much wider range of markets. To come back to your question, that cluster would need to be such that it really did engage with academics, clinicians, companies, regulators and government. How does it do that? It does it by showing that there is a way forward. A lot of the problem at the moment is that people cannot see that there is a way forward. They can see brick walls and they cannot see the long-term future. If we said as a country that we would invest in a cluster for what I call advanced therapies—gene and cell therapy—and I would like to come back to that later, then there would be a way forward, people would get excited about it and just as translation has got on to the academic agenda, so will commercialisation, and we will move the whole field forward.

Q139 Baroness Sharp of Guildford: Do you therefore feel that there should be some form of incentive or disincentive in order to encourage the growth of this embedded cluster?

Professor Chris Mason: You need an incentive to get the cluster off the ground. It needs to be in the right location. The UK is ideally positioned for Europe and the MENA (Middle East and North Africa) markets because we have airports at Stansted, Gatwick, Heathrow and

the City airport. We have a phenomenal clinical base and a phenomenal base in the City in terms of potential future funding. We have pharma involved. The EMA (European Medicines Agency) is in London. Everything is there. Every bit of the jigsaw is currently in the UK. We are ready to go. What is needed now is for the Government to say that they will back a single cluster which will bring in academics and clinical business and get them all together. The Government need to say, “Yes, we will fund it properly and we will deliver on commercialisation, not just translation but commercialisation”. It is a unique moment in time. This window will probably be open only for a few years. We have possible sites for the cluster, now it needs government will and funding to drive it forward. I believe that we can deliver.

Q140 Baroness Sharp of Guildford: How do you envisage that the Government would back it?

Professor Chris Mason: What is needed is leverage. The Government cannot do everything on this and I appreciate that but we could propose where we set up a centre for cell therapy for Europe and the Middle East and gene therapy for the global market. The UK is extremely strong in this space. We are global leaders. We have a massive chance here. There is a convergence of cell and gene therapy. If we say that we will back a single centre—not a virtual cluster but a real one—the Government could talk to people like Ruth and other big pharma players and bring together the interested partners. We will have some open innovation in there; there is no doubt that we need some common tools. That is really important. Then we will see little companies growing in the UK and inward investment. I hope that we will see other Pfizers establishing their regenerative medicine companies in the UK. However, this has to be a joined-up plan and the investment and leverage must be in place.

Q141 Lord Cunningham of Felling: I should like to ask Dr McKernan what she thinks of this.

Dr Ruth McKernan: I would be very positive about partnerships with academics in the UK. We work with many different groups. We work on making IPS cells with Ludovic Vallier; the Sanger centre is just down the road from where we are. We have a collaboration in Scotland and we work with the guys in London at Moorfields. It is quite straightforward to collaborate with people in the UK. The academic environment here is very open to it. We run into a little bit more trouble as regards intellectual property. The IP position on cell therapy is very complex. There are many small pieces of IP involved in making a product. Sometimes university business groups do not have a good sense that their one piece of IP may not be quite as valuable as they believe it to be, and that slows us up sometimes. The other thing that can be an issue is the high full economic costs. The last time I looked at the cost of sponsoring a postdoc in different parts of the world—these are not recent data but come from a few years back—I found that for the full cost of sponsoring a postdoc in the UK you could get two in the United States and 10 in China, so maybe there are some things to be done there to enable good, close collaborations to take place at a more competitive rate. As regards other areas, I like Chris’s idea of having a centre in the UK. It would certainly help in terms of running clinical studies, understanding reimbursement, how products are valued and how they get through the NHS. That example is relevant to the rest of Europe, at least for some countries. Therefore, I think there would be real value in that. However, from a pharma perspective the most important thing we can do is to show that there is good robust efficacy with cell therapies. That will, I think, will open up a lot of

competition and value creation. If the UK is in a position to take advantage of that, it would be great for us.

Q142 Lord Patel: I seek a brief answer, please. Does the Office for Life Sciences have a role in any of this?

Professor Chris Mason: I think the UK has become much more joined up over the past 10 years on this whole thing. It started out with the DTI (Department of Trade and Industry) and its technology strategy and the original programme was called the TSB programme. We have seen a number of government departments feeding in very well, which bodes well. To come back to the points that have already been made by Ruth and Michael, reimbursement is critical. We are moving into therapies that are transformative. By that we mean that they are either curative or, as Ruth said, people take them very infrequently; maybe you will have a top-up of your pancreas cells every five years. That is a very different business model from what we have seen up until now. Clearly, we need to take that into account when we reimburse these therapies. They will cost more because cells cost more to manufacture. That means they have to deliver more. We cannot compare, say, a tissue-engineered piece of skin with a simple bandage or, as I say, pancreas cells with insulin injections. The business model actually changes, which means that it is not just the DoH that has to stump up the money but bodies such as the Department for Work and Pensions as these therapies will enable patients to return to work, or maybe they do not have to give up work as they once would have done. The therapies will certainly help carers and benefit UK plc. We are now in a situation where reimbursement will be higher and we cannot expect the DoH to fund all that. We need now a joined-up thing from BIS. To come back to the question, we certainly need the DoH on board, the Treasury and other government departments. A bit of shuffling round of money will be needed to pay for these therapies, and that will help with market pull.

Q143 Lord Wade of Chorlton: To follow up Professor Mason's point about that, I agree entirely with you about the value of clusters, but generally clusters evolve and are not imposed by government. How does government make the decision to impose a cluster in this area? From your knowledge of the industry, where would you expect that a cluster is likely to evolve?

Professor Chris Mason: Clusters can be generated, you are absolutely right. The I28 corridor in Boston has emerged. The clusters on the west coast were very much helped by defence funding, and they did help with silicon chips at that stage. Where this is slightly different is that we want an embedded industry. We do not want this to be sucked out of the UK once it gets a little bit bigger. We want the jobs and the high-value manufacturing to stay here. That is entirely possible. These are fresh therapies. Some are autologous, which means that the material comes from the patient and goes back to the same patient. That needs a short journey time. So we have a big plus here. We cannot just make a big pot of these products anywhere in the world and ship them in. These are actually made locally. They are made using high-value manufacturing techniques, which we are very good at in the UK. So can this process evolve? Yes, it can, it is a combination. We have a lot of good companies, a lot of good pharma, a lot of interest and a phenomenal reputation. It is just a question now of bringing all the bits on to one space. We have had a jigsaw dotted around.

Q144 Lord Wade of Chorlton: That is what I do not quite understand. How are you going to turn this into a practical application when you can put the responsibility on to government to suddenly turn this disparate organisation into a cluster?

Professor Chris Mason: It is not just Government. Big pharma and others all have a role to play in this but we have to have a joined-up plan that says, “Yes, we are going to be the winners”, and I do not think we have that at the moment. We are saying that we may be one of the players and we may be a leader, but we have to say that the UK could be the No. 1 in Europe. We need to make it the go-to place to be, so that if you are thinking about setting up in Europe, you think of London or elsewhere in the UK. I do not mind where it is as long as it is in the UK.

Q145 Lord Wade of Chorlton: Where does the leadership come from?

Professor Chris Mason: It needs to come from government. At the very top, yes, it has to have the Government wishing to do this.

Q146 The Chairman: Could I ask Michael Hunt to comment on the cluster concept?

Michael Hunt: There is maybe a more fundamental issue here that goes back to the question that was asked earlier regarding the interplay between academia and industry. We have a very solid and deep academic base of research in cell therapy and regen med in this country. They are well resourced and there is a huge amount of very valuable work being done, but there is no emerging industry. Why is that? Purely and simply, historically there has not been enough academia/industry collaboration, by which I mean both industry and academia understanding the respective roles, and respecting those roles, that each of those cohorts play in bringing a product out of a university and into development. If there is a greater understanding of the role that both parties can play, and those parties work together more strongly with those aims in mind, then I think we might see more of an emerging industry. I do not think it need take any more money and it probably does not necessarily need a cluster. What it needs is a sensible balance of basic research funding—RC funding—and translational funding through the TSB and the Catapult. By the way, the Catapult can act as a quasi-cluster in bringing together some of these academic centres of excellence. There is no need to move them or base them anywhere in particular, but someone is needed to co-ordinate this excellent research and try to steer it towards the generation of an emerging industry. That is the Catapult’s remit and it is a hugely valuable entity which is just being set up here in London to try to bring some of these things to fruition. If you can address that, we have the basis for an industry where you have the strengths of the UK working absolutely hand in hand with an emerging industry. At the moment there is just a disconnect. I do not necessarily know why that is because, in common with any business, we work quite closely with our own academic partners at King’s here in London and beyond the UK. Something is not quite right here in terms of there being all this great basic research but it is not being translated. Until we start seeing some translation, the issues that come further down the pipe are less relevant because there will be nothing to feed into that pipe. We have to get the basics sorted first. You are right to point this out. The interplay between academia and how we translate this science into solid businesses that are adequately funded to get the job done is absolutely critical. The Catapult has a huge role to play there.

Q147 Lord Rees of Ludlow: Just to follow this up, you emphasise the issue of critical mass, even when we do have the cluster. I have a worry that I would like you to address. Given that what we are spending is still rather small compared with the US and California, can we avoid the situation which prevails all too often in the existing high-tech cluster around Cambridge whereby companies—SMEs—are built up but then get taken over by the US and we lose the full benefit? How can you avoid that situation happening again?

Professor Chris Mason: It is built into the therapies themselves. A number of these therapies are fresh, so to manufacture them in the States and bring them over is unlikely. The other thing is that the therapies can be split into two: ones which are more universal, where you have a common donor and maybe treat 5,000, 10,000 or 100,000 patients, and others which are autologous, where the cells come from the patient and go back to the same patient. Again, they need a local supplier—let us put it that way—but one local supplier could cover the whole of Europe, the Middle East and north Africa.

Q148 Lord Rees of Ludlow: Could not the US companies take over this?

Professor Chris Mason: They could come into the UK. I think the UK economy for cell therapy would be a combination of inward investment, divisions of big pharma which see the light and small companies wanting to build up. I think we do need a critical mass. As regards attracting good people in from the US, why would you want to move out of San Diego, the Bay area or Boston, where you can lose your job on a Friday because the company goes down and join another one on the Monday, and instead come to the UK where you might work in, say, Guildford and then your next job might be in Scotland, so you have to move around? Cluster is really important. This is about logistics. If you want to serve those markets, you have to be in the right place and the US is not in the right place for that. The biggest US contract manufacturer is Lonza at Walkersville. The company would have to ship its products into the UK and then starburst out to the rest of Europe. I say that the operation needs to be based in Europe.

Q149 Lord Wade of Chorlton: Has sufficient thought been given to the long-term infrastructure requirements in the UK to support the expansion of regenerative therapies as they develop in the future? If not, who should be thinking about it?

Dr Ruth McKernan: No, sufficient thought has not been given to it. Very often we end up developing the infrastructure when we have the product and we understand more about what is required. We need to think about this much more in advance.

Q150 Lord Wade of Chorlton: Who should think about it?

Dr Ruth McKernan: As a pharma company, obviously we need to think about it because, should our clinical trials prove successful, we need to consider where we will manufacture the cells, how we will get them out to patients, which specialist centres we will use to get them to patients and who will reimburse them. Therefore, we certainly have a part to play in that. However, there is an opportunity for countries that want to have this as part of their life sciences strategy to encourage biotech companies in. One example where we are beginning to see this, although it is very early days, is the Cell Therapy Catapult Centre. That is the only example of its type that I know where, if you want to get an early stage clinical trial done as a company or as an SME, there is somebody that you can go and talk to who will help design it “soup to nuts” and make sure that it can happen. Had that existed when we were setting up our clinical studies, I would certainly have looked at it as an option. I know that companies in the United States are looking at the Cell Therapy Catapult Centre and asking themselves how they can use this resource to try to advance the understanding of their products and get their clinical trials done. That would certainly be a useful thing. We worry a lot about stem cell tourism and people going to other parts of the world, getting unvalidated cell therapies and doing themselves damage. However, the UK has a unique perspective. We have a robust regulatory environment. The quality of the work here is respected the world over. Should not we be in a position to set up specialist

centres and encourage the rest of the world to come here rather than the other way round?

Michael Hunt: I agree. It sounds as though I am promoting the Catapult left, right and centre here, but basically it has a huge role to play. One of the first generic challenges it is addressing is scoping out what infrastructure actually exists on the manufacturing side in this country at the moment. It is a fair enough place to start. If you move beyond manufacturing, where clearly there is an issue about what we have, how good it is and whether it serves the needs of the emerging industry, those are all good questions for the Catapult to address. I go back to what I said earlier—namely, that the National Health Service is a very valuable infrastructure in which to conduct and promote clinical trials of innovative products like cell therapies. That side of the infrastructure equation is already in place. It is just a matter of getting clinicians and other interested parties in the NHS behind these treatments and using the NHS infrastructure to conduct these trials. There is so much good stuff there in terms of registries and information flows that link centres across the country. That does not exist elsewhere in the world. It is an incredibly valuable resource to be able to access patients and to track them before, during and for a long time after a clinical trial has taken place, as well as obviously having co-ordination mechanisms like the NIHR to help promote this type of clinical activity. Manufacturing and the NHS are two key infrastructure issues. One can be used as it is already there, and one is currently being explored anyway by the Catapult. Perhaps at this stage it is difficult to say whether we have the manufacturing infrastructure that we need. I believe that there are enough centres in the UK to serve the immediate needs of the industry in the near term but that those centres need a bit of co-ordination. Again, the Catapult should take it upon itself to provide that co-ordinating activity so that companies like us know where to go to get these products manufactured.

Q151 Lord Wade of Chorlton: The NHS blood transfusion service has also been suggested in this regard. Do you agree with that?

Michael Hunt: Yes, I think so. There are other centres such as NHS Blood and Transplant up in Speke. There are various centres dotted around that are looking to move into supporting the emerging cell therapy industry. That is great. Where that infrastructure exists—maybe there is some latent capacity there—we should be using it, so, yes, I certainly support that.

Professor Chris Mason: The other bit of the equation is that we need to make this a very friendly environment for the contract manufacturing organisations. If we could embed them in the UK, that would greatly help us build the whole clustering arrangement within the UK. There are not that many of them so if they all set up in Germany, it is likely that Germany may well be the hub for all this. The two things here are, first, that contract manufacturers are part of the equation and, secondly, I think it is a race with other centres in Europe to establish the European centre.

Q152 Lord Dixon-Smith: This may sound a silly question. I understand completely what a wonderful asset the NHS is but I wonder if it appreciates how critical it is in this sort of situation. Is it working with you and trying to help you or is it merely what I would call a passive sleeping partner, hoping that at some point it may get a benefit?

Michael Hunt: Speaking from our own experience, we found that we were pushing at an open door. What it takes first and foremost are clinicians within the NHS who are innovation friendly so they are willing to explore innovative areas in their own centres. Once you get a good principal investigator behind you, a lot of other things will start to

happen. As regards the underlying infrastructure, we have made great use of the NIHR to help get our approaches adopted. Once you get through that first hurdle you are on your way, but I do not sense that there is resistance. Probably the knowledge base is low at the moment, but if we can feed more of these innovative therapies through the NHS I do not sense that there will be major resistance because, ultimately, everyone agrees that cell therapies have the ability to crack some very significant problems, at least in principle, in terms of dealing with chronic disease conditions, as we are doing. The NHS should have a major role to play in that.

Q153 Lord Dixon-Smith: Presumably, in theory, if what you say is correct, you should have a hand in reducing the cost pressures on the NHS?

Michael Hunt: Absolutely, that is very much what we would hope to do. Ultimately, that is why we are in business.

Dr Ruth McKernan: There is something else that we need to add to that, though, because at the moment new therapies need to be approved for use by NICE and they need to be reimbursed. We have to be prepared to pay for innovation and I am not sure that the UK has been fully prepared to pay for innovative new drugs. Therefore, we still have a lot of work to do on the cost-benefit and the way that stem cell therapies are going to be reimbursed because they will be expensive and they will be very different in terms of the way that patients are treated.

Q154 Lord Willis of Knaresborough: Good morning. I am particularly interested in the confusion that arises around GMP facilities. We have heard from some witnesses that there are adequate numbers. You have said that this morning and Michael Hunt said that a couple of minutes ago. Yet, Professor Mason, you have said that there is a need to bring facilities together to create large manufacturing facilities which can sell into Europe and the Far East, which I find an attractive proposition. We have also stated that the NHS is a remarkable resource, which we can use in developing the throughput of these therapies and long-term studies, and that the NHS blood transfusion service is a good depository or, if you like, manufacturing facility, for stem cells. Am I all right so far? Do we agree on that?

Professor Chris Mason: Absolutely.

Q155 Lord Willis of Knaresborough: Is there a sense, then, that the NHS blood transfusion service could be used as the central stem cell bank, and that that could be our main manufacturing facility?

Professor Chris Mason: My gut feeling is that we should be thinking of the next 10, 20 or 25 years. The answer is no. I think we have enough resource to do early clinical trials very well in the UK if the resources and facilities that we have are co-ordinated, used well and brought up to the right spec. I think that is true.

Q156 Lord Willis of Knaresborough: So we simply have this plethora of different manufacturing facilities?

Professor Chris Mason: We have little ones—little workshops. This industry is like the motor car business in about 1900 when lots of people were making great hand-built cars. We are moving towards a genuine industry, which we want to embed in the UK, but we are not equipped for that at the moment. Manufacturers are not going to be part of an NHS facility. I would think that they are going to be a stand-alone, proper manufacturing resource.

Q157 Lord Willis of Knaresborough: So we simply wait until Germany, France or Singapore develop those facilities and then sucks it all over there. Is that what we are saying?

Professor Chris Mason: We do not wait; we attract the business to the UK, and many of us are working on that aspect. We are talking to manufacturers like Lonza, trying to get them to bring their business to London instead of putting down a base in Germany, so there is activity. However, the model has changed. Pharma companies were always vertically integrated so they made the discovery and did everything, including manufacture, sales and marketing, and that was very much the model. The model which we are now going to work on for cell therapies is a very horizontally integrated one where we have different parts of a jigsaw. You may have a manufacturer, a consultant, a patent lawyer or someone working for a small SME, all working together. However, they cannot function in isolation, so we need the bigger manufacturers to make sure that the whole eco system moves forward as the whole thing expands.

Q158 Lord Willis of Knaresborough: I want to ask you, Dr McKernan, about Pfizer, because clearly you are a key player in that. From the pharma point of view, where do you get your stem cells from for your research?

Dr Ruth McKernan: For our retinal pigment epithelial product we acquired a small company in Sheffield called Axordia, which makes the embryonic stem cell line that we use. That is a UK-made line and we will use it for our clinical studies in the UK. If that works, I think there will be challenges because the regulations around the world are not harmonious. Different countries may have different regulations regarding the cell type or the exact way the cells are made, so a bit of work will need to be done on that. In the other cell study that we are doing, the cells are made in the United States but are shipped to European countries where we also run some of our clinical studies. We need to separate autologous therapies, where the patient receives their own cells, from allogeneic therapies, where they can be made in large batches. Although the shelf life is short, we have shown that these products can be shipped around, perhaps with some intermediate lab that expands them or does some of the preparation, so there are models that use that. However, my next point is very important. As we look at allogeneic therapies and scale them up, we may choose to do that ourselves because of the know-how that is required which involves proprietary information that we may not choose to outsource. Alternatively, we may choose to outsource that to another company such as Lonza or to a UK manufacturing site, so there are many different models here.

Q159 Lord Willis of Knaresborough: Would you say from Pfizer's point of view that the small personal stem cell therapies are likely to be incredibly expensive in the UK base simply because they are personalised?

Dr Ruth McKernan: Do you mean the autologous therapies?

Q160 Lord Willis of Knaresborough: Yes. But would you ship in the large-scale products from the States or somewhere else?

Dr Ruth McKernan: We have focused only on allogeneic therapy. So far we have not devoted our efforts to developing autologous therapy because it is very individual and personalised. I am sure that cost-effective autologous products can be developed in the way that fertilisation clinics have developed cost-effective products, but they are not something that we have chosen to make.

Q161 Lord Willis of Knaresborough: What I am trying to say is that you seem to have already decided that you have a model which simply says, “We bring them in from the States because they can manufacture them in bulk”.

Dr Ruth McKernan: No, we have made no decision about that.

Q162 Lord Willis of Knaresborough: But Professor Mason is saying we can continue with all these little bits because it does not matter. It seems to me that we are missing a trick somewhere.

Professor Chris Mason: May I clarify one little bit? I am saying that we have all those little bits. They are super for doing early clinical trials on autologous or allogeneic products. They are perfect for long-term autologous products, but even for that bigger organisations may need to be involved. However, this allows us to embed manufacturing in the UK. You start small. If you look at Detroit, it had 700 car companies in the 1900s. They built an industry. I think that is what will happen. We will get a coalescence but you have to have that little nidus there in the first place.

Q163 Lord Willis of Knaresborough: We said that about microchips and plastic electronics and we have lost them all. Are we going to lose this as well while we wait for them to grow?

Professor Chris Mason: We do not wait; we have to do something now. The window is small and the Government need to react quickly.

Q164 Lord Patel: That brings us very nicely to my question. Professor Mason, you have been very passionate—today you have demonstrated that again—about the fact that the United Kingdom has the opportunity because of our good science to address the issues of translation, regulation and commercialisation, and that if we miss that opportunity others will step in such as the United States, China, Singapore or somewhere else. Will all three of you say what we must do so that we do not miss that opportunity?

Professor Chris Mason: From my perspective, the bits of the jigsaw are present in the UK—we have everything. As you said, we have an outstanding research base. Translation is coming more to the fore. The Catapult is a great thing to have, as is the Biomedical Catalyst Fund. We obviously need more of those translational activities. We need academics to feel comfortable in the translation space so they do not feel that they will ruin their careers by engaging in translation and development, although they are interchangeable in my mind. We now need to engage more with the pharma that we have left and the pharma outside the UK to get inward investment in the space from small companies or SMEs. We also need to persuade the pharma companies that this is the best possible place, or maybe the only place, to put down their fledgling units, for want of a better name, as Ruth has done in Cambridge. She probably did so because Cambridge had a lot to offer. If we use those bits of the jigsaw and the leverage, we will move forward.

Q165 Lord Patel: What is it that the United States, Israel, Singapore or China are doing to encourage their companies to grow?

Professor Chris Mason: I think they have better state-delivered programmes. Not everywhere is doing well in this area, but if we look at California, for example, the California Institute for Regenerative Medicine with its \$3 billion worth of grants has clearly focused companies. I do not think that it has the best science but it certainly has the incentives for companies to set down there and work well. The same applies to Singapore and Israel,

which have the same sort of drivers. A driver from the top is needed to put commercialisation properly on the agenda.

Dr Ruth McKernan: I would say that Japan is a very good country to look at because it has recognised that its expertise is in IPS cells with Shinya Yamanaka. It has built four separate and distinct units that are developing IPS cell based therapies. Japan has made that its strategy. The scientists from Japan that I have spoken to are very excited and focused on doing that. We cannot do everything as we are not a huge country, so we have to bite off the pieces that we can do. Certainly, from a scientific perspective, we are very good at blood and liver and we have some nice heart studies.

Q166 Lord Patel: But the question was: if this science is good, what is it that we have to do to make the companies grow?

Dr Ruth McKernan: We need specialist centres. The Catapult centre is a good generic centre, but we need specialist cell therapeutic centres. I do not know how this fits into the NHS but if we want to be world-leading we have to have therapies available that others see as something they cannot get in their own countries and therefore are prepared to come here and pay for them. That does not fit very well with our NHS system and is probably outside the remit of pharma. However, building that expertise is important, as is building the specialist centres to give people therapies and measure their efficacy.

Q167 Lord Patel: I need to explore a sideline. Ruth, you said that as a pharma you were less interested in autologous treatments. Of course, pharma are less interested in autologous treatments because there is less money to be made out of them. On the other hand, for individual patients, a treatment is a treatment, and therefore somebody has to pick that up in terms of looking at patient care as opposed to making money.

Michael Hunt: I do not think you need to make that distinction. As I mentioned in a previous session, there are companies in the States in mid to late stage clinical trials with autologous treatments. These are companies with private investors backing them. I am sure that if you spoke to them they would not take the view that there is less money to be made or other commercial disadvantages with these treatments.

Q168 Lord Patel: Who is doing that autologous treatment development in the UK on a rival scale?

Michael Hunt: There are few examples of small companies that are translating either allogeneic or autologous treatments. We try not to make that distinction because autologous treatments have their appropriate setting. It depends on the disease condition, what you are trying to treat and how you are trying to treat it. The bigger issue here is: where are all the companies? I keep going back to this. We have this amazing capacity for basic research and trying to understand what is going on with cell therapy and how it all works but we have not generated any kind of emerging industry up to this point. The catalysts are starting to come through now. Very recently, we have seen some significant changes in the regulatory environment and it is great to see that. We are seeing the establishment of funding schemes like the Catapult and the Biomedical Catalyst, which can and will make a difference because the amounts of money involved here are not huge. To develop a small emerging industry of high-class players is not going to be a king's ransom; it does not need to be. We need to allow these mechanisms to play out and allow these companies to flourish. That cannot be done without at least some seed backing through these schemes from people who understand the longer-term implications because the other

investors who come in will inherently have shorter timeframes. The most fundamental issue for the industry is the timescales that investors tend to think in. That applies as much to VCs as it does to public institutions or private investors. None of them will think in terms of a timeframe that is as long as is required to realise value in this space, so there have to be other backers sitting to one side who can get these things off the ground and allow at least a degree of confidence for those other investors to want to come in who understand the longer-term aim. We need to keep those investors interested in what these companies are looking to achieve ultimately. If, ultimately, the UK can never grow an industry through to revenue-generating businesses—in other words, businesses license themselves off or flog themselves off to non-UK based businesses—that is another issue which goes far beyond regen med.

Lord Patel: I am getting slightly confused.

Q169 The Chairman: I am afraid we are running out of time. We are up against the wall, so just one brief comment, please.

Dr Ruth McKernan: I just want to make a quick comment on the business model. There are autologous therapies that will treat patients very well, but this is not the area that pharma has worked in. Setting up one therapy for one patient is not our area of expertise. We are moving into cell therapy from the aspect that we know and understand. Other companies will move into autologous therapy from areas such as stem cell transplants and bone marrow transplants—from the things that they know and understand. Ultimately, these things will join but we can move only incrementally and develop things incrementally.

The Chairman: Thank you very much. I am sorry; we have run out of time. I thank the witnesses very much indeed for their helpful comments this morning. You will in due course receive a transcript of the session, which will give you a chance to make any corrections. If there are any points that you have not been able to make as we have been quite pressed for time, and which you would like to make, please do not hesitate to send them to us in writing and they will form part of the published evidence.

Dr Mahendra Rao, National Institutes of Health – Written evidence

Chief, Laboratory of Stem Cell Biology, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

Note: Dr. Rao is responding as an individual scientist to this request.

Regenerative Medicine in the UK

Stem Cell Research in the UK

In the UK today, stem cell efforts in both academic and commercial areas continue to play a significant role in the field of regenerative medicine. Outlined below are those considered to be the UK's chief ambassadors to this vital and exciting field – whether through individual research breakthroughs or leverage behind the scenes.

In England, notable scientists include Robin Lovell-Badge, Austin Smith, Roger Pederson, and Azim Surani. Academic research programs with particularly strong research records include those headed by Chris Mason and Pete Coffey, respectively (University College London), and Peter Andrews (Sheffield University). The groundbreaking nature of Chris Mason's research draws, in large part, on its integration of basic science and bioengineering efforts through his commercial endeavor (RegenMed). Further, undertaking the complete bioengineering process has necessarily involved close collaborations with other leading UK researchers, including Pete Coffey and Peter Andrews. Pete Coffey's multidisciplinary stem cell research, especially his London Project to Cure Blindness which led to a macular degeneration clinical trial at UCL, has garnered international attention; he was recruited last year to the University of California, Santa Barbara, in the United States, leveraged in part by a grant from the California Institute for Regenerative Medicine (CIRM). He is continuing his efforts on the UCL projects, as well as heading the new California Project to Cure Blindness, co-funded by Britain and CIRM. Peter Andrews participated in the same London Project to Cure Blindness, as part of his research efforts focused on the biology of pluripotent stem cells. Like Chris Mason, his approach is quite collaborative, as illustrated by his coordination of the International Stem Cell Initiative, and efforts with the ESTools organization involving 20 companies. Collaborative efforts such as these greatly facilitate and expedite stem cell research and, ultimately, the path to therapy.

In addition, the Wellcome Trust has a long history of supporting excellent research and actively encouraging stem cell banking efforts. Outside of academia, England also has built a strong biotech infrastructure that supports regenerative medicine research efforts, with a focus on therapeutic potential. Notable biotech groups are Pluricell, Angel Biotechnology, TriStem, VetCell, Odontis, Plasticell and Stemride International (London); CellCentric, Intercytex and ViaCell (Cambridge); CellTran Ltd. (Sheffield); EpiStem and Renovo (Manchester); Relnnervate (Durham); RegenTec Ltd. (Nottingham); and ReNeuron (Surrey).

In Scotland, academic research is similarly supplemented by national support through the new Health Science Scotland and Scottish Development International (SDI) efforts. Health Science Scotland's support is particularly integral to regenerative medicine, given its focus on translational medicine. Biotech companies in Scotland with notable contributions to the

field include Stem Cell Sciences (Edinburgh), Geron Bio-Med (Roslin), StemCell Services (Glasgow), and CXR Biosciences Ltd. (Dundee).

In addition, the UK as a whole has pioneered pragmatic policies related to human embryonic stem cells (hESC) that have enabled them to be at the forefront of hESC research, including the recent UK Stem Cell Bank deposit by King's College London of xeno-free clinical grade ESC lines that will be freely available to the research community and stand to become the "gold standard" for their research community. Allowable in vitro fertilization (IVF) options have likewise been clearly delineated in policies, including research donations from IVF procedures.

A key element for speeding up translation into therapy is the ready availability to the research community of functional stem cell lines. In line with this goal has been the UK's longtime commitment to stem cell banking. In addition to support from institutions such as the Wellcome Trust, for example, their UK Stem Cell Bank headed by Glyn Stacey both generates cell lines and enables outside deposits of valuable stem cell resources that are made available to researchers worldwide. High impact cell lines that have also been made available are clinical grade iPSC lines from Peter Andrews.

Finally, it should be noted that the US and UK have long collaborated successfully in significant scientific endeavors, with stem cell and related projects being no exception. An important example is in the area of genome-based analysis, including the 1000 Genome Project supported by both the National Human Genome Research Institute at the National Institutes of Health (NIH) and the Wellcome Trust. Another long-term sequencing collaboration has been with the Wellcome Trust Sanger Institute. A broader long-term partnership has been that between NIH and the Wellcome Trust, coordinating a joint PhD training program at UK universities and the NIH Bethesda campus.

Opportunities:

Key roadblocks to stem cell therapy hamper not just UK research efforts, but also those in the field at large. Chief among these is the need for greater coordination and standardization. To that end, the NIH Center for Regenerative Medicine (NIH CRM) has worked with a team of experts in the field to develop several key standardized tools and is actively sharing these with the stem cell community. These tools include the following: a standard consent form developed to address critical consent issues, to avoid later impediments to the use of the materials for research and eventual stem cell therapy in patients; a stem cell deposit information form, to help standardize information about stem cell lines that are being made available through stem cell banking; a model stem cell deposit agreement that avoids downstream limitations on use and freedom to operate; and standardized protocols. The opportunity exists for the UK to explore the feasibility of adopting these standardized resources in their research and banking efforts.

As an example, several large US-based repositories have been quite supportive of NIH efforts toward standardization, and have facilitated patient-specific cell line deposits. Indeed, coordination is proving to be mutually beneficial, thereby underscoring its usefulness. Deposit arrangements based on resources developed by NIH CRM are in development with Coriell and Wisconsin International Stem Cell (WISC) Bank, and an agreement with the Rutgers repository is already in place. Researchers in receipt of these model forms and agreements have, in turn, been developing similar agreements.

With multiple repositories expanding to support stem cell research, their infrastructure could similarly benefit from coordination. Establishing a common database for all stem cell lines could greatly streamline the process for researchers locating appropriate cell lines, as well as more easily identify issues or gaps in what is currently available to the community. Here in the US, we are exploring options involving PubMed, dbGAP and/or BLAST.

Stakeholder societies could undoubtedly play an important role in supporting stem cell research in the UK, as they do in the US. Chief among these in our experience have been cord blood societies, the American Society of Hematology (ASH), the Alliance for Regenerative Medicine, and the standard setting International Society for Stem Cell Research (ISSCR). These societies provide established networks for rapidly sharing expertise, new and existing resources, and new directions.

Always keeping in mind that the end goal is to develop clinical therapies, strengthening cGMP facilities with the capability of manufacturing clinical grade cell lines (including iPSC lines and their derivatives) is an essential part of the translational process. For the academic biotechnology industry, equally critical are widely available engineered lines unfettered by IP constraints. University cGMP facilities are important for autologous therapy and should be supported, but industry-based contracting manufacturing organizations with the necessary expertise also should be supported.

Lastly, as these stem cell efforts culminate in clinical trials for potential therapies, coordination of regulatory efforts will also become critical. Close coordination by the EU and the Food and Drug Administration in the US would greatly facilitate the clinical phase of our translational efforts.

13 December 2012

Regener8 – Written evidence

Author: Dr Mike Raxworthy, Operations Director, Regener8, on behalf of Regener8.

The research base

1. How does the UK rank internationally in the scientific field of regenerative medicine?

It is frequently said that the UK has a world-leading position in regenerative medicine (RegenMed) although we are not sure of the objective basis for this statement. However, with the exception of the US in several sub-sectors of RegenMed, the UK can justifiably claim to have a leading position in stem cells (adult and embryonic; via Leeds, Newcastle, York, Bristol, and Sheffield universities in particular), scaffolds and matrices (synthetic and biologic; via Keele, Sheffield and Leeds universities in particular) and development and delivery of regenerative therapies in the surgical setting (via UCL, Bristol, Nottingham and Southampton universities in particular). It should be noted that many of these research strengths have been developed in collaboration with other universities and with industry partners.

2. Where does the UK have strengths and weaknesses in the field?

See responses to the previous question for strengths. The UK suffers from having a relatively weak industry base for the transfer and translation of technologies and therapies emerging from academia. Some very strong and technically-excellent companies do exist (eg Reneuron, Tissue Regenix) but funds are limited even with these relatively mature companies. The majority of companies in the RegenMed space are SMEs without access to sufficient funding to progress expensive development of regenerative therapies to the clinic and the market. New funding arrangements will help (see below) but this remains a weakness.

The connectivity of the UK RegenMed community (academia, companies and clinicians) is a strength and the work of organisations such as the KTNs (Health Tech and Medicines, Nano), the UK National Stem Cell Network (which ceased to exist at the end of 2011), the Scottish Stem Cell Network (which will cease to exist at the end of 2012), the IKC in Medical Technologies, as well as our own work at Regener8, has resulted in this favourable position. The work of the Technology Strategy Board (TSB) in supporting regenerative medicine has also contributed strongly to this connectivity. TSB have invested £21.5m in a programme of competitions in the area of regenerative medicine in the period from September 2009 to March 2012. This has allowed the progression of feasibility studies (31 projects) to research and development projects (16 grants awarded) through to clinical evaluation of qualifying projects (4 grants awarded).

Regener8 itself has a strong position with academic members (principally from the N8 universities of Durham, Lancaster, Leeds, Liverpool, Manchester, Newcastle, Sheffield and York but with significant national strength) and an industry membership of over 170 companies involved in regenerative medicine. Our remit is to improve the translation of regenerative technologies into therapies.

3. Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

As noted in the previous question, TSB have played an invaluable part in supporting and nurturing the emergent RegenMed industry in the UK. Their regenerative medicine programme has provided vital funding to allow emergent companies to form partnerships and consortia in order to progress novel regenerative therapies to the stage of clinical evaluation. There is also reasonable support from the Research Councils (although mostly directed at the science/research base) and the Wellcome Trust. The recent establishment of the Biomedical Catalyst fund and of the Cell Therapy Catapult are welcome additions to the funding landscape in RegenMed (although neither is devoted exclusively to RegenMed)

Application of the science

4. Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

Clinical and commercial translation continues to be a major challenge. Some regenerative therapies have progressed to the clinic and are available for purchase and use (eg Tissue Regenix' dCell Vascular Patch; TiGenix' ChondroCelect for cartilage repair) and the latter is available through private healthcare providers in the UK. However the majority (eg Reneuron's treatment for stroke and treatments for age-related macular degeneration (AMD)) will not be available before 2018 at the earliest. Adoption by the NHS is seen as a major barrier.

5. What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

Regenerative medicine approaches utilising the medical device approval route (ie through the use of scaffolds and matrices to support the body's own regenerative and repair mechanisms; and/or through minimally-manipulated adult autologous stem and donor cells) have a strong chance of making an impact in the treatment of diseases (particularly in cardiovascular, musculoskeletal and wound repair fields) in the next 5 years. The regulatory route is more straightforward and safety concerns are much reduced compared to treatments classified as Advanced Therapy Medicinal Products (ATMPs). In our view, treatments classified as ATMPs (eg substantially-manipulated cells or tissues) will mostly take until the end of the 10 year period to be in a position for routine use (although it should be noted that ChondroCelect is an ATMP and lessons should be learned from TiGenix' testing and registration strategy for this product).

Barriers to translation

6. Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

- 6.1. What difficulties are encountered when conducting clinical trials and how could these be overcome?
Clinical trial approvals and the steps needed to prepare and qualify materials for clinical trial require a skill set not normally found within academic or small company settings. Specialist knowledge and the ability to navigate around the approval process are required and can be a steep learning curve for the novice. Greater provision of (and expansion of the current) support from the National Institute for Health Research (NIHR) at the local level would be a benefit in overcoming this difficulty. This would require an earlier engagement with trials in preparation and awareness of this facility by industry. A further means of overcoming difficulties would be the provision of dedicated funds to allow companies to engage specialist clinical management organisations and statisticians to help develop clinical testing strategies, prepare submissions and monitor and manage the clinical live phase and data collection and analysis.
- 6.2. What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?
Access to research-minded clinicians; classification of clinical trial as either commercial or non-commercial (most first-in-man trials conducted by SMEs should be classed as non-commercial as they will require further testing to reach regulatory-level standard, however, it can be difficult to convince hospital trusts of the validity of this approach). The cost of insurance for clinical investigations can also be prohibitive for SMEs.
- 6.3. What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?
Adoption by NHS is commonly cited as a significant barrier to the availability of regenerative therapies. Regenerative approaches tend to have a higher purchase cost than conventional pharmaceutical interventions – however, this is usually a one-off cost for curing a disorder rather than the cost of a daily or weekly pill to manage the patient's disease. Lifetime costs for RegenMed treatments will therefore often work out less expensive. High quality health economics studies will be vital to make the argument for adoption.

Barriers to commercialisation

7. What is the current and potential future, commercial value of the sector to the UK economy? What is its value to society?
Globally, the size of the regenerative medicine market is estimated as being around \$5bn now rising, according to some commentators, to as much as \$20bn by 2014. Growth rates (CAGR) are between 18 and 29%. The UK stands to gain a significant proportion of this given its acknowledged prominent position. We would estimate as much as 20% of the global market could be accounted for by UK companies. Revenues of this size will have benefits to patients, the NHS and stakeholders involved in RegenMed which will in turn generate wealth and benefit the UK economy as a whole.
8. Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

See response in (11) below. We would urge government to make available specific funds for conducting clinical trials and health economic studies (through the MRC or TSB and in conjunction with the Wellcome Trust. Many companies would be prepared to surrender a proportion of equity (to Wellcome) for receipt of funds to allow first in man or Phase I trials which would in turn allow these companies to be stronger investment propositions for venture capital funds.

9. What role does patenting play in the commercial development of regenerative treatments?

A strong IP position is vital for companies and academic groups developing new RegenMed therapies. Development of a new product will require considerable investment (minimum of £5m for a therapy following the medical device route and at least 10 times this amount for ATMPs) and so companies need to protect their technology from competitors. All companies involved in RegenMed will be active in filing and progressing patent applications in as many territories as their budgets permit.

10. What business models are most appropriate to support the development of regenerative treatments?

Regener8 does not believe there is an ideal business model to exploit regenerative technologies and therapies. However, the joining up of players in the UK RegenMed landscape (thus making all skills needed for development and commercialisation) is extremely important for the success of these treatments and organisations involved in doing this, as well as initiatives that facilitate this, should be adequately supported and promoted nationally.

11. What are the barriers to securing finance to develop such treatments?

See comment above on the cost of bring RegenMed treatments to the market. Funding at this level needs either corporate partnering (eg with big pharma) or venture capital investment. Both are currently extremely difficult to secure in the UK.

12. Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

See our earlier comment on the need for health economic analysis of the value and effectiveness of RegenMed therapies.

13. What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

Barriers include the lack of a centralised approval system for RegenMed clinical trials and no guaranteed adoption route for therapies demonstrating a positive effect through these trials. Hard infrastructure (clean rooms, licensed GMP facilities etc) exist and are well supported within the RegenMed community as a whole. Regener8 is engaged in raising the translational awareness and capability of the UK academic RegenMed community.

International comparisons

14. What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

The US has made significant investment in translational centres (eg \$3bn funding for stem cell research alone to CIRM; an \$85m federal grant recently made to the Wake Forest Institute of Regenerative Medicine). Although recent public funding for the Biomedical Catalyst and Cell Therapy Catapult is extremely welcome, considerably greater funding will be needed to maintain and secure the UK's favourable position in the development of regenerative therapies.

15. How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

The ATMP system is an EU-wide regulation as are medical device regulations (governed by the Medical Device directive). Regulations governing the development of regenerative medicines in the US are undergoing review at the present time and the resulting uncertainty causes difficulties for UK companies wishing to enter the US market. To realise the return on investment for developing a regenerative therapy, companies will expect to sell their products in all major healthcare markets.

16. Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

See previous question

17. What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

There are considerable risks attached to “stem cell tourism” and UK citizens should be strongly advised to steer clear of this. This can even apply to unregulated and inadequately tested treatments available in the US. An adequately funded, rigorous but streamlined approval route in Europe and the UK is the only safe and reliable way to make potentially life saving/life enhancing RegenMed therapies available in the UK.

20 September 2012

ReNeuron – Written evidence

About ReNeuron

1. ReNeuron is a leading, clinical-stage stem cell business. Its primary objective is the development of novel stem cell therapies targeting areas of significant unmet or poorly met medical need. ReNeuron has used its unique stem cell technologies to develop cell-based therapies for significant disease conditions where the cells can be readily administered “off-the-shelf” to any eligible patient without the need for additional immunosuppressive drug treatments. ReNeuron’s lead candidate is its ReN001 stem cell therapy for the treatment of patients left disabled by the effects of a stroke. This therapy is currently in clinical development. The Company is also developing stem cell therapies for other conditions such as critical limb ischaemia, a serious and common side-effect of diabetes, and blindness-causing diseases of the retina such as retinitis pigmentosa. ReNeuron has also developed a range of stem cell lines for non-therapeutic applications – its ReNcell[®] products for use in academic and commercial research. The Company’s ReNcell[®]CX and ReNcell[®]VM neural cell lines are marketed worldwide under license by USA-based Merck Millipore. ReNeuron’s shares are traded on the London AIM market under the symbol RENE.L. Further information on ReNeuron and its products can be found at www.reneuron.com.

ReNeuron’s response

2. ReNeuron is aware of the content and recommendations of the responses made by the various trade bodies representing the regenerative medicine industry in the UK and beyond, such as the BIA, the Alliance for Regenerative Medicine and the Alliance for Advanced Therapies. As a member of these bodies, we support the observations and recommendations made in those submissions. In particular, we support the comments made regarding the relative strengths and weaknesses of the UK research base with respect to the international scene; the likely development horizon for new regenerative medicine advanced therapy products coming into clinical development; and lack of sufficient funding for overcoming generic barriers to commercialisation in our field.
3. Rather than merely repeating these broader comments and recommendations, which are well-elucidated and evidenced in those submissions, ReNeuron’s response therefore focuses in a little on a number of specific issues it sees, or has faced, from its somewhat unique perspective as the UK’s first commercial developer of a fully GMP-compliant stem cell therapy medicinal product in clinical development in the UK. ReNeuron’s peer group (in respect of clinical-stage stem cell therapy companies) predominantly resides outside of the UK, being a cohort of small to medium sized companies based primarily in the US but also in mainland Europe.
4. **Regenerative medicine and the NHS.** As part of its broader clinical development strategy, ReNeuron wishes to promote the clinical application of its three pipeline products: ReN001 for stroke disability, ReN009 for critical limb ischaemia and ReN003 for retinitis pigmentosa, in the UK. More specifically, we wish to develop our therapies as far as possible in conjunction with the clinical research infrastructure offered by the NHS, perhaps the UK’s most valuable asset to

be leveraged when considering the translation of regenerative medicine from the lab bench to the bedside in the UK. The ongoing Phase I clinical trial of our ReN001 therapy for disabled stroke patients is being undertaken through the NHS at Glasgow Southern General Hospital, Greater Glasgow and Clyde NHS Board. Our ReN001 therapy has also been adopted by the National Institute for Health Research (NIHR) Stroke Research Network. The NIHR is the UK public body responsible for promoting and enabling clinical research through the NHS infrastructure.

5. ReNeuron has been able to realise the NHS's potential for patient recruitment, using local GP services to identify potential stroke patients in the community who can be contacted about the ongoing clinical trial. The NHS has also provided exemplary surgical support. The NHS teaching hospitals have excellent radiological facilities and expertise, essential for patient selection and follow-up. Furthermore, long-term patient review and registry access in the NHS, an essential requirement for compliance with Advanced Therapy regulations, are the envy of our non-UK peers.
6. ReNeuron believes that the NHS provides an excellent environment for developing specialist regenerative medicine products within a hospital environment. We therefore strongly support the recommendations made by other submissions to promote clinical research in the NHS as applied to regenerative medicine, and the eventual adoption of these advanced therapies into the NHS via appropriately designed cost-effectiveness assessments. Additional benefits would accrue if the MHRA Early Access to Medicines scheme, currently under consultation, were to be applied in due course to ensure rapid pre-approval and adoption into the NHS of regenerative medicine treatments demonstrating clinical proof-of-concept and with the potential to reduce healthcare costs.
7. **UK regulatory environment.** We believe ReNeuron was the first commercial sponsor to fully navigate the Department of Health's stem cell regulatory Roadmap. This map was designed to clarify the various statutory and non-statutory approvals required to undertake clinical research using stem cell products in the UK. However, it exemplified the complexities and overlaps within the UK's regulatory process, with between 6 and 10 separate authorities required to review some or all of the required documentation. ReNeuron is supportive of the Government's efforts to streamline the regulatory process by coordinating all regulatory and ethics bodies within the new Health Research Authority, thereby ensuring a proportionate and timely review process and avoidance of duplication between the different agencies or committees that review clinical trial proposals in the UK. In our view, it is essential that this streamlining is seen to work in practice if the UK is to be seen as an international centre of excellence for translational clinical research in regenerative medicine. We would add that clarity of regulatory requirements and process needs to be applied not only to the therapeutic agent itself but also to any bespoke device that might need to be deployed to administer the therapy, or to scaffolds or similar devices on which or within which cells may be seeded or grown (i.e. a cell/device combination therapy).
8. **Manufacturing.** Manufacturing of stem cell therapy and regenerative medicine products represents a significant challenge. ReNeuron has engineered stem cell products that can be effectively scaled in an outsourced contract manufacturing environment. The cost of GMP facilities and their validation, along with cell bank

9. **Funding.** The financing of regenerative medicine businesses faced with significant translational costs (clinical, manufacturing, etc) remains a fundamental issue. Funding the progression from early pre-clinical proof-of-concept to Phase II clinical proof-of-concept is extremely challenging in the regenerative medicine field because of cost and risk of failure in the mind of any potential investor. Many regenerative medicine companies are targeting indications that, by definition, have been unresponsive to, or untested by, traditional pharmaceutical approaches. Investors therefore lack a measurable investment risk perspective and are therefore reluctant to invest the sums required for the regenerative medicine business to successfully negotiate the “valley of death”. If anything, the attitude of both generalist and specialist healthcare investors has hardened over the last couple of years, as the challenges faced by the field, and the timelines involved, have become clearer to all involved. For its part, we believe that industry players developing higher risk interventions (e.g. where surgical delivery is required) can help to de-risk their programmes by innovative clinical trial design, involving endpoints that represent meaningful improvements in patient benefit, rather than merely statistically significant changes in clinical scales. The goal of such designs is to de-risk future investment by treating enough patients to reject the null hypothesis that the treatment does **not** work, as well as minimising surgical intervention in case the treatment is ineffective. The case for government-assisted funding of such cost-effective designs is clear - success can lead to subsequent and lower risk pivotal trials with the more substantial costs associated with such trials being borne by investors or commercial partners.
10. Anticipated future successes in the field from those players that are making headway, from a regulatory, clinical or commercial partnering perspective, will help to boost investor confidence, leading to greater and wider private investment into the field. In the meantime, ReNeuron supports the recommendations made in other submissions regarding the careful co-ordination of available government/RC funding streams in the UK field to ensure that an appropriate and sufficient weighting is given to translational (clinical) research, most especially that done in partnership with the NHS.
11. In this context, UK government initiatives to assist the funding of the emerging UK regenerative medicine industry include £10 million in funding to the TSB in 2013 and £50 million funding over 5 years to the Cell Therapy Catapult Centre. While such initiatives are welcome, the sums available are relatively small (when the costs of taking a therapy from pre-clinical proof-of-concept to Phase II are considered) and are likely to be distributed widely in the sector. It is unlikely therefore that these initiatives alone will be sufficient to address the continuing funding concerns of the regenerative medicine sector. By way of illustration, funding initiatives abroad, such

as the state of California bonds, totalling \$3 billion, to fund the California Institute of Regenerative Medicine (CIRM), are making a significant difference to the emerging regenerative medicine industry beyond the UK. For example, one California-based stem cell business (StemCells Inc) has been awarded two major grants from CIRM of \$20 million dollars apiece, one for translational studies in spinal cord injury and another matched funding grant for pre-clinical studies in Alzheimer's disease. We believe that the potential impact of a successful regenerative medicine industry for UK patients, the UK healthcare system and UK jobs, together with widespread UK public support for the development of therapies in this area, also warrants the consideration of further innovative and cost-effective funding vehicles, possibly based on the French Citizen's Innovation Funds (CIFs) model, as recommended by the BIA in their submission.

19 September 2012

ReNeuron, Pfizer and Professor Chris Mason, University College London – Oral evidence (QQ 128-169)

ReNeuron, Pfizer and Professor Chris Mason, University College London – Oral evidence (QQ 128-169)

[Transcript to be found under Pfizer](#)

Research Councils – Supplementary written evidence

EPSRC and MRC Regenerative Medicine Portfolio Update

1. Purpose

To provide the House of Lords Science and Technology Select Committee with a an update to the 2010 regenerative medicine portfolios of the Engineering and Physical Sciences Research Council (EPSRC) and Medical Research Council (MRC), to inform the Committee’s inquiry into regenerative medicine.

2. Background

The joint Research Council and Technology Strategy Board’s “A Strategy for UK Regenerative Medicine” (see [Annex I](#)) presented an analysis of the sponsor group’s research portfolio in regenerative medicine based on grants live on 19 November 2010 (the “sponsor 2010 portfolio”). In response to the Committee’s request for an update of this portfolio, EPSRC and MRC, which together accounted for c. 68% of the 2010 portfolio by value, have analysed their regenerative medicine portfolios based on grants live on 1st October 2012 (the “2012 portfolio”). This paper presents an analysis of the 2012 portfolio versus the MRC and EPSRC contributions to the sponsor group 2010 portfolio (the “2010 portfolio”).

3. EPSRC and MRC 2010 and 2012 regenerative medicine portfolios

3.1 Spend by Funder

The sponsor 2010 portfolio consisted of 353 awards with a total annualised spend of £72.6 million. The split per sponsor was as follows

<u>Sponsor</u>	<u>Number</u>		<u>Value (£m)</u>	
ESRC	6	2%	0.9	1%
EPSRC	58	16%	11.3	16%
BBSRC	97	27%	12.8	18%
MRC	137	39%	37.7	52%
TSB	46	13%	8.8	12%
NIHR	9	3%	1.1	1%
TOTAL	353	100%	72.6	100%

The total MRC and EPSRC annualized spend on regenerative medicine in 2010 was c. £49.0 million, accounting for c. 68% of the total sponsor 2010 portfolio. In 2012, total MRC and EPSRC annualized spend on regenerative medicine was c. £47.5 million, split as follows

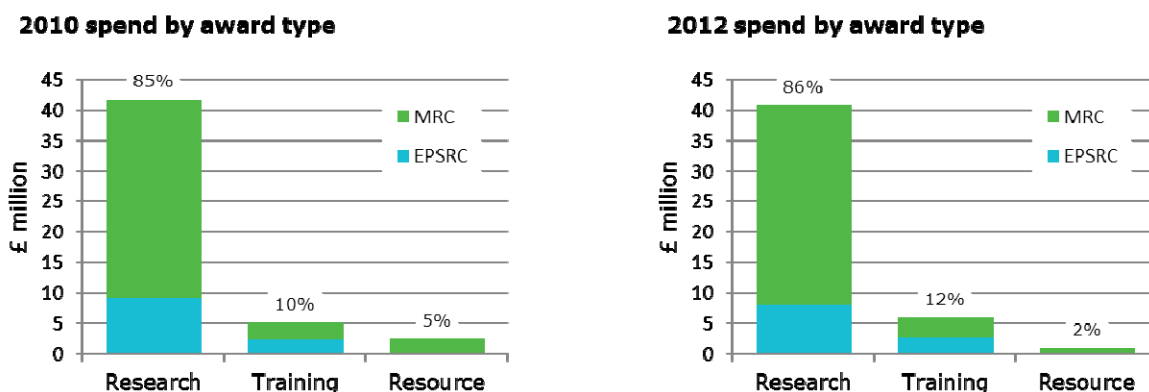
<u>Sponsor</u>	<u>Number</u>		<u>Value (£m)</u>	
EPSRC	38	16%	10.4	22%
MRC	120	39%	37.2	78%
TOTAL	158	100%	47.5	100%

This represents a modest decrease of c. 3% by value between the 2012 and 2010 portfolios, which is accounted for, in part, by certain strategic initiatives, including a joint call between EPSRC and the Technology Strategy Board, not being repeated.

It is worth noting that the 2012 portfolio does not reflect the recent significant joint BBSRC, EPSRC and MRC investment in the UK Regenerative Medicine Platform (UKRMP); a £25 million initiative that seeks to address the technical and scientific challenges associated with translating promising scientific discoveries in this area towards clinical impact, as recommended in “A Strategy for UK Regenerative Medicine”. Nor does it include the joint c. £13 million Wellcome Trust and MRC investment (MRC contribution = £4 million) in the Human Induced Pluripotent Stem Cell Initiative, which seeks to provide a knowledge-base to underpin the use of such cells in studying the effects of genes on health and disease.

3.2 Spend by Award Type

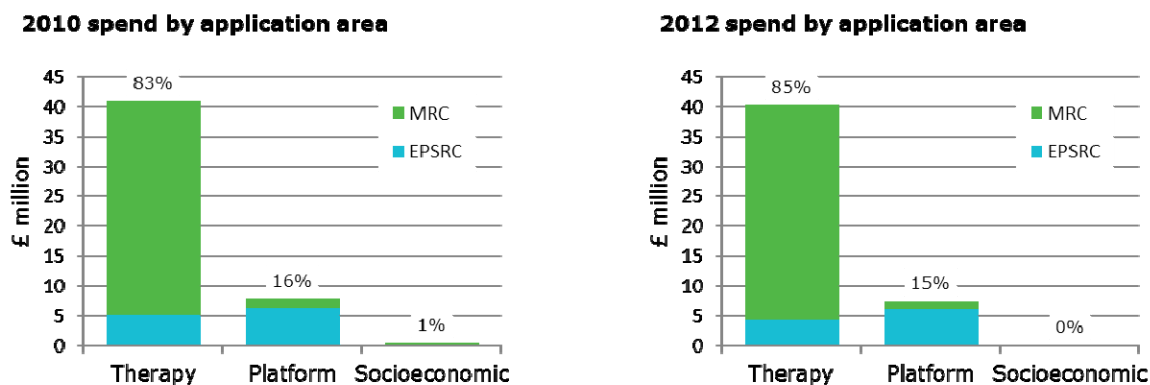
Awards were categorised for the type of funding. These figures do not include RC studentships, as grant details were not available.



As with total investment, only modest changes in spend by award type are seen between 2010 and 2012.

3.3 Spend by Application Area

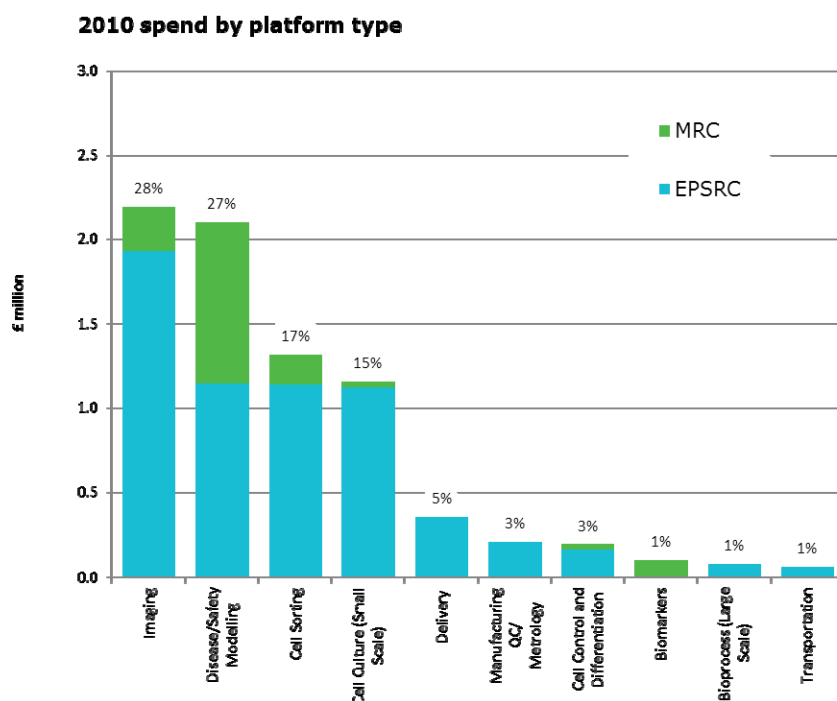
Each award has been categorised by whether it falls within a Therapy, Platform or Socioeconomic application area. Therapy awards cover underpinning investigations that may inform therapy developments (examples include stem cell biology, studies of endogenous repair mechanisms) and the development of specific therapies. Platform awards support the development of therapies but are not embodied within the end therapy (examples include the development of a safety/efficacy model or a new manufacturing process). Socioeconomic awards include, for instance, studies on the patient acceptance of regenerative medicine therapies and cost effectiveness.

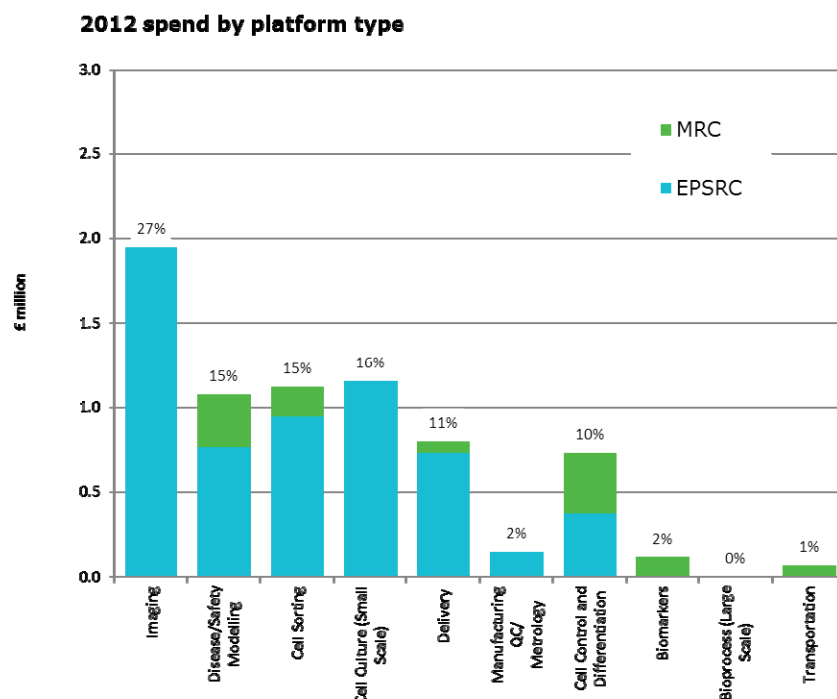


As in 2010, the majority of EPSRC and MRC investment is in the therapy area. The relative balance between therapy and platform is expected to be changed in the platforms favour with the recent UKRMP investments. The relative balance of EPSRC and MRC contributions to the therapy and platform areas, with MRC leading in therapy and EPSRC leading in platforms, reflects the remits of the councils.

3.4 Spend by Platform Type

All Platform Awards were further classified by the type of platform they were seeking to develop.

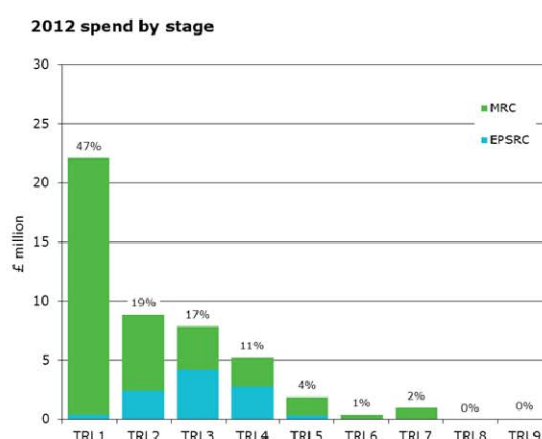
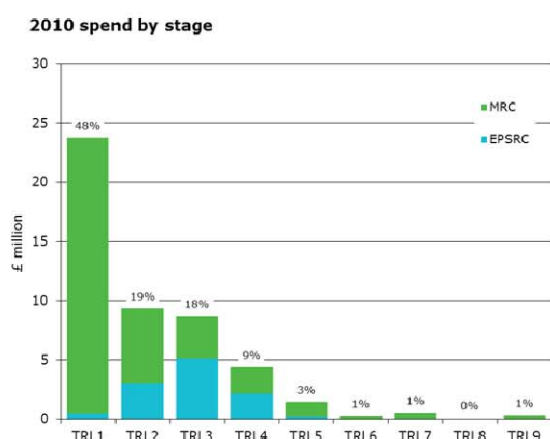




While the total spend in the platform area has not changed significantly, it is apparent that more of the spend is being directed towards activities, such as delivery and cell control and differentiation, at the more applied rather than discovery end of the spectrum.

3.5 Spend by Stage

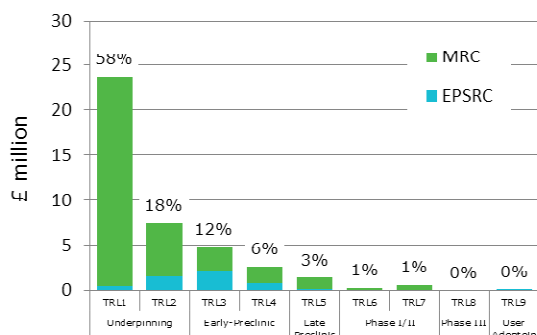
In line with the relative immaturity of the field, in 2010 it was found that the majority of sponsor funding was focused on the earliest Technology Readiness Levels (TRLs), supporting investigations probing the field's underlying science, with levels reducing as projects move further down their developmental path.



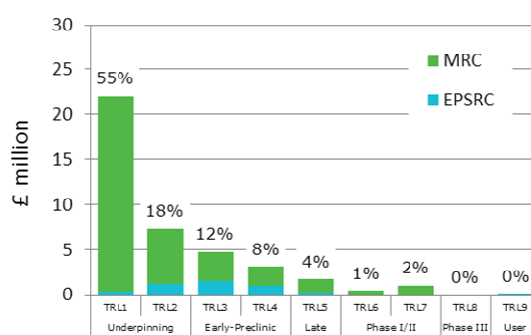
While the EPSRC and MRC portfolios remain weighted towards the lower TRLs, increases can be seen in the proportion of spend in TRLs 4 and 5, indicating a maturation of the pipeline.

Spend by stage can be broken down further by examining the distribution of spend for the therapy and platform application types.

2010 therapy spend by stage

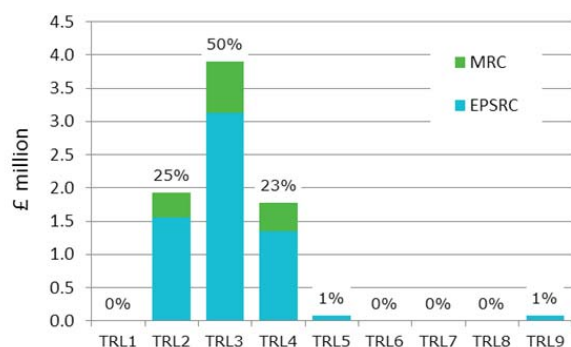


2012 therapy spend by stage

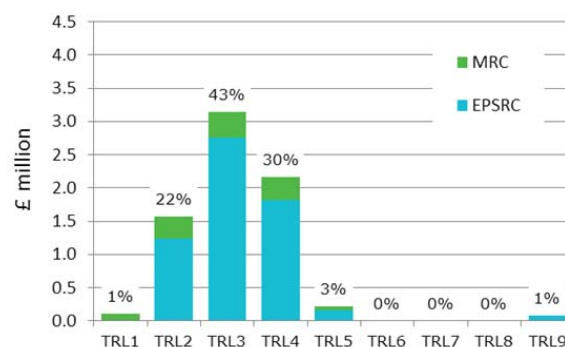


As with overall spend, therapy spend shows increases in the higher TRLs

2010 platform spend by stage



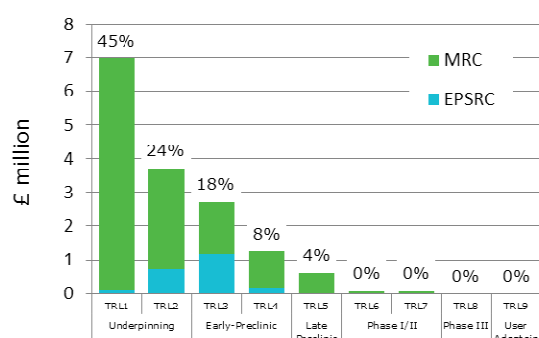
2012 platform spend by stage



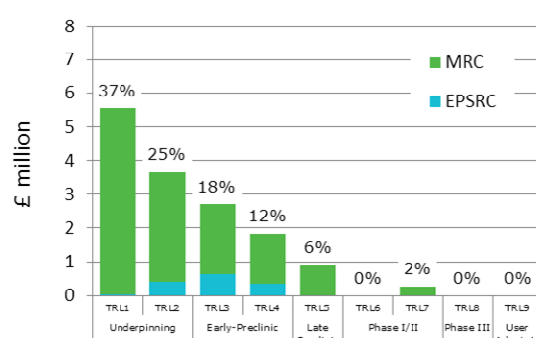
Platform TRL1 and TRL2 investments may be underrepresented due to the challenge of identifying awards at this phase, as these may not yet be linked to an application in regenerative medicine.

A possible reason for the relatively modest shift of spend towards later TRLs is that a significant proportion (c. 65% by value) of the 2010 awards are present in the 2012 portfolio. This is due to the average duration of awards in the portfolios (c. 42 months) being much greater than the interval between the census dates of the two portfolios (19th November 2010 and 1st October 2012, interval = c. 23 months). To account for this, an analysis has been made comparing the 2010 portfolio absent shared awards versus the 2012 portfolio absent shared awards, thereby providing a better account in shifts in recent funding behaviour.

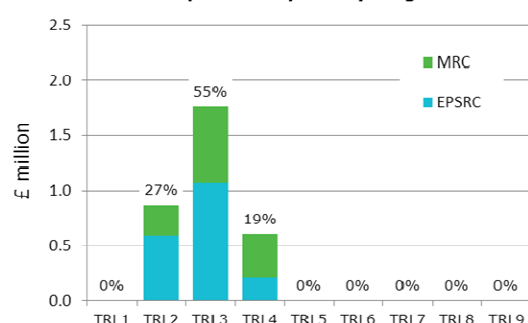
2010 not in 2012 therapy spend by stage



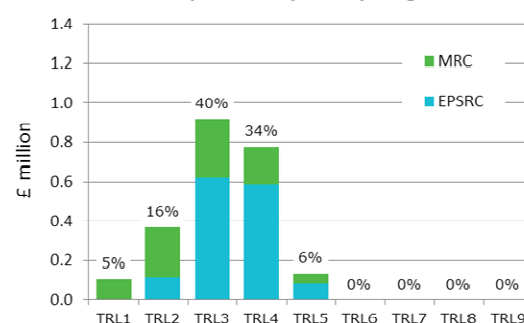
2012 not in 2010 therapy spend by stage



2010 not in 2012 platform spend by stage



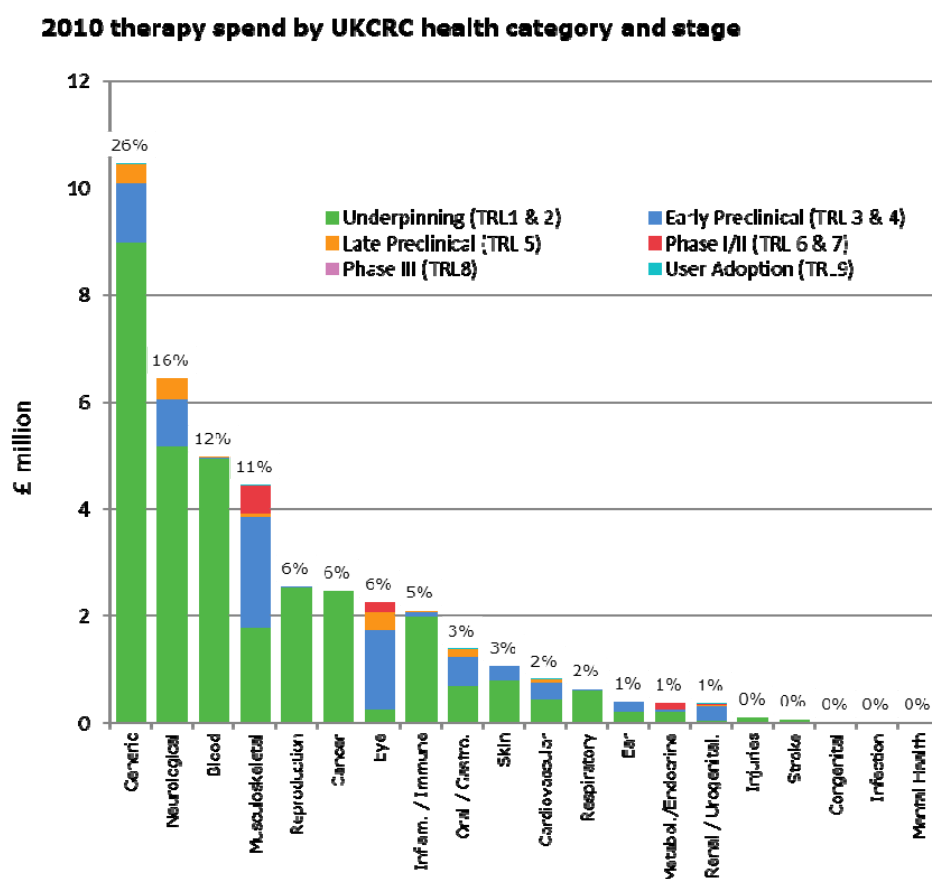
2012 not in 2010 platform spend by stage



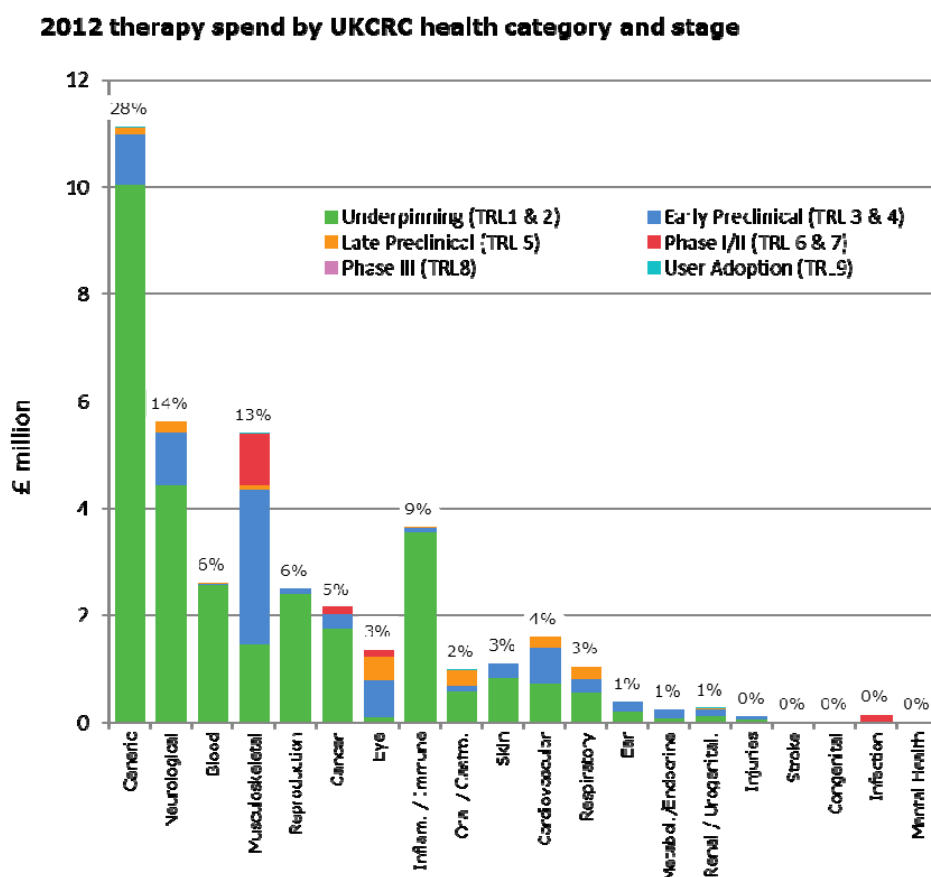
This analysis shows a more pronounced shift in investment towards the later TRLs, suggesting that the councils have been promoting and supporting the maturation of the therapy and platform development pipelines.

3.6 Therapy Spend by UKCRC Health Category and Stage

The coding of the portfolio enables additional analysis to be undertaken including an investigation of spending on therapy awards by UKCRC Health Category and Stage.



The prominence of musculoskeletal awards and their relative higher proportion of late stage projects reflect the fact that this area has been an early and significant focus of regenerative medicine activity. The significant preclinical development in Eye likely reflects the emergent understanding of the tractability of this application area



The overall balance of the portfolio by therapeutic area has remained broadly the same with the exception of changes in the relative proportions of investment between blood and inflammatory and immune, which reflects the maturation of programmes within the hematopoietic stem cell field.

23 April 2013

Research Councils UK (RCUK) – Written evidence

INTRODUCTION

1. Research Councils UK (RCUK) is a strategic partnership set up to champion the research supported by the seven UK Research Councils. RCUK was established in 2002 to enable the Councils to work together more effectively to enhance the overall impact and effectiveness of their research, training and innovation activities, contributing to the delivery of the Government's objectives for science and innovation. Further details are available at www.rcuk.ac.uk.
2. This evidence is submitted by RCUK on behalf of the Research Councils listed below and represents their independent views. It does not include or necessarily reflect the views of the Science and Research Group in the Department for Business, Innovation and Skills (BIS). The submission is made on behalf of the following Councils:
 - Biotechnology and Biological Sciences Research Council (BBSRC)
 - Economic and Social Sciences Research Council (ESRC)
 - Engineering and Physical Sciences Research Council (EPSRC)
 - Medical Research Council (MRC)
 - Science and Technology Facilities Council (STFC)
3. This response focuses only on those questions or parts of questions relevant to RCUK or the individual Councils who have contributed to the response.

SUMMARY

Regenerative Medicine – state of play

4. Regenerative medicine is a dynamic field of research that holds the promise of providing new therapeutic approaches for a variety of conditions, many of which have limited or no effective treatments. To realize this goal there will need to be a concerted and interdisciplinary effort encompassing academics, clinicians and commercial entities, that builds on a solid understanding of the underlying science. At this point the field is only just beginning to make strides towards the translation of this potential into clinical application, and there is still much to be learnt about regenerative processes and how cells might be manipulated and controlled to deliver functional replacement of damaged or diseased tissue. However, substantial progress has been made in recent years in better understanding the underlying biology of cell maintenance and differentiation and of the role of the surrounding cellular microenvironment or 'niche', which in turn has led to more researchers moving into translational regenerative medicine. Related advances in biomaterial technology, gene therapy and nanobiology have also contributed to renewed optimism that real advances may be made in the clinical arena in the not too distant future.

A cross-Research Council priority

5. The Research Councils (RC) have a history of working synergistically in the stem cell area, for example through the £40m cross-Council stem cell programme (2003-7) and more recently in delivering the targets set out in the 2005 UK Stem Cell Initiative, for example in establishing the infrastructure and regulatory framework for human embryonic stem cell (hESC) derivation and delivery, supporting training programmes to build research capacity, and establishing shared communication and public understanding activities. As well as implementing individual research programmes in a coordinated manner, joint RC funding has also supported the UK National Stem Cell Network, the UK Stem Cell Bank and the Stem Cells for Safer Medicine PPP.
6. More recently the RCs joined the Technology Strategy Board (TSB) under a £19m programme in regenerative medicine (2009-11) which formed part of the Office of Life Sciences blueprint (detail provided in the TSB submission), while added coherence and momentum has been provided through the implementation activities promoted under the [Strategy for UK Regenerative Medicine](#)²⁶², published in March 2012. This set out the opportunities and challenges faced by the UK regenerative medicine community, spanning discovery and translational science through to the requirements for clinical delivery, and provided a route map for future investment in UK regenerative medicine research.
7. This submission will not seek to reiterate the background and recommendations of the strategy, except to highlight key points of direct relevance to the questions posed, but will rather expand on developments since its publication, which encompass the investment of more than £30m RC funding through the UK Regenerative Medicine Platform and additional strategic initiatives undertaken in partnership with the Wellcome Trust.

RESPONSE

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

8. The most recent assessment of the strength of the research base was undertaken through the 2010 BIS/DH report 'Taking Stock of Regenerative Medicine in the UK', which established that the UK retains a leading position, in Europe and globally, in the science and commercial translation of regenerative medicine. The report further identified that UK research in this field has higher impact than equivalent research in life sciences more generally. However, although the UK is at the forefront of this rapidly evolving field, it is recognised that we cannot be complacent given increasing global competition in this field, notably from N America and SE Asia.
9. A key UK advantage over other global regions is that investigators are able to explore the full spectrum of potential regenerative medicine interventions, including both adult and embryonic stem cell based approaches which, as well as offering distinctive options for therapeutic development according to disease area, provide important cross-fertilisation of biological understanding. The UK's well developed legislative and

²⁶² RC/TSB Regen Med Strategy: www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008534

regulatory framework has helped build and maintain broad public support for this position.

Where does the UK have strengths and weaknesses in the field?

10. The UK has particular strengths in the areas of stem cell biology (developmental, mechanisms of pluripotency) and in the clinical areas of blood, neurology and ophthalmology. It is internationally competitive in most other areas, but arguably slightly behind the curve in terms of integrating the related areas of physical science, such as in materials science and chemical biology. The need to drive interdisciplinarity is being targeted under the RC/TSB Strategy for regenerative medicine.
11. The UK is a world leader in human embryonic stem cell (hESC) research, with supportive infrastructures and legislation, but lags behind the US and Japan in terms of the volume of its outputs in induced pluripotent stem cell (iPSC) research. Again, investment is being targeted to support this area through the recent award of a new WT/MRC-funded national iPSC programme (see para 29), while broader impetus is being provided through the establishment of a new WT/MRC Stem Cell Institute in Cambridge, launched in August this year²⁶³.
12. Translational research in regenerative medicine is a challenge globally, given the knowledge gaps that remain, and the high costs of developing complex and multidisciplinary therapeutic approaches for which the commercial market is uncertain. The UK is well positioned to undertake clinical development in this field, given the potential to draw on high quality clinical research infrastructure (through the National Institute of Health Research) and established capacity in the procurement, processing and distribution of cells and tissues for human application (through NHSBT). Nevertheless, the development of regenerative medicine products is ultimately dependent on commercial investment, at this time through the biotech sector, which is much stronger in the USA and increasingly so in the tiger economies of Asia.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

13. The most comprehensive analysis of the UK regenerative medicine portfolio was recently undertaken as part of the RC/TSB strategy development exercise, which mapped projects supported by the UK Government. This identified a total of 353 awards, with a total annualized spend of £72.6m. The split per sponsor was as follows:

	Number		Value (£m)	
MRC	137	39%	37.7	52%
BBSRC	97	27%	12.8	18%
EPSRC	58	16%	11.3	16%
TSB	46	13%	8.8	12%
NIHR	9	3%	1.1	1%
ESRC	6	2%	0.9	1%
TOTAL	353	100%	72.6	100%

²⁶³ WT-MRC Stem Cell Institute: www.mrc.ac.uk/Newspublications/News/MRC008805

14. In addition to the investments identified above, STFC has also provided investment for technology development in support of the field, which for example has led to a successful start-up company (The Electrospinning Co.) that supplies advanced substrates to UK stem cell researchers.
15. When this research spend is analysed by application type or disease area, the following headline messages are apparent:
 - i) approaching half of the investment is focussed on research involving adult stem cell or progenitor cells, with 19% directed to embryonic stem cell research, and 8% to acellular technologies;
 - ii) reflective of the state of scientific understanding, 79% of the funding supports basic or early preclinical research, with less than 10% invested at the stage of clinical investigation;
 - iii) the major areas of therapeutic investigation are neurological, musculoskeletal, and blood disorders. The prominence of the latter two reflects the fact that these areas represented the earliest focus of activity in regenerative medicine due to their relative tractability. In terms of emerging areas, ophthalmology has the highest proportion of preclinical development, in line with the emergent understanding and potential for application in this area.
16. In addition to the portfolio identified above, research support is also provided through the charitable sector, notably the WT and British Heart Foundation (BHF) but including other disease-focussed research charities, as well as through the EC's 7th Framework Programme. The majority of this funding, as for the RC portfolio, is focussed at the basic end of the research spectrum.
17. In the main, RC support is allocated through research grants, provided in response-mode in open competition with other areas of life science. Specific, targeted schemes have also been put in place to support the translational agenda; for example the MRC established a Translational Stem Cell Research Committee in 2008 to address the translational gap between hypothesis-led discovery science and its application, under which £21.4m has been awarded in support of preclinical development and early phase clinical trials. Going forward, support for product development may also be provided through the new £180m MRC/TSB Biomedical Catalyst funding stream, established to promote the development of products up to proof of concept in man, whether academically or industrially. Strategic awards are also provided to a number of centres of excellence (MRC/EP SRC), while infrastructural awards support key resources such as the UK Stem Cell Bank and hESC GMP derivation facilities. Further detail on these investments is provided within the RC/TSB Strategy document.
18. In terms of capacity building, RC training awards are available in competition with other areas, as well as being provided within RC centres of excellence. In the past studentships and fellowships have been targeted through earmarked funding, although it is apparent that stem cell biology is now mainstream and popular amongst biomedical graduates, meaning that dedicated funding schemes are no longer necessary to promote this area. Instead, the focus has shifted to promoting interdisciplinary training.
19. Lastly, international partnership is actively promoted in this area, given the need to keep at the forefront of a rapidly developing field. The MRC in particular has developed a number of strategic alliances, and in the past three years funding has been

made available to support stem cell research collaboration with the US (Californian Institute of Regenerative Medicine), China and Israel. MRC has also chaired the International Stem Cell Forum²⁶⁴ since its inception in 2003, through which funding has been provided to promote international harmonisation in stem cell characterisation, stem cell banking, and ethics and governance.

20. It is noteworthy that the European Parliament is currently debating the constitution of Horizon 2020, the EU's programme for research and innovation running from 2014 to 2020. Provisions in the draft regulation provide for the funding of stem cell research including hESC research, which is currently allowed under the 7th Framework Programme. However, these provisions are under threat from 'pro-life' MEPs who believe that public funds should not be spent on hESC research. While policy changes at the EC level would not directly affect UK research funding, any reversal of the current position is likely to send out a negative message to researchers entering the field as well as commercial investors. Accordingly, MRC, as part of coalition of leading funders of biomedical research and patient groups, issued a joint statement in June this year calling on the European Parliament to continue funding hESC research²⁶⁵.

Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease?

21. Application is being taken forward in two main areas; i) therapeutic development and ii) as a preclinical tool to model disease and provide predictive screens for drug development and toxicity testing.
22. **Therapeutics:** In the therapeutic domain, approaches are for the most part focussed on using autologous cells, with only a handful of studies exploring the use of hESCs, or the exogenous manipulation of endogenous cells to promote self-repair. The number of regenerative medicine studies²⁶⁶ close to or in clinical testing is in the region of 25 in the academic sector, and 15 in the commercial sector, indicating that the field is still at an early stage in relation to clinical pull-through. This should not be surprising given that the field is relatively young in comparison to other areas of biomedicine, and what is key at this stage is that clinical trials are developed on a foundation of well developed science, and under a methodology that provides knowledge on safety, efficacy and mechanism in order to inform the further refinement of promising studies.
23. To catalyse progress in this area, BBSRC, EPSRC and MRC have jointly established the UK Regenerative Medicine Platform (UKRMP) as a £25m national programme to promote translational research in the field and address the knowledge gaps and obstacles where more development is needed to underpin the delivery of new therapeutic approaches²⁶⁷. The UKRMP will operate in close cooperation with the TSB Cell Therapy Catapult Centre, and will provide critical linkage between the discovery science base and efforts to promote application and ensure continued UK competitiveness in this area.

²⁶⁴ www.stem-cell-forum.net

²⁶⁵ www.mrc.ac.uk/Newspublications/News/MRC008738

²⁶⁶ defined as those targeting a known regenerative process, as opposed to, for example, other cell therapies or anti-cancer stem cell treatments [based on data supplied by MRC, PDUK, Diabetes UK, MNDA, MS Soc, CRUK and the CT Catapult]

²⁶⁷ www.ukrmp.org

28. **Disease modelling and drug development:** Nearer term application is being delivered through the establishment of disease models and drug screening assays, increasingly based upon iPSC technology, which can be utilised to provide specific cell types from patients via skin, blood or hair biopsies. As well as offering new approaches for studying the mechanisms of disease in the lab, this technology is of increasing interest to the biopharmaceutical sector, as it offers the potential to create drug and toxicology screens reflective of specific patient/population genotypes, as well as providing renewable supplies of human cells such as neurons, which would previously have been inaccessible for study. It should also be recognised that the science underlying iPSC reprogramming, and the technologies utilised for differentiating iPSCs into specific cell lineages and their subsequent purification and scale-up, will be informative for future therapeutic development, whether using hESC, iPSC or directly differentiated cell types.
29. In support of this area, the WT and MRC have recently made a £12.75m joint award to establish a human iPSC initiative²⁶⁸. This programme will address stem cell phenotyping, disease-modelling and protocol standardisation to provide increased understanding of how to control the many variables currently limiting the full application of iPSC technology, as well as providing a bank of quality controlled iPSC lines for use by the UK research community. It should also support pre- competitive industrial partnerships developing in this area, such as the UK-led €52m disease-modelling platform recently funded under the EU Innovative Medicines Initiative.

What potential does regenerative medicine hold to treat disease in the next 5-10 years ? What is the reality versus the headlines about what will deliver?

30. Regenerative medicine offers the potential for new treatments for numerous debilitating diseases such as Parkinson's, motor neurone disease, multiple sclerosis, cardiovascular conditions, diabetes, liver damage, spinal cord damage and blindness. Many of these conditions are degenerative conditions, the prevalence of which will increase with an ageing population which Europe is facing.
31. A number of regenerative medicine products are already being marketed, for skin, bone, adipose, cartilage and blood disorders, but in most other cases proof of concept has only been established in animal models, with much more development work needed prior to clinical application. Nevertheless, there is reason for optimism, with a number of phase I clinical trials using adult stem cells now underway, as well as ReNeuron's UK based trial for disabled stroke patients, which represents the first of its kind for a neural stem cell product. The MRC's strategic investment in hESC research is also beginning to bear fruit, with a pipeline of more than 20 clinical-grade hESC lines now starting to be deposited in the UK Stem Cell Bank. The first hESC-based clinical trial has just commenced in the UK, to treat Stargardt's macular dystrophy²⁶⁹, with the promise of another to follow soon in the related area of age-related macular degeneration.
32. In terms of future areas of potential clinical impact, several MRC-funded studies have recently published high profile papers demonstrating preclinical proof of concept in

²⁶⁸ www.hipsci.org

²⁶⁹ www.ucl.ac.uk/stemcells/News/stem-cells-news/news111

animal studies for iPSC-mediated repair of genetic liver disease²⁷⁰, photoreceptor transplantation into damaged retina²⁷¹, and most recently hESC-mediated repair of the inner-ear²⁷². However, such preclinical studies remain some years away from clinical testing, and much further from clinical use. The challenges of moving firstly into clinical trials and then for successful therapies into product manufacture should not be underestimated, both in terms of the science and level of investment required, and it is therefore essential that we maintain the message of 'hope not hype' in relation to public engagement in this area.

Barriers to translation

What difficulties are encountered when conducting clinical trials and how could these be overcome?

33. Clinical trials of cell therapies for regenerative medicine pose unique challenges including the difficulty of predicting potency, dose and risk. A number of uncertainties/issues remain, as elucidated in the RC/TSB Strategy and briefly outlined below:
- scalable and controlled processes must be established to produce products of an appropriately reproducible potency and safety;
 - new biomarkers and technologies are needed to monitor therapeutic effect and safety;
 - controlling potential transplant rejection is an unsolved problem;
 - the selection of the clinical indication to be pursued must reflect an appropriate risk:benefit ratio for the patient, while strategies must be established to target those patients who might respond most favourably to such interventions;
 - outcome measures need to be defined to give early indications of successful regeneration, while lengthy follow-up periods are likely to be required given safety issues - both will impact upon commercial investment;
 - new clinical trial designs will be required, perhaps more adaptive in nature, that consider the specific challenges around small study size (in terms of number of participants), patient selection and follow-up;
 - ethical issues remain re. donor selection, screening and traceability;
 - processes and procedures need to be developed to support the storage and delivery of regenerative medicine products to the clinic, requiring research into cryopreservation/cell hibernation and transportation;
 - considerable regulatory uncertainty remains due to the issues listed above, as well as in relation to EU-legislation.
34. The new investments being made by the RCs through the UKRMP, coupled to the new Cell Therapy Catapult Centre, are intended to directly address many of these challenges. In further support of this agenda, MRC and ESRC, in partnership with the Association of the British Pharmaceutical Industry (ABPI), the Academy of Medical Sciences (AMS) and the Medicines and Healthcare products Regulatory Agency (MHRA), are also convening a workshop with academic and industrial experts in

²⁷⁰ Yusa et al, Nature 478, October 2011 – www.mrc.ac.uk/Newspublications/News/MRC008230

²⁷¹ Pearson et al, Nature 485, May 2012 – www.mrc.ac.uk/Newspublications/News/MRC008595

²⁷² Chen et al, Nature ePub, Sep 2012 – www.mrc.ac.uk/Newspublications/News/MRC008848

October to explore the challenges of pre-clinical development and clinical testing. The aim is to identify the key areas of regulatory uncertainty and improve the transparency and utility of the UK's regulatory framework. It is anticipated that the outputs will inform the further development of the *MRC/DH stem cell tool-kit*²⁷³ to embrace the full spectrum of regenerative medicine. Follow-up activity is also being planned to explore international harmonisation in partnership with overseas agencies.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

35. The predictions of the global market potential for regenerative medicine vary wildly, with market analysts and academic analyses predicting exponential growth of between 5 and 10 fold over the next 5 years, potentially to anywhere between \$1 and \$5billion by 2014. Given this variation, plus the varying definitions of baseline value and field definition, it is almost impossible to place a figure on its value to the UK sector.
36. The primary value to society is about providing cures for chronic, debilitating or incurable conditions, which as well as improving the quality of life for patients, families and carers, will potentially have a major impact in reducing NHS costs in the long term. Regenerative therapies have the potential to provide permanent cures, as opposed to the long-term use of most pharmaceutical products, which will necessitate new health economic paradigms to evaluate their worth. The timeline for the delivery of next generation regenerative medicine products is uncertain, but many observers believe that these will begin to have significant clinical impact in 10-20 years time. Success in the application and commercialisation of regenerative medicine would also provide economic growth for the UK, and help maintain the competitiveness of the UK life sciences sector.

What role does patenting play in the commercial development of regenerative treatments?

37. Conventional wisdom has been that, in order to attract private investment, scientific discoveries must be patentable. This consensus has emerged over the past 50 years given the background of pharmaceutical companies chasing big returns by developing small molecule drugs – as easy to copy, once known, as they are to patent.
38. In the area of regenerative medicine, this thinking has been challenged in interpreting the effects of the 2011 European Court of Justice ruling that material derived from hESCs and procedures involving their use could not be patented. While this ruling has no immediate impact on the regulatory framework or research that can be undertaken in the UK, it does have the potential to undermine commercial investment which is made in an international context. The implications of the ECJ ruling will not be fully apparent for some time, and its impact has received mixed views. It remains possible that the uncertainty regarding intellectual property protection might be offset by the importance of 'know-how' in the field, whereby those developing hESC-based therapies may seek to protect IP as 'trade secrets'. Indeed, the enormous complexity of stem cell technologies make them inherently more difficult to reproduce, and this

²⁷³ www.sc-toolkit.ac.uk

reliance on scientific ‘know how’ could dissuade competitors even in the absence of underlying patent protection, as is seen in other therapeutic areas such as biopharmaceuticals which share the requirement for complex manufacturing protocols. On the other hand it has also been argued by some commentators that the ruling may in fact provide freedom to operate in an area where fear of patent infringement might have limited innovation.

39. Nevertheless the ruling is likely to further damage investor confidence in an area that already holds a lot of uncertainty as to how commercial return can be attained, which could have a negative impact on the development of hESC-based therapies, which are now beginning to enter early phase clinical trials.

What business models are most appropriate to support the development of regenerative treatments?

40. Across the regenerative medicine field there will be very diverse ‘pathways to impact’ and commercial models are likely to emerge based upon marketed regenerative products for therapy, health service driven models as seen in the area of bone-marrow transplants for example, cosmetic and sports medicine, and in the development of tools and technologies and platform companies. This remains an area of uncertainty where existing biopharma paradigms based on traditional drug development are not suitable. Accordingly the ESRC co-funded two studies through the 2009 TSB-led ‘Value Systems and Business Models’ call, which aimed to provide archetypal business models for use by SMEs and start-ups to help them attain sustainability and to provide tools to enable UK regenerative medicine businesses to realise value more effectively. The reports of the REALISE and VALUE projects have recently been published²⁷⁴.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

41. The RCs maintain good connections with their overseas counterparts, many of whom are engaged with translational activity and commercial partnership in this area. A number of different approaches are being pursued by agencies around the world, and it will be important for the UK to monitor their implementation, and absorb any lessons accordingly. This intelligence gathering is facilitated by MRC's involvement through the International Stem Cell Forum, and the Foreign and Commonwealth Office's Science and Innovation Network.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

42. As mentioned in paragraphs 20 and 38, for hESC research the EC's policy for supporting R&D under its Framework Programmes and the 2011 European Court of Justice ruling on patenting have the potential to impact on UK activity, albeit indirectly.

²⁷⁴ www.genomicsnetwork.ac.uk/innogen/publications/policyreports/title.26059.en.html
www.biolatris.com/Biolatris/News_&_events_files/VALUE%20Final%20Report.pdf

In considering this, it should be highlighted that the UK regulatory framework in this domain is as developed as any in the world, and the result of the widespread debate and consultation that led to the 2008 revision of the Human Fertilization and Embryology Act. Public support for hESC research in the UK remains high²⁷⁵.

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

43. Differences in regulatory approach across global regions pose challenges for both researchers (for example in transferring or accessing cell lines) and companies (seeking regulatory and /or market authorisation). As mentioned in paragraph 34, MRC and ESRC are currently scoping an international meeting with regulators and N American agencies with a view to identifying areas where further harmonisation might be possible, while the International Stem Cell Forum²⁷⁶ has also issued guidelines to help provide common standards and best practice for stem cell banking and distribution.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

44. There are many people with incurable or debilitating illnesses who in seeking routes to improve their condition might consider the possibility of getting treatment overseas. However, in very many cases these treatments are likely to be unregulated and not thoroughly tested, meaning they could be ineffective or harmful. It is therefore important that UK patients have access to the necessary information to allow them to evaluate the risks when researching the possibility of going abroad for regenerative/stem cell-based treatment. The RC-sponsored UK Stem Cell Network issued a position statement on stem cell tourism in 2009²⁷⁷. More broadly, the MRC chairs a national 'communications coalition' of research funders that meets regularly to help ensure that information on the progress of research and clinical testing in this domain is both accurate and available.

27 November 2012

²⁷⁵ www.mrc.ac.uk/Newspublications/News/MRC005308

²⁷⁶ www.stem-cell-forum.net

²⁷⁷ www.uknscn.org/downloads/stem_cell_tourism.pdf

Professor Stephen Rimmer, Professor Sheila MacNeil and Professor John Haycock, University of Sheffield – Written evidence

The following provides comments for consideration by the select committee and provides the views of three Sheffield University Professors, who are highly involved in developing technologies for Tissue Engineering and Regenerative Medicine. Both MacNeil and Rimmer also have significant commercial experience and all three have long track records of working in collaborative teams with both academics and industry, in this area.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

Cell biology and stem cell science: The UK is an international leader in basic cell biology and basic stem cell science. It is our view that research strengths are evident across a number of UK institutions. Other countries may have a greater volume of activity (e.g. USA) but it is hard to see countries that are more advanced in developing an understanding of basic stem cell science. However, Asian and Australian economies are rapidly expanding capability in this area and this is a genuine threat. Reasonably good funding exists for basic cell biology and stem cell science in the UK.

Translation to the clinic: The UK lags behind the USA, Asian and Australian economies, despite the significant advantages of the NHS. New thinking is needed here so it becomes easy to take science from TRL 1/2 through to TRL 3 to 5. It is our firm view that far too much of the research funding is being concentrated into too few opportunities, with the result that much early stage science does not progress to early stage clinical evaluation. Translation is a major weakness of the UK and the route of the problem lies now in over concentration of resource and a peer review system that is both confused and counter productive. Outstanding creativity evident in early stage research is being halted. Equally, too much funding and effort is being directed to scaling up of technologies of poor quality. Translatable progress is impeded by regulatory complexity, when the issues are to develop more effective solutions that make real clinical impact. Good examples of areas of clinical importance that require new innovative thinking include the treatment of chronic wounds and solving the problems of angiogenesis. Addressing this problem in the UK has been made worse in recent times and a clear decrease in real impact from the UK in terms of translation to products has arisen as a result. Progress overseas (e.g. USA) is seeing real inroads being made in these areas. This is directly evident with a decrease in the frequency of patents being filed, and minimal performance in terms of IP generation arising from a small number of highly funded centres in the UK.

UK Biomaterials is part of the Soft Matter community in the most part and in the recent EPSRC review Soft Matter was highlighted as world leading and a major strength of UK chemistry research. Leading institutions such as Nottingham, Manchester, Sheffield and Durham are producing truly world class innovative work in the area and this is one of the areas where increased support at the early translation stage will deliver new companies and significant UK IP, with real opportunities for new growth. UK academics in this area are continually at the forefront of major innovations yet there is a clear problem in that most of these innovations are rarely taken forward to translation because often times early translation grants are assessed both on hard commercial grounds and scientific excellence.

Hard materials are also a feature of the UK Biomaterials scene and there a number of major leading groups at Bristol and Leeds in this area.

The NHS is an extraordinary asset in the UK, and a major potential strength for implementing UK regenerative medicine strategies, but there are problems. It's integration with leading universities in taking research development and translation through to clinical trial is notably weak. A few examples of good practice exist - in particular within London excellent communication between basic science, engineering and NHS professionals are beginning to result in translation to the clinic but such examples are few and far between, and not seen elsewhere. A major problem here is the recent changes on the training of NHS consultants such that the best and brightest of clinicians are no longer advised to do research as part of their career. The few proposed routes to train academic clinicians are very difficult to integrate into current NHS training. In some disciplines, notably Burns, Plastics and Reconstructive Surgery the academic base of this discipline has withered to an almost unrecoverable level for the UK. In recognition of this a charity *The Healing Foundation* has tried to fund academic centres for improving the situation. While commendable this small funding is insufficient to enable a rescue for the UK in this area. The lack of joined up thinking in training NHS consultants and funding academic posts for academic clinicians has put the UK at a major disadvantage internationally. Generations of bright keen energetic young clinicians are being lost from research in general, but a lack of clinical academic champions for regenerative medicine is presently the single biggest problem the UK is suffering from at this time.

The NHS is a powerful resource, its role however and the expertise of clinical staff therein is focussed almost predominantly on 'front-line' delivery, with little emphasis given to technology development, research training and integration with UK universities, compared to other countries in Europe, the USA and more recently Asia. The UK is potentially in a very powerful position to lead the world in regenerative medicine, but much needs to be done to enable this.

Who are main funders

Existing funders include the EPSRC, the MRC and BBSRC typically as separate entities. We believe that a BBSRC/EPSRC/MRC single panel with the remit to fund across the TRLs so they are in position to assess the pipeline would be of benefit. This would solve many issues, as scientists and clinicians currently have to make their science fit the frequently narrow remits of each funding body.

Is science being translated into applications?

Some very good examples of UK translation exist e.g. Myskin autologous skin cell therapy for restoring a skin barrier in burns and chronic wounds, autologous chondrocytes for cartilage defects and a GSK hydrogel for wounds. Internationally it is accepted that autologous skin cells benefit patients with extensive burns and cultured limbal stem cells benefit patients with reduced vision due to loss of these cells. Cell free natural scaffolds such as decellularised porcine scaffolds are seeing success for small site clinical repair but scientific evidence supports the integration of cell therapy for larger site defects – delivered either as autologous cells, or as a stem source. Here it is likely that a naturally derived or synthetically based delivery vehicle (i.e. scaffold) will be required. Considerable UK expertise exists in the basic science underpinning these areas - but applications and the translation of these technologies are few and far between.

A key example of where cell-free meshes are failing is in the thousands of women who have received cell-free meshes for pelvic organ prolapse repair who are now suffering major complications (natural cell-free meshes failing after a year or two and synthetic scaffolds causing erosion through the patient tissues in up to at least 10% of patients) The problems associated with synthetic vaginal mesh are well documented, recently highlighted by an FDA warning and an IUGA/ ICS standardization report on mesh complications. Reported erosion rates of around 10%, with the use of these cell-free non-bioabsorbable materials strongly highlights the need for alternative strategies in the treatment of POP.(Please see Abed H, Rahn DD, Lowenstein L, Balk EM, Clemons JL, Rogers RG. Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. International urogynecology journal. 2011;22(7):789-98

Boennelycke M, Gras S, Lose G. Tissue engineering as a potential alternative or adjunct to surgical reconstruction in treating pelvic organ prolapse. International urogynecology journal. 2012. Epub 2012/09/04. and [Haylen BT](#), [Freeman RM](#), [Swift SE](#), et al An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. [Neurourol Urodyn](#). 2011 Jan;30(1):2-12.).

Why are we not translating?

1. The regulatory environment has effectively closed down many research groups who were on track to work with clinicians to move to the clinic. While patient safety is paramount the regulatory barriers have become so high that most academic groups will not engage with them - and there is no real funding support for this. There is significant fear of regulation within the community, which is hampering progress. However our position is that strong regulation is necessary to protect patients but this should not impede early stage work from taking place.
2. A major weakness in the UK is reluctance of universities to support IP over the required timeframe and a very poor appreciation of commercial realities within 'traditional' University business units. Immediate commercial returns are not expected, within 5-10 year timeframes for simple technologies and longer timeframes are required for more demanding strategies. This is not attractive to the majority of UK universities.
3. Difficulties exist in getting funded for EARLY stage translation. Funding for basic science, while competitive, is reasonably commonplace, as long as ideas are of high quality and contain novelty. Opportunities for second stage (follow-on) funding are far and few between, usually with unrealistically short timeframes for commercial return and unrealistically small amounts of funding. Business models followed are more appropriate for semi-conductor technologies and mature market products. RCUK do not typically consider this to be their remit, and when they do, the opportunities are proportionately small and timeframes too short to be realistic.
4. Poor joined up thinking between NHS and universities – the NHS is focused almost entirely on clinical delivery rather than investing and integrating with research and development. Universities have good expertise in research application, but limited opportunities to catalyse this.

5. Too much funding is concentrated into too few institutions and old technologies, much of this funding needs redistributing and these older technologies should be competing for funds in the private markets – this model works successfully in the USA. Indeed, a major new strategy in the USA now integrates R&D driven industries together on university sites. Both share jointly in the gap we have in UK (TRL3/4). Significant Federal, State and private funding (\$bn's) is seeing single high technology sites being created and utilised by multiple users, with immediate cost savings for industry, with no need to develop independent R&D, and significant investment for universities. The model integrates early stage development, application and translation between scientists and industry, while simultaneously maintaining basic and applied research therein (for example the College of Nanoscale Science and Engineering model, University at Albany, NY, USA).

Potential

Most in the field globally would agree that regenerative medicine and tissue engineering will change the future direction of medicine. However, many advances are required, most notably in taking basic science through to application. Expectation however should be realistic, with 5 to 50 year timeframes, not 1-2 years, as with present expectation and short-term translation models. This can be divided into the respective areas:

Acellular biomaterials both synthetic and natural have been the mainstay of materials based therapies for many years. Technology is already available for improving these devices by improving cellular integration and thus biological performance in 2 dimensions, i.e. we already now how to encourage cells to grow over surfaces. However, despite early ideas based on the use of decellularised scaffolds and the use of porous and fibrous materials long-term, 3D integration remains difficult. Angiogenesis is clearly the key here and the UK will need to devote significant effort in this area if acellular 3D scaffolds are to reach their potential. The problems are significant and ground-breaking advances are required. Use of the immune system to enhance healing and integration may be a way forward as will biochemical approaches but progress in this area will require investment on the 10 to 50 year timescale and will require significant investment in basic science. However, the UK can develop a lead in this area once institutions are coordinated and managed to this objective: controlling angiogenesis in 3D. Major IP can be developed that will support new companies.

Stem cells. Considerable world-leading effort is focused on understanding stem cell biology, and this is to be applauded. Clearly, on the 10 to 50 year time scale stem cell therapy will be important but probably these therapies will mainly be used for treatment of potentially fatal conditions where the risks will be balanced by the fatality from doing nothing. The bottlenecks at the moment appear not to be either upscaling or understanding signalling mechanisms, areas where significant funding has been directed, but rather on effective delivery. None of the strategies that involve simply adding stem cells to a site have been successful. On the other hand treatment of corneal dysfunction is routinely being carried out in India using amniotic membrane carriers loaded with stem cells. Clearly, the field of stem cell therapy will be important, but new technology will be required for delivery and perhaps the field is now beginning to pass from the stage of early hype to become a more mature field, where real therapies can be developed over the next 20 years.

Cell therapy with autologous cells. This is already a reality in the clinic and probably provides the best chance of real clinical impact in the 5 to 10 year time. Delivery of autologous cells in 2D is already possible. However, delivery in 3D is more difficult and increased activity at the basic science level will be key. The advantages of delivery of autologous differentiated cells are significant both in commercial and technical terms:

autologous cells can be the safest cellular alternative and they can often be produced in the required numbers. They do not carry the immediate potential risks of stem cell delivery. Therefore, many in the field would be of the opinion that for non-life threatening conditions autologous cell delivery will be the key technology. On the other hand in the long-term, more stem therapies are likely to be directed at more critical illnesses. In both, cell therapy scale up will be required but technology already exists for this aspect and it will not be necessary for the UK government to invest further. Rather private enterprise is already well equipped to carry out the necessary process developments and we consider that no or little new IP or growth is possible by investigating in scale up from an academic standpoint.

We do not agree with one of tenants of the “A Strategy for UK Regenerative Medicine” document, which states that autologous therapies are expensive and therefore should not be considered. The reality is that autologous therapies demonstrably work, and investment is required to further this via a more stratified approach. Many burns patients and patients with corneal defects worldwide have reason to be grateful for cultured autologous cell therapy.

In terms of the cost for autologous one-to-one therapy we should consider that televisions and motorcars used to be expensive, but are now common place as with initial development of all high technology innovations. The UK has considerable strength in this area and the cost of such therapies can be addressed readily by investment in the logistics for autologous cell delivery – in particular single site facilities. Current UK infrastructure for this is poor and consequently the cost is high. We consider autologous cell therapy to be a key part of the stratification of regenerative medicine for providing safer and more effective therapies. Therapy and the systems to support the delivery of autologous cells are already in practise overseas (autologous chondrocytes by Genzyme in the USA). On the other hand, allogeneic donor cells cannot be produced in sufficiently large numbers for clinical requirements. We were concerned that this technology was absent in the report, and it is not proven that the facilities required for a one to many approach will ever be cost-effective. As far as we aware there have been no advances that address the major difficulties that surround the large-scale production of allogenic cells. Of major concern is the safety of allogenic cells and issues with responses of individual patients to foreign cells. As more patients are treated with single source cells that are multiple passaged it is inevitable that problems will arise. In this respect the stratification that is implicit in the use of autologous cells is a significant advantage that is already driving their application.

Barriers

A major short falling and weakness in the UK concerns how clinicians are trained in scientific research and development. While such training will only be attractive for a select number of newly qualified doctors, the training of research-orientated clinicians is essential for establishing the UK as a leader of Regenerative Medicine – or indeed any form of clinical translation. Introduction of the new Modernising Medical Careers (MMC) programme (in 2005), while beset with problems for individuals wishing to pursue a medical-only career, has been nothing far short of a national disaster for clinicians interested in clinical research and development. Ironically, the UK had a reasonable strength in enabling this 10+ years ago. The current system actively discourages early on against clinical trainees considering higher research (MD/PhD) degrees at the most timely point in their career, typically just after SHO positions, or early on in Registrar training. Such an undertaking now results in a real threat in not obtaining a Specialty Registrar position thereafter for hospital posts. For those with a training position, the usual progression is to a Consultant post thereafter. This

reveals a second major problem in almost all such individuals now work in an entirely clinical environment, with no available time for research and development. Furthermore, the trend for UK clinicians coming in to Consultant posts is to have never experienced or ever had an opportunity to train in a research environment. Consequently such individuals are lacking basic research skills or an understanding of research environments. Those individuals who historically undertook such training understood how research was conducted and how basic scientific research was applied to clinical problems. More importantly, such individuals established, during the higher degree training process, a critical network and link between laboratories and clinics - facilitating the workflow between University research and the NHS. This is rapidly now being eroded in the UK due to major short sightedness of the MMC programme and needs addressing coherently and as a matter of urgency.

Market failure

There is major market failure in this sector much of which is driven by a short-term investment culture and poor business understanding of the new markets. In particular we believe that government can do much more to incentivise business to work closely with the science base and we would welcome schemes that allow low risk funding to enable business to work closely with early stage projects. However, such projects need to have minimal managerial input from government and they must allow for large degrees of failure with potential sideways opportunistic utilisation. Probably, all that is required are significant tax incentives for funding rather than direct use of public funds. The market is also failing because short termism is not allowing small companies to admit failure and perhaps refocus. Government can help here by allowing more early stage work to take place in the public sector, i.e. companies are being formed too early because it is not possible to obtain early translational funding and it is very difficult to produce IP positions and preliminary work that is attractive to companies

Patents

Patents are key to the development of technology because it is almost impossible to either spin out or develop partnerships without an IP position. As far as we are aware no spin out company has ever progressed without strong patent positions. The UK needs to find a way to support academics into national regional filing, perhaps in a collective government sponsored manner with no risk to PIs, who rarely get benefits from IP. Only when patents are in this stage will companies and private capital follow.

Funding for platform technology

The document “A Strategy for UK Regenerative Medicine” highlighted the recent advances in “biomaterials research and nanoscience” and produced a high level conclusion that these developments “mean that the field is now poised to move beyond its historic focus on blood, bone cartilage and skin repair.” (page 7). Also, (page 13) “Biomaterials development for structural support and the direction of propagation and differentiation” is highlighted as one of twelve underpinning areas that warrant investigation. On page 13 the report also makes a clear statement on the necessity of supporting basic research. On page 15 there is an implicit statement that “The fund (Biomedical Catalyst) will be complimented by EPSRC responsive mode funding that will continue to provide support for early stage development of products incorporating or made of biomaterials including tissue engineered products.” Also, the report promotes the use of endogenous repair processes: an area where the use of designed active biomaterials will be key.

In this context, Appendix II provides some clear insights into the current funding landscape and given the context outlined above we believe that there is cause for concern presented by the data “Platform Spend By Stage”, page 29. Although the data in “Therapy spend by stage” is as might be expected for an emergent technology with significant spend at TRL1 and TRL2. Given the strength of the UK in biomaterials and nanoscience in particular it is worrying that the TRL1 spend is zero for Platform technologies and only 15% at TRL2. The data suggest that most of the funding is directed at older technologies and we question the reasoning proposed within the report “Platform TRL1 and TRL2 investments may be underrepresented due to the challenge of identifying awards at this phase, as these may not yet be linked to an application in regenerative medicine.” This seems unlikely because, given the high profile nature of regenerative medicine and the drive to show national significance and relevance, there would be clear drivers for PIs to highlight applications in regenerative medicine. The data appear to provide a clear need to redistribute spend away from TRL3 and TRL4 into TRL 1 and TRL2. Failure to do this will significantly damage the UK’s competitiveness in this area. Support for endogenous repair strategies would also be enhanced as many of the newer materials strategies are directed at control of healing and angiogenesis etc. using advanced materials.

20 September 2012

Roslin Cells Limited, Scottish National Blood Transfusion Service (SNBTS) and UK Stem Cell Bank – Oral evidence (QQ 244-266)

Evidence Session No. 10

Heard in Public

Questions 244 - 266

TUESDAY 11 DECEMBER 2012

Members present

Lord Krebs (Chairman)
Lord Broers
Lord Crickhowell
Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord O'Neill of Clackmannan
Lord Patel
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
Lord Turnberg
Lord Willis of Knaresborough
Lord Winston

Examination of Witnesses

Aidan Courtney, Chief Executive Officer, Roslin Cells Limited, **Professor Marc Turner**, Medical Director, Scottish National Blood Transfusion Service, and **Dr Glyn Stacey**, Director, UK Stem Cell Bank.

Q244 The Chairman: I would like to welcome our second witness panel this morning, for this second half the evidence in relation to our inquiry into regenerative medicine, and in a moment I would like the three panellists to introduce themselves for the record. If you wish to make any brief opening statements please feel free to do so, but please also keep it brief because we have a lot of questions to get through. Perhaps I could start with the first witness, Aidan Courtney.

Aidan Courtney: Good morning. My name is Aidan Courtney. I am Chief Executive of Roslin Cells.

Professor Turner: My name is Marc Turner. I am Professor of Cell Therapy at the University of Edinburgh, and Medical Director of the Scottish National Blood Transfusion Service.

Dr Stacey: My name is Glyn Stacey. I am the Head of Division of Cell Biology and Imaging at the National Institute for Biological Studies and Control in the UK, and I also have the title of Director for the UK Stem Cell Bank project funded by the Research Council.

Q245 The Chairman: Thank you very much. I would like to kick off with a rather general question about the challenges that are associated with the manufacturing of viable cell lines in the UK. We are interested in both the production of cell lines for research and the scaling up for commercial use. Perhaps starting with Aidan, you could give us a view on this and then we will ask the other witnesses on the panel as well.

Aidan Courtney: I think I should start by saying that stem cells and viable cell lines are difficult. They are tricky and they are liable to be unstable, so bringing a manufacturing process to bear on a biological material that is inherently capable of developing in many different ways will always be challenging, and, from a manufacturing point of view, one is always having to work hard at both validating that the material that one starts with is what you expect it to be and that all the steps in the process of developing—transforming it to a different type of cell or just expanding it to a larger quantity, or both—actually has happened, and controlling that process. So looking at it from my experience and our experience at Roslin Cells, I will just say a little about the company: we have 25 staff. We are based in Edinburgh, and we are in the business of making stem cell lines. I think it is quite interesting to note that, of the staff in the company, we have three PhDs and the vast majority of staff are technically trained, extremely capable in what they are doing, but their job and their challenge is to develop procedures and then knuckle down and complete the process. So in that regard, I think a lot of the challenge for manufacturing cell lines is about having the human capital, the people who are trained and capable of doing it. That is probably one of the most important aspects of what we do.

Professor Turner: To build on what Aidan has said, there is one order of magnitude and complexity obviously for generating research grade cell lines, but then when one starts to talk about potential clinical grade stem cell lines, be they human embryonic stem cell derived or induced pluripotent stem cells derived there are further orders of complexity. There is complexity around the issues of registered donors—things such as donor-informed consent, procurement, donor selection and testing, particularly for clinical-grade cell lines that may go on to be administered; or the therapeutics derived from there from might be administered to many patients over a prolonged period of time and traceability of the product needs to be retained. So whereas with a research-grade cell line one can break the link between a cell line and a donor, in a clinical-grade cell line that will not be possible. There are a number of elements around that. There are complexities around a manufacturing process that has to be driven to GMP grade in compliance with UK and European pharmaceutical law, and then there are complexities at the other end where one starts to come to clinically trialling these very novel products, which may behave in a very different kind of way in the human body from the pharmaceuticals we are used to managing through the clinic.

Dr Stacey: There are clearly still, although we have clinical trials developing with human ES cells, fundamental issues relating to scientific aspects of generative stability. Also microbial infection, particularly for the UK prion disease contamination which—

The Chairman: I am very sorry. I am having difficulty hearing.

Dr Stacey: Sorry, yes. Particularly for the UK, there are issues around microbial contamination and potential prion contamination of these products. It is also important to bear in mind that the research now developing is very close to clinical application so there may be, relatively speaking in terms of past products that we see in biotech, a relatively short period between discovery and application, and clearly we need to have careful scientific evaluation scrutiny of those products as they are coming through and on each cell

line that has been developed. I think those are probably the key issues that I would mention at this stage.

Q246 The Chairman: Do you think that the regulatory framework governing the development and maintenance of viable stem cell lines strikes the appropriate balance between facilitation of new discoveries and commercial development and ensuring the quality of product. Do you think the regulatory framework is appropriate?

Aidan Courtney: Others would speak of it from other facets. From a commercial perspective, I think the companies and investors wishing to develop new cell therapies most importantly need to understand what the regulatory framework is, how long it will take to overcome it and what that duration is. Clarity of the process is more important than brevity in many respects because one can then account for how long it will take to put the programme together to develop a new cell therapy, or indeed a cell product that is not a therapy. There are many cell products that are developed that are not heading in a clinical direction; they are heading for drug discovery reasons as well. In that regard, the importance in the UK is to say that, yes, we do have a good regulatory framework. It is reasonably clear, it is robust and I think people have confidence in it, so I would not be critical of the UK regime.

Clearly at times regulators are a bit like buses. There are none around and then three turn up at once and there is an overlap, or has been an overlap, in various aspects of the regulation in the UK. Even if there is no overlap, the plurality of regulators may cause complexity in contrast to perhaps the US, where there is perhaps perceived to be just a single regulator. But most importantly, I would not be critical of the UK regime particularly.

The Chairman: Professor Turner, do you agree with those?

Professor Turner: Yes, I broadly agree. The regulatory regime is complex and I think that is a reflection of the legacy in the way it has evolved and particularly the way that the EU directives and regulations have come into UK law, particularly the tissues and cells directive, for example, the ATMP regulations and the cross-reference, then, to pharmaceutical standards, but we have a lot of interaction with our colleagues in HTA and MHRA – they come to see us a great deal, we have a very good relationship with them and there is a fair amount of dialogue between colleagues who have a regulating responsibility and those of us who are producing cell therapies of various kinds as the field evolves and the regulatory science evolves. So it is a learning curve for all.

Dr Stacey: Yes, I think while there are, as Aidan has alluded to, some complexities in the regulation, the regulators have been very keen to engage with the users of that regulation and to develop and promote a way forward on adapting a regulation that is needed for future cell therapies. One example is the interaction with a national group called the Clinical Human ES Cell Forum, which is formed of the various groups deriving human ES cells for clinical application in the UK stem cell bank, and that got a very good engagement from all three of the regulators involved in this area. Some of that discussion has led to recommendations on revisions to the European Union tissue and cells directive. So I think they are very keen to engage with the users; that has been a very positive experience and the regulators are keen to learn. I think that is very important.

Q247 Lord Cunningham of Felling: The Bio Industry Association tells us that the requirement that all new human embryonic stem cell lines be deposited in the stem cell bank is a barrier to commercial investment and prevents long-term exclusive use of that

line. Very recently, last week in fact, in the United States of America the Committee encountered someone working in this field who told us he had spent two years trying to secure commercial access to a British stem cell line and in the end gave up and went somewhere else. Do you have any comments on that?

Dr Stacey: Yes. The UK model for managing the issues around human ES cells has been to make sure that any of those human ES cells that are derived in the UK or are coming from the UK are used only for certain purposes. The bank has been there to provide the repository for those cell lines both derived in the UK and that have been deposited from outside. I have to say it has been a very positive engagement from research from outside of the UK to use the UK stem cell bank in that way. One of the issues that the bank has to deal with is that all of these cells are owned by other people and there have been delays in progressing some of the research-grade cells through the process of getting agreements and the acceptance that the principle of having these cells derived in the UK is that they are then made available for research purposes broadly.

On the issue of commercial-grade cell lines, that is not a discussion that has been had with the UK stem cell bank because we do not have any cells that we consider to be suitable for clinical application at this time. That would have been a discussion with another organisation. I am not familiar with that.

Q248 The Chairman: As Lord Cunningham has said, we heard from a researcher in the States about the fact that he had given up on trying to access stem cell lines from your bank. Could you just tell us how many international researches have successfully accessed stem cell lines from the UK stem cell bank?

Dr Stacey: Just one point: if that person applied through the steering committee to the UK stem cell bank to use the cells for clinical application, of course that would not have been progressed because we have only research-grade cells available at this time. Next year, when we will be receiving clinical-grade cell lines, it will be a different matter. We are also putting all those cells through an additional due diligence process to make sure that they are fit for purpose under the EU tissue and cells directive and that some of the other issues, such as IP issues, have been addressed and anyone applying for cells made aware of them.

The Chairman: That is not the answer to my question.

Dr Stacey: I apologise. Could you repeat the second part of the question?

The Chairman: The question was how many international researchers have successfully applied to use lines from your bank?

Dr Stacey: We have had requests from international companies and a number of companies have received cell lines from us for international use, as well as researchers outside. In fact, the first cell line we released went to a lab in Turkey.

The Chairman: Could you perhaps write to us and give us the numbers?

Dr Stacey: We could send a break down by the types of cell lines we have.²⁷⁸

Q249 Lord Patel: Can I go back to this regulatory regime? You all seem to be comfortable that our regulatory regime in this country is paying attention and you can talk to them, but unlike some other countries we have several different regulatory organisations.

²⁷⁸ Dr Stacey clarified after the session that there have been 40 human embryonic stem cell lines sent to 17 different institutes/organisations abroad.

So what are the challenges in our environment for developing translational therapies, particularly the cell therapies, and having to address all the regulators, including the European Medicines Commission?

Aidan Courtney: There are two points to be observed. One is that, yes, for reasons of history we have several regulators and now one might say, “Would it not be nice just to have one?” Some people might say, “Would it not be nice to have zero?” but we will ignore them. In many respects the important issue is not so much how many regulators you have but having people who are experts, who would be able to guide one through the process so that the overlap between them or the negotiations through the different regulatory process work smoothly. So long as one is not in a situation where one has regulators who are asking for conflicting data or other factors, which puts one in a closed loop and unable to progress, the number of regulators is not the issue. I think the challenge we have in cell therapy is that with the very notable exception of blood transfusion services in NHS, most of the people coming into developing cell therapy are likely to be either academics trying to start a company or new companies who are probably going through that regulatory process for the first time, and it is very difficult for them to find someone to give them the guidance to take them through the regime.

I think the other example of people trying to develop therapies, for which the regulatory landscape is terribly important, is overseas businesses that want to develop a therapy or bring one into Europe, and will be asking the question: is the UK the place for them to make that investment? I think having a solid regulatory regime is very important and that is a tremendous asset so long as it is articulated as such and we can demonstrate to people that, yes, if you are bringing your cell therapy into clinical trial in the UK you will be supported to take that through, which is also very important. But the number of regulators, Lord Patel, is not the issue in itself.

Q250 Lord Patel: In answer, Dr Stacey, to both Lord Cunningham and the Lord Chairman, I thought you suggested that for the embryonic cell lines that were derived in this country there were some restrictions, whether they be ethical restrictions or scientific restrictions, for lines to be transferred to institutions or individuals outside this country. It was Parliament that established the stem cell bank; are you suggesting that we need a different kind of governance policy for the stem cell bank for this to happen more often?

Dr Stacey: I think the Government—

The Chairman: Can I just ask all witnesses to speak up?

Dr Stacey: Yes, indeed.

The Chairman: Because the transcriber cannot hear and we are having difficulty hearing at this end of the room.

Dr Stacey: Sorry, yes. The field has moved a tremendous amount since 2000, when the stem cell bank and the steering committee were first thought of, and clearly governance needs to progress as time goes on. This is a discussion we have had with the steering committee in the past couple of years to give the bank a greater freedom to act within the community. That has been very important. It has to be a gradual process, it is not something we can do overnight because we do not want suddenly to unravel all of the good that we have done in increasing confidence that people have in the UK system. We take that on as a very serious responsibility for the bank. However that does mean that we have constraints

that would not be felt by another company supplying cell lines that owns those cells, such as Wi-Cell in the US.

Q251 Lord Winston: Yes, one of the issues is to do with GMP facilities and the technical help to support them, and we have heard a lot of evidence to suggest that they have enough to do phase 2 and phase 3 trials. Does the UK have sufficient number and spread of the GMP manufacturing facilities and clean rooms to meet demand, both for research and for potential clinical use?

Professor Turner: In my opinion there are a fair number of GMP-grade clean rooms available throughout the United Kingdom. UK Blood Services between them hold quite a lot of clean rooms that can be used for minimally manipulated products or short-term culture projects, things such as corneal epithelial stem cells for example. There are fewer very high-grade GMP facilities of the kind of quality that would be required to drive through potent stem cell-derived cell therapies but there are some; we have some in Edinburgh, there are some in Newcastle, for example, and there are some down here in London. One of the things to be borne in mind is that often people think it is a matter of the clean rooms and the facilities, when in fact you can always build clean rooms if you so wish—it is expensive but it can be done. It is much more about the quality management system and, as Aidan said earlier, the people with the capability and the knowhow to lift research protocols off the academic bench and drive them through that very complex process. My personal view is that we have capacity at present. I also think that as time goes on the nature of the manufacturing is very likely to change. It will probably move much more towards closed systems and more automated systems, so I personally would not recommend significant further capital investment in clean rooms at this juncture. Let us use the facilities we have and see how the industry develops and how the science develops over the next four or five years.

The Chairman: Would the other witnesses like to add to that?

Dr Stacey: Through my own experience what I think would be very helpful is more driven co-ordination of these kinds of facilities across the UK. Some may be available, some may not. I very much reflect what Professor Turner has said but there is also a need for a driver to encourage this interaction. My experience is when you put people in contact, where you can see there is a need and a capacity, they will very often take up that opportunity if they can. I have seen that work in one or two cases in the UK, even with centres that work at quite distant locations. So I think it would be very helpful to have a central driver to utilise the UK facilities.

Q252 Lord Winston: Does it matter that there are other urban areas where there are not these sorts of facilities. Does that discourage workers from thinking about the need for them in the future?

Aidan Courtney: From my experience, the process often starts with the company or the entity that has developed the therapy, wants to move into the clinical trial. The first question in their mind is: where are they going to find the clinician that will take forward that trial?

The Chairman: Could you speak up a bit?

Aidan Courtney: I do apologise. The point I am making is that the sequence of decisions for a company wishing to develop a new cell therapy would be along the lines of, first of all,

identifying a clinician who would be willing to take forward the clinical trial itself. That then grounds where the business is going to take place and one then moves back upstream to say, “Where are we going to do the manufacturing?”, which is shaped quite often by how long the cells will be viable between the end of the manufacturing process in the GMP facility and when they have to be used in a clinic. That logistical challenge, which can be down to a few hours, can shape whether you need to have the GMP in the cluster. Therefore, lack of GMP would limit a region. If that durability in the supply chain is greater, then I would not see that as a problem.

Professor Turner: Could I add to that? To give you an example, we have manufactured corneal epithelial stem cells in Edinburgh, which will be transplanted in, for example, Liverpool and we have shipped pancreatic islet cells, which have a very short shelf life, down to Bristol for transplantation. To emphasise Aiden’s point, it does not so much matter where you have a manufacturing facility; it is more a matter of capability and premises, so long as you have the proper logistic infrastructure to deliver that to the clinical site in a timely way.

Q253 The Chairman: Thank you. Could I just ask who is doing the thinking about large scale manufacturing when finding one wants to treat tens of thousands or hundreds of thousands of patients with stem cells? Are you doing that sort of thinking or is that being done by commercial companies? Can you tell us what is going on?

Professor Turner: We are doing some of that thinking. For example we have a programme of work funded by the Wellcome Trust that is looking toward the manufacture of red blood cells from pluripotential stem cell lines. In that case you have to consider that we transfuse about 2 million red cell concentrates in the United Kingdom alone each year and each of those contains about 2.5×10^{12} , so of all the cell therapies that is a real challenge in terms of scale-up. What I would say is that there are scale-up issues. How would one possibly manufacture cells on that kind of scale? There are also issues of process control because the current way in which we manufacture small numbers of cells up to 10^{11} are very intensive in terms of hands-on scientific time and the kinds of reagents that we use. There is process modification and there are issues of increasing the density of cell culture. We can see the problems but I think a lot of that work still has to be done in the engineering and process control space.

Aidan Courtney: If I could just pick up that and a couple of other points as well. Going back to the manufacturing question, looking at the products which are currently in early stage, either in research or phase one, phase two, the volume the cells required and the number of patients being treated is quite small. But one is looking over a time of five years or 10 years to have those therapies move through into a large scale situation. It would be a mistake not to anticipate that the technology used to process cells would be transformed in that same period, so the question is not just who is thinking about doing large scale manufacturing for some abstract endpoints, the question is what will cell manufacturing look like in 2018 or 2020? Looking at it, coming from elsewhere, I think that the cell manufacturing industry is on a very similar trajectory to what one might find in microelectronics going back to the 1960s and the 1970s, when the computers were in air-conditioned rooms that were locked and there were hatches, very much like in a clean room, and everyone else was outside. Now the computer is ubiquitous and the idea of processing power has been changed. So that relationship between the processing and the rest of the organisation, whether it is the clinic or the patient, is completely transformed and I think that over the next 10 years the bioengineering and automation developments will

transform the question. The question, “How are we going to treat 10,000 patients with a new cell therapy?” is absolutely correct but on the question, “How are we going to do it in 2018 or 2020?”, we have a little more flexibility than saying we need a large factory-type facility to do it.

The Chairman: Dr Stacey, do you wish to come in?

Dr Stacey: Yes, I think one other thing I would like to add is clearly the biomanufacturing capacity is not just the facilities—it is not just about having the scale-up models—but about a broad range of expertise, particularly in the cell culture aspects and the issues that come out of using cell cultures and cell culture methodologies, which we need to have a bit more people trained in and co-ordinating with the distribution networks and the people producing these in the clean rooms, and having trained people working those clean rooms. It is not a straightforward process. It involves quite a bit of expertise. The other thing is that it would be increasingly important to utilise the experience that the UK has from more than 40 years in the biotechnology sector over which cell cultures have been expanded and grown to make vaccines and biotherapeutics. The knowledge that has been built over that time is very relevant to this area. Again, it is a co-ordination activity, getting that expertise co-ordinated with these new manufacturing centres.

Q254 The Chairman: What about existing networks such as NHSBT and SNBTS, those networks, are they being utilised to supply commercial scale products in the future?

Dr Stacey: I think they will be very important. However, in general, those systems that are working with tissues, organs and cells that are minimally manipulated, and the issues relating to the cell culture technology and expansion, become very relevant then. So there would be a need for cross-training, possibly involving the other groups with expertise in culture and pluripotent stem cell lines to feed into that, helping that distribution network work, particularly where there maybe local production centres at the end of that supply chain.

Q255 Lord Patel: We talked about this problem of manufacturing issues and large-scale manufacturing, but beyond that large-scale manufacturing there will be challenges about distribution of cellular therapies, particular to wherever is required. I know you gave two examples, saying that it is not such a problem to manufacture the therapies in Edinburgh and transfer them to Newcastle and Bristol, but when we are talking about hundreds of thousands of patients—let us hope—how are we going to manage that? What challenges will there be and what thinking are we doing about it?

Professor Turner: Lord Patel, the UK Blood Services take 2.5 million donations each year from all around the United Kingdom from Land’s End right up to Orkney, and we also “manufacture” or produce components in a relatively small number of our production facilities across the United Kingdom and then redistribute blood, platelets and fresh and frozen plasma. So we do have a lot of that infrastructure already and some of those cellular products are really quite fragile. Platelets, for example, have to be held at 22 degrees Celsius plus or minus two degrees, constantly oscillated, and they have a three or four-day shelf life by the time that processing is completed. I am not saying it is an easy problem but it is the kind of problem that we have solved in other kinds of contexts. What I would also say as an addendum is that we not only supply cells within the United Kingdom. We have supplied cytotoxic T lymphocytes, for example, which we are manufacturing in Aberdeen, to a patient in New Zealand and we are about to treat a patient in Sweden. So there are ways of transporting these kinds of products through a secure quality-controlled delivery chain. I

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would say this, would I not, but I think we need as a country to leverage the infrastructure we already have through UK Blood Services to aid in that.

Q256 Lord Patel: Is it just an issue of building more capacity, rather than new thinking?

Professor Turner: Yes, hopefully in due course we will need to look to build more capacity but I think at the moment we can probably use the capacity that we have.

The Chairman: Would anybody else wish to comment on this? Sorry, Lord Turnberg wished to come in.

Q257 Lord Turnberg: I was fascinated by the pancreatic islet cell you are sending off to Bristol. I just wonder whether you are making recommendations for us to make recommendations and we want to move now from Liverpool to the rest of the UK and the world. What would speed it up, what hurdles are in the way and what should we do to make it happen quicker from the point that it is at to generalisation?

Professor Turner: In building the cell therapy industry in the UK as a whole, do you mean?

Lord Turnberg: Take the pancreatic islet cell that you already have.

Professor Turner: That probably is not a good example for this context because pancreatic islets are derived from cadaveric organ donors so the supply is limited. But in terms of developing cellular therapies as a whole, I think that one of the assets or capabilities that the UK has built and is building is something I talked about earlier, which is the ability to take new research protocols off the research bench and take them through what is actually quite a complex process of GMP reduction translation to manufacture, quality control and into clinical trial. That requires a series of different assets and capabilities, and that they be joined up. I think that is a real asset for us, as a country. That is something that we need to further invest in and leverage. The speed of taking a new therapy through to the clinic is what will position us internally and will attract companies and inward investment externally and therefore builds the industry in the United Kingdom.

Q258 Lord Willis of Knaresborough: Can I just come back to two issues? First of all, this inquiry is very specific and looking at commercialisation of these therapies, not only for UK patients but, of course, as an economic generator. It concerned me, Dr Stacey, that when we were in the States we heard the very negative comments about the bank, which you have tried to address, but on your website it says that the lines are not suitable and may not be used for development of cellular therapies, which does seem to be a pretty big put-off for any commercial organisation. You have explained that they are not commercial-grade lines. Is that because of problems with CJD in the past, or are there other reasons for that? Because if you do not have commercial-grade lines very quickly, and you thought you might have one next year, we are out of the game, are we not?

Dr Stacey: All the lines we have had so far have been submitted for research only. They have a background that means they could be used only for research purposes. Some companies or countries might be willing to develop them for clinical applications, but in our situation we do not have the evidence to show that they can be safely transferred into a clinical trial. However, next year, as you reminded us, we will have not just one but around 28 embryonic stem cell lines with suitable provenance coming to the bank. Those are the cells that we will be putting through an additional due diligence process to make sure that we have added a further risk reduction process to those lines that are available from the UK Stem Cell Bank. Then these could be seen as relatively low risk cell lines, in terms of

commercial application, that could be taken forward for clinical application. Although those will still be owned by the originators, we do not own them, so there will still be a discussion to be had between the owners of the lines and the recipients.

Q259 Lord Willis of Knaresborough: But on that part can we press the button to go? Okay. Can I ask you a second question? Take this in the spirit in which it is intended, but I thought there was an element of complacency about the regulatory burden. It seems to me that if you have embryonic stem cells, for instance, and you then have to satisfy the HTA, the HFEA and the MHRA in order to progress further, there are three barriers there, which, if they are taken as a continuum, create a huge timeline. Why are you not pressing for—and perhaps you are doing with the current consultation—to have all that pulled together into one particular regulator?

Dr Stacey: Those regulators have been there for different purposes.

Lord Willis of Knaresborough: I appreciate that.

Dr Stacey: To some extent that was complicated by the development of the EU tissue and cells directive, which brought human embryonic stem cell lines into the framework of tissues and cell delivery. In the UK we have a situation that would separate, if you like, *in vitro* artefacts such as the stem cell lines from the original tissues and cells. We now have the EU tissue and cells directive to do that, which has now come through the HTA under the quality and safety regulations for human use, which was an additional regulation that came in, to some degree, externally. So I think the regulators have tried to do a good job in managing that complicated situation. They have recognised that there are areas of overlap and there has been agreement, I think this was mentioned earlier, not to duplicate inspection, and to accept that there are certain areas that have already been covered by the HFEA and the HTA, and then the MHRA are going to come to clinical trials. So I think it is less burdensome than it might appear at first sight, it would be, by natural intuition, easier to have a single regulator. That might be something that could work in the future.

Q260 Lord Willis of Knaresborough: Just a year ago we were fighting hard in this House through the Health and Social Care Bill, or Act as it now is, to follow up the Academy of Medical Science's strong suggestion that there should be a single regulator through the Health Regulatory Authority. Everyone has gone quiet on that, why? We had an opportunity to do exactly what you wanted, to have a single regulator.

Dr Stacey: We have many changes going on at the moment, with the HTA and HFEA being absorbed into what was Public Health England. So I had anticipated that this was the direction of movement. My anticipation is that something simpler would come out the other side.

Aidan Courtney: I think, from a commercial point of view, the first thing is that in the timeframe you have to develop your therapy you just have to get on with it in terms of what the regulations are. So you just accept it and get on with it. There are two or three different broad challenges that one has to address, and whether they are addressed by speaking to different regulators or one regulator, they still have to be addressed. The first is one of consent and ethics, which is very much from the embryonic procurements addressed by the HFEA. But for other tissue types, they would not be addressed by HFEA; it would be HTA or elsewhere. But essentially one has to be very clear and robust about one's consents and how one goes about the procurement tissue. Whether one has one or three regulators, it is the same question one has to get those challenges right. The second is the entire

handling and processing of the tissue through the whole process of developing, moving towards a product. That is something that needs to be handled and should be regulated, whether by HTA or whoever. Thirdly, if one is developing a medicinal product, one will have to be asked questions about the specifics of that medicinal product and its safety in the context in which it is intended to be used. That third one is addressed by the MHRA in this country.

In many respects those three questions have to be addressed. Whether one has to fill in one form or three forms, the questions are still there. Three sets of fees, three sets of inspections—in fact my company has a joint inspection in early January, which we are pleased about, and we almost had a triple inspection, which I think would have been a very interesting record. But one is happy to have joint inspections. I think the fees are a burden for small companies, but other than that the questions will always be there no matter how many regulators you have.

Q261 Lord Patel: I have a question for Mr Courtney. What are the challenges for commercial companies such as yours in developing commercial embryonic stem cell lines, or any other lines in this country? Do we have regulation that plays against you developing them?

Aidan Courtney: There is a difference between the UK and other countries, from my perspective, when working with embryonic stem cell lines, which of course are only one subset of all the types of cells one might be working with within regenerative medicine. Within the UK we have the Human Fertilisation and Embryology Authority; we have a licence from the HFEA, because we are making embryonic stems cells and that obliges us to deposit the cells with the UK Stem Cell Bank, which is fine.

The challenge in the embryonic stem cells is that there is a one-size-fits-all type of regulation, so we do not have the flexibility to restrict access to a small number of lines that might have commercial potential. There is a blanket treatment of all the lines that we must put in the bank and the bank has a policy. That is the way the UK regulations work for embryonic stem cells. I would say that it has been challenging and distracting because other countries within Europe do not have that, and therefore the UK contrasts differently and, from a commercial perspective, disadvantageously for embryonic stem cells. That is a feature of the embryonic stem cell landscape in the UK. Obviously, in the past few years the major developments in cell therapy and regenerative medicine are in other aspects of cell therapy and regenerative medicine, particularly for the development of induced pluripotent stem cells, and those do not fall within that nexus of regulation.

If I may just finish by saying that it is terribly important to identify that, from a commercial perspective in order to attract the investments needed to develop the therapy, one has to be able to indentify some form of monopoly in order to secure future profits. How that monopoly is identified and established can come in many forms. It may be in patents or it may be in restricted access to the physical tissue itself and the cell line. Other commercial businesses develop things around brand and other aspects. There are other ways of building up a monopoly in market position. It is terribly important, if you want to attract private investment into regenerative medicine, that the potential investors can see clarity over the length of the regulatory landscape, in order to get themselves to commerciality and that when they get there there will not be someone coming around in double-quick time, stealing that market because they cannot protect their market position. As to how that market is protected, there were many different strategies. Patenting is one but it is not the only one for you to look at.

Q262 Lord Cunningham of Felling: Do you have any advice for the Committee about lessons we may learn from other countries in this area of inquiry that we are undertaking? I should say that we met one American commercial developer who had a higher opinion of our regulatory system than he did of the Food and Drug Administration, because he had a very bad experience with it. What advice would you give us about the development of viable cell lines, for both research and commercial use, and what lessons can we learn from other countries?

Dr Stacey: I think one point to start with is to say that the UK has had a big influence in this area because it has led in producing the early seed stocks of these cells and the banking of the cells. There is quite a large international scientific and banking consortium called International Stem Cell Bank Initiative funded by more than 20 countries internationally to support collaborations on stem cell research. This group has brought together numerous centres distributing these cell lines to agree on best practice and a number of other issues in relation to delivery, and has published on best practice in this area. The UK led that group. Generally speaking, groups such as Wi-Cell and the other formal groups that have been supplying for even longer than we have, respect the quality assurance and the standards that we have established in the UK in this area and look to learn from that. In that particular area we are not looking to necessarily learn so much from others, although we never stop learning, but we do in fact seek to teach other people how to do some of these things. I think we are not far from being on the back foot in that respect. I think there are some other commercial approaches we could learn from foreign activities in particular, probably in areas where, for the UK, we are purchasing highly expensive complex reagents to put into the culture of these cells. We could get supplies of those cheaper and driving down some of the prices for delivery. That could be done possibly on a UK basis and would be a very positive move. It is something we have looked at before from a stem cell bank but you need some investment to get that going.

Q263 The Chairman: Would others like to offer lessons from international experiences?

Aidan Courtney: In danger of sounding complacent, I think it is worth reinforcing that we do have, obviously a very good science base, and I generally think we have robust and better-quality regulation—

Q264 Lord Cunningham of Felling: Forgive me for interrupting you: I think everyone acknowledges we have a pretty good science base in this country, but my question is not just about research it was about in commercial development. That is where the perceived weakness is.

Aidan Courtney: That is not a weakness that is restricted to regenerative medicine as one might see that it is systemic elsewhere. The challenges will always come down to funding. How does one bring private funding that goes beyond where public sector funding can take things. In that regard, I think one can look at the United States and say that there is a greater body of private investors. That might be philanthropically motivated investment, rather than hard-nosed venture capital, but there is a greater body of investors who are willing to put funding into companies. I can think of one company that has raised \$120 million to develop without going to venture capitalists: that was through private individuals investing. In many respects what we lack in the UK, and I know that this is something the Committee will have heard several times in other areas as well, is a willingness of people to invest at a very early high risk stage when the financial model just is not there yet, so it is a matter of having faith. That is the challenge we have more than any others in the commercialisation side.

Dr Stacey: Could I just add one thing? I detect a shift in the commercial exploitation of these lines. The industry in general is focused in smaller companies very often struggling to get established and to get products being developed. Very often all that they have in these early stages is a cell line or a group of cell lines to exploit. So the focus is very much on ownership of the lines, and who has the lines and who does not have the lines. How the field develops is reflected in the history of development of vaccine production where a single cell line, the Vero cell line of the WHO bank, is now used by numerous manufacturers to make polio vaccine. They are putting this vaccine into millions and millions of children and adults, it is all based on one cell line so you think there would be huge risk, but having that common source of cells that has been qualified internationally has been important. I see the first signs of this in the cell therapy area, where some of the commercial companies who are developing clinical trials are now looking to license out their cell lines to other commercial operations in a not entirely dissimilar way to how it would operate through UK Stem Cell Bank and the other developers of stem cell lines in the UK. I think there will be a gradual shift in the field so that these banking operations are not seen as a block but as a benefit—they are risk-reduction activities from a commercial perspective.

Q265 The Chairman: What about international differences in approaches to GMP requirements? Are they a significant challenge for the development of cell lines?

Dr Stacey: This is a discussion we have had within this international forum that I mentioned for banking. Although there are differences between the regulators, the regulators are always working at this, there are collaborations between the EMA and the FDA looking towards harmonisation. That is not 100% successful necessarily, but it is progressive. I think some of the manufacturers are still critical, but it is moving in the right direction. This is not something that will be resolved overnight; it involves bigger organisations. But it is progressing in that direction of harmonisation. There are positive signs; there are also activities such as the International Conference on Harmonisation, which co-ordinates activities in these areas between Japan, western Europe and the US, which will also be important in harmonising these issues.

Q266 Lord Patel: Can Mr Courtney comment on what Glyn just said about being able commercially to use a single line for manufacturers or commercial companies will take on to produce their own products?

Aidan Courtney: I think Glyn is describing a mature state of play in vaccine production. I think that there are two or three factors I would comment on to draw a distinction. First, to the extent that in vaccine production there may be other types of monopoly protections in terms of patentability and the such like for the product development downstream, that means that they do not need to hold tight to the cell line itself in the same way because they can protect their commercial products lower down in a different way. The other aspect of it is that in a mature sector one knows that that initial cell line, how it performs and one is not expecting any adverse reaction due to the choice of cell line. In a more nascent sector, where new products are coming through and they are only just being put into people for the first time, from a commercial point of view one may be developing a new cell product with the cell line investing a very substantial part of the company's resources in that one product. Then, even within the company, you may be thinking, "I will choose not to use that cell line in a different therapy, and I certainly would not give it to a third party" simply because maybe in those other examples something goes wrong that is not expected and that causes the regulators to question the quality of the whole line itself, which would underpin my first product. We are in a slightly different space from what Glyn was defining.

The Chairman: I would like to draw this session to a close. I thank the three witnesses for their very helpful comments to inform our inquiry. You will, in due course, receive a transcript and you are able to make minor corrections to that if you wish. There was one particular point that Dr Stacey agreed to send us on the number of overseas researchers and companies that have successfully applied for cell lines from your stem cell bank. If there are any other comments you wish to make in writing, please feel free to do so and we will incorporate them into the evidence. Thank you very much.

Professor Anne E. Rosser and Professor Stephen B. Dunnett, Cardiff University – Written evidence

Professor Anne E. Rosser and Professor Stephen B. Dunnett, Cardiff University – Written evidence

[Submission to be found under Professor Stephen B. Dunnett, Cardiff University](#)

Royal College of Pathologists (RCPATH), the British Society for Blood and Marrow Transplantation (BSBMT) and the British Society for Haematology (BSH) – Written evidence

Royal College of Pathologists (RCPATH), the British Society for Blood and Marrow Transplantation (BSBMT) and the British Society for Haematology (BSH) – Written evidence

[Submission to be found under British Society for Blood and Marrow Transplantation \(BSBMT\)](#)

Royal Society of Chemistry (RSC) – Written evidence

The Royal Society of Chemistry (RSC) welcomes the opportunity to respond to House of Lords Select Committee on Science and Technology call for evidence on Regenerative Medicine.

The RSC is the largest organisation in Europe for advancing the chemical sciences. Supported by a network of 47,000 members worldwide and an internationally acclaimed publishing business, its activities span education and training, conferences and science policy, and the promotion of the chemical sciences to the public. This document represents the views of the RSC. The RSC has a duty under its Royal Charter "to serve the public interest" by acting in an independent advisory capacity, and it is in this spirit that this submission is made.

The importance of the chemical sciences to the UK economy cannot be underestimated. In 2010 the RSC and Engineering and Physical Sciences Research Council (EPSRC) published a joint report, *The economic benefits of chemistry research to the UK*.²⁷⁹ This report found that chemistry research broadly underpins 6 million jobs in the UK and enables the UK to generate £258 billion each year, or 21% of GDP.

The RSC will comment on questions relevant to its remit.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

1. Regenerative Medicine in the UK has seen growth in recent times with increasing number of publications (52% growth in total number of publications, 2005-2009).²⁸⁰ The UK has domestic strength within this field, indicated by a higher normalised citation impact compared to equivalent research in Biological Sciences and Clinical/Medical Sciences.²⁸¹
2. According to *Taking Stock of Regenerative Medicine in the United Kingdom* report,²⁸² the UK performs well internationally, producing higher impact papers indicated by an average citation impact (aci) of 1.62 compared with Germany (1.53 aci) and Japan (1.22 aci). The UK also produces a high volume of papers (5725 between 2005-2009), but is outperformed in terms of impact by European countries such as Switzerland (1.92 aci), Sweden (1.72 aci) and the Netherlands (1.79 aci). The UK also publishes significant levels of collaborative research (43%), the UK's top collaborators include the US, Japan and Germany.²⁸³
3. Without doubt, the US outperforms all other countries in terms of high volume output (26,744 papers between 2005-2009) and high average citation impact (1.87 aci).²⁸⁴

²⁷⁹ [The economic benefits of chemistry research to the UK](#), RSC/EPSRC, 2010

²⁸⁰ [A bibliometric analysis of Regenerative Medicine](#), Thomas Reuters, 2011

²⁸¹ *Ibid.*

²⁸² [Taking Stock of Regenerative Medicine in the United Kingdom](#), Office of Life Sciences, BIS, 2011

²⁸³ *Ibid.*

²⁸⁴ [A bibliometric analysis of Regenerative Medicine](#), Thomas Reuters, 2011

Where does the UK have strengths and weaknesses in the field?

4. The UK Chemical Science community has considerable opportunity for growth in the Regenerative Medicine sector. Already, the UK has a network of research centres²⁸⁵ based in Leeds, Loughborough, London, Oxford, Cambridge and Edinburgh and an EPSRC Doctoral Training Centre (DTC) comprising three universities based at Loughborough, Keele and Nottingham.²⁸⁶ There are also DTC awards in Regenerative Medicine and Tissue Engineering (spanning Leeds, Sheffield and York).
5. A long term strategy for support for centres such as the Cell Therapy Technology Catapult (London), and a connected approach between Biomedical Research Units (BRUs) (Birmingham, Bristol, Imperial, Leeds and Oxford) and Biomedical Research Centres BRCs (Cambridge) with specialism in regenerative medicine, needs to be informed and linked to the research centres outlined in paragraph 4. The key here is to link fundamental science with its subsequent translation to the patient.
6. In 2008, the RSC carried out a 2-day workshop, at which materials scientists, chemists, biologists and engineers were asked to identify areas that would revolutionise the fields of regenerative medicine and tissue engineering. The workshop outlined the technological advances and underpinning science required to achieve maximum impact in areas such as biomechanics, responsive materials, stem cells and strong adhesive gels.²⁸⁷ Opportunities for the chemical sciences were identified including: development/understanding of polymerisation reactions; development of smart scaffolds; understanding surface chemistry, biological interactions/processes and the development of small molecule libraries for the interrogation of fundamental pathways that control stem cell differentiation.²⁸⁸
7. Developments in lab-on-a-chip technologies and the invention of novel material scaffolds for tissue culture/engineering are showing real commercial promise, e.g. research on synthetic scaffolds at Imperial College London and Nottingham, and natural scaffolds at Leeds and UCL. A recent review illustrated the important role of small molecules both in enabling novel cell therapies as well as in the modulation and differentiation of stem cells.²⁸⁹ Chemistry can potentially improve the efficacy of differentiation, proliferation and the survival of stem cell sculptures. In addition, the ability to procure specific stem cell cultures will allow researchers to gain access to more relevant screening tools for biological targets for drug discovery programmes.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

8. *A Strategy for UK Regenerative Medicine*²⁹⁰ mapped the sponsor portfolio (BBSRC, EPSRC, ESRC, MRC and TSB) for 2010. The Regenerative Medicine Portfolio included 353 awards, equivalent to a total spend of £72.6 million.²⁹¹ The Medical

²⁸⁵ [A Strategy for UK Regenerative Medicine](#), MRC, 2012

²⁸⁶ <http://www.dtcregen-med.com/>

²⁸⁷ [Chemical Strategies in Tissue Engineering and Regenerative Medicine](#), RSC, 2009

²⁸⁸ *Ibid.*

²⁸⁹ T E Allsopp, M E Bunnage and P V Fish, *MedChemComm.*, 2010, 1, 16-29

²⁹⁰ [A Strategy for UK Regenerative Medicine](#), MRC, 2012

²⁹¹ *Ibid.*

Research Council (MRC) has the greatest annualised award spend, followed by Biotechnology and Biological Sciences Research Council (BBSRC) and EPSRC. Of the total spend by research council, 89% is allocated to research grants, 7% on training (not including research council studentships) and 3% on resources. The majority of this funding is used for research to inform therapy developments and the development of specific therapies (78% of total) with 19% directed towards platform development and the remainder towards socioeconomic understanding (3% of total).²⁹²

9. Regenerative Medicine has also received significant funding from the third sector. For example, the British Heart Foundation's latest fundraising campaign for research, *Mending Broken Hearts*, focuses on raising £50 million to fund research in regenerative medicine.
10. Funding for therapy development needs to be accompanied by investment in key partnering disciplines (chemistry, chemical biology, materials science, systems biology, surface chemistry, supramolecular chemistry etc.). Funding is also required for development of the safety and efficacy models that are essential to delivering viable therapies.
11. In particular, chemical biology has been identified as a key facilitating area that develops the necessary understanding of the biological processes that underpin innovative therapeutics.²⁹³ The 2008 report, *Face-to-Face UK Chemistry-Biology Interface*,²⁹⁴ called for funding bodies to ensure that support routes for interdisciplinary research were clear and that education in chemical biology disciplines ensures that graduates have the correct practical and theoretical expertise. Cross-disciplinary collaborations between the BBSRC, EPSRC and MRC should be encouraged and communicated to the research community e.g. MRC/BBSRC/EPSRC UK Regenerative Medicine Platform. This is not being adequately facilitated by the current research council structure, which is organised around traditional scientific disciplines.
12. It has been noted that endogenous repair solutions (likely to be small molecules or biologic products that stimulate endogenous repair mechanisms) are currently underrepresented in terms of funding compared to their perceived potential.²⁹⁵ This is an area of particular relevance to pharmaceutical companies, with an easier path to development that is well characterised. Investments in stem cells could also facilitate drug discovery by providing a source of specialised cells used for *in vitro* toxicology testing, e.g. Stem Cells for Safer Medicines (SC4SM)²⁹⁶ initiative. Basic funding directed applications for clinical scenarios are also required e.g. cell adhesion to biocompatible polymers rather than glass cover slips.

Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease

²⁹² [A Strategy for UK Regenerative Medicine](#), MRC, 2012

²⁹³ *Ibid.*

²⁹⁴ [Face-to-Face UK Chemistry-Biology Interface Report](#), RSC, 2008

²⁹⁵ [A Strategy for UK Regenerative Medicine](#), MRC, 2012

²⁹⁶ <http://www.sc4sm.org/>

in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

- I3. Translation of fundamental research into clinical applications takes time and coordination. Therapeutic areas with the most marketed regenerative medicine products are for skin, bone, adipose, cartilage and skin disorders. At present, most research spending is focussed on the hypothesis-driven exploratory research phase.²⁹⁷ There is a need to also support research and translation into the clinic. This translation piece relies on bringing together complementary skills across a range of disciplines, including chemistry.
- I4. Partnering with other learned societies, the RSC can provide a platform for medicinal chemists, materials scientists and clinicians to identify challenges and propose solutions going forward. The RSC has previously hosted pre-competitive workshops designed in partnership with UK/EU pharmaceutical industry on themes such as “Imaging for Human Health” and “The Emerging Model for Medicines Research”.²⁹⁸ Outputs from these initiatives are used to inform policy, funding and lead to the establishment of networks across the disciplines. Importantly, clinicians must be able to outline problems in the context of the chemical sciences, whilst scientists must be encouraged to collaborate to provide solutions in clinical terms.

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

- I5. The restoration of diseased cells, tissue or organs through cell or gene therapies could potentially offer hope to patients suffering from chronic disease such as neurodegenerative disease (e.g. Parkinson’s disease), heart disease, stroke and diabetes. Regenerative Medicine will also provide alternative/complimentary options to patients facing long periods of drug treatment or major surgery.
- I6. Tissue engineering and regenerative medicine approaches to modern healthcare require the use of chemicals and/or chemically derived materials. Novel chemistry is being deployed on surfaces to promote cell adhesion, improve cell function and encourage the development of functioning tissue.
- I7. Several examples of currently approved scaffolds (acellular and cellular), cell based products and exogenous stimulators of repair are listed in *A Strategy for UK Regenerative Medicine*.²⁹⁹ **To deliver future advances in regenerative medicine, chemical science research that develops the tools and materials for such therapies must be developed and funded concurrently.**

Barriers to translation

Are the actions outlined in the Government’s Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board’s Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory

²⁹⁷ [A Strategy for UK Regenerative Medicine](#), MRC, 2012

²⁹⁸ <http://www.rsc.org/ConferencesAndEvents/RSCEvents/PrecompetitiveWorkshops/Index.asp>

²⁹⁹ [A Strategy for UK Regenerative Medicine](#), MRC, 2012

barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

18. Effective collaboration between the research communities will be crucial to ensuring the safe development of regenerative medicine treatments. In order to truly realise the benefits of tissue engineering and regenerative medicine, effective chemical strategies need to be exploited in the creation of novel scaffolds, materials and the understanding of fundamental pathways that control stem cell differentiation.
19. As mentioned in paragraph 11, research councils need to work together to provide interdisciplinary research grants in regenerative medicine. This would greatly increase the pace of advancement in the field. The Biomaterials Chemistry Group and Chemistry Biology Interface Division of the RSC provide a forum for chemists to interact with a variety of scientific disciplines to advance knowledge in all molecular aspects of biomaterials and chemical biology.

What difficulties are encountered when conducting clinical trials and how could these be overcome?

20. Clinical trials for regenerative medicine pose difficulties, in particular with respect to predicting potency and therapeutic effect. Chemical science can help by developing new and better tools for biomarker validation and identification, and protein expression to track cell integration and therapeutic effect. Implementation will require improved collaboration between clinicians and research groups and, if successful, would be expected to have a major impact on the cost, timescale and risk associated with development of Regenerative Medicine therapies.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

21. The potential economic impact of Regenerative Medicine as a whole is estimated to be between \$2-5 Billion, and the annual growth of the global stem cell component of this market is forecast to be 30%, with sales of \$11 billion by 2020.³⁰⁰ Savings in direct health care costs in the USA are projected to be \$250 billion per year from chronic diseases such as heart failure, stroke, late-stage Parkinson's disease, spinal cord injury, and insulin-dependent diabetes.³⁰¹
22. Plasticell is an excellent example of successful UK based start-up company in the field of stem cell research. Plasticell, established in 2002, develops regenerative drugs using high throughput stem cell technologies for a wide range of biomedical applications. Plasticell's award-winning technology, Combinatorial Cell Culture (CombiCult™), is a bead-based high throughput screening platform which allows numerous leading biotechnology and pharmaceutical industry clients to develop efficient protocols for Embryonic Stem (ES) cell differentiation.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

³⁰⁰ [TSB/ESRC REALISE Project](#), Innogen Working Paper, 2010

³⁰¹ [C Mason and P Dunnill, Regen Med, 2008, 3\(3\), 351](#)

23. Funding difficulties are experienced at seed and start-up stages, the kind of funding that is often provided by venture capitalists. Analysis carried out by Regenerative Medicines in Europe project³⁰² (REMEDIÉ) found that the landscape is dominated by SMEs with a few Pharma companies beginning to invest, e.g. Pfizer, Sanofi-Aventis, Smith&Nephew and Shire.
24. In the UK, investment by venture capitalists in the commercialisation of research has fallen to very low levels falling from £930 million in 2008 to £677 million in 2009.³⁰³ The RSC has included a number of recommendations in its response to the House of Commons Science and Technology Committee inquiry on *Bridging the “valley of death”*³⁰⁴ addressing mechanisms to improve commercialisation of research. These recommendations would also be relevant to the translation of Regenerative Medicine research. In particular, actions³⁰⁵ for Government to encourage funding include:
- de-risk the proposition to investors by introducing co-financing measures (e.g. R&D tax credits, public procurement policies, collaboration on R&D projects, including research clusters together with academic institutions).
 - improve the taxation system to incentivise private investors offering seed and start-up funds.
 - increase public funding for public private partnerships.

What role does patenting play in the commercial development of regenerative treatments?

25. According to a report³⁰⁶ compiled by the Intellectual Property Office, the largest subject areas in terms of patent classification are “Materials for grafts/prostheses/coating containing added animal cells”, “Cells from the blood or immune system: haematopoietic stem cells, uncommitted or multipotent progenitors”, and “Embryonic cells: pluripotent cells e.g. embryonic stem cells”. Within the UK, five of the top ten applicants are Universities.³⁰⁷

What business models are most appropriate to support the development of regenerative treatments?

26. Parameters and criteria required for reimbursement (and therefore, commercialisation) of a particular therapy need to be well understood and transparent so that research and clinical efforts can be targeted towards delivering these end-points. As indicated in the RSC response to the *Bridging the “valley of death”*,³⁰⁸ this requires improved communication across the sector, including regulatory authorities, funders, industry, academia and investors.

What are the barriers to securing finance to develop such treatments?

27. Life sciences, biotechnology, pharmaceuticals, medical devices and clean technology research areas are perceived as cash intensive and slow at providing return on investment due to long lead in times and high attrition rates. Difficulty in being able

³⁰² http://ec.europa.eu/research/social-sciences/projects/428_en.html

³⁰³ [Venture Capital - Now and After the Dotcom Crash, NESTA, 2010](#)

³⁰⁴ *Bridging the “Valley of Death”*:improving the commercialisation of research, Paragraph 5, RSC, 2012

³⁰⁵ *Ibid.*

³⁰⁶ [Regenerative Medicine – The Patent Landscape in 2011, IPO, 2011](#)

³⁰⁷ *Ibid.*

³⁰⁸ *Bridging the “Valley of Death”*:Improving the commercialisation of research, Paragraph 6-12, RSC, 2012

to attract venture capital for spin-outs or start-ups has a knock-on effect in incurring delays in commercialisation.³⁰⁹ See paragraph 24 for recommendations to Government.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

28. Researchers (Industry and Academia), NHS and the government need to agree a fair process to look at drug pricing approval systems that reflect the investment made in research and development as well as ensuring that drugs are made available to the patients that need them.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

29. The *Taking Stock of Regenerative Medicine in the United Kingdom* report³¹⁰ outlines the landscape for Regenerative Medicine in USA, Japan and Germany in terms of national strategy, funding, investment and regulation. As outlined previously in Paragraph 18, there is a need for effective collaboration and communication across research communities; initiatives seeking to address this challenge include, for example: Regenerative Medicine Initiative in Germany³¹¹ and The NIH Centre for Regenerative Medicine in the US.³¹²

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

30. The British Standards Institution PAS 93:2011 *Characterisation of human cells for clinical application* best practise guide and the Department of Health/ MRC's UK Stem Cell Tool Kit contain information relevant to organisations and researchers for the development of cells as building blocks or use in Regenerative Medicine, 80% of visits to the Stem Cell Toolkit website were recorded from outside the UK.³¹³
31. Unified mechanisms across the EU involving researchers, manufacturers, clinicians and regulatory communities should be encouraged, **but need to be based on risk not hazard**. Hence, a balance needs to be found between the benefits of novel materials and treatment to the patients and the potential risks they pose. Consultation with the research and implementation communities affected by such legislation would be essential in the process for its development.

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³⁰⁹ [SCI Riding the funding rollercoaster](#) (2011)

³¹⁰ [Taking Stock of Regenerative Medicine in the United Kingdom](#), Office of Life Sciences, BIS, 2011

³¹¹ <http://www.rmig.org/welcome/>

³¹² <http://crm.nih.gov/>

³¹³ [A bibliometric analysis of Regenerative Medicine](#), Thomas Reuters, 2011

Dr Angela J. Russell, University of Oxford, Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant and Dr Graham M. Wynne, University of Oxford – Written evidence

Dr Angela J. Russell, University of Oxford, Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant and Dr Graham M. Wynne, University of Oxford – Written evidence

Authors:

*Dr Angela J. Russell, Departments of Chemistry and Pharmacology, University of Oxford
Professor Stephen G. Davies, Waynflete Professor of Chemistry, Department of Chemistry, University of Oxford*

Professor Dame Kay E. Davies, Dr Lee's Professor of Anatomy, Department of Physiology, Anatomy and Genetics, University of Oxford

Dr Robert Westwood, Independent Consultant, ex Pharma & Biotech Industry

Dr Graham M. Wynne, Department of Chemistry, University of Oxford, ex Biotech Industry

Summary

The ability to harness the potential of stem cells represents a significant opportunity to revolutionise medicine by offering new and improved treatment options for a wide range of diseases. To manipulate exquisitely the expansion or lineage commitment of stem cells would be a major advance in the treatment of diseases in man. The use of small molecules to control cell fate for regenerative medicine is an emerging discipline which offers unprecedented advantages over other techniques in terms of greatly reduced costs, scalability and the ability to control cell fate reversibly at will. One of the potentially most powerful applications of using small molecules to direct stem cell fate would be the ability to manipulate these cells in vivo. There would be enormous advantages with the capability to safely proliferate and specify the fate of a patient's own endogenous stem cells solely through administering a drug, thereby precluding the need for cell therapies.

The UK academic community, including the University of Oxford, has established itself as a world leader in the area of regenerative medicine, with the use of small molecules to manipulate stem cell fate being an area of particular expertise and impact. The regulatory restrictions in place in the US and Japan have inhibited their capability to exploit the full potential of the area of regenerative medicine, and this has allowed the UK to steal a march on other nations, thereby providing a unique and timely opportunity to consolidate our lead, and importantly to regenerate UK plc.

The Research Base

[1] The UK pharmaceutical and biotechnology industries, whilst having undoubtedly faced significant challenges over the past several years have an established and unrivalled track record in discovering and most importantly developing game-changing therapeutics. This development experience, combined with the discovery potential of multidisciplinary academic and biotech collaborations will be pivotal in reducing to practice the promise of regenerative medicine therapeutics.

[2] Although significant opportunities for collaboration exist at the current time, one of the main factors holding back progress is the lack of financial support for the area. Funding exists in the UK and EU for new therapeutic opportunities through bodies such as the EPSRC, BBSRC, MRC, Wellcome Trust etc, and through mechanisms like the Innovative Medicines Initiative, but the majority of this, as applied to regenerative medicine, is focused on cell-based therapeutics. Whilst undoubtedly offering potential for the treatment of disease and the establishment of the principles on which regenerative medicine is based, it is

Dr Angela J. Russell, University of Oxford, Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant and Dr Graham M. Wynne, University of Oxford – Written evidence

our belief that small molecule based strategies to stimulate or augment endogenous repair processes for regenerative medicine strategies offer significant advantages over cell based approaches to revolutionise medicine, based on the ease of administration and control of dosing we associate with such drugs.

Application of the Science

[3] The mechanisms to translate small molecules from initial discovery through to a commercial product, whilst high risk and expensive, are well established. To date there have been limited demonstrations of this in the regenerative medicine arena, with most approaches being the development of cell-based therapies. A notable exception is Eltrombopag (an oral thrombopoietin receptor agonist) which increases platelet numbers, approved by the FDA in 2008. Other examples are in clinical development including Plerixafor, currently in Phase III clinical trials for Haematopoietic Stem Cell (HSC) mobilisation from the bone marrow.

[4] Stem cell based technologies, and particularly small molecule based approaches to them have the potential to fundamentally change drug treatment from a symptomatic to curative outcome. Multiple therapeutic applications can be envisaged, starting initially from 'topical' applications like retinal repair and wound healing whereby the small molecule is introduced directly at the intended site of action and avoiding systemic circulation, through to systemic applications such as neurodegenerative diseases where it is anticipated that orally delivered treatments could be applied.

[5] The current emphasis is currently concentrated in two areas – firstly on 'large' molecules (biologics / peptides) which provide therapeutic proof of concept and/or treatment in areas such as red blood cell production (erythropoietin, EPO), HSC expansion (Granulocyte Colony Stimulating Factor, G-CSF), wound healing, corneal and cardiac repair (thymosin β 4) but are often difficult to administer and control. The second area is cell based therapies, and whilst the media interest that areas such as retinal therapies, tissue repair and cardiac function attract is encouraging and highlights the potential in the area; this needs to be tempered with a lot more realism about the scope and limitations of cellular and biomolecule approaches to medicine.

[6] Notwithstanding the contribution that these biological approaches will make in establishing the principles of regenerative medicines we believe that it is vital that there is a greater awareness of, and focus on the application of small molecules in this area.

[7] For all resident stem cell based, or *in situ* repair approaches the choice of resident stem / progenitor cells for targeting must be rigorously informed. An example of a logical and arguably optimal approach in this regard is to target "residual" adult cells of developmental origin. For example, in the cardiovascular system, there is much more promise in targeting progenitor cells which contribute multiple cell types to the developing heart for cardiac regeneration, as opposed to the rare adult-only cardiac "stem cells" or the ill-defined "side-population".

[8] The potential of stem cells goes significantly beyond the accepted opportunities for tissue and organ repair and regeneration with the discovery of molecules that can reprogram cells (i.e. which can respecify the fate of cells). Once the principle of reprogramming of cells using small molecules is more established the potential that hitherto undesirable cell types, such as cancer cells, could be reprogrammed is envisaged, such that they are no longer malignant and life threatening.

Barriers to Translation

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[9] Development of small molecule therapeutics is therapeutically agnostic – the pathway is well trodden, and whilst it is certainly high risk, pharmaceutical companies have a proven track record in progressing new compounds through clinical development and onto the market. Likewise, academia and biotechnology companies have a worldwide reputation for innovative target discovery and providing proof-of-principle for novel therapeutics. The required skills, technologies and infrastructure are in place and available to use. Indeed, within the UK, we are leaders in this area, having brought many ground-breaking new therapeutics to market over the past 70 years, starting from the first commercial applications of the β -lactam antibiotics like penicillin, continuing through the discovery and development of beta-blockers, anti-ulcer drugs, treatments for erectile dysfunction and anti-virals.

[10] This success and experience has provided the infrastructure both in academic and industrial environments, and more especially in collaborations between the two to capitalise on the emerging field of regenerative medicine.

[11] Most of the technologies are well practiced, and their application to the emerging targets involved in cell proliferation and differentiation will enable discoveries to be made in this area which will lead to potential curative disease treatments, which will be developed using the established industrial paradigms. They will rejuvenate the industry model from the current ‘target centric’, symptomatic treatments where success rates are falling, to a wholly new regenerative approach. Phenotypic (cell-based) screens are an emerging trend in pre-clinical assay development within pharma/biotech/academia, and identification of the molecular target(s) of efficacious small molecules, whilst not essential for development and translational work can be incredibly important in facilitating progress towards the clinic and commercialisation.

[12] Hence the use of libraries of known drugs and/or small molecules with known targets and modes of action, are highly relevant here and would be pivotal. Clinical evaluation will be facilitated by the use of suitable biomarkers, enabling patient selection and clinical trial stratification to be approached with a greater chance of a successful outcome than has historically been the case: such approaches are gaining increasing momentum across many therapeutic areas, and particularly in the development of cancer therapies.

[13] There have been enormous scientific and technological advances in recent years which now enable us to start to apply the existing expertise to the possibility of discovering and delivering small molecule approaches to the control of stem cell proliferation and differentiation, and ultimately to translate into therapeutics for regenerative medicine providing sufficient financial resources and backing can be obtained through Government support.

Barriers to Commercialisation

[14] In order to attract significant investment for projects (from industry and the investment community) it is currently essential to have demonstrated proof of concept in Phase IIA clinical trials; therefore mechanisms for funding the work up to and including this point are required. This is the well known, and widening, ‘funding gap’ in biomedical research, and it is critical that this is addressed, not only for regenerative medicine, but more widely in drug discovery.

[15] The UK pharmaceutical industry provides massive economic benefit; in fact ABPI figures show that it brings to the UK greater economic benefit than any other technology-based industry, and the potential impact that small molecule stem cell therapeutics could have on UK plc would extrapolate this benefit many times. Furthermore, it would enable

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the whole UK pharmaceutical and biotechnologies industries, which have faced enormous challenges, including significant downsizing in recent years, to be rejuvenated, providing much needed highly skilled jobs in the sector as well as the obvious wider healthcare benefits to society. One only needs to look at the work of innovators like Sir James Black, and the effect his contributions had on the industry, both in the UK and abroad to see this in practice. Undoubtedly, and as evidenced by the publication rates in this area, other countries will exploit this area in a competitive environment with the UK.

[16] Intellectual property (IP) and patenting are essential parts of protecting the significant investment made in bringing any new therapeutic agent to market. For small molecule modulators of stem cell function, the patenting of these important new discoveries will present no additional new challenges, as the pathway involved is well established, and encourages the development of these agents. Conversely, the most appropriate way to exploit the IP of cell based regenerative medicine therapeutics is far less clear and unproven, thereby showing that there is a very clear advantage to pursuing small molecule based approaches.

[17] Spin outs from academia are the preferred and established method for reaping most benefit from this new technology. The Chemistry Department at Oxford has an enviable reputation of reducing to practice its innovative new discoveries, and many commercial successful organisations have resulted. We believe that the future of medicine lies in regeneration, and small molecule regenerative medicine approaches have the potential to regenerate UK plc, providing massive and transformative healthcare benefits at the same time.

[18] At the current time there is little seed corn money available in order to start the process and allow innovators to capitalise on their ideas, though once concepts start to be proven and demonstrated then we expect funding to become more readily available. We cannot afford to be risk averse, and the Government needs to be proactive in supporting innovators and strategies of this type.

[19] Pricing structures are largely irrelevant, as for the first time we will be adopting a curative approach to currently unmet medical needs, rather than alleviating symptoms. In turn, as the technology develops, and more diseases can be treated using regenerative medicine type approaches, hospital visits will decrease, waiting lists will shorten and lead to better health within the population, and a lower healthcare burden to Government. We envisage the end truly justifying the means, as the (relatively) short term investment in bringing the technology to fruition will pay off with the longer term benefits.

International Comparisons

[20] When approaching regenerative medicine we need to learn lessons from the past, and take clear and decisive action now to enable the UK to ensure its leading position in this highly competitive field is maintained. There are both legislative barriers and public misconceptions elsewhere, for example the US, which complicates the approach, and we need to be more forward thinking and ensure there are no such barriers.

[21] Our small molecule approach to regenerative medicine and stem cell technology is unencumbered by many of the issues surrounding the development of cell based therapies, and the reduction to practice of developing ‘small molecule’ drugs is well practiced and should be no more problematic than developing a drug for any other therapeutic areas. Taken together with the enthusiasm industry has to develop regenerative medicine based therapeutics, and with the right level of financial and legislative support from central

Dr Angela J. Russell, University of Oxford, Professor Stephen G. Davies, University of Oxford, Professor Dame Kay E. Davies, University of Oxford, Dr Robert Westwood, Independent Consultant and Dr Graham M. Wynne, University of Oxford – Written evidence

Government, the UK is now uniquely positioned to capitalise on this, and maintain its leading position.

20 September 2012

Professor Steven Sacks, King's College London, Professor Michael Linden, King's College London, Professor Charles Ffrench-Constant, University of Edinburgh and Dr Ludovic Vallier, University of Cambridge - Oral evidence (QQ 1-20)

Professor Steven Sacks, King's College London, Professor Michael Linden, King's College London, Professor Charles Ffrench-Constant, University of Edinburgh and Dr Ludovic Vallier, University of Cambridge - Oral evidence (QQ 1-20)

[Transcript to be found under Professor Charles Ffrench-Constant, University of Edinburgh](#)

Professor Steven Sacks, King's College London – Supplementary written evidence

One additional point I would have liked to mention is that we really need a new system of recognition that promotes teamwork and brings competitive programmes of work together. Investigators may have issues of leadership/authorship position on a grant/published work – on which recognition and reward of the REF system are based. At present it can provide a significant barrier to collaborative work. A possible solution is a new system of recognition that is seen as fair and equitable. This could for example identify the author contribution rather than position in the author line. It is part of a generic challenge which may require a global solution. Nonetheless, the problem should be recognized as a potential barrier to joined up work on stem cell solutions, and be discussed.

To clarify another point, I was not suggesting that the entire MRC portfolio should be aligned to NIHR money, but where an MRC award is made out of a translational pot, then alignment with NIHR funding may create more opportunity for translation. This is exactly how it happened in my own Centre.

30 October 2012

Chiaki Sato, University of Tokyo – Written evidence

From Chiaki Sato, Assistant Professor, policy Alternative Research Institution, at the University of Tokyo; Guest Scholar, Engelberg Center for healthcare Reform, at the Brookings Institution

Please note this submission is on an individual basis

1. Application of the science

There are two cases: (1) J-TEC has received reimbursement approval for the autologous cultured epidermis "JACE" in Japan. The reimbursement under the national healthcare insurance started in Jan. 2009, though it was very restrictive. (2) J-TEC has also received government approval to manufacture and sell autologous cultured cartilage "JACC" for traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints in July 2012.

Potential for regenerative medicine are in the next 5-10 years:

- (1) Japan Chemical Research Pharmaceuticals Co., Ltd.-human mesenchymal stem cells to treat GVHD (graft versus host disease), a life-threatening immune reaction occurring in leukemia patients following bone marrow transplantation. Currently, the phase II/III study is ongoing, following positive results from the phase I/II study.
- (2) JTEC- Stem cell for corneal, pre-IND
- (3) ArBlast, Co., Ltd.- cultured corneal epithelial cell sheet for ophthalmologic use, getting IND
- (4) Terumo, Co., Ltd.- Human Skeletal Muscle Myoblast Cells for ischemic heart disease, getting IND

The headline generally does not deal with trans-relational period from clinical trials to therapies.

2. Barriers to translation

- What difficulties are encountered when conducting clinical trials and how could these be overcome?

It is difficult to find targeting patients for clinical trials in Japan, and if possible it costs very much. CRO and hospital networks could solve this weak point.

In Japan, there is a difference in regulations between clinical researches and clinical trials. This means the pathway to marketing or application to therapy is completely divided and change from clinical researches to clinical trials are practically impossible. Clinical researches shall be initiated by researchers and involvement to the researches from industries is very difficult. Clinical trials, which means in Japan researches must follow ICH-GCP standards for collecting data to marketing approvals and industries can easily involve in them. Ministry of Health, Labour and Welfare is thinking to make quality and compliance in clinical researches better for reducing differences between clinical researches and clinical trials.

- What other difficulties are encountered conducting translational research within national healthcare systems and how could these be overcome?

Financial costs and compensations for accidents in clinical researches are big issues in Japan. Clinical trials are funded by mainly industries but clinical researches are paid by hospitals and patients (sometimes some grants from the government and industries).

- What barriers are encountered when seeking approval for the use of such treatments in national healthcare systems or through private healthcare?

There is no specific and clear rule for regenerative medical products and technologies. All products shall be a pharmaceutical drug or medical device for marketing approvals with reimbursements from the national healthcare insurance. In other words, even if there is no marketing approval, physicians provide therapies as clinical researches.

3. Barriers to commercialisation

- What is the current, and potential future, commercial value of the sector? What is its value to society?

There are several projections: From US\$10 billion to US\$50 billion.

- Does your Government, where there is market failure, provide incentives to attract investment in companies working in this high risk area?

Less incentive is offered to regenerated medical products compared with pharmaceuticals and medical devices. No clear pathway and no special reimbursement rule are my reasons.

- What role does patenting play in the commercial development of regenerative treatments?

The patent rule is also unclear and it must be disincentive for investments. In Japan, medical process patents are disallowed but what is medical process is not so clear. Some professionals said it is a problem of how to apply for patents but others think it came from the patent act and its practice.

- What business models are most appropriate to support the development of regenerative treatments?

In Japan, in light of marketing approvals and reimbursement issues, to treat a product as a pharmaceutical drug is the best.

- What are the barriers to securing finance to develop such treatments?

No expectation about review times and reimbursement levels are the barriers.

- What pricing structures does your national healthcare system have for such treatments? Are they appropriate to supporting the development of regenerative treatments?

There are three ways for pricing: as drugs, devices, and medical procedures. However, from the standpoint of industries, medical procedure is less attractive because there is no specific price for the product which is used for the procedure. Treated as a drug or device allows prices to be set by itself.

Pricing in drugs and devices is two type: (1) comparative approach with similar drugs and devices and (2) relative costs approach. (1) is adding on pricing based on HTA appraisals or other requirements for similar products. (2) is calculating costs including R&D and marketing etc. (2) is attractive for industries but unclear rules work for calculating.

There is a big difference between drugs and devices: devices can be priced in a group for similar function devices and reset of pricing levels after launching is also done in the group. This sometimes could be disincentive for launching innovative products in Japan, because a product cannot be valued by itself.

The most disincentive is to ceiling the launching heist price to 1.5 times of the average marketing price among the U.S., U.K, France, Germany and Australia. Japan's approvals take more time than other countries, so this rule is critically important.

- What infrastructure barriers exist within healthcare systems, or externally, that prevent the scaling-up or commercial development of such treatments?

Access to venture capitals are limited. We need some risky money to launch regenerated medical products but in Japan it is not so easy to find such money. This comes from unclear rule for clinical researches/trials and approvals, our long review time, and reimbursement rules.

4. International comparisons

- What could the UK learn from its competitors about supporting the Development and commercialisation of regenerative medicines?

I believe the UK could learn from Japan's failures in making pathway to launch in light of both regulatory affairs and reimbursement issues. Then, the UK learns from the U.S. patent issues and regulatory affairs. As to patents, medical process patent will be an issue for making new incentives. Also, making a distinction between practice of medicine and products which shall be regulated in marketing should be discussed.

- How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

As I explained, in Japan, there is no specific regulation for regenerative medicine. That means a regenerative medical product shall be treated a drug, device, or practice of medicine. In other words, we have regulations as drugs and devices with general clinical trials regulations. Japan has just finalized discussions about issuing a guidance for clinical trials and future legislation in 2013.

- Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

I think no. The regulatory concept in the E.U. and the U.S. is similar but details are different. Then, Japan's involvement to such harmonization is very slow though we want to catch up with other countries' advancement.

- What risks do citizens face when travelling to other countries for regenerative treatments? What safeguards does your country have in place to protect the interests' of citizens travelling abroad for such treatments?

Quality assurance is not clear and surely there can be an accident in therapies. I am not sure about liability insurances or contractual agreements in foreign regenerative therapies.

It is surprising for me that there have been few warnings about such risks. Probably, the government is less concerned about provided medicine abroad.

30 November 2012

Professor Michael Schneider, Imperial College London, Professor Peng Tee Khaw, UCL Institute of Ophthalmology and Professor Roger Barker, University of Cambridge – Oral evidence (QQ 21-41)

**Professor Michael Schneider, Imperial College London,
Professor Peng Tee Khaw, UCL Institute of Ophthalmology and
Professor Roger Barker, University of Cambridge – Oral evidence
(QQ 21-41)**

[Transcript to be found under Professor Peng Tee Khaw, UCL Institute of Ophthalmology](#)

Scottish Enterprise – Written evidence

Scottish Enterprise is pleased to present the following evidence to the Select Committee. In line with the call for evidence, we have answered those questions we are best placed to address.

The research base

1. How does the UK rank internationally in the scientific field of regenerative medicine?

- 1.1 The Department of Business, Innovation & Skills Report, “Taking Stock of Regenerative Medicine In The UK” presents a comprehensive analysis of the UK’s international rankings across a range of metrics. In addition, regular discussion with senior figures from a range of international regenerative medicine companies suggests that the UK is increasingly perceived as an attractive location to translate early-stage regenerative therapies into new products, and this is reflected in Scottish Development International’s inward investment pipeline.

2. Where does the UK have strengths and weaknesses in the field?

- 2.1 The UK has several major centres of academic excellence in stem cell and developmental biology including London, Cambridge and Scotland and the resources and capabilities to translate research protocols through to clinical grade cellular therapeutics and /or small molecules. The UK also has considerable strength in its clinical infrastructure and the role the NHS plays in clinical trialling, evaluation and adoption of new therapeutics. The UK regulatory system gives confidence in the quality, safety and cost effectiveness of novel products. Within Scotland, the Scottish National Blood Transfusion Service (SNBTS) has been instrumental in driving forward the development of the industry, working with public- and private-sector partners, including Scottish Enterprise, to ensure that the clinical, regulatory, manufacturing and distribution logistics expertise built up over many years of providing blood products and bone marrow transplantation.
- 2.2 This expertise is supporting the development of a number of new cell therapies that are currently entering clinical trial – including Reneuron’s stroke therapy and US-based Advanced Cell Technologies’ therapy for Stargardt’s Macular Degeneration.

3. Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

- 3.1 Scottish Enterprise has invested £32.4m since circa 2005 across a strongly co-ordinated series of initiatives supporting regenerative medicine research and commercialisation. This has leveraged in excess of £46m from other funders, including public sector partners and charities. Initiatives include the creation of the Scottish Stem Cell Network; establishing Roslin Cells Ltd – a not-for-profit company to develop a range of cell lines to tightly-defined standards (“Good Manufacturing Practice”) suitable for clinical usage; and the Scottish Centre for Regenerative Medicine at the University of Edinburgh. Based at Edinburgh BioQuarter – a flagship science park featuring the University of Edinburgh’s medical research and teaching

facilities, a major teaching hospital, clinical research facility and flexible accommodation for life science companies - the SCRM is home to the MRC Centre of Regenerative Medicine, with over 200 interdisciplinary researchers as well as the most advanced pilot-scale cell therapy facility in the UK.

- 3.2 One of the biggest “funding gaps” has been for translational development: the pre-clinical and clinical development activities that lie between basic research and a marketable product. Scottish Enterprise has worked closely with the worked closely with the UK Stem Cell Foundation since the charity was established in 2005, and together have jointly funded 4 projects.

Application of the science

4. **Is the science being translated into applications? What are the current applications of the science of Regenerative Medicine in the UK and internationally? Which treatments are available in the NHS or through private healthcare?**

- 4.1 Yes, in two broad market categories: new therapeutics and cell-based tools & technologies. In Scotland, two cell therapies have been developed into clinical practice:
- **Pancreatic islet programme** (a collaboration between Scottish Liver/Islet Transplant Unit and SNBTS);
 - **EBV Cytotoxic T lymphocyte (CTL) bank** established to treat patients internationally with post-transplant lympho-proliferative disease. This is one of the first cellular therapies in the country to achieve a MHRA Manufacturing Licence. The first CTL have been released to treat a child with refractory EBV-driven non-Hodgkin's lymphoma
- 4.2 Four regulatory-approved stem cell therapies are in clinical development in Scotland:
- Reneuron's REN001 **stem cell therapy for stroke**
 - ACT's **retinal pigment epithelium (RPE)** treatment for Macular degeneration (Stargardt's disease)
 - **Corneal epithelial** stem cell treatment
 - Study of CD133 cells in **chronic liver failure**
- 4.3 There are significant applications of regenerative medicine in the area of tools and technologies, including
- Provision of hepatocytes (liver cells) for use in toxicity testing (a core component of testing any new drug) by companies like University of Edinburgh spinout Fibromed (www.fibromed.co.uk);
 - Development of disease-specific cell assays for use in drug discovery, for example the Motor Neuron Disease assay developed by the scientists in Edinburgh, Cardiff and Cambridge (<http://www.crm.ed.ac.uk/news/press/stem-cell-study-could-aid-motor-neurone-disease-research>); and for Parkinsons disease (<http://www.crm.ed.ac.uk/news/press/dopamine-producing-nerve-cells-grown-stem-cells-parkinsons-patient>)
 - New reagents for stem cell research, for example Deliverics' Safectin (<http://www.deliverics.com/home/index.php/products/safectin-stem>)

- 4.4 The development of regenerative medicine-based tools and therapeutics is supported by a rapidly-expanding supply chain, with companies developing new products and services to support the industry. Scotland has over 20 companies that are active in this area, including Angel Biotechnology, who have significant expertise in manufacturing cell therapies and BioOutsource who provide specialised safety testing – both are working with Reneuron’s ground-breaking trial in Glasgow; Sistemic, who use microRNA technology to characterise cells; Charles River’s preclinical development capabilities; and many others.

Barriers to commercialisation

5. What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

- 5.1 Current commercial value of this sector in the UK is small, but growing rapidly. Scotland has seen a rapid expansion from 3 companies operating in the sector in 2004 to in excess of 20 companies today, with a mix of Small- and Medium-sized Enterprises (SMEs) and large multinationals. Very few are focussed exclusively on regenerative medicine, but are developing a range of new products and services to support the emerging industry. This activity is likely to generate commercial value in the short- to medium-term.
- 5.2 Maximum commercial value is unlikely to be realised until new regenerative therapies complete clinical trials and are routinely adopted by healthcare providers. The 2011 BIS report “Taking Stock of Regenerative Medicine in the UK” highlighted that today 80% of healthcare costs go towards treating the late stages of illnesses, such as heart failure, which in the future could be either cured early or better managed using cell therapies, indicating a very large potential commercial value. This value is likely to be derived from the companies involved in the developing these new therapeutics, as well as the supply chain including cell therapy manufacturing specialists, packaging and distribution suppliers, and quality control companies.

6. What role does patenting play in the commercial development of regenerative treatments?

- 6.1 Patenting regimes differ significantly across major healthcare markets – particularly in the area of stem cells and cells derived from stem cells, so companies appear to be using alternative methods of protecting their knowledge. This can be by using “trade secret” approaches to protect essential process or regulatory know-how, or by relying on being the first-in-market to build a competitive position. Rather than pursuing patents for the specific cell types used in a therapy, companies appear to be patenting devices and processes for delivering the cells into a patient. For example Tigenix have 3 patent families for ChondroCelect (Europe’s first and only approved cell therapy product), covering cell stability tests, marker genes, biopsy device (see <http://www.tigenix.com/public/uploads/files/Presentation%20Tigenix%20Kempen%20March%2022,%202012.pdf>)

7. What business models are most appropriate to support the development of regenerative treatments?

- 7.1 To support the **development** of regenerative treatments, highly collaborative “virtual” business models would appear to be the most appropriate. This allows companies to outsource large areas of work to specialist providers – for example pre-clinical development from Contract Research Organisations such as Charles River, clinical expertise sourced from the NHS, manufacturing expertise from companies like Angel Biotechnology. These models are supported by funding schemes from Scottish Enterprise, the Technology Strategy Board and others.
- 7.2 Compelling business models for the **commercial exploitation** of regenerative treatments have not yet emerged. These may differ significantly from today’s pharmaceutical industry-based models, and will be inextricably linked to suitable healthcare reimbursement models for potentially expensive, curative treatments, but still provide enough of an incentive to make companies attractive to private investors.

8. What are the barriers to securing finance to develop such treatments?

- 8.1 New regenerative medicine therapies mostly appear to be developed by small, innovative biotechnology companies like Reneuron, Advanced Cell Technologies, Tigenix and Viacyte. These businesses are early-stage and carry inherent risks due to the long-term timescales and high costs for product development, uncertain clinical pathways and regulatory guidance. Even if a product can demonstrate clinical effectiveness, reimbursement mechanisms are not clear. These factors combine to make it extremely difficult for companies to attract investors.
- 8.2 Some of these barriers are beginning to be addressed – for example, NHS Research Scotland is able to identify suitable lead clinical investigators, and co-ordinate rapid approvals for multi-site clinical trials. This can significantly reduce clinical trial lead-time, and in some circumstances co-sponsor clinical trials.

9. What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

- 9.1 As part of a long-term, major investment to support the development of a regenerative medicine industry in Scotland, Scottish Enterprise, the Roslin Foundation and the University of Edinburgh, supported by the Scottish National Blood Transfusion Service, established Roslin Cells Ltd – a not-for-profit organisation which had the remit of addressing the challenge of producing high-quality clinical-grade cell lines for use in developing new therapies.
- 9.2 Many of the regenerative therapies currently in development are aimed at “orphan indications”, which are characterised by having relatively few patients with that particular disease. This can make it challenging to identify, and recruit, suitable patients for clinical trials. Scotland has created NHS Research Scotland, which helps to address this challenge, by coordinating rapid approval of multi-centre clinical trials right across Scotland. Combined with extensive pan-Scotland patient records, and comprehensive disease-specific databases, Scotland’s healthcare informatics capabilities enable suitable patients to be identified and recruited in to trials.

- 9.3 Barriers exist around lack of clarity over reimbursement mechanisms and lack of clarity and support for navigating the approvals process. It is possible commercialisation of new NHS-developed therapies **may** be accelerated by seeking to engage private-sector partners at an earlier stage of the development process. As noted in previous answers, many therapies are still at an early stage of clinical development, so major scale-up issues have not yet been addressed. These scale-up barriers are likely to be technological in nature, so significant work in this area needs to be investigated – possible via the Catapult centre.
- 9.4 Given the investment to date in developing a suitable infrastructure and commercial supply chain in Scotland, it is anticipated that the Catapult Centre will complement and utilise these existing capabilities, rather than duplicate them.

18 September 2012

Scottish Government – Written evidence

Letter from Alex Neil, MSP, Cabinet Secretary for Health and Wellbeing

As Cabinet Secretary for Health and Wellbeing I enclose a submission on behalf of the Scottish Government on the points highlighted by the Select Committee in the Regenerative Medicine call for evidence. The submission was produced in consultation with the Scottish National Blood Transfusion Service (SNBTS), Scottish Stem Cell Network and the Scottish Regenerative Medicine community. Scottish Enterprise will be providing a separate submission focussing on economic impact.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

1. There are no formal rankings as such, but the report commissioned by BIS (June 2011) and carried out by Thomson Reuters: (<http://www.bis.gov.uk/assets/biscore/innovation/docs/b/11-1059-bibliometric-analysis-of-regenerative-medicine.pdf>) provides a good assessment. The report's aim was to map the global landscape of regenerative medicine research using bibliometric analysis of research publications and their citations as a proxy for impact and to compare the overall UK strength in the field with the rest of the world. The report provides a high degree of granularity on specific aspects and should be considered in full, but the overview analysis presents a consistent picture of a very dynamic and globally competitive field in which the UK is performing well.

There has been an increase of around 60% in volume of publications over the 5 years analysed, with UK providing around 8% of regenerative medicine publications in 2009. UK average citation impact was high and rising in 2009 (1.72) compared to world average (1.4) and is higher than the UK research base generally. The UK is also amongst the countries with the greatest proportion of highly cited papers (19.1% in 2009). The UK's impact profile is better than that of emerging Asian competitors, somewhat better than Europe generally and comparable with that of North America.

Where does the UK have strengths and weaknesses in the field?

2. The UK has several major centres of academic excellence in stem cell and developmental biology in London, Cambridge and Scotland and the resources and capabilities to translate research protocols through to clinical grade cellular therapeutics and /or small molecules. The UK also has considerable strength in its clinical infrastructure and the role the NHS plays in clinical trialling, evaluation and adoption of new therapeutics. The UK regulatory system gives confidence in the quality, safety and cost effectiveness of novel products.

3. However, joining up these resources can be challenging, particularly now that many of the stem cell networks have closed. The BIS Strategy for UK Life Sciences (Dec 2011) points to pockets of excellence in the UK which, if they could be rolled out UK-wide, would enhance the UK's competitive position in regenerative medicine. In addition, some of our major competitors are making significantly greater Governmental investment in regenerative

medicine research, e.g. the US, who, in California alone, are investing more than \$3bn in the sector. Another significant UK weakness is the lack of availability of venture capital investment or a strong commercial sector which, in other fields, shoulders some of the development cost for new technologies.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

4. The UK Research Councils fund research in stem cell biology, regenerative medicine and associated tools and technologies. MRC and TSB have recently (December 2011) jointly created a Biocatalyst fund of £180m to fund specific areas of healthcare, including regenerative medicine.

5. The Technology Strategy Board has also provided funding for the development of a Cell Therapy Catapult. The Wellcome foundation is a major funder as are the charities such as the MS Society, British Heart Foundation, Diabetes UK etc. There is also a welcome degree of philanthropy (e.g. J. K. Rowlings' £10m donation to build the Anne Rowling Regenerative Neurology Clinic in Edinburgh) but it is still at a lower level than is seen in, for example, the US.

6. From a Higher Education viewpoint in Scotland, the Scottish Funding Council has changed our research funding formula to focus more resource on world class research areas. We are also trying to push the translation of research – across all key areas, not specifically regenerative medicine - through a number of knowledge exchange initiatives funded by or managed by the Scottish Funding Council (in collaboration with Scottish Enterprise and Highlands and Islands Enterprise), which should start to have an impact over the next couple of years.

The intention is that these initiatives will help increase the level and impact of university-business collaboration and will lever in private sector funding to increase the commercial applications of economically significant research.

Application of the science

Is the science being translated into applications? What are the current applications of the science of Regenerative Medicine in the UK and internationally? Which treatments are available in the NHS or through private healthcare?

7. Broadly speaking Cellular Therapies can be categorised according to the complexity of cell manipulation involved during manufacture and therefore the quality and regulatory challenges and difficulty in bringing a product to commercial development and clinical application:

Category 1: minimally manipulated cell therapies either of autologous or allogeneic origin. The paradigm here is Haematopoietic Stem Cells derived from bone marrow, mobilised peripheral blood or umbilical cord blood which are usually cryopreserved as a mononuclear cell preparation and thawed just prior to transplantation. This is a routine NHS clinical practice (around 3,000 transplants *per annum* in the UK). However preparation of enriched cell populations on the basis of immunophenotypic markers such as CD34 or CD133 either for haematopoietic transplantation or under clinical trial for other indications (for example to improve post-myocardial infarction perfusion) would also fall into this category.

Separation of islet cells from pancreata through digestion, centrifugation and washing also falls into this category and is in clinical practice (around 30 transplants *per annum* in the UK). These products are regulated under the EU Tissues and Cells Directives and Human Tissues (Quality and Safety for Human Application) Regulations by the Human Tissue Authority.

Category 2: somatic cell therapies in which autologous cells or allogeneic cells donated by living or deceased donors, are isolated or cultured for a limited period of time *in vitro* (usually a matter of days or weeks) prior to transplantation into one, or potentially a handful of, recipients. Examples include corneal epithelial stem cell transplantation for the treatment of ocular surface disorders; mesenchymal stem cells for the treatment of autoimmune diseases or to ameliorate graft versus host disease or solid organ graft rejection; CMV- or EBV-specific cytotoxic T lymphocytes to treat disseminated infection or lymphoma respectively in immunosuppressed patients. These cellular therapies are regulated as Advanced Therapy Medicinal Products (ATMPs) by the Medicines and Healthcare products Regulatory Agency.

Category 3: pluripotent stem cell lines are derived either from *in vitro* blastocysts (human embryonic stem cells [hESC]) or genetic reprogramming of adult cells (induced pluripotent stem cells [iPSC]). Such cell lines will proliferate indefinitely in culture and can also differentiate into most if not all of the cell types present in an adult. They therefore open the possibility of scalability and of a single (allogeneic) donor contributing multiple cell or tissue products to multiple recipients over an extended period of time. Examples include hESC-derived retinal pigment epithelium cells for Stargardt's Macular Dystrophy (Advanced Cell Therapies) and neural stem cells for patients disabled by ischaemic stroke (ReNeuron), both of which are currently in clinical trial. These kinds of cellular therapy products are also regulated as ATMPs.

8. In our opinion the complexity of cellular therapy products is likely to increase in the longer term since tissues do not comprise single cell suspensions but complex three dimensional structures comprising multiple cell types and extra-cellular components. In addition, it is likely that we will see the emergence of small molecules and biopharmaceuticals capable to direct therapeutic administration over the coming years.

What potential does regenerative medicine hold to treat disease in the next 5-10 years?
What is the reality versus the headlines about what the science will deliver?

9. Like most other developed economies the age structure of the UK's population is changing. Approximately 17% of the population are currently aged 65 or over and 2.2% are over 85 years old. By 2035, the proportion of people over 65 is projected to rise to 23% and those over 85 to 5.5% of the population. In 2010, 28% of deaths were caused by cancer, and the majority of the rest by degenerative conditions including ischaemic heart disease (15%), cerebrovascular disease (9%), other cardiovascular diseases (7%), respiratory diseases (7%), liver and other gastrointestinal disease (6%), neurological disease (3%), renal failure (2%) and diabetes mellitus (2%). The evidence suggests that people are living longer with chronic and sometimes multi-factorial degenerative disease. It is estimated that in the coming decades just under 2/3rds of people over the age of 65 will suffer from a life-limiting disability. Most of our current pharmaceuticals ameliorate symptoms or prevent progression of disease, but there is little that will restore function to damaged tissue short of organ transplantation. The development of a new generation of Regenerative Therapeutics is therefore likely to be of direct health, economic and social benefit over the coming decades.

10. The range of diseases where regenerative treatments have been shown to be beneficial in responsibly conducted clinical trials is mainly restricted to haematopoietic stem cell transplantation to treat various diseases of the blood and immune system. However the Canadian health regulators approved Osiris Therapeutics' mesenchymal stem cell therapy for acute graft-versus host disease in children and in Europe TiGenix have a chondrocyte product approved for cartilage repair in the knee. In addition, there are many products now in clinical trials (1768 open trials on clinicaltrials.gov) some of which are looking very promising. We should therefore expect some cell therapy products to move through clinical trial and into routine clinical practice over the next 5-10 years.

Barriers to translation

Are the actions outlined in the Government's Strategy for UK Life Sciences, their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and the Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of Regenerative Medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field?

11. The Research Councils and the TSB report identifies many of the key issues associated with the development of regenerative medicines and outlines some of the steps required to address the challenges. However, the key hurdle is the cost of translating research protocols to clinical GMP and conducting clinical trials which are a key milestone in proving principle and attracting commercial investment. The amount of funding available (£72.6m in 2010 spread over 353 projects) is insufficient for this purpose. In 2011, Geron halted its hESC programme, largely led by GRNOPCI, a treatment for spinal cord injury, having spent \$87.5m (£56m) (Geron Annual Report 2011) over 3 years. In our experience even small Category 2 cell therapy proof of principle clinical trials require in the order of £1m over 2-3 years.

If not, what more action is required? In particular:

What difficulties are encountered when conducting clinical trials and how could these be overcome?

12. Specific challenges include the time and cost of translating research protocols to clinical GMP grade, of obtaining regulatory approval and of conducting the clinical trials themselves. There may be challenges in defining suitable patient subgroups, appropriate short or medium term clinical end points and achieving sufficient recruitment to demonstrate clinical efficacy. Further work on joining up the various elements required to drive products from the research laboratory through commercialisation to routine clinical application is necessary.

What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

13. Broadly speaking the NHS is focused on routine service delivery within an increasingly challenging financial environment and the amount of discretionary time available for clinicians and managers to support academic or commercial clinical trials is limited. A broad responsibility on NHS Boards to support clinical trialling activity along with specific

partnerships would help to improve this process and make the UK a more attractive place to conduct clinical trials.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

14. Whilst approval from the competent bodies is a prerequisite for cellular therapies to be marketed in the UK, other considerations come into play in regard to adoption including cost effectiveness, service pathway change requirements and affordability. The NHS is a large complex organisation with competing priorities such that new developments must prove value and have strong supporting evidence of benefit. Barriers tend to be seen differently from different stakeholders and the proposed Innovation Partnership Board and its Health Innovation Partnership in Scotland will focus on joint work to link medical technology companies with the NHS³¹⁴.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

15. The current commercial value of this sector in the UK is small, but growing rapidly. For example, Scotland has seen a rapid expansion from 3 companies operating in the sector in 2004 to in excess of 20 companies today, with a mix of Small- and Medium-sized Enterprises (SMEs) and large multinationals.

Only a few are currently focussed exclusively on regenerative medicine, but are developing a range of new products and services to support the emerging industry. This activity is likely to generate commercial value in the short- to medium-term. Maximum commercial value will be realised in the longer-term when new regenerative therapies complete clinical trials and are routinely adopted by healthcare providers. The 2011 BIS report “Taking Stock of Regenerative Medicine in the UK” highlighted that today 80% of healthcare costs go towards treating the later stages of illnesses, such as heart failure, which in the future could be either cured early or better managed using cell therapies, indicating both a very large potential direct commercial value and indirect value in mitigating health and social care costs. Long-term value is therefore likely to be derived from cell therapeutic and pharmaceutical development companies, as well as the supply chain including cell therapy manufacturing specialists, packaging and distribution suppliers, and quality control companies.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

16. There is a continuing market failure between very promising academic research data and early stage clinical proof of principle which will attract larger scale investment. Most countries competing in this space are now providing second phase public-sector funding in order to build their regenerative medicine industries of the future. The Scottish and UK Governments will need to do the same if they want to build on the investment made thus far and not cede our hard won comparative advantage to our competitors.

³¹⁴ Statement of Intent for Innovation in Health
<http://www.scotland.gov.uk/Topics/Health/NHS-Scotland/InnovationinHealth>

What role does patenting play in the commercial development of regenerative treatments?

17. Patenting regimes differ significantly across major healthcare markets – particularly in the area of embryonic stem cells and cells derived there-from, so companies appear to be using alternative methods of protecting their knowledge. This can be by using “trade secret” approaches to protect essential process or regulatory know-how, or by relying on being the first-in-market to build a competitive position. Rather than pursuing patents for the specific cell types used in a therapy, some companies appear to be patenting devices and processes for delivering the cells into a patient. For example Tigenix have 3 patent families for ChondroCelect (Europe’s first and only approved cell therapy product), covering cell stability tests, marker genes and a biopsy device.

What business models are most appropriate to support the development of regenerative treatments?

18. To support the development of regenerative treatments, highly collaborative “virtual” business models would appear to be the most appropriate. This allows companies to outsource large areas of work to specialist providers – for example pre-clinical development from Contract Research Organisations such as Charles River, clinical expertise sourced from the NHS, manufacturing expertise from companies like Angel Biotechnology. Compelling business models for the commercial exploitation of regenerative treatments have not yet emerged. These may differ significantly from today’s pharmaceutical industry-based models, and will be inextricably linked to suitable healthcare reimbursement models for potentially expensive treatments with long-term benefits to both the patient and the healthcare system, but still provide enough of an incentive to make companies attractive to private investors.

What are the barriers to securing finance to develop such treatments?

19. New regenerative medicine therapies mostly appear to be developed by small, innovative biotechnology companies like Reneuron, Advanced Cell Technologies, Tigenix and Viacyte. These businesses are early-stage and carry inherent high risks due to the long-term timescales and high costs for product development, uncertain clinical pathways and regulatory guidance. Even if a product can demonstrate clinical effectiveness, reimbursement mechanisms are not clear. These factors combine to make it extremely difficult for companies to attract investors.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

20. It is difficult to say at the present time. Most cellular therapies are likely to have high up-front costs but long-term benefits both to the patient and to the wider healthcare and social systems by mitigating the impact of chronic degenerative conditions. These wider longer-term societal benefits will need to be included in evaluation of cost-effectiveness though the assessment thereof are likely to prove challenging. The short-term affordability of proactive treatments with longer-term preventative or anticipatory benefits is also likely to be challenging for current reactive healthcare systems.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

21. The main current barriers are around the length of time required for translation of research protocols through to clinical-grade products, the complexity of approvals processes and the duration and difficulty of mounting good quality clinical trials. Some of these barriers are beginning to be addressed – for example, in Scotland NHS Research Scotland is able to identify suitable lead clinical investigators and co-ordinate rapid approvals for multi-site clinical trials. This can significantly reduce clinical trial lead-time, and in some circumstances provide co-sponsorship clinical trials. Going forward, the awareness of industry of the cost-effectiveness measures normally associated with the NHSScotland, the new methods that may be required, the funding of these studies and the understanding of how clinical adoption is dependent on the evidence and priority setting within NHSScotland provides further challenges to the commercial development of this new generation of therapies. It is likely that better collaboration between the NHS and academic and private-sector partners at an earlier stage of the development process will mitigate some of these challenges and could enhance the UK as an international location for development of these therapies: in NHSScotland better collaboration is the aim of the Innovation Partnership Board which should be in operation by the end of 2012.³¹⁵

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

22. The regenerative medicine sector has the potential to address the health issues presented by an ageing demographic but the technology is at an early stage and largely unproven. This presents a development risk that the private sector, with a few notable exceptions, is unprepared to take, resulting in a lack of translation of academic research into companies. If the promise of the technology is to be realised two things need to be provided, firstly a source of funding that is sufficient to develop the academic research into investable opportunities for the private sector to take forward, and secondly, an organisation tasked with commercialising (translating) the technology. The Cell Therapy Catapult has the required features to achieve this and its long-term strategy is awaited with interest. A key challenge for such an entity is to embed the technology into the UK economy; there may be a risk of the ‘investable opportunities’ being acquired by foreign entities and the technology and jobs being exported.

23. The Catapult has some features in common with the Canadian Centre for the Commercialisation of Regenerative Medicine (www.ccrm.ca). This entity has been seeded with CAN\$15m for the period 2011-2016 with the remit to turn research into commercial outcomes. It has the ability to do its own research and controls the IP coming from 17 Canadian Universities through MaRs innovation (www.marsdd.com). It has attracted a consortium of 22 companies (e.g. Pfizer, GE, Lonza) who have paid a fee to join and who get priority access to the IP and to participate in collaborative projects. The ability to pool IP and control its dissemination would be a feature for the Catapult to consider. It is this that has led to companies being prepared to pay to join.

³¹⁵ Statement of Intent for Innovation in Health <http://www.scotland.gov.uk/Topics/Health/NHS-Scotland/InnovationinHealth>

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

24. The UK has transposed the EU Tissues and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC into UK law as the Human Tissues (Quality and Safety for Human Application) Regulations 2007 and is subject to Regulation (EC) No: 1393/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amended Directive 2001/83/EC and Regulation (EC) No 726/2004.

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

25. There is reasonable harmonisation across Europe though variations in the transposition of EU law into national law and in the approach of different Competent Authorities does present challenges in conducting pan-European clinical trials. The single marketing authorisation under the European Medicines Agency should help commercialisation, which is valid in all European Union countries, as well as in Iceland, Liechtenstein and Norway. Significant differences exist with other parts of the world and more convergence between these regulatory frameworks would establish a common playing field and assist the development of regenerative medicines.

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

26. Within the UK patients are fully protected by regulation. However, in other countries, even in Europe, regulation varies with procedures being offered and some make claims unsupported by clinical evidence. Some target vulnerable individuals who, understandably, are willing to try and pay anything to find a cure. Whilst some patients have reported beneficial effects, others have suffered significant morbidity or have died following procedures. The International Society for Stem Cell Research has published a very useful website to provide impartial advice to people contemplating such therapy (www.closerlookatstemcells.org//AM/Template.cfm?Section=Home1). UK citizens should be strongly encouraged to only accept established regenerative therapies or participate in properly controlled clinical studies. A central register of the latter would be of value both to patients and to the development of the field.

20 September 2012

Scottish National Blood Transfusion Service (SNBTS) and Cambridge National Institute for Health Research (NIHR) – Written evidence

**Scottish National Blood Transfusion Service (SNBTS) and
Cambridge National Institute for Health Research (NIHR) – Written
evidence**

[Submission to be found under Cambridge National Institute for Health Research \(NIHR\)](#)

Scottish National Blood Transfusion Service (SNBTS), UK Stem Cell Bank and Roslin Cells Limited – Oral evidence (QQ 244-266)

Scottish National Blood Transfusion Service (SNBTS), UK Stem Cell Bank and Roslin Cells Limited – Oral evidence (QQ 244-266)

[Transcript to be found under Roslin Cells Limited](#)

Shire – Written evidence

Shire warmly welcomes the House of Lords Science and Technology Committee's inquiry into Regenerative Medicine and is pleased to be able to respond to the call for evidence. Shire Regenerative Medicine (Shire RM) is a leader in providing regenerative medicine solutions for people with life-altering conditions. We aspire to harness the power of regenerative medicine to address society's unmet medical needs, and are focused on developing and delivering solutions that support the body's natural healing process in the areas of diabetic complications and dermal repair.

As Shire RM's commercial activities currently focus on the US, we offer some thoughts and reflections specifically around barriers to translation and our interaction with the regulatory authorities which we hope will be of use and interest to you in the course of your inquiry.

Barriers to translation

Q: Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field?

From our experience as a Clinical Trial Authorization (CTA) Sponsor in the UK and through national protocol assistance with the Medicines and Healthcare Regulatory Agency (MHRA), we believe regulatory expertise is being developed in the UK and, as such, have not encountered any specific regulatory barriers or challenges.

Additionally, European Union (EU) regulatory framework for clinical development for many of these products, Advanced Therapeutic Medicinal Products (ATMPs), has been addressed providing Sponsors with guidance on specific quality, nonclinical, and clinical considerations and specific expert reviews from the Committee for Advanced Therapies (CAT). The categorization of ATMPs has also allowed for more specialized and more frequent interactions at a reduced fee, aiding Sponsors in the development of regenerative medicines.

Q: If not, what more action is required?

Whilst the EU and UK regulatory framework for some products is advancing, such as for ATMPs, further clarity regarding classification of medicinal products, medical devices, and combination product pathways, especially for cell therapies, would be useful.

This includes development of clarity regarding regulatory review authority, regulatory approach and requirements for initiation and fulfilment of clinical development for products containing a drug and device, but that are not defined according to the definition of combination products (example: drug/device not integral based upon the characteristics of one or both of the combined components). This situation for Sponsors becomes complex when more than one reviewing authority (example: MHRA and BSI) is needed for the initiation of clinical development.

About us

Shire enables people with life-altering conditions to lead better lives. Through our deep understanding of patients' needs, we develop and provide healthcare in the areas of:

- Behavioural health and Gastrointestinal conditions
- Rare Diseases
- Regenerative Medicine

as well as other symptomatic conditions treated by specialists.

We aspire to imagine and lead the future of healthcare, creating value for patients, physicians, policymakers, payors and our shareholders.

19 September 2012

Smith & Nephew, Intercytex Ltd and Professor Anthony Hollander, University of Bristol and Azellon – Oral evidence (QQ 81-127)

Smith & Nephew, Intercytex Ltd and Professor Anthony Hollander, University of Bristol and Azellon – Oral evidence (QQ 81-127)

[Transcript to be found under Intercytex Ltd](#)

Dr John Snowden, Sheffield Teaching Hospitals NHS Foundation Trust and University of Sheffield – Written evidence

Haematopoietic stem cell transplantation (hsct) in severe autoimmune and inflammatory diseases

1. History

1.1 Autoimmune diseases are relatively common, affecting 5-8% of the population. The vast majority of patients are managed successfully by disease specialists with an evolving array of therapeutics and supportive care measures. However, exceptional patients with autoimmune and inflammatory diseases develop refractory, life-threatening states. In this context, various types of haematopoietic stem cell transplantation (HSCT) have been administered as intensive immunomodulatory treatment in the last 15 years (Snowden et al, 1996, Snowden et al 2011, Farge & Gluckman 2011, Snowden et al 2012a).

1.2 Initial support for this intensive therapeutic approach to poor risk autoimmune and inflammatory diseases was provided by a wealth of pre-clinical studies where animal models were observed to be cured, or otherwise ameliorated, by myeloablation and lympho-haematopoietic regeneration with allogeneic, syngeneic or autologous HSCT. In humans, further support was provided by serendipitous observations of patients undergoing HSCT for 'standard' indications (e.g. leukaemia) in which co-existing autoimmune diseases were cured or controlled (Hough et al, 2005).

1.3 Following the early clinical reports of HSCT delivered specifically for severe autoimmune diseases in 1996, consensus guidelines were published by the Autoimmune Diseases Working Party of European Group for Blood and Marrow Transplantation (EBMT) in 1997. Retrospective database analyses and prospective studies subsequently demonstrated the feasibility and safety of autologous and allogeneic HSCT, and also initial efficacy in various specific autoimmune diseases (Hough et al, 2005, Burt et al, 2006, Mancardi & Saccardi 2008, Burt et al, 2011, Snowden et al 2012a). In tandem, scientific studies characterised the biological changes induced by autologous HSCT associated with stabilisation or reversal of organ damage and for the first time demonstrated the possibility of resetting the immune balance through thymus mediated immune tolerance and/or generation of T-regulatory cells (Farge et al 2005, Muraro et al 2005, Roord et al 2008, Zhang et al 2009, Alexander et al 2009).

2. Current status in Europe

2.1 The European guidelines have recently been updated to provide haematologists, rheumatologists, neurologists, gastroenterologists and other specialists with specific guidance on patient selection, treatment protocols, and data registration. (Snowden et al, 2012a).

2.2 To date, worldwide registries have accumulated around 2000-3000 HSCT procedures. The status of the EBMT registry (personal communication, Professor Dominique Farge, Head of Internal Medicine and Vascular Disease Unit, St Louis Hospital, Paris 7 University, Elected Chair of EBMT Autoimmune Disease Working Party), including different types of HSCT and autoimmune disease indications is as follows:



HSCT for ADs: EBMT Registry

September 2012 *

*All transplants not yet registered for 2012

- Transplant procedures 1440
- Patients 1400
- Male/Female % 39/61
- Centres /Countries 223/32
- Overall Follow up 2.9y (<1-24)

	Autografts n=1329	Allografts n=100
First	1324	75
Second	15	21
Third		4
Median age at 1st transplant	36y (3-76)	14y (<1-69)



Number of HSCT: 1440- EBMT Registry

September 2012 *

*All transplants not yet registered for 2012

MULTIPLE SCLEROSIS	504	HAEMATOLOGICAL	81
CONNECTIVE TISSUE D.	448	ITP	25
SSc	300	Evans'	19
SLE	103	AIHA	19
PM-DM	20	Other	17
Sjogren	3		
Antiphosph. syndrome	3	VASCULITIS	43
Other/Unknown	15	Wegener's	10
ARTHRITIS	173	Behcet's	8
Rheumatoid arthritis	88	Takayasu	2
Juvenile chronic arthritis :		Microscopic poly. nodosa	3
- Systemic JIA	50	Classical poly. nodosa	1
- Other JIA	18	Churg-Strauss	2
- Polyarticular JIA	10	Other/ Unknown	17
Psoriatic arthritis	3		
Other	4	OTHER NEUROLOGICAL	41
INFLAMMATORY BOWEL	107	Myasthenia gravis	5
Crohn's disease	95	Other/Unknown	38
Ulcerative colitis	4		
Other	7	INSULIN DEPENDENT DIABETES	10
		OTHER/UNKNOWN/MISSING	31

3. How does the UK compare with Europe?

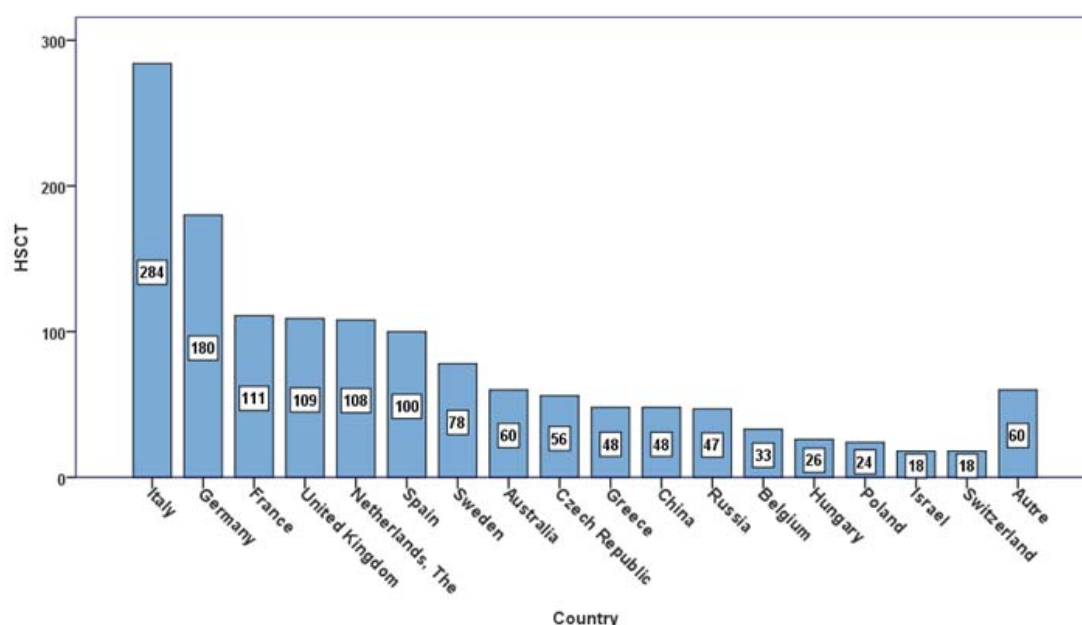
3.1 The British Society for Blood and Marrow Transplantation (BSBMT) registry was used to analyse patients undergoing HSCT for severe autoimmune and inflammatory diseases in the UK between 1997-2009 (55 autologous HSCT, 15 allogeneic HSCT). In this evolutionary period, treatment of autoimmune diseases with HSCT was relatively rare in the UK, averaging 5 per year, and comprising 0.22% of UK HSCT activity (Snowden et al 2012b).

3.2 Over the equivalent time period, there were 1198 registrations in the EBMT autoimmune disease database throughout Europe and thus UK activity comprised 5.8% of EBMT activity for SADs, and the UK is the 4th largest contributor to this field (Snowden et al 2012b and see figure/personal communication Professor D Farge).



Number of HSCT per country (n=1408)

EBMT registry April 2012



3.3 UK outcomes of HSCT in severe autoimmune diseases mirror published EBMT data. Because of compromised multisystem organ function in many patients with severe autoimmune diseases, there are relatively high procedural risks of treating patients with autoimmune diseases compared with other indications, such as haematological cancers, although greater experience has led to better patient selection (Snowden et al 2012a, Snowden et al 2012b).

3.4 Overall severe autoimmune diseases have been a rare indication in HSCT practice in the UK. Compared with many other European countries, the UK has not seen the increase in activity in the two main indications, multiple sclerosis and systemic sclerosis, nor played a substantial role in randomized clinical trials in these diseases. The reasons for this are unclear, but may relate to inter-specialty relationships, the availability of alternative biological treatments, the developing evidence base and NHS funding arrangements for HSCT in rare and novel indications. Prospective clinical study enrolment was reported in only a minority (20%), and therefore most procedures are performed in case-by-case, ad

hoc fashion. Logistical and financial challenges to setting up non-pharma based clinical trials involving complex procedures (such as HSCT) are likely to have contributed to the UK failing to be a European leader in this field.

3.5 There is therefore a case for a national network linking experienced HSCT centres with relevant regional level autoimmune disease specialists (rheumatologists, neurologists, gastroenterologists etc) who are able to identify poor prognosis patients with refractory disease, before advanced, irreversible organ damage and chronic immunosuppression compromise the potential benefits of HSCT. Dedicated infrastructural support is essential. Ideally, patients should be enrolled onto prospective clinical studies in centres with a special interest.

4. Conclusions and future directions

4.1 There is now well over fifteen years of clinical experience of HSCT in patients with various autoimmune and inflammatory diseases. The field has brought about fruitful multidisciplinary collaborations between to address one of the most challenging of groups of patients in clinical practice. In parallel, scientific studies have started to elucidate mechanisms of reset and control of dysfunctional immune systems. However, the evolving industry of biological therapies and small molecule drugs has proved a constant challenge to establishing the role of HSCT in severe AD (Illei et al 2011). Other related cellular therapy based approaches (such as mesenchymal stem cells) have also been the focus of investigation in autoimmune diseases.

4.2 Long-term outcomes of efficacy and safety of this approach are of major importance. Health economic considerations are also central to the development of such therapeutic strategies, i.e. whether a single intensive episode of HSCT treatment may be more cost-effective than the current practice of high-cost biological therapies administered over many years.

4.3 Ultimately, biological, HSCT and other cellular therapy based approaches (such as mesenchymal stem cells and T-regulatory cells) may not be mutually exclusive, and optimal outcomes may be achieved with combinations of intensive treatments combined with long-term consolidation and maintenance approaches. For the present time, it is intended that the recently updated EBMT guidelines promote patient safety and facilitate harmonization of procedural aspects, patient selection, data collection, and coordination of prospective studies, with the goal of identifying the most appropriate clinical niche of HSCT in each AD, as well as supporting basic scientific research.

5. Acknowledgement

I thank Professor D Farge for permission to use EBMT ADWP data.

6. Declaration of potential conflict of interest

Dr Snowden is a long-term member and current secretary of the EBMT ADWP.

5 October 2012

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TAP Biosystems, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine and Cell Therapy Catapult Centre – Oral evidence (QQ 267-282)

TAP Biosystems, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine and Cell Therapy Catapult Centre – Oral evidence (QQ 267-282)

[Transcript to be found under EPSRC Centre for Innovative Manufacturing in Regenerative Medicine](#)

Technology Strategy Board (TSB) – Written evidence

Introduction

1. The Technology Strategy Board is a business-led organisation with a leadership role to stimulate technology development and innovation for the benefit of UK business in the areas which offer the greatest potential for boosting UK growth. The organisation operates across Government and advises on policies which relate to technology, innovation and knowledge transfer. The Technology Strategy Board is the UK innovation agency and acts as the prime channel through which the Government incentivises business-led technology innovation.
2. The Technology Strategy Board was established in July 2007 and has invested more than £1 billion to date, the majority of the funding being matched by business. It has directly supported around 4,000 companies and works with nearly every University in the UK as well as many further education organisations.

Background

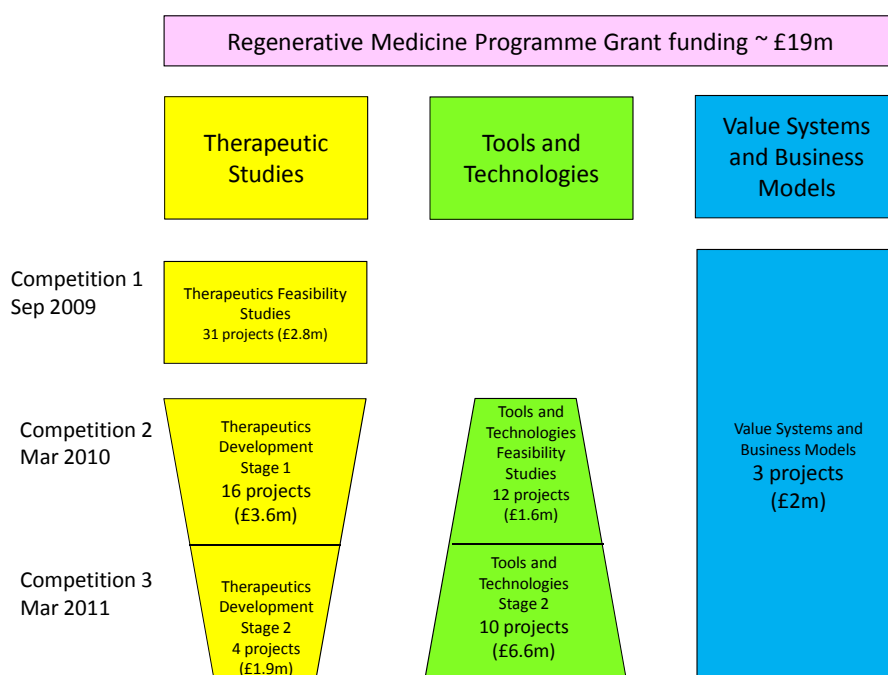
3. Since its formation in 2007, the Technology Strategy Board has supported work to address translation and commercialisation challenges in the area of regenerative medicine and cell therapies. In the period 2005 to 2009 the Technology Strategy board (and its predecessor the Technology Programme in the DTI) had committed more than £20million in cell therapy/regenerative medicine technologies, tissue engineering and cell bioprocessing. This covered a portfolio of some 30 projects involving 20 different companies. Support was also provided through the Knowledge Transfer Networks (KTNs) to support community building and the public private partnerships Stem Cells for Safer Medicine (SC4SM) with MRC, BBSRC, DH and BIS, GlaxoSmithKline, UCB, AstraZeneca and Roche to enable the use of stem cells in early drug discovery. In addition the Technology Strategy Board invested in the Leeds University Innovation and Knowledge Centre, with EPSRC and BBSRC with a focus on Medical Devices exploring how emerging research in the regenerative therapies and devices areas can be applied.
4. In 2008-9 as part of a need to focus on particular sectors the Technology Strategy Board undertook to develop programmes that could support the emergence of new industries. One of those areas was regenerative medicine and the development of the Regenerative Medicine Programme (announced in July 2009) allowed the opportunity for Technology Strategy Board to undertake a more strategic approach to supporting this nascent industrial sector.
5. As part of the development of the Regenerative Medicine Programme, the Technology Strategy Board needed to gain a better understanding of the challenges being faced by companies. It worked closely with the Bioindustry Association Regenerative Medicine Industry Group (now the Cell Therapy and Regenmed advisory Committee) and other industry colleagues to build the Regenerative Medicine Programme.
6. Many of the challenges required engagement with the science and clinical bases to address fundamental questions associated with validation of the technology or to access

new ideas. Therefore it was important to ensure that companies had the potential to identify and work with key academics and clinicians and engagement with the Research Councils particularly MRC, BBSRC, EPSRC, ESRC and the Scottish Government allowed the Regenerative Medicine Programme to develop as a partnership of UK funders working together to address the challenges.

The Regenerative Medicine Programme

7. Technology Strategy Board launched Regenerative Medicine Programme in Sept 2009. The programme was developed in partnership with MRC, BBSRC and EPSRC and was overseen by a Regenerative medicine advisory group to provide strategic insight to the development of the programme. The aims of the programme were to ensure that UK businesses could achieve a commercially competitive edge with global impact, we aimed to:
 - Underpin and enable to flourish the best regenerative medicine businesses in the UK, and
 - Build a connected regenerative medicine community by forming well-linked programmes of work and activities to develop medicines and technology platforms.
8. The programme has a focus on addressing challenges in 3 areas
 - Therapeutic Development – to support companies to progress products towards or into the clinic
 - Tools and Technologies – to address manufacturing and safety/efficacy challenges and to build linkages in the supply chain, both business to business and business to academia
 - Value systems and business models – to allow companies and stakeholders develop a better understanding of where and how value will be created in the emerging regenerative medicine value chain and develop business models to enable businesses to best capture that value.
9. The programme funded a total of 76 projects and committed £16.25m of Technology Strategy board funding with an additional £3m committed by MRC, BBSRC EPSRC ESRC and the Scottish Government. These projects were matched with £7.5m of funding from industry.
10. Critical to the design of the programme was:
 - ensuring companies, particularly the SMEs could participate in the competitions for funding in a manner which matched their cash-flow and business strategies
 - building linkages within the community with supporting activities and workshops being run by the Knowledge Transfer Networks and the regional and national stem cell networks.
11. **Some of the highlights of the programme include**
 - Direct financial support to 5 commercially led projects to start clinical studies.
 - Tissue Regenix – received support through the Programme enabling AIM listing raising £4.5m. Tissue Regenix was incorporated in May 2006 in order to commercialise the research of the University of Leeds.

- Reneuron received support through the Programme for ReN001 and ReN009 products. Reneuron gained regulatory approval and have embarked on a Phase I clinical trial in the UK for their lead ReN001 stem cell therapy for disabled stroke patients. Recently also announced filing for 2 new clinical studies for ReN001 and ReN009 from Critical Limb Ischemia.
- Cellmedica – received support throughout the programme and have successfully completed a fund raising exercise raising £17m.



12. The findings of the programme demonstrated many of the challenges of supporting the commercial development of new technologies. It also highlighted that different support mechanisms were to address the needs of this nascent industry. The Regenerative Medicine Programme is a start and the Technology Strategy Board are committed to the area with the establishment of the Cell Therapy Catapult (funded at £50m over the next 5 years) and additional funding calls. However as products begin to enter later stage clinical development, additional financial resources and investment will be required by companies to exploit their discoveries and to secure the industry in the UK.

The responses to the questions below are based on Technology Strategy Board's findings from the Regenerative Medicine Programme.

Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally?

13. The Regenerative Medicine Programme Therapeutic Feasibility Studies allowed us to create a snapshot of the UK commercial regenerative medicine pipeline. While this does

not cover all commercial products currently in development in the UK it creates a starting point. The therapeutic areas these products aim to address is in table 1 below. The nature of products is approximately split evenly with around half being cell based approaches and the rest being biomaterials, or proteins.

Table 1: Snapshot of the UK commercial regenerative medicine pipeline

Therapeutic area	Number of products
Blood product	2
Bone	3
Eye	2
Immunotherapy	1
Liver	1
Skin	1
Stroke	1
Tendon/Cartilage	11
Vascular repair	3
Wound healing	4

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

14. The Therapeutic feasibility study projects were asked to indicate when they were likely to get into the clinic (for clinical trials purposes). The results were based on self-reported company estimates. Results are shown in Tables 2 and 3 below. It is worth noting that the non cell based products were more advanced in getting to clinic trials stages. While the fate of products progressing through the clinical research phases is still unknown the indications are that companies recognise the need to generate clinical evidence to support product development strategies and also to raise finance.

Table 2 Number of products likely to enter clinical study phase (all product types)

All RM therapies Pipeline	First in man	Phase I	Phase ½	Phase 2
2010	2	1	1	1
2011	2	4	1	1
2012	5	2		
>2013	2			

Table 3 Number of products likely to enter clinical study phase (cell based products)

Cell therapies Pipeline	First in man	Phase I	Phase ½	Phase 2
2010				1
2011		1	3	
2012	4			
>2013	2			

15. Through the Therapeutic Studies strand of the Regenerative Medicine Programme, 4 commercial projects will be embarking on clinical studies in the coming year. These are in the areas of wound healing, joint repair, eye and immunotherapy.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy?

16. Calculating future value of the sector in the UK is fraught with difficulties and is partly driven by how the sector is defined (eg Cell therapies versus Regenerative medicine). An opportunity analysis was carried out on the 16 'Regenerative Medicine therapeutic development - stage one' projects (9 of which were cell based therapies), to estimate their potential revenue generating prospects. Market estimates and potential to capture market share were estimated by the companies as part of their submissions. This was then balanced against risk and likelihood of success. It was estimated that the projects (as a portfolio) could potentially generate ~ £500m of sales revenues per annum in 7-10 years. A similar exercise using the 12 'Tools and Technologies' feasibility studies resulted in an estimated figure of ~ £180m of sales revenues per annum over the same period.
17. This is a first pass estimation and further analysis will be carried out by the Technology Strategy board through the cell therapy catapult centre, to gain more detailed insight into the UK sector.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

18. The Technology Strategy Board has committed to providing long term support to the area of regenerative medicine and cell therapy for UK businesses. The Regenerative Medicine Programme will continue with an additional commitment of up to £10m of funding to go into the programme in 2013. In addition the recently announced Cell Therapy Catapult centre will see Technology Strategy Board investing £50m over 5 years to build a centre with critical mass of infrastructure and expertise to support businesses in addressing challenges in pre-clinical, manufacturing and clinical development as well as address exploring health economics and reimbursement routes for these novel treatments.

19. Furthermore the joint MRC/TSB Biomedical Catalyst was also recently announced to deliver some £180m to support translational activities bridging academic and commercial activities in therapeutic development, medical devices, diagnostics and e-health/m-health solutions. Regenerative medicine is within the scope of the programme.
20. The Technology Strategy Board will continue its close partnership working with the Research Councils in this area and particularly the Regenerative Medicine Platform which will focus on earlier stage research challenges.

What business models are most appropriate to support the development of regenerative treatments?

21. The Technology Strategy Board funded three consortia led projects in the area of 'Value systems and Business modelling' with co-funding from ESRC and the Scottish Government. The challenge was to help companies and stakeholders better understand where and how value will be created in the emerging regenerative medicine value chain and develop business models to enable businesses to best capture that value. The reports from two of these projects ('Value' led by Biolatris, and 'Realise' led by the Scottish Stem Cell Network) have been submitted separately as evidence to the inquiry. The generic outputs of the projects are being disseminated amongst the UK community and delivered a set of tools to enable the industry better understand the potential route by which companies will best capture value in the UK.

What are the barriers to securing finance to develop such treatments?

22. Emerging industries have a number of common characteristics (Calori *et al* 1985) however particularly pertinent to regenerative medicine are the following :
 - Strong technology uncertainty;
 - Regulatory uncertainty;
 - Market uncertainty;
 - Strategic uncertainty;
23. Furthermore particular challenges are being faced by the overall Life Sciences sector with regards to access to finance due to the long development times necessary to demonstrate product safety and efficacy. Through our consultation with the regenerative medicine companies during the Regenerative Medicine programme and in establishing the Cell Therapy Catapult, it was particularly felt that focussed support to enable companies to build the clinical evidence base was necessary to de-risk their value propositions and leverage the significant funding necessary to bring products to market.
24. However Technology Strategy Board believe that more needs to be done, particularly as the later stages for the development of these therapies becomes increasingly more expensive for companies. The Cell Therapy Catapult and the Regenerative Medicine Programme funding is a good stepping stone. However to realise the full potential of regenerative medicine and cell therapy, additional funding and resources to support the later stages of clinical development are required.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

25. Technology Strategy Board has been working with the community to explore where infrastructure can play a role in supporting commercial development. This has led to the establishment of the Cell Therapy Catapult with its base at Guy's Hospital. The Catapult will build its capabilities and will attempt to address some of the key infrastructure challenges, either through the centre itself or through partnerships with others (academia, NHS and commercial partners). However we recognise the fact that physical infrastructure must also house the multi disciplinary expertise necessary to address the complex challenges in product development and building this expertise and knowledge base within the Catapult and accessing academic, clinical and commercial knowledge is part of the role the catapult will play to enable the industry to develop in the UK.

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

26. The Technology Strategy Board has been in discussion with international companies, funding bodies and translation centres to understand regenerative medicine development in the global context. This has helped inform our strategy and ensuring the Cell Therapy Catapult was internationally competitive. We will continue this international activity and work with the Science and Innovation Network and UKTI to identify potential international partnerships.

20 September 2012

Technology Strategy Board (TSB) and Cell Therapy Catapult Centre – Oral evidence (QQ 283-294)

**Technology Strategy Board (TSB) and Cell Therapy Catapult Centre
– Oral evidence (QQ 283-294)**

[Transcript to be found under Cell Therapy Catapult Centre](#)

Technology Strategy Board (TSB) – Supplementary written evidence

In response to a request for additional information relating to the size and location of projects that the Technology Strategy Board has invested in and geographic location, through the Regenerative Medicine Programme. Attached below are summary tables for the following competitions:

- Regenerative Medicine Feasibility Studies 2009 – exploratory work on potential therapies
- Regenerative Medicine Value systems 2009 – to understand business models associated with regenerative therapies
- Developing therapeutics 2010 – preclinical development
- Developing Therapeutics 2011 – clinical development
- Tools and Technologies Feasibility studies 2010 – exploratory development of manufacturing of safety/efficacy technologies for Regenerative medicine development
- Tools and Technologies 2011 full scale development of manufacturing of safety/efficacy technologies for Regenerative medicine development

Points to Note

- There are currently 3 projects that are progressing towards or are in the clinic (TAP Biosystems, Neotherix and CellMedica). Cellmedica have embarked on the Phase ½ study and have treated 15 patients (source CT catapult clinical trials database <https://catapult.innovateuk.org/documents/10726/1553967/CTC+UK+Clinical+Trials+Database/0451f336-4e2a-4907-a909-355e940b67b4>). The remaining projects are aiming to start human studies in 12-18months. A fourth project that was initially funded has withdrawn (led by Orthox)
- The Technology Strategy Board has also funded pre-clinical development work for Reneuron and Azellon which has progressed products to clinical studies (Reneuron trial started in 2010, Azellon trial started in 2012)

15 January 2013

Technology Strategy Board (TSB) – Supplementary written evidence

Competition Title	Year	Participant Name	Is Lead	Project Title	Project Status	Project End Date	Offer Grant (£)	Region
Regenerative Medicine feasibility studies 2009	2009	Regentec Limited	Lead	Scale-up and Manufacture of an Injectable Regenerative Bone Matrix	Closed	n/a	98900	East Midlands
Regenerative Medicine feasibility studies 2009	2009	MedCell BioScience Limited	Lead	Characterisation of human bone marrow-derived mesenchymal stem cells for the treatment of tendon injuries	Closed	n/a	86747	East of England
Regenerative Medicine feasibility studies 2009	2009	Pfizer Regenerative Medicine	Lead	Therapeutic Human ES cells: A Study to Map Sustainable Supply	Closed	n/a	100000	East of England
Regenerative Medicine feasibility studies 2009	2009	Renovo Ltd	Lead	Skin Regeneration and Scar Reduction Following Injury	Closed	n/a	150500	North West
Regenerative Medicine feasibility studies 2009	2009	Plasticell Ltd	Lead	Animal Component-Free Bioprocess Development for MSC-Derived Osteoblasts	Closed	n/a	97998	South East
Regenerative Medicine feasibility studies 2009	2009	Orthox Ltd	Lead	High strength regenerative tissue scaffolds for large lesion articular cartilage repair	Closed	n/a	82080	South East
Regenerative Medicine feasibility studies 2009	2009	Intercytex Ltd	Lead	Allogeneic Fibroblast therapy for Epidermolysis Bullosa	Closed	n/a	100000	North West
Regenerative Medicine feasibility studies 2009	2009	AGT Sciences Limited	Lead	Regenerative Cartilage Hydrogel Implant for the Remediation of Osteoarthritis	Closed	n/a	100000	Yorkshire & Humberside

Technology Strategy Board (TSB) – Supplementary written evidence

Regenerative Medicine feasibility studies 2009	2009	Biopharma Technology Limited	Lead	Formulation and processing of cell-containing regenerative medicine products to enable long term storage.	Closed	n/a	97800	South East
Regenerative Medicine feasibility studies 2009	2009	Bioceramic Therapeutics	Lead	Bioceramic Therapeutic's Porous Bone Scaffold-Manufacturing and pre-CE Technical File Project	Closed	n/a	93489	South East
Regenerative Medicine feasibility studies 2009	2009	Cell Medica Ltd	Lead	Novel T cell immunotherapy to treat adenovirus infections in paediatric patients following allo-HSCT	Closed	n/a	85800	South East
Regenerative Medicine feasibility studies 2009	2009	ImmunoSolv Limited	Lead	Improving Bioprocessing of Therapeutic Cells via Dead-Cell Removal	Closed	n/a	99400	Scotland
Regenerative Medicine feasibility studies 2009	2009	Bioceramic Therapeutics	Lead	Bioceramic Therapeutic's Porous Hybrid Bone Substitute - Technical File and Quality Design Control	Closed	n/a	97580	South East
Regenerative Medicine feasibility studies 2009	2009	ReNeuron Group plc	Lead	cGMP manufacturing, formulation and delivery challenges for a proprietary clinical grade stem cell product for peripheral arterial disease	Closed	n/a	82072	South East
Regenerative Medicine feasibility studies 2009	2009	Neotherix Limited	Lead	EktoTherix: development of a regenerative tissue scaffold for repair of surgical excision wounds	Closed	n/a	99196	Yorkshire & Humberside

Technology Strategy Board (TSB) – Supplementary written evidence

Regenerative Medicine feasibility studies 2009	2009	Orthomimetics Ltd	Lead	Process Development and Optimisation for Large Scale GMP Manufacture Capacity for the Production of a Clinical Grade Cartilage Regeneration Product	Closed	n/a	80000	East of England
Regenerative Medicine feasibility studies 2009	2009	Tissue Regenix Limited	Lead	Implementation and certification of an ISO 13485:2003 quality system	Closed	n/a	100000	Yorkshire & Humberside
Regenerative Medicine feasibility studies 2009	2009	Smith & Nephew	Lead	Peptide amphiphile technology for the repair of cartilage lesions in osteoarthritic patients	Closed	n/a	100000	Yorkshire & Humberside
Regenerative Medicine feasibility studies 2009	2009	AedStem Ltd	Lead	Disposable device to produce a serum-based chondrogenic reagent from a patient's own serum sample	Closed	n/a	67181	Yorkshire & Humberside
Regenerative Medicine feasibility studies 2009	2009	The Automationpartner-ship (Cambridge) Ltd	Lead	Towards GMP Production of RAFT Tissues for Cornea Regeneration	Closed	n/a	95000	East of England
Regenerative Medicine feasibility studies 2009	2009	The Ideas Studio Ltd	Lead	Design & development of an automated process design for controlled (GMP) manufacture and final verification of a fibrin-based biomaterial tissue regen	Closed	n/a	98171	South East
Regenerative Medicine feasibility studies 2009	2009	Tissue Regenix Limited	Lead	dCELL® Meniscal Repair Device in vivo pilot study	Closed	n/a	100000	Yorkshire & Humberside

Technology Strategy Board (TSB) – Supplementary written evidence

Regenerative Medicine feasibility studies 2009	2009	Aqix Limited	Lead	AQIX® RS-I - A therapeutic formulation for the regeneration of donor tissues and organs otherwise regarded as 'marginal' for transplantation	Closed	n/a	100000	South East
Regenerative Medicine feasibility studies 2009	2009	Progenteq Limited	Lead	Development of an allogeneic articular cartilage stem cell therapy	Closed	n/a	100000	Wales
Regenerative Medicine feasibility studies 2009	2009	Biocompatibles UK Ltd	Lead	CellBeads for the Prevention of Vein Graft Disease	Closed	n/a	79593	South East
Regenerative Medicine feasibility studies 2009	2009	Tissue Regenix Limited	Lead	dCELL® Vascular Patch manufacturing process scale-up	Closed	n/a	100000	Yorkshire & Humberside
Regenerative Medicine feasibility studies 2009	2009	ReNeuron Group plc	Lead	The Glasgow Stroke Disability Stem Cell Trial - Steps to clinical trial initiation	Closed	n/a	86271	South East
Regenerative Medicine feasibility studies 2009	2009	Roslin Cells Ltd	Lead	GMP Master Cell Bank for Red Blood Cell Production	Closed	n/a	97900	Scotland
Regenerative Medicine feasibility studies 2009	2009	Orthomimetics Ltd	Lead	Development of a Multi-Centre Trial and Patient Registry for a Cartilage Regeneration Natural Implant Product	Closed	n/a	100000	East of England
Regenerative Medicine feasibility studies 2009	2009	MedCell BioScience Limited	Lead	Engraftment and role of mesenchymal stem cells in extrinsic tendon healing - a feasibility study for intra-	Closed	n/a	90890	East of England

Technology Strategy Board (TSB) – Supplementary written evidence

				thecal clinical use				
Regenerative Medicine feasibility studies 2009	2009	LiverCyte Ltd	Lead	Allogeneic Cell Therapy for Acute Liver Failure (ACT-ALF) - a scoping study:	Closed	n/a	99500	South East
Regenerative Medicine feasibility studies 2009	2009	Stem Cell Development	Lead	Determining the Efficacy of candidate cell therapy products	Closed	n/a	87631	North East
Value Systems 2009	2009	Biolatris Limited	Lead	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	67070.	East of England
Value Systems 2009	2009	Consulting on Advanced Biologicals Limited	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	73557.	London
Value Systems 2009	2009	NHS Blood and Transplant	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	50000.	London
Value Systems 2009	2009	NHS Technology Adoption Centre	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	20565.	North West
Value Systems 2009	2009	Quy BioSciences Limited	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	71669.	East of England
Value Systems 2009	2009	The British United Provident Association	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	37224.	London
Value Systems 2009	2009	Loughborough University	Collaborator	Regenerative medicine value systems: navigating	Closed	31/03/2012	98391.	East Midlands

Technology Strategy Board (TSB) – Supplementary written evidence

				the uncertainties				
Value Systems 2009	2009	Cell Medica Limited	Collaborator	Regenerative medicine value systems: navigating the uncertainties	Closed	31/03/2012	149156.	London
Value Systems 2009	2009	Scottish Stem Cell Network Limited	Lead	A Therapy Realization Pathway Tool (TRPT) applied to three representative regenerative medicine therapeutic products: REALISE	Closed	30/04/2012	160210.	Scotland
Value Systems 2009	2009	KLCE Consulting Limited	Collaborator	A Therapy Realization Pathway Tool (TRPT) applied to three representative regenerative medicine therapeutic products: REALISE	Closed	30/04/2012	26000.	Scotland
Value Systems 2009	2009	Roslin Cells Limited	Collaborator	A Therapy Realization Pathway Tool (TRPT) applied to three representative regenerative medicine therapeutic products: REALISE	Closed	30/04/2012	109000.	Scotland
Value Systems 2009	2009	University of Edinburgh	Collaborator	A Therapy Realization Pathway Tool (TRPT) applied to three representative regenerative medicine therapeutic products:	Closed	30/04/2012	154055.	Scotland

Technology Strategy Board (TSB) – Supplementary written evidence

				REALISE				
Value Systems 2009	2009	Lonza Biologics Public Limited Company	Lead	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	200000.	South East
Value Systems 2009	2009	LGC Limited	Collaborator	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	49654.	South East
Value Systems 2009	2009	Future Medicine Limited	Collaborator	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	90000.	London
Value Systems 2009	2009	London Regenerative Medicine Network	Collaborator	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	150000.	London
Value Systems 2009	2009	University College London	Collaborator	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	364174.	London
Value Systems 2009	2009	University College London	Collaborator	British Regen Industry Tool Set (BRITS)	Live	30/06/2013	345747.	London
Developing Therapeutics 2010	2010	Orthox Limited	Lead	Evaluation, Manufacturing Scale up and Regulatory Validation of FibroFix: a Mechanically Advanced, Tissue Regenerative, Meniscal Cartilage Repair Device	Closed	31/03/2011	136266.	South East
Developing Therapeutics 2010	2010	Northwick Park Institute for Medical	Collaborator	Evaluation, Manufacturing Scale up and Regulatory Validation of FibroFix: a Mechanically Advanced, Tissue Regenerative, Meniscal Cartilage Repair	Closed	31/03/2011	125119.	London

Technology Strategy Board (TSB) – Supplementary written evidence

				Device				
Developing Therapeutics 2010	2010	Orthox Limited	Lead	Evaluation of a tissue regenerative load bearing two phase silk-hydroxyapatite composite scaffold in large legion osteochondral knee cartilage regeneration	Closed	31/03/2011	106211.	South East
Developing Therapeutics 2010	2010	Northwick Park Institute for Medical	Collaborator	Evaluation of a tissue regenerative load bearing two phase silk-hydroxyapatite composite scaffold in large legion osteochondral knee cartilage regeneration	Closed	31/03/2011	96257.	London
Developing Therapeutics 2010	2010	Projenteq Limited	Lead	Regenerative Medicine Programme: Developing Therapeutics	Closed	31/03/2011	64981.	Wales
Developing Therapeutics 2010	2010	University of Cardiff	Collaborator	Regenerative Medicine Programme: Developing Therapeutics	Closed	31/03/2011	93904.	Wales
Developing Therapeutics 2010	2010	University College London	Collaborator	Regenerative Medicine Programme: Developing Therapeutics	Closed	31/03/2011	155786.	London
Developing Therapeutics 2010	2010	Aqix Limited	Lead	AQIX RS-I - Basic development of a therapeutic formulation for the assessment and	Closed	31/03/2011	160740.	London

Technology Strategy Board (TSB) – Supplementary written evidence

				regeneration of donor organs otherwise regarded as marginal for transplantation				
Developing Therapeutics 2010	2010	Freeman Hospital	Collaborator	AQIX RS-I - Basic development of a therapeutic formulation for the assessment and regeneration of donor organs otherwise regarded as marginal for transplantation	Closed	31/03/2011	131843.	North East
Developing Therapeutics 2010	2010	Pfizer Limited	Lead	Preparation for Evaluation of a diabetes interventional cell therapy	Closed	30/04/2011	10000.	South East
Developing Therapeutics 2010	2010	Athersys Limited	Collaborator	Preparation for Evaluation of a diabetes interventional cell therapy	Closed	30/04/2011	87000.	Scotland
Developing Therapeutics 2010	2010	Newcastle University	Collaborator	Preparation for Evaluation of a diabetes interventional cell therapy	Closed	30/04/2011	173672.	North East
Developing Therapeutics 2010	2010	King's College London	Collaborator	Preparation for Evaluation of a diabetes interventional cell therapy	Closed	30/04/2011	84207.	London
Developing Therapeutics 2010	2010	RepRegen Limited	Lead	StronBone and StronBone-P - Formulation Optimisation Scale Up Pre-clinical Testing Clinical Trial Design and Planning	Closed	31/03/2011	102679.	South West

Technology Strategy Board (TSB) – Supplementary written evidence

Developing Therapeutics 2010	2010	Imperial College London	Collaborator	StronBone and StronBone-P - Formulation Optimisation Scale Up Pre-clinical Testing Clinical Trial Design and Planning	Closed	31/03/2011	86600.	London
Developing Therapeutics 2010	2010	University College London	Collaborator	StronBone and StronBone-P - Formulation Optimisation Scale Up Pre-clinical Testing Clinical Trial Design and Planning	Closed	31/03/2011	134804.	London
Developing Therapeutics 2010	2010	University College London	Collaborator	RAFT Tissues for Cornea Regeneration: Standards and Sustainability	Closed	31/03/2011	101454.	London
Developing Therapeutics 2010	2010	The Automation Partnership (Cambridge) Limited	Lead	RAFT Tissues for Cornea Regeneration: Standards and Sustainability	Closed	31/03/2011	86406.	East Midlands
Developing Therapeutics 2010	2010	King's College London	Collaborator	Phase II clinical trial to examine Allogeneic Fibroblast therapy for Epidermolysis Bullosa	Closed	31/03/2011	111342.	London
Developing Therapeutics 2010	2010	InterCytex	Lead	Phase II clinical trial to examine Allogeneic Fibroblast therapy for Epidermolysis Bullosa	Closed	31/03/2011	162613.	North West
Developing Therapeutics 2010	2010	Regentec Limited	Lead	Regenerative Matrices for Orthopaedic Repair	Closed	31/03/2011	79200.	East Midlands
Developing Therapeutics 2010	2010	RepRegen Limited	Collaborator	Regenerative Matrices for Orthopaedic Repair	Closed	31/03/2011	49500.	South West

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Developing Therapeutics 2010	2010	Molecular Profiles Limited	Collaborator	Regenerative Matrices for Orthopaedic Repair	Closed	31/03/2011	32934.	East Midlands
Developing Therapeutics 2010	2010	University College London	Collaborator	Regenerative Matrices for Orthopaedic Repair	Closed	31/03/2011	128737.	London
Developing Therapeutics 2010	2010	InterCytex	Lead	Towards the clinical examination of Allogeneic human dermal fibroblast therapy for scar contractures particularly in injured military service personnel	Closed	31/03/2011	78956.	North West
Developing Therapeutics 2010	2010	Selly Oak Hospital	Collaborator	Towards the clinical examination of Allogeneic human dermal fibroblast therapy for scar contractures particularly in injured military service personnel	Closed	31/03/2011	56100.	West Midlands
Developing Therapeutics 2010	2010	Livercyte Limited	Lead	Clinical use of CD34+ stem cells to treat acute liver failure	Closed	30/04/2011	162500.	London
Developing Therapeutics 2010	2010	Lab2Launch	Collaborator	Clinical use of CD34+ stem cells to treat acute liver failure	Closed	30/04/2011	29000.	Scotland
Developing Therapeutics 2010	2010	Neotherix Limited	Lead	EktoTherix: translation from R&D of a regenerative tissue scaffold for repair of surgical excision wounds	Closed	31/03/2011	116558.	Yorkshire & Humberside
Developing Therapeutics 2010	2010	Lorien Engineering Solutions Limited	Collaborator	EktoTherix: translation from R&D of a regenerative tissue	Closed	31/03/2011	21000.	West Midlands

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				scaffold for repair of surgical excision wounds				
Developing Therapeutics 2010	2010	Matrix Knowledge Group	Collaborator	EktoTherix: translation from R&D of a regenerative tissue scaffold for repair of surgical excision wounds	Closed	31/03/2011	17500.	London
Developing Therapeutics 2010	2010	Smith & Nephew UK Limited	Collaborator	EktoTherix: translation from R&D of a regenerative tissue scaffold for repair of surgical excision wounds	Closed	31/03/2011	17500.	London
Developing Therapeutics 2010	2010	Roslin Cells Limited	Lead	Clinical translation of endothelial cells derived from human embryonic stem cells	Closed	31/03/2011	103000.	Scotland
Developing Therapeutics 2010	2010	University of Glasgow	Collaborator	Clinical translation of endothelial cells derived from human embryonic stem cells	Closed	31/03/2011	55991.	Scotland
Developing Therapeutics 2010	2010	Altrika Limited	Lead	Development of a combinatorial Smart Matrix pro-angiogenic scaffold with micro-structured silicone backing for full-thickness skin reconstruction	Closed	31/03/2011	22500.	Scotland
Developing Therapeutics 2010	2010	RAFT Institute	Collaborator	Development of a combinatorial Smart Matrix pro-angiogenic scaffold with micro-	Closed	31/03/2011	92476.	South East

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				structured silicone backing for full-thickness skin reconstruction				
Developing Therapeutics 2010	2010	University of Cardiff	Collaborator	Development of a combinatorial Smart Matrix pro-angiogenic scaffold with micro-structured silicone backing for full-thickness skin reconstruction	Closed	31/03/2011	38000.	Wales
Developing Therapeutics 2010	2010	AedStem Limited	Lead	Pre-clinical development of a novel technology to improve the cost-effectiveness and clinical uptake of cell-based cartilage repair therapies	Closed	31/03/2011	21000.	North East
Developing Therapeutics 2010	2010	University of Leeds	Collaborator	Pre-clinical development of a novel technology to improve the cost-effectiveness and clinical uptake of cell-based cartilage repair therapies	Closed	31/03/2011	15000.	Yorkshire & Humberside
Developing Therapeutics 2010	2010	Cell Medica Limited	Lead	Adenovirus-specific paediatric immune reconstitution (ASPIRE)	Closed	31/03/2011	76239.	London
Developing Therapeutics 2010	2010	University College London	Collaborator	Adenovirus-specific paediatric immune reconstitution (ASPIRE)	Closed	31/03/2011	90568.	London

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Developing Therapeutics 2011	2011	The Automation Partnership (Cambridge) Limited	Lead	RAFT: Corneal Stem Cells - First in Man Safety Study	Live	31/03/2015	159540.	East Midlands
Developing Therapeutics 2011	2011	University College London	Collaborator	RAFT: Corneal Stem Cells - First in Man Safety Study	Live	31/03/2015	365977.	London
Developing Therapeutics 2011	2011	Neotherix Limited	Lead	EktoTherix: Initial clinical evaluation of a regenerative tissue scaffold for repair of surgical excision wounds	Live	30/09/2013	137870.	Yorkshire & Humberside
Developing Therapeutics 2011	2011	Lorien Engineering Solutions Limited	Collaborator	EktoTherix: Initial clinical evaluation of a regenerative tissue scaffold for repair of surgical excision wounds	Live	30/09/2013	43158.	West Midlands
Developing Therapeutics 2011	2011	Smith & Nephew Medical Limited	Collaborator	EktoTherix: Initial clinical evaluation of a regenerative tissue scaffold for repair of surgical excision wounds	Live	30/09/2013	26210.	North East
Developing Therapeutics 2011	2011	Cell Medica Limited	Lead	Phase I/II study investigating safety and efficacy of adenovirus-specific T-cells given to high-risk paediatric patients post-HSCT to treat reactivation of ADV	Live	28/02/2015	334069.	London
Developing Therapeutics 2011	2011	University College London	Collaborator	Phase I/II study investigating safety and efficacy of adenovirus-specific T-cells given to	Live	28/02/2015	327730.	London

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				high-risk paediatric patients post-HSCT to treat reactivation of ADV				
Tools and Technologies 2010	2010	Plasticell Limited	Lead	Lineage-specific hES reporter lines for combinatorial highthroughput screening	Closed	31/03/2011	57480.	London
Tools and Technologies 2010	2010	Sigma-Aldrich Company Limited	Collaborator	Lineage-specific hES reporter lines for combinatorial highthroughput screening	Closed	31/03/2011	38550.	South West
Tools and Technologies 2010	2010	Queen Mary University of London	Collaborator	Lineage-specific hES reporter lines for combinatorial highthroughput screening	Closed	31/03/2011	23679.	London
Tools and Technologies 2010	2010	InterCytex	Lead	New clinically compatible system for hESc derivations	Closed	31/03/2011	58000.	North West
Tools and Technologies 2010	2010	University of Manchester	Collaborator	New clinically compatible system for hESc derivations	Closed	31/03/2011	49294.	North West
Tools and Technologies 2010	2010	Lonza Biologics Public Limited Company	Lead	Clinical Cell Purification using Antibody Drug Conjugates - Feasibility Study	Closed	31/03/2011	15000.	South East
Tools and Technologies 2010	2010	University College London	Collaborator	Clinical Cell Purification using Antibody Drug Conjugates - Feasibility Study	Closed	31/03/2011	134982.	London

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Tools and Technologies 2010	2010	Asymptote Limited	Lead	Cryopreservation platform for clinical delivery of regenerative medicine therapeutics	Closed	31/03/2011	86963.	East Midlands
Tools and Technologies 2010	2010	University College London	Collaborator	Cryopreservation platform for clinical delivery of regenerative medicine therapeutics	Closed	31/03/2011	27000.	London
Tools and Technologies 2010	2010	University of Manchester	Collaborator	Cryopreservation platform for clinical delivery of regenerative medicine therapeutics	Closed	31/03/2011	21766.	North West
Tools and Technologies 2010	2010	Clinimed Limited	Lead	Reporter Tissue Engineering Scaffold for Wound Healing	Closed	31/03/2011	30939.	South East
Tools and Technologies 2010	2010	University of Brighton	Collaborator	Reporter Tissue Engineering Scaffold for Wound Healing	Closed	31/03/2011	98251.	South East
Tools and Technologies 2010	2010	Orla Protein Technologies Limited	Lead	GMP substrates for culture & derivation of clinical grade hESC cells	Closed	31/03/2011	65000.	North East
Tools and Technologies 2010	2010	Health Protection Agency	Collaborator	GMP substrates for culture & derivation of clinical grade hESC cells	Closed	31/03/2011	35000.	East of England
Tools and Technologies 2010	2010	Newcastle University	Collaborator	GMP substrates for culture & derivation of clinical grade hESC cells	Closed	31/03/2011	37634.	North East
Tools and Technologies 2010	2010	ImmunoSolv Limited	Lead	Improving Quality of storage and supply of therapeutic cells through dead-cell removal	Closed	31/03/2011	81894.	Scotland

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Tools and Technologies 2010	2010	Lab2Launch	Collaborator	Improving Quality of storage and supply of therapeutic cells through dead-cell removal	Closed	31/03/2011	35628.	Scotland
Tools and Technologies 2010	2010	Altrika Limited	Lead	Cell labelling for in vivo use and in-process quality control	Closed	31/03/2011	39470.	Scotland
Tools and Technologies 2010	2010	University of Edinburgh	Collaborator	Cell labelling for in vivo use and in-process quality control	Closed	31/03/2011	48263.	Scotland
Tools and Technologies 2010	2010	Pharmidex Pharmaceutical Services	Lead	Development of new generation biofunctionalised nerve conduits	Closed	31/03/2011	87900.	London
Tools and Technologies 2010	2010	University College London	Collaborator	Development of new generation biofunctionalised nerve conduits	Closed	31/03/2011	53106.	London
Tools and Technologies 2010	2010	Zyoxel Limited	Lead	3D Human Neuronal Tissue Model for the Safety Assessment of Stem Cell Therapies	Closed	31/03/2011	75480.	East of England
Tools and Technologies 2010	2010	Aston University	Collaborator	3D Human Neuronal Tissue Model for the Safety Assessment of Stem Cell Therapies	Closed	31/03/2011	68500.	West Midlands
Tools and Technologies 2010	2010	Domainex	Lead	Novel assays and platforms for testing and controlling regenerative medicine products	Closed	31/03/2011	102060.	London

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Tools and Technologies 2010	2010	Sigma-Aldrich Company Limited	Collaborator	Novel assays and platforms for testing and controlling regenerative medicine products	Closed	31/03/2011	43987.	South West
Tools and Technologies 2010	2010	Avanticell Science Limited	Lead	Preclinical control of stem cells using functionalised self-assembling hydrogels	Closed	31/03/2011	50905.	Scotland
Tools and Technologies 2010	2010	University of Brighton	Collaborator	Preclinical control of stem cells using functionalised self-assembling hydrogels	Closed	31/03/2011	89202.	South East
Tools and Technologies 2011	2011	Plasticell Limited	Lead	High Throughput Platform for the Discovery of GMP Compatible Stem Cell Manufacturing Protocols	Live	31/12/2014	407241.	London
Tools and Technologies 2011	2011	Cell Guidance Systems Limited	Collaborator	High Throughput Platform for the Discovery of GMP Compatible Stem Cell Manufacturing Protocols	Live	31/12/2014	99409.	East Midlands
Tools and Technologies 2011	2011	LGC Limited	Collaborator	High Throughput Platform for the Discovery of GMP Compatible Stem Cell Manufacturing Protocols	Live	31/12/2014	68644.	South East
Tools and Technologies 2011	2011	NHS Blood and Transplant (NHSBT)	Collaborator	High Throughput Platform for the Discovery of GMP Compatible Stem Cell Manufacturing Protocols	Live	31/12/2014	161224.	London
Tools and Technologies 2011	2011	Stabilitech Limited	Lead	Enhanced Cell Stability during manufacture and administration	Live	31/05/2014	44000.	London
Tools and Technologies 2011	2011	University College	Collaborator	Enhanced Cell Stability	Live	31/05/2014	261724.	London

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2011		London		during manufacture and administration				
Tools and Technologies 2011	2011	Altrika Limited	Lead	Cell labelling for in vivo use and in process quality control	Live	31/01/2015	186248.	Scotland
Tools and Technologies 2011	2011	University of Edinburgh	Collaborator	Cell labelling for in vivo use and in process quality control	Live	31/01/2015	51108.	Scotland
Tools and Technologies 2011	2011	Roslin Cellab	Collaborator	Cell labelling for in vivo use and in process quality control	Live	31/01/2015	52435.	Scotland
Tools and Technologies 2011	2011	Queen Mary University of London	Collaborator	Cell labelling for in vivo use and in process quality control	Live	31/01/2015	162282.	London
Tools and Technologies 2011	2011	Lonza Biologics Public Limited Company	Lead	CPrep - Closed point-of-care-Preparation Device	Live	28/02/2015	226875.	South East
Tools and Technologies 2011	2011	eXmoor Pharma Concepts Limited	Collaborator	CPrep - Closed point-of-care-Preparation Device	Live	28/02/2015	313200.	South East
Tools and Technologies 2011	2011	Amercare Limited	Collaborator	CPrep - Closed point-of-care-Preparation Device	Live	28/02/2015	134007.	South East
Tools and Technologies 2011	2011	Asymptote Limited	Lead	Development of a GMP cryogenic cold chain for clinical delivery of regenerative medicine therapeutics	Live	31/03/2015	447282.	East Midlands
Tools and Technologies 2011	2011	InterCytex	Lead	Expandable Clinical Grade Human Feeder Cells for hESc Derivation	Live	31/03/2014	119937.	North West

TiGenix NV – Written evidence

1. TiGenix NV (NYSE Euronext: TIG) is a leading European cell therapy company with a commercial product and an advanced clinical stage pipeline of adult stem cell programs.

The company's lead product, ChondroCelect®, for cartilage repair in the knee, is the first and only approved cell-based product in Europe, and is currently being launched in different European countries.

TiGenix's stem cell programs are based on a validated platform of allogeneic expanded adipose-derived stem cells (eASCs) targeting autoimmune and inflammatory diseases. Built on solid pre-clinical and CMC packages, they are being developed in close consultation with the European Medicines Agency. The company has initiated a Phase III clinical trial in complex perianal fistulas in patients with Crohn's disease, is conducting a Phase IIa trial in rheumatoid arthritis, and successfully concluded a Phase I trial to investigate the potential of intra-lymphatic administration of eASCs for autoimmune disorders.

TiGenix is based out of Leuven (Belgium), and has operations in Madrid (Spain), and Sittard-Geleen (the Netherlands).

The Committee invites submissions on the following points, with practical examples where possible (please only answer the questions of relevance to you):

The research base

- *How does the UK rank internationally in the scientific field of regenerative medicine?*
- N/A
- *Where does the UK have strengths and weaknesses in the field?*
- N/A
- *Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?* N/A

Application of the science

- *Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?*
2. ChondroCelect gained its central market authorisation as an ATMP (Advanced Therapy Medicinal Product) in October 2009 and as such has been available for prescription in the UK and EU since then. The ATMP regulation (EU: 1394/2007) came into force on 30th December 2008 and decreed that any ATMP product on the (local) markets prior to this date must have submitted and received a Central Marketing Authorisation from EMA (European Medicines Agency) by the end of 2011 for gene or somatic cell therapies) and the end of 2012 for tissue-engineered products. Non-compliant products would have to remove themselves from the market. To date ChondroCelect is the only product that has been granted such a marketing authorisation (gene product Glybera might be the second one having a positive Opinion from CHMP), and is indicated for the “Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults.” (Summary of Product Characteristics).

3. ChondroCelect is only used within a surgical in-patient setting, and as such can only be prescribed by a qualified, trained, certified orthopaedic surgeon.

4. Patient Access to Therapy

Access to CCI (Characterised Chondrocyte Implantation) with ChondroCelect for an NHS patient and for one who is covered by private medical insurance is in stark contrast. Since the product availability at the end of 2009, five (5) patients have been sanctioned for CCI using ChondroCelect on the NHS via the “Pass-Through Payment Mechanism” (since evolved to “Innovations Payment Mechanism”) from Sandwell and South Birmingham PCTs. See later paragraph on Barriers to Commercialisation for further details on Patient Access in the NHS. Patient Access for those covered by Private Medical Insurance is markedly different. Two of the largest Private Medical Insurers are now routinely authorising appropriately indicated patients for CCI with ChondroCelect, and to date all privately insured patients have been covered by their PMI (Private Medical Insurance) provider for CCI therapy when appropriately indicated, using a Single Case Decision methodology.

- *What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?*

5. Taking Rheumatoid Arthritis as a concrete example, we have moved from symptomatic treatment (of pain and inflammation) with PHARMACEUTICALS to disease-progression control with BIOLOGICALS. The next big step to advance therapeutic excellence would be to cure/ repair through REGENERATIVE MEDICINE. Today, regenerative medicine in general might be at a point where biologicals (biotech products) have been 20 years ago: considering development and commercialization challenges, they can be considered now at a critical turning that will determine their future course. With some first products available in some markets, from a “big picture perspective” we would expect within the next 5-10 years in defined areas substantial proof-of-principle that regenerative medicine can deliver on its high expectations and substantially advance public health.

Barriers to translation

- *Are the actions outlined in the Government’s Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board’s Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:*
 - *What difficulties are encountered when conducting clinical trials and how could these be overcome? N/A*
 - *What other difficulties are encountered conducting translational research within the NHS and how could these be overcome? N/A*
 - *What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?*

6. Further to the answer above and below, there are no longer barriers to approval in private healthcare. For the NHS the major barrier is the inappropriate use of an existing NICE Guidance (TAG89) by PCTs as a reason to not fund CCI. In 2000 NICE

conducted a HTA (TA16) on ACI (Autologous Chondrocyte Implantation) which was subsequently reviewed in 2005 (TA89). CCI with ChondroCelect was not included in either the original HTA or the subsequent review. NICE currently do not intend to conduct a HTA on CCI with ChondroCelect rather preferring to wait until two other trials for RM products within a similar therapeutic area report next year. This means that the earliest possible guidance that could be issued would be in 2014, with an estimated NHS impact in 2015. In the meantime patients are still presenting with an unmet clinical need (estimated to be in the region of 1250 per year), and the suggestion from Andrew Dillon of NICE is that PCT/CCG's should assess whether to provide access to therapy or not by investigating the business case at a PCT level. For the moment PCT/CCG's are seemingly unwilling to use the Innovation Payment Mechanism to fund individual patients for therapy, although interestingly the Joint Medical Command is providing patient access to CCI with ChondroCelect for Military patients.

There is therefore a total absence of equality amongst the UK population in terms of an individual's ability to be treated with an approved medicinal product for its licensed indication: Privately Insured and Military patients can gain access, whereas seemingly an NHS patient cannot.

Barriers to commercialisation

- *What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?* No insight.
 - *Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?*
 - o *What role does patenting play in the commercial development of regenerative treatments?* N/A
 - o *What business models are most appropriate to support the development of regenerative treatments?* N/A
 - o *What are the barriers to securing finance to develop such treatments?*
7. Due to the lack of a national reimbursement mechanism, there is uncertainty as to NHS adoption, and therefore return on investment. Additionally there is an uncertain regulatory framework.
- Hospital exemption in Europe (See below)
 - Specials scheme in UK

The specials scheme appears as an eventual back-door for "non routine"/hospital exempted ATMPs in UK (for specials more degrees of freedom in interpretation, no real guidelines on how to evaluate 'non routine' delivery and importantly enough possibility to import which conflicts with the lack of import that the hospital exempted products allow.

o *Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?*

8. No. The current HRG system and annual budgeting constraints of the PCT/CCGs does not allow sufficient flexibility to make the upfront investment required for a disruptive innovative technology whose cost-effectiveness is only realised many years in the future. For as long as PCT/CCG's are challenged with balancing an annual budget, then it will prove to be extremely difficult for them to make the - sometimes large - additional

spend on a therapy which is potentially curative as opposed to palliative. The current reimbursement system within the NHS is ill-equipped to cope with the introduction of Regenerative Medicine Therapies.

o *What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?*

9. As per answer above, in a market where there is no national reimbursement, it is difficult to “sell” the ROI model to potential investors when routine patient access to such technologies does not follow. Until the NHS is funded in such a way as to support patient access to cost-effective technologies whose upfront cost is significantly higher than existing therapies, but where their cost-effectiveness is only demonstrated in future years, then the development of the Regenerative Medicine Industry in the UK is under threat. The barrier to the development of the UK RM Industry is not so much product/technology development capabilities, but rather patient access to those RM therapies once they have been developed, and subsequently gained commercial approval.

International comparisons

- *What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?*

10. Belgium and the Netherlands, for example, have taken the lead to provide market access of a regenerative medicine product like ChondroCelect. In close collaboration between the manufacturer, payers and medical providers/ organizations (here: orthopaedic societies) precise treatment algorithms and patient target profiles have been institutionalised – to ensure a controlled introduction into the markets. In line with this spirit, the manufacturer has committed itself to tightly monitor the clinical effectiveness (e.g. in a registry and will report regularly on progress to the concerned authorities) as well as offering a risk-share program. On the other side, appropriate prices have been granted to allow the company to achieve a return of its significant investment, development risk and maintain the supply of a product that comes with substantial cost-of-goods.

- o Overall, the framework of development and commercialization is driven by
 - close cooperation between the key players
 - control
 - the intent that (only) the right patient receives the right therapy
- *How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK? N/A*
- *Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?*

11. With respect to the called “Hospital Exemption (HE)” - outlined in article 28 of the European Regulation for ATMPs 1394/2007, which provides for the implementation of national procedures and control measures to regulate the manufacturing and use of certain non-routinely produced Advanced Therapy Medicinal Products (ATMPs) - an harmonized and transparent implementation is crucial to bring more innovative, effective and safe therapies to all European patients.

12. HE is appreciated as a mean to offer individual patients a treatment with a customized, innovative and safe product, particularly when a disease occurs so rarely that the regular development and validation of the required therapy is not feasible. However, the inconsistent implementation of the HE in the Member States (MS) and routine preparations of treatments under an exemption might impede the development of new safe and effective treatments. An harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients. It is in the best interest of patients to limit Hospital Exemptions to non-routine preparations of treatments based on article 28 of European Regulation 1394/2007 under all applicable safety and quality rules. Furthermore, HEs should no longer be allowed when a fully validated, centrally approved ATMP is available. At this moment, there is no European-wide legal certainty on this point. The development of advanced therapies for patients requires large investments in time and money that cannot be done without legislation that offers a clear regulatory situation assuring fair and beneficial market conditions for new therapies.
13. It is especially important to note that misuse of the HE might limit the market size and the potential return on investment for future, centrally approved products. Use of the HE might therefore make it unaffordable to develop a centrally approved product. This means that certain advanced therapies will only remain available for a limited number of patients in a MS. These local therapies will not be tested for safety and efficacy the same way centrally approved therapies are tested. Furthermore, these local therapies will not become available for all European patients. It is therefore crucial for the development of new advanced therapies that the European Regulation is correctly implemented in all of the MS, so companies can count on a transparent and harmonized use of the HE in the Europe Union without unwanted and unfair competition, with the aim to benefit all eligible patients in Europe.
14. The implementation of article 28 requires national policy to accommodate the existing national and local healthcare specificities in each MS. However, these national policies have to fit within the boundaries set by Regulation 1394/2007. National policies should also foster innovation according to the intentions formalized in the ATMP Regulation. In other words, national policies should help foster the development of new and safe ATMPs with approval by EMA, while allowing for strictly non-routine treatments for individual patients.
15. In a number of countries, the eligibility criteria for the HE are applied liberally, while the exempted products do not have to adhere to the same standards as EMA approved products. This situation undermines the effectiveness of the central ATMP Regulation to ensure the quality, safety and efficacy of advanced therapy medicinal products. Allowing parallel circuits of nationally exempted products with lower standards also presents a barrier for the development of non-exempted products by causing unfair competition.
16. Article 28 of the Regulation was published in November 2007. The implementation of the Regulation into national legislation is ongoing since then. Quite a few MS are still developing the required national framework. A first screening of the existing national / guidelines and legislation shows a lack of legal clarity on the interpretation of the criteria in Article 28, resulting in very different interpretations of the

Regulation by stakeholders and by MS as well as large differences in the national implementation of the Regulation. Terminology such as ‘preparation on a non-routine basis’ used in the ATMP Regulation leaves room for different interpretations. An EU-wide harmonization of the definitions and criteria is needed to remedy the problem.

17. In conclusion, an harmonized and transparent implementation based on article 28 of European Regulation 1394/2007 is crucial to bring more innovative, effective and safe therapies to all European patients. It is in the best interest of patients to limit HEs to non-routine preparations of treatments under all applicable safety and quality rules. Furthermore, HEs should no longer be allowed when a fully validated, centrally approved ATMP is available.

- *What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas? N/A*

20 September 2012

TiGenix NV, Bupa Health and Wellbeing UK and National Institute for Health and Clinical Excellence (NICE) – Oral evidence (QQ 214-243)

TiGenix NV, Bupa Health and Wellbeing UK and National Institute for Health and Clinical Excellence (NICE) – Oral evidence (QQ 214-243)

[Transcript to be found under National Institute for Health and Clinical Excellence \(NICE\)](#)

Tissue Regenix Group plc – Written evidence

1. Introduction to Tissue Regenix

Tissue Regenix is a regenerative medical devices company. It was incorporated in May 2006 to commercialise the ten years of academic research of Professor Eileen Ingham and Professor John Fisher from the University of Leeds in the field of tissue decellularisation, (the reduction of soft tissue into a biological scaffold).

1.1 Our dCELL® Technology comprises a patented process which removes cells and other components from animal and human tissue allowing it to be used without anti-rejection drugs to replace worn out or diseased body parts. The unique feature about the Tissue Regenix biological scaffold is that it has the architecture of natural tissue and so that provides the right environment for the cells to regenerate.

1.2 The potential applications of this process are diverse and address many critical clinical needs such as vascular disease, heart valve replacement and knee repair. Our process can be applied to soft tissue repair in any part of the body so the potential market is enormous. This is truly a platform technology.

1.3 Our technology is already in use clinically and we have a pipeline of products to address significant medical market opportunities.

1.4 Tissue Regenix received European approval in August 2010 for its first product, a vascular patch, which replaces tissue removed during a procedure to unblock leg vessels, and the company is in the process of obtaining U.S. clearance. We have a growing bank of clinical trial data that will allow us to commercialise some of these products in the next 12 months.

1.5 We have a partnership with NHSBT. NHSBT has the right to carry out pre-clinical and clinical evaluations using Tissue Regenix's dCELL® technology for development purposes and the manufacture of human tissue derived clinical products for use by the NHS. Tissue Regenix will be able to fast-track clinical evaluations of additional human tissue applications using NHSBT's development capacity and clinical network. Tissue Regenix has the exclusive commercialisation rights to all data generated from the NHSBT trials.

1.6 We also have a commercialisation and IP agreement with one of our long term clinical collaborators, the Pontifical Catholic University of Parana (PUCPR), Brazil, and Professor Francisco da Costa. Under the terms of the agreement Tissue Regenix obtains exclusive worldwide commercialisation rights (excluding Brazil) to all data generated from over eight years clinical use of decellularised human donor heart valves as heart valve replacements.

1.7 The company joined the Alternative Investment Market in August 2010 and at the end of 2011 successfully raised £25m through a share placing that is being used to invest in further research and development. Major shareholders include: Invesco; ORA Capital Partners, the Northern Entrepreneurs Fund; the University of Leeds and IP Venture Fund.

1.8 We believe that as a company that: is built on world-leading research from a British university; is partnering with the National Health Service to trial and commercialise its

products so that they can not only help patients with long-term conditions faster but also save the NHS and the taxpayer money and bring them to a world market with benefits to UK plc exemplifies what the Government's *Strategy for UK Life Sciences* is trying to achieve.

2. The research base

2.1 The UK is the European leader in investment in university regenerative medicine research and start-ups, second only to the US in terms of the number of patents registered and businesses launched worldwide.

2.2 Currently the UK Government, through the research councils, and charities are the major funders of research. In the current climate it is very difficult for university spin-outs to obtain funding at seed, Series A and B stages. The only significant funders at this stage are Imperial Innovations and IP Group.

2.3 Concern has also been expressed that funding appears to be focused on universities and centres in the South-East of England. Our own experience demonstrates that there is leading edge research taking place within the N8 Research Partnership - a collaboration of the eight most research intensive universities in the North of England: Durham, Lancaster, Leeds, Liverpool, Manchester, Newcastle, Sheffield and York.

2.4 It is only at the later stages that private equity companies are willing to consider investment and given the funding climate currently naturally they are risk-adverse. However this is where regenerative medicine companies like ourselves do have an advantage as it is a lower risk, lower cost and more predictable business model than, for example, a biotech business. This is why Tissue Regenix has been able to attract funding even in the current downturn.

2.5 The building of the Francis Crick Institute to create a research hub is to be applauded but it is a consortium of Government, academia, the MRC and charities. Currently it does not appear to be seen as a UK equivalent of the German Fraunhofer-Gesellschaft, whose € 1.8 billion annual research budget is made up of €1.5 billion generated through contract research. How will industry be involved in the Institute's work? What it should be is an academic-industrial complex but will it be?

3. Application of the science

3.1 The system of academic preferment in the UK is based principally on the publication of peer-reviewed research papers. Academics are not given credit for the commercial application of that research. This should not be the case particularly as academic institutions do receive income from licensing or equity participation. We understand that universities quite rightly cherish their independence and it is this objectivity that the commercial sector values but successful commercialisation reinforces the validity of the research and should be recognised in academic career development.

We applaud the Government's intention, set out in its report, *Investing in the UK Health and Life Sciences*,³¹⁶ to amend the way academics are appraised and make it easier for them to be involved in applied research. The report stated, "*academics will now be judged to a significant degree on the impact created by the translation of their work into social and economic benefit.*"³¹⁷

³¹⁶ Investing in UK Health and Life Sciences, HM Government, 5TH December 2011.

³¹⁷ Investing in UK Health and Life Sciences, HM Government, 5TH December 201, page 5.

It goes on to say that industry will be included “*in the panel that makes those decisions.*”³¹⁸ We would have to say that we have not been approached to participate in such panels or to comment on the judging criteria.

It is well-known that there is a chronic shortage of human donors. The total number of people registered on the Organ Donor Register was 18,693,549 – or or 30% of the population – by the end of March 2012 but despite this three people die every week waiting for transplants.³¹⁹

3.2 The chronic shortage of human donor organs has led clinicians to seek alternative sources of tissue that can be safely and effectively used to replace diseased or dysfunctional human body parts. This coupled with the established fact that people are living longer and demanding better quality of life over that period is driving the growth of regenerative medicine. Typically people think of stem cells when they consider regenerative medicine, however, there are significant challenges associated with their routine use in the clinical setting as well as the expense involved.

3.3 Tissue Regenix believes that the markets with the biggest potential and consequently significant savings for the NHS are: Advanced Woundcare (e.g. decellularised dermis); Cardiac (e.g. heart valves); and Orthopaedics (e.g. meniscus). For example, the removal of damaged meniscus tissue is the most common orthopaedic procedure in the U.S. and is a contributory factor to the early onset of osteoarthritis. Peel Hunt, the broking and advisory house, estimates the size of the replacement meniscus market globally at \$3 billion.

3.4 There is significant competition in the US, where LifeCell and Integra have established a dominant position in their respective fields. However, in Europe the market is still largely undeveloped, with limited penetration of biologic patches against non-surgical patches, and even less penetration into the cardiac, vascular, woundcare and orthopaedic markets.³²⁰ Estimates put the size of the global woundcare market alone at \$13 billion.³²¹ We believe that regenerative medicine can provide treatments to conditions such as chronic leg ulcers from diabetes and provide heart valve replacements to younger patients suffering from cardiac disease who have to undergo multiple replacements during their lives as currently they can only be given mechanical heart valves. However we believe there are issues which have been recognised but still need to be tackled before those opportunities is realised.

³¹⁸ Investing in UK Health and Life Sciences, HM Government, 5TH December 2011, page 5.

³¹⁹ The Organ Donation and Transplantation Activity Report 2012.

³²⁰ Tissue Regenix, Peel Hunt, 3rd August 2011 i.

³²¹ Peel Hunt, citing Shire Pharmaceuticals, August 2011.

Figure 9: Biologic market in General Surgery

Source: Medtech Insights 2011

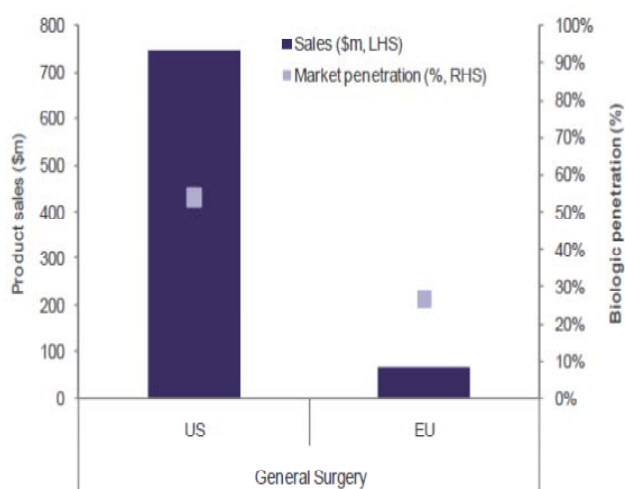
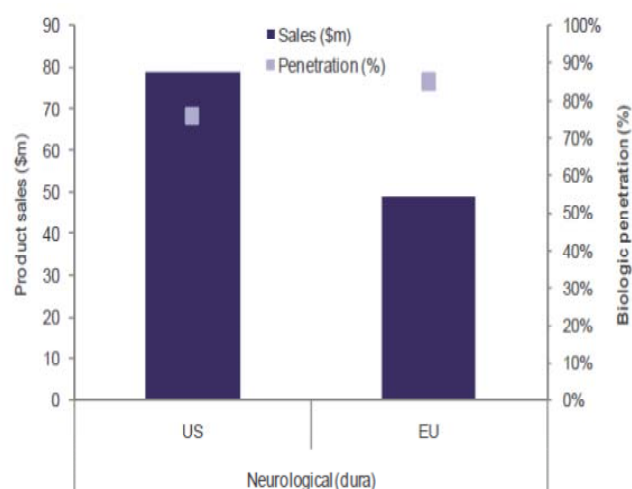


Figure 10: Biologic market in Neurosurgery

Source: Medtech Insights 2011



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4 Barriers to translation

4.1 This Government and organisations such as the MRC and the TSB have all identified the barriers and challenges to translating innovation into commercial reality. As we have mentioned earlier in this submission, Tissue Regenix has a partnership with NHSBT which has been recently expanded and extended. We are convinced that the Government's intention to "*place clinical research at the heart of the NHS*" is absolutely right and we are undertaking successful pre-clinical trials with the University Hospital of South Manchester and NHSBT. The National Institute for Health Research, (NIHR), was set up to, "*to create the best possible research environment in the NHS and build an international reputation for excellence in translational and applied research,*" a laudable aim but the multifarious levels of bureaucracy we, as a partner have, to be involved with is confusing and ultimately unproductive, wasteful of time and money and this is meant to be a streamlined process.

4.2 We draw the Committee's attention to the NIHR Innovation Pathway. We do not understand why so many groups, units and individuals have to be involved in negotiations and participate in decisions regarding trials? (see next page.)

³²² Size of the US/European Biologic general surgery and neurosurgery markets 2011, Meditech/Peel Hunt.



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4.3 We are currently attempting to set up a post-market trial with three NHS hospitals, (Leeds, Doncaster and Bedford), but we have to deal with three separate organisations. Surely there needs to be one body that we could negotiate with to secure the necessary consents?

4.4 The NHS's reliance on full economic costing means that when working with it on clinical trials it has to take the total overheads of the individual organisations into account rather than just the department that is undertaking the trial. This of course makes working with the NHS more expensive than going to another jurisdiction. There need to be tax breaks for undertaking clinical trials in this country; a simplified infrastructure to partner with and a lower cost or these trials will not take place within the NHS.

5 Barriers to commercialisation

5.1 The Government has introduced a preferential regime for profits arising from patents known as Patent Box. It appears to us that if you wish to preserve the Patent Box benefit and minimise the risk of the patent being revoked that patents which have a narrow scope will be more advantageous than patents of broad scope.

5.2 The Patent Box will also complicate how licences are drafted to ensure a clean separation between patent box eligible and ineligible income streams. Even so Patent Box will be helpful to companies at our stage of development but will do nothing to help early-stage pre-revenue companies.

³²³ NIHR website.

5.3 Traditional business models are not appropriate for early stage companies. It is very difficult to get outside investment pre-revenue and the technological challenges can mean that the cash-burn is very high. We believe that early-stage companies might find it beneficial to adopt a hybrid business model selling consultancy services as well developing their products. Early-stage companies have to demonstrate some kind of revenue stream or they will be unable to raise funding.

5.4 The Committee raised the issue of pricing structures for the use of treatments in the NHS. The truth is there aren't any pricing models. NICE reviewed Carticel, a stem cell treatment for cartilage repair and rejected it as too expensive despite the fact that this could provide better long term results than current treatment options and decrease the amount of knee surgery that takes place within the NHS which is predicted to increase by 20 per cent over the next 10 years and every knee replacement operation costs £7,600. The NHS is not able to capture the quality of data to generate pricing models. In our experience NHS trusts do not share data as they compete for resources in a cash-strapped system.

6 International comparisons

6.1 We have been impressed by the work of Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) and its SME Engagement Centre which helps SMEs define their technical issues and identify the best way to address them. It also licences public sector technology to commercial companies, helps build alliances domestically and internationally. It is very difficult for any SME in the UK to navigate around the various funders, public and private, regulatory organisations and academia. We believe a CSIRO-like organisation in the UK would be very valuable.³²⁴

6.2 The biggest market for regenerative medicine is the United States. The FDA requires more clinical analysis for non-pharmaceutical medical devices than European regulators and tissue products like those derived from our dCELL's scaffold are categorised as medical devices since they are implanted and not metabolised by the body. We continue to work towards the US approval of our first generation vascular patch, with a 510(k). Greater harmonisation of standards has been discussed for many years and would be desirable but has made little or no progress.

24 September 2012

³²⁴ CSIRO website, <http://www.csiro.au/Portals/Partner.aspx>.

Sir John Tooke, University College London (UCL), Professor Robin Ali, UCL and Professor Graham Lord, King's College London – Oral evidence (QQ 64-80)

Sir John Tooke, University College London (UCL), Professor Robin Ali, UCL and Professor Graham Lord, King's College London – Oral evidence (QQ 64-80)

[Transcript to be found under Professor Robin Ali, University College London](#)

UCB Pharma Ltd – Written evidence

Author: Dr Neil Weir, Vice President of Discovery, UCB Pharma Ltd

Executive summary

UCB is a global research led global biopharmaceuticals company. We have a significant scientific presence in the UK and base our principle immunology research in Slough, where we carry out early stage research into severe disease. We have already successfully commercialized drug treatments invented at our Slough research site and continue to invest in new treatments for Parkinson's, epilepsy, rheumatoid arthritis, lupus and osteoporosis, with around 400 scientist and research support staff through our research UK subsidiary UCB Celltech. To give context to this investment, UCB ranks in the top five pharmaceutical companies investing in the UK and is the largest EU inward investor into medical science.

This submission has been drafted for the House of Lords Science and Technology committee following their call for evidence into regenerative medicine. It will address the challenges of carrying out research in the UK and commercializing new, innovative treatments, in terms of pricing, access to the NHS and uptake by clinicians. UCB has significant experience of early stage research in the UK and has also been engaging with the translational research project team (TRP) to co-develop a novel treatment for severe lung disease. We have a significant level of academic and clinical joint projects, supporting a 30 strong PhD programme across the UK, which give us a very relevant perspective on the challenges facing scientific development.

The UK is one of the premier research environments in the world, with an established and successful university sector and a high level of science and education investment by government. However the UK is becoming less competitive as a result of increased bureaucracy and a lack of patient focus when prioritizing science investment. Great improvements have been brought about by the Office of Life Sciences in 2009, the Life Sciences Strategy in 2011 and the Innovation, Health and Wealth report, also in 2011. However a review of access to funding for all research led companies is necessary and better co-ordination between the different funding and regulatory bodies (MRC, TSB, TRP, NIHR, MHRA) is vital to keep the UK competitive.

Barriers to translation; what difficulties are encountered in conducting translational research within the NHS and how could these be overcome?

1. The NHS should be a world leading environment in which to carry out innovative early stage research, but it is falling behind other countries in terms of attractiveness and ease of working
2. This has been the subject of the **Life Sciences Strategy**, launched last year by the government, which looks to address the low level of early stage clinical research in the UK. We applaud the approach taken by government as part of this initiative; but

- UCB's experience has been that the implementation of policy has not matched the expectations at the time of launch of the strategy
3. One of the main vehicles for increasing the level of early stage translational research was the creation of the Translational Research Partnerships (TRP's). This initiative brings together the lead NHS hospital specialists in a defined disease area and allows access to specialist guidance and advice. The aim is to increase the level of technologies moving from proof of concept and the lab, to the first in human stage.
 4. We found the process helpful, however it reached an impasse when we needed to look at funding and support for ongoing commercialization. When we embarked on the discussions with the TRP group we had intended to jointly develop one of our compounds in an area of high unmet need in respiratory disease. We intended the lead hospital trust to become a partner and share the benefits of commercialization, as is common in many hospital and academic centers in the US. **The TRPs are a potential incubator for high level joint research between the pharmaceutical industry and the NHS.**
 5. The only mechanism open to our NHS partner to raise funding was the MRC grant system, which could take up to a year to secure approval; as a result we will no longer involve the NHS as a direct partner. It has been helpful for us to be involved with the TRP to validate and develop our thinking on the clinical aspects of the technology; however it has taken significant time and resource on behalf of both parties to reach this stage and it is frustrating to find that the block has become one of access to funding. **UCB asks that consideration is given to better alignment between the MRC, NIHR and TSB to allow funding based on the quality of the science and the potential for breakthrough in areas of unmet patient need rather than the size of the organization involved.**
 6. As part of the Life Sciences strategy a £180m fund was made available by government to support novel early research in the UK to act as an "incubator" fund. However this is not solely directed on a project basis and is restricted to smaller size companies (classified as SME's). Funding should be available to all companies on the basis of the quality of the scientific project; in addition there should be an alternative mechanism to allow NHS trusts and academic partners to rapidly access MRC funding for novel and innovative research projects in areas of high unmet patient need. The level of recent investment into BRUs and BRCs are boosting clinical trials infrastructure, but are still not providing a benefit over commercial CROs.
 7. By way of comparison, the Michael J Fox Foundation has launched a "rapid response innovation awards" programme which aims to support high-risk, high-rewards projects with little or no preliminary data, but with potential to significantly impact our understanding or treatment of Parkinson's disease. The programme aims for a funding decision in six weeks or less. We would ask that an element of the MRC / TSB programme is available for similar high risk high reward research projects on a rapid turnaround decision basis to bring research to the UK. Clinical trials approval in the UK still lags behind other countries, either because of resource limits or procedures, meaning that early stage work is less likely to be placed here.

Barriers to translation; what barriers are encountered when seeking approval for such treatments on the NHS?

1. There are several barriers to approval within the NHS and they cover three categories; cost effectiveness approval by NICE, payer planning arrangements, prescribing access and uptake.

2. **NICE cost effectiveness approval** typically will occur between six months pre-launch and one year post-launch of a new medicine. Although the dossier is developed and submitted to NICE in line with the marketing authorization, the NICE committee will not discuss the medicine in committee until marketing approval has been granted. As a result the minimum delay caused by the NICE committee will be three months. However more innovative medicines will frequently encounter significant delays due to the complexity of the treatment or the lack of familiarity of the clinical and health economic experts; the recent review of belimumab, a novel treatment for lupus by GlaxoSmithKline has taken over one year since the medicine gained approval and there is currently little sign of a resolution for this innovative medicine where there has been little clinical development for nearly forty years. It is likely that as the complexity of the treatment increases that NICE will take longer to make approval decisions, denying patients access to new, effective treatments
3. **Payer planning** is the process whereby access to funding is gained for new medicines from the PCT so that patients can be treated by hospital clinicians. Often this will take the form of implementing NICE guidance for new treatments that have been assessed as cost effective. In the absence of a NICE review (not all products will be reviewed by NICE, or they may be the subject of a later review as part of a Multiple Technology Appraisal) it will require an individual funding request (IFR) whereby a clinician must apply to the PCT for payment. If there is no agreement between the PCT and the treating hospital there will be no funding stream allocated. Again, as with NICE, if there has not been a process of work with the PCT prior to the marketing authorization, then the response of payers will be to “red light” a product and prevent it from being used in the NHS – regardless of the clinical merit of the treatment or the needs of the patient. This will also be the case even where the treatment is resource or cash sparing.
4. **Prescribing access and uptake** is a lengthy process that follows from payer planning. After funding has been identified with the PCT or commissioning body there are inevitably local protocols that will control which clinicians can use the treatment and how it will fit into a local hospital or regional formulary. Often even medicines that are approved by NICE will not be placed onto a formulary, or the formulary will place significant restrictions onto the access to a treatment. It is rare and unusual for a formulary to specify how a patient will access a treatment or therapy; only what products must be used beforehand. As a result patients will be maintained on failing or suboptimal therapies as there is little clarity about when patients move from an open to a newer, but more restricted, treatment.

Barriers to commercialisation; are the pricing structures for the use of such treatments on the NHS appropriate to support their development

1. The DoH is currently renegotiating the PPRS scheme in the UK and looking to introduce Value Based Pricing to control the cost of new medicines in the UK, so this area is subject to significant change. There are significant barriers to commercialization under the current scheme and we hope they will be resolved under the new VBP process.
2. The pricing barriers to commercialization occur firstly in obtaining a reasonable price compared with other EU markets, secondly in gaining a price that reflects the wider value of the medicine and finally in maintaining this price across the EU.
3. **Reasonable prices at launch** have become a significant challenge in the UK which has some of the lowest prices amongst the developed health economies. Routinely France, Germany, Italy and Spain will all allow higher prices for new, innovative

treatments. The UK, through the work of NICE and other agencies, places an up limit on the price that will be paid for a medicine that is often set without regard to patient need or the level of innovation brought by a new treatment. The most obvious manifestation of this challenge is the Cancer Drug Fund. Many of the most recent cancer treatments are freely available through social healthcare systems in Europe, but only available in the UK through the support of the cancer drugs fund which allows access to treatments that have been refused by NICE.

4. **Obtaining a price that reflects the wider value of medicine** is more challenging in the UK and the narrow definition of the benefit of a new medicine is one of the main reasons for refusal by NICE. A new technology will have benefits that go beyond the improvement of the health state of the patient, or the avoidance of other medical interventions, the current measure of cost effectiveness from NICE. In many cases – and particularly with regenerative medicines - there will be much wider societal benefits such as a return to work, or the avoidance of social care costs which in many chronic diseases can dwarf the direct NHS costs, particularly in diseases of the elderly like Alzheimers. Amgen/UCB are currently developing a treatment for osteoporosis which is an example of where pricing in the UK (as currently defined through NICE review) will not support the true value of the treatment as much of the cost from osteoporosis are managed in the social care sector rather than the NHS. We would be happy to submit a detailed case study that will outline more of the issues if this would prove valuable

25 September 2012

UK Regenerative Medicine Community – Written evidence

The UK Regenerative Medicine Community

The Community is a network of clinicians, basic and translational researchers, engineers, health economists, companies and other interested people that has grown over the last five years out of the UK National Stem Cell Network and through interdisciplinary collaboration on projects sponsored by the Research Councils, charities and the Technology Strategy Board. The Community is informal; individuals put their name to this submission in a personal capacity. Some individuals have also contributed to other submissions on behalf of their organisations.

The research base

How does the UK rank internationally in the scientific field of regenerative medicine?

As one of the scientific leaders in the field, the UK is well placed to begin to drive therapies through the clinic to widespread adoption. We are aware of two estimates that have been made. Research shows that the UK houses 15 of the 138 cell therapy companies worldwide, ranking the UK third in the world.³²⁵ According to data from the York SATSU-led EC REMEDiE programme (www.york.ac.uk/satsu/remedie/) the UK contributes substantially to the European cell therapy industry: eight cell therapy biotech companies are based in the UK of a total of 51 across the EU and the UK has almost a quarter (26) of all the regenerative medicine companies in Europe.

Academically, the UK is very strong with an average of 10 publications per million in habitants.³²⁶ Though this figure matches the performance in the US, the UK engages in twice as much collaborative research.³²⁷ We believe that interdisciplinary collaborative research is a key element in the successful development of cellular therapies.

Where does the UK have strengths and weaknesses in the field?

As mentioned above the UK has a strong research presence in Regenerative Medicine and an industry is emerging. It is important now that the well funded science is translated into clinical application; that regenerative medicines become widely available and adopted by the healthcare system.³²⁸ The constraints to this happening are a lack of translational funding, a strict regulatory environment and lack of penetration into the NHS.

Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

The major funders of regenerative medicine in the UK are the MRC, the Wellcome Trust and the Technology Strategy Board. Funding is also available from the EPSRC and the BBSRC. Disease-based charities, notably Arthritis Research UK and the British Heart Foundation are committing tens of millions of pounds to basic and translational research in

³²⁵ D Williams RA, A Dent, R. Archer: Building a viable regenerative medicine industry: a guide for stakeholders. Loughborough. (2010).

³²⁶ Luo J, Flynn JM, Solnick RE, Ecklund EH, Matthews KRW: International Stem Cell Collaboration: How Disparate Policies between the United States and the United Kingdom Impact Research. PLoS ONE 6(3), e17684 (2011).

³²⁷ *Ibid.*

³²⁸ Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

the field. Historically the regional development agencies made major investments in regenerative medicine, funding now lost to much of the UK. Traditionally funding has been available for basic science and engineering in addition to clinical application. However there is a need for more translational funding that combines the key features to move a therapy through clinical trials and make it commercially ready. The TSB funded Cell Therapy Catapult Centre hopes to bridge this gap, though the £10-30m funding provided annually by the Catapult Centre and its partners will be insufficient in itself.

Application of the science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

It has been identified that most cell therapies are clinician led, that is, they come out of academic clinical practice.³²⁹ It has also been identified that though there are many cell therapies in clinical trials (389),^{330,331} the time horizons to market approval are long. Based on evidence from Tigenix and Dendreon, clinical trial duration is twice as long as that for traditional medicines,³³² the limiting factor being the lack of both private and public funding available to take cell therapies quickly through clinical trials.

There are many cell therapies being developed internationally.³³³ The potential for cell therapies is large; some are disease specific, such as Reneuron's RN001 for stroke (www.reneuron.com) ; others such as Athersys' Multistem are developed to treat a range of diseases (www.athersys.com) . In the UK we have cell therapies in development for both orphan diseases (such as Epidermolysis Bullosa) and highly prevalent diseases such as coronary heart disease.

The cell therapy industry in the UK is not new. Genzymes Carticel has been available privately for over ten years (although the National Centre for Clinical Excellence (NICE) requires that the patient be enrolled in a clinical trial). NHS funded cell therapies include cadaveric islet transplantation, have been funded by the National Commissioning Group.

It is expected that, of the cell therapies in development in the UK, the majority would seek to be NHS funded.

What potential does regenerative medicine hold to treat disease in the next 5-10 years? What is the reality versus the headlines about what the science will deliver?

³²⁹ Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

³³⁰ *Ibid.*

³³¹ Note that while a figure in excess of 2500 trials in regenerative medicine is correct and often quoted, over 80% of these trials use blood stem cells to treat cancer, a regenerative therapy that has been available for 40 years.

³³² Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

³³³ Prestwich GD, Erickson IE, Zarembinski TI, West M, Tew WP: The translational imperative: Making cell therapy simple and effective. Acta Biomaterialia (0),

The future of regenerative medicine is hopeful. It is believed that over the next 10 years at least 7 cell therapies will reach the stage of market approval;³³⁴ unfortunately none of these are UK developed cell therapies. As cell therapies in the UK are regulated under EU legislation as advanced therapeutic medicinal products, the speed with which products can traverse the route to market is slow, hindered further by the lack of funding available.

That said, cell therapies will continue to enter later stage clinical trials and our understanding of the regulatory requirements will increase such that the process becomes shortened.

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: *Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

There remain very significant challenges.

In particular:

What difficulties are encountered when conducting clinical trials and how could these be overcome?

Until recently most clinical trials in regenerative medicine were exempt from MHRA oversight. The introduction of EU regulations defining Advanced Therapeutic Medicinal Products had the consequence that cell therapies manufactured locally, close to the clinic were immediately required to comply with MHRA regulations. This led to a delay of 2 years or more in clinical trials that had already been approved and funded. A positive outcome has been that there are now 12 MHRA accredited cell manufacturing centres (representing 47 processing suites) embedded close to the clinic in the UK.³³⁵ Despite the action promised in the government report 'Taking Stock of Regenerative Medicine in the UK' the regulatory burden for conducting clinical trials in the UK is still very high, there is deep concern that government budget constraints are going to lead to further delays in regulatory approval.³³⁶

What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

The very welcome changes in the Department of Health that resulted in the establishment of the National Institute of Health Research have much improved both the climate and resources for translational research. The research councils, in their strategy for UK Regenerative Medicine have also committed funding for translational research. It remains a challenge to engage consultants in the NHS in regenerative medicine; they remain the least well-connected and smallest part of the regenerative medicine community nationally. NIHR should ensure that its clinical research training schemes produce active practitioners in translational research in regenerative medicine

³³⁴ Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

³³⁵ *Ibid.*

³³⁶ Tooke J: A new pathway for the regulation and governance of health research. (2011). A report of the Academy of Medical Sciences.

What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

The Nicholson report 'Innovation Health and Wealth'³³⁷ acknowledged the high barriers to diffusion within the National Health Service which should indeed be the major route to adoption in the UK for Regenerative Medicine. The report recommends that we establish a more systematic delivery mechanism for diffusion and collaboration within the NHS. This remains a challenge. More positively the National Specialist Commissioning Group has been active in funding regenerative medicine for low prevalence indications nationwide, an example is the commissioning of islet transplantation therapy for severe type I diabetes. Local specialist commissioning groups had also indicated their willingness to fund regenerative medicine therapies, however there is now a hiatus as the commissioning arrangements within the health service are altered; it remains unclear whether these commissioning groups' willingness to consider funding regenerative therapies will carry through to the new commissioning body. It should also be noted that while private health insurers have proved willing to fund treatment with Tigenix's ChondroCelect (the first licensed ATMP in the EU), NHS commissioners seem unwilling to fund this treatment and NICE has yet to review its use. In our view, although some cell therapies may be offered privately the expertise and critical mass are insufficient for private healthcare to act as a route to proof of feasibility. The new National Commissioning Board should top slice and ring fence funding for regenerative therapies.

Barriers to commercialisation

What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

Using the ONS pharma figures and assuming an average of 20 employees per company, regenerative medicine and regenerative medicine related companies contribute around £150m of production and £80m GVA to the UK economy, that is around 1% of current production figures for UK pharma manufacturing and around 10% of the global cell therapy market. The argument for cellular therapies as a major benefit to the UK economy is based on three premises: substitution, comparative advantage and the indirect economic benefits of curative, compared to palliative, health care. Substitution: Global pharma is searching for a new business model. It is facing a patent cliff; costs of drug development are rising as new drug approval is falling. The UK is facing increased competition for investment from Pharma relative to far-eastern markets, including India and China: disinvestment in the UK is a severe threat, given the GVA and rents accruing to the UK from the pharma industry. Growth in cell therapies offers a strategy to substitute and safeguard high value jobs in the UK. Comparative advantage: the UK is losing its comparative advantage in pharma manufacturing, R&D and clinical trials, despite the resilience of UK pharma manufacturing, the very positive changes brought about by NIHR and the recent Government initiative to reduce regulatory barriers. The UK retains a comparative advantage in cellular therapies and is for the moment pre-eminent in Europe. Action to support regenerative medicine nationally will ensure that this comparative advantage is enhanced. Indirect economic benefits: These benefits accrue to patients wherever treated, so therapies developed, manufactured in the UK and exported will benefit economies globally. Nonetheless, the NHS in being an early adopter of cell therapies will give the UK an advantage in labour factor productivity, relative to its global competitors, through reduced levels of sickness absences.

³³⁷ DoH: Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS. (2011).

With appropriate action on regulation and NHS involvement/adoption the value of regenerative medicine activity can be increased ten-fold. On 2010 prices, this will increase production to £1.5bn, and generate £800m GVA. This will generate (or safeguard, given pharma contraction) 5000 highest value manufacturing jobs and deliver around £200m in economic rents, excluding terms of trade. This would substitute or enhance therapeutic (conventional pharma + cell therapies) GVA by around 10%. Looking solely at the National Account, ten-fold growth over ten years will yield 5000 jobs, and £800m GVA.

It is important to develop economic models that go beyond current health economics analyses, given the curative potential of cellular therapies. The Milken Institute calculates that the better treatment of chronic disease translates into a potential gain of 20% US GDP over 40 years, due 80% to productivity gains and amounting to 0.5% GDP growth pa (<http://www.milkeninstitute.org/>). CTs offer curative potential that may ultimately enhance GDP growth by perhaps 1-2% , an important consideration given the UK's forward demographic, where the decreasing working population's factor productivity must support an increasing retired population. 1% of UK GDP is £20bn.

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area?

The main challenge to companies in the regenerative medicine sector is to develop a viable business model. Thus not only is this sector a very high risk area for investment it is also very uncertain how any investment might ultimately recouped. The government has through NIHR, TSB and the research councils, made funds available to support proof of concept that may ultimately increase the currently small number of phase I/II trials but this alone will not solve the problem of the absence of a plausible business model for the sector.

If not what more should Government do?

The government should encourage co-development of regenerative medicine therapies in partnership with the NHS and commit to the adoption of cellular therapies funded through the NHS budget. Regenerative medicine offers the promise of reducing overall societal costs of care for chronic disease. It is important that the cost effectiveness of these long-term therapies are assessed not just on within year savings but on the lifetime savings that they will offer. NICE must play a key role in the development of economic models for the cost effectiveness of regenerative medicine.

What role does patenting play in the commercial development of regenerative treatments?

In our view regenerative therapies can be protected by knowhow, that is, the process developed to manufacture and administer the therapy, as regulatory barriers effectively operate as barriers to market entry. There is however a concern with patents as a threat: freedom to operate may be hampered and investors made cautious by the possibility of a patent infringement claim.

What business models are most appropriate to support the development of regenerative treatments?

The current standalone biopharma business models are, for the reasons we have given above, unlikely to succeed. Co-development of commercial therapies in partnership with the NHS together with a clear commitment from government to provide the resource and the route to adoption by the National Health Service is needed to attract the substantial

investment that will be required. The 2012 Health Act permits joint venture companies between NHS Trusts and commercial companies; this may be a promising route. However, the NHS does not have a strong track record of collaboration with private companies.

What are the barriers to securing finance to develop such treatments?

As we have stated the very high risk associated with investment in regenerative medicine and the long lead times to financial return as well as the absence of exemplary business models are the major barriers.

It is instructive to consider the example of Advanced Biohealing, a very successful regenerative medicine company. Advanced Biohealing was acquired by Shire for \$750million dollars in 2011; however total investment in the therapy that Shire ultimately acquired is likely to have been close to the sum paid by Shire. The product was developed by Advanced Tissue Sciences in the early 1990's; this company ceased trading in the late 2000s and Smith and Nephew who had acquired the product withdrew it from the market in 2006 for commercial reasons, selling it on to Advanced BioHealing (www.slideshare.net/SafeguardScientifics/abh-and-shire-panel-discussion) so that even this ultimate success represents a substantial loss of investment capital

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

Pricing structure for regenerative medicine treatments in the NHS are not yet well developed. This is a further source of uncertainty for companies and their investors. In general, current NHS pricing structures reflect within year savings. It is questionable whether this is appropriate for regenerative medicine therapies as these therapies will lead to cure rather than palliation and save many times their cost in future years' savings on palliative therapies that the patient no longer needs.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

In general, when clinicians lead or are very closely involved in developing a novel regenerative therapy, the therapy is developed paying close attention to existing clinical procedures.³³⁸ This is the case largely because the individual clinician does not have the means to alter markedly either the procedure or the clinical pathway. When companies develop novel regenerative therapies they pay close attention to manufacture but pay less attention to any changes in clinical procedures or clinical pathways, ignoring the fact that the customer is the health care provider and the end user is the clinician. Conversely, clinicians rarely consider the manufacturing challenges that arise from their potentially successful regenerative therapies. Both companies and clinicians are very sensitive to clinical need, but each ignores a key component of the procedure-product dimension. Ideally, if cellular therapies are to be readily adopted, clinical procedures and cellular products should be brought much closer together. There is evidence that some companies are considering means to deliver their regenerative medicine product using a clinical procedure, as half of the cellular products in company trials involve a clinical procedure. Nonetheless it remains a challenge to adapt these new procedures to the clinical pathway of treatment. Time to market for cellular therapies should be reduced markedly if clinicians think more about manufacturing and distribution and companies think more about minimizing disruptions to

³³⁸ Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

existing clinical pathways. This is most easily achieved if clinicians, health economists, and companies are speaking to one another from a very early point in the development of a cellular therapy.^{339,340}

In general, research and development is not high on NHS Trusts' Executive Boards' Agendas. Regenerative medicine offers the prospect of changing the demand curve for the NHS and so is of national importance. It needs to be placed alongside other major national NHS initiatives

International comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

The most successful examples of the development of regenerative therapies by companies have been in the US. In general, investment in biotech as a whole has been greater and has been more successful in the US than in the UK. There is a more robust attitude to risk from investors and a more focussed presentation to investors of the merits of a biotech product. This is illustrated by a war game style simulation that pitched British born executives and investors working in the states against their British born counterparts working in the UK.³⁴¹

There are currently 12 regenerative medicine products on the market in the US (Orcell (Ortec), Appligraf (Organogenesis), Allogeneic Hematologic Progenitor Cells (HemaCord), Provenge (Dendreon), Laviv (Fibrocell Technology), Carticel (Genzyme), Gintuit (Organogenesis), HPC (Clinimmune Labs), Dermagraft (Advanced Biohealing), Dermagraft T-C (Advanced Tissue Sciences), Epicel (Genzyme), Integra Artificial Skin (Integra Life Sciences)), we predict there will be a further 9 products in the clinic by 2022 (extrapolation of data from³⁴² and www.clinicaltrials.gov). There is also the observation that the US healthcare market is much less price sensitive than the NHS. An example being the company Dendreon whose product is priced at \$93,000 and prolongs the life of cancer patients for 6 weeks.

In our view, we cannot reproduce these conditions in the UK. However, the National Health Service is a huge asset and partnership between companies and the NHS can be turned to our advantage and enable us to develop a different, but equally successful business model.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

There is a lack of harmonisation of EU regulations at the operational level that leads to confusion amongst academic and commercial developers. This lack of regulatory harmonisation is leading to such insecurity within the field that commercial funding is only very sparsely available. As an example, ChondroCelect is the only licensed cellular

³³⁹ Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

³⁴⁰ Trounson A, Baum E, Gibbons D, Tekamp-Olson P: Developing a Case Study Model for Successful Translation of Stem Cell Therapies. Cell Stem Cell 6(6), 513-516 (2010).

³⁴¹ This means war. Nat Biotech 26(9), 954-954 (2008).

³⁴² Foley L, Whitaker M: Concise Review: Cell Therapies: The Route to Widespread Adoption. Stem Cells Translational Medicine 1(5), 438-447 (2012).

regenerative medicine in the EU but some member states are allowing hospitals to manufacture an unlicensed “biosimilar” in order to avoid the cost of the licensed alternative. More common is the problem of definition of these novel products. A regenerative therapy may not meet the definition of a medicine if it is “not substantially modified” and so be exempt from the ATMP regulations. EU member states are not obliged to accept EMA classifications as binding and this has already led to at least one product being regulated differently between member states in the EU.

Investors are citing this as sufficient regulatory uncertainty to refuse to invest in commercial trials which is a barrier to the development of UK SMEs.

Additionally, cell:device combinations are regulated as ATMPs in the EU but as medical devices in the US which greatly complicates the commercial development of this type of product (in Australia they are mostly deemed devices). The principal market is still seen to be in the US and data arising from EU-based trials as medicines are not directly transferrable to the FDA for approval as a medical device.

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

EU directives governing the use of regenerative medicines are intended to harmonise regulation across the EU but the degree of rigour with which this directive is implemented and enforced varies considerably from country to country (see above) with the UK MHRA being unusually diligent in this regard.³⁴³

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

UK citizens face substantial risk when travelling to some other countries for regenerative treatments. In other countries regenerative treatments are often not adequately supported by clinical research data to prove their safety and efficacy. This is a consequence of the lack of safeguards to protect their interests in some countries overseas. The International Society for Stem Cell Research has considered these matters carefully <http://www.isscr.org/ForThePublic.htm> and offers advice to those considering travelling overseas for treatment. It should be recognised that one clear reason that UK citizens seek regenerative medicine treatments overseas is that they are not available in the UK yet.

25 September 2012

Signatories

Affiliations are given but all sign in a personal capacity

Richard Daniel	Archer Brison	Managing Director Scientific Director	Two BC Ltd St Mary's Hospital, Manchester
Andrew Beining Aidan	Butters Chen Courtney	Director Reader in Medicinal Chemistry Chief Executive Officer	Frontline University of Sheffield Roslin Cells Ltd

³⁴³ Tooke J: A new pathway for the regulation and governance of health research. (2011). A report of the Academy of Medical Sciences.

UK Regenerative Medicine Community – Written evidence

Paul Anil	De Sousa Dhawan	Senior Research Fellow Director -Paediatric Liver GI Nutrition Centre Clinical Director-Child Health Joint CAG Lead, Child Health – King's Health Partners	University of Edinburgh King's College Hospital, London
Paul	Fairchild	Fellow of Trinity College Co-Director of the Oxford Stem Cell Institute	University of Oxford
Sian John Anthony	Harding Haycock Hollander	Professor of Cardiac Pharmacology Professor of Bioengineering Arthritis Research UK Professor of Rheumatology and Tissue Engineering Head of The School of Cellular and Molecular Medicine	Imperial College London University of Sheffield University of Bristol
James John	Huckle Hunt	Group Director Biologics and Spine Clinical Engineering (UK CTE)	Smith & Nephew Research UK BioTEC University of Liverpool
Hugh Sue	Ilyine Kimber	Managing Director Professor of Stem Cells and Development	Ilyine Ltd University of Manchester
Sheila Andrew Patricia	MacNeil McCaskie Murray	Professor of Tissue Engineering Professor of Orthopaedic Surgery Lecturer in Stem Cell and Developmental Biology	University of Sheffield Newcastle University University of Liverpool
David Richard	Newble Oreffo	CEO Chair in Musculoskeletal Science & Associate Dean International and Enterprise, Faculty of Medicine	TAP Biosystems University of Southampton,
Margaret	Parton	Sector Specialist in Medtech and Healthcare	UKTI
Julia Catherine Kevin	Polak Prescott Price	Honorary Principal Research Fellow Director Chief Executive Officer	Imperial College London Biolatris Ltd The Scottish Stem Cell Network, Roslin Biocentre King's College London
Brian	Salter	Professor of Politics and Director of Research	University of Nottingham Newcastle University
Kevin James	Shakesheff Shaw	Head of School of Pharmacy Professor of Regenerative Medicine for Diabetes and Honorary Consultant Physician Institute of Cellular Medicine	University of Nottingham Newcastle University
Marc Andrew Michael David	Turner Webster Whitaker Williams	Medical Director Director Dean of Research & Innovation Professor of Healthcare Engineering Director of the Research School of Health and Life Science	SNBTS HeadQuarters SATSU, University of York Newcastle University Loughborough University

UK Stem Cell Bank, Roslin Cells Limited and Scottish National Blood Transfusion Service (SNBTS) – Oral evidence (QQ 244-266)

UK Stem Cell Bank, Roslin Cells Limited and Scottish National Blood Transfusion Service (SNBTS) – Oral evidence (QQ 244-266)

[Transcript to be found under Roslin Cells Limited](#)

UK Stem Cell Bank – Supplementary written evidence

International Supply of Human Embryonic Stem Cells (2006-2012)

Recipient Country	No. Cell Lines	Organisations	Academic/Industry
Australia	3	1	Academic
Canada	1	1	Academic
Denmark	3	1	Academic
France	2	1	Academic
Germany	7	3	Academic
Italy	6	1	Academic
Netherlands	2	1	Academic
Portugal	1	1	Academic
Saudi Arabia	4	1	Academic
Singapore	1	1	Academic
Spain	5	2	Academic
Sweden	2	1	Academic
Thailand	1	1	Academic
USA	2	1	Industry
Total 14	Total 40	Total 17	

3 January 2013

UK Stem Cell Foundation – Written evidence

1.0 Introduction

The House of Lords Science and Technology Committee is conducting an inquiry into regenerative medicine. The Committee wishes to look, in particular, at whether the UK is in a position to facilitate the translation of knowledge from world-leading research to treatments, and to benefit from the commercial opportunities that they present. It also seeks to explore how realistic some of the reported claims of regenerative treatments and therapies are, both in the UK and internationally.

The UK Stem Cell Foundation is the only UK charity that focuses specifically on raising funding for translational stem cell research in the form of projects with potential to enhance or lead to treatment of a wide range of conditions and diseases. It aims to speed up the progression of promising stem cell research and technology into treatments and therapies for patients. Since its establishment in 2005, the Foundation has enabled over £15 million to be invested in stem cell research projects in the UK through a combination of fundraising, co-funding and collaboration. These include projects into spinal cord repair, bone and cartilage repair, hip revision surgery, corneal blindness, glaucoma, liver disease, heart attack recovery, multiple sclerosis and tendon repair.

This submission collates a range of views from the Foundation's eminent and well informed Board of Trustees, executive and Principal Investigators.

2.0 Evidence Requested by the Committee

2.1 The Research Base

How does the UK rank internationally in the scientific field of regenerative medicine?

The UK ranks highly internationally in the scientific field of regenerative medicine - probably second to the USA in terms of research activity. However, it ranks significantly lower in term of its number of small to medium-sized enterprises (SMEs).

Where does the UK have strengths and weaknesses in the field?

The UK's main strengths are in its sound science base in universities and academia, and the knowledge, innovation and skills of its scientists and researchers.

The UK's main weaknesses in the field are:

- Regulatory barriers to clinical trials that are slowing up progress of therapies to clinical development, in particularly GTAC;
- Inefficiencies in the NHS in conducting clinical trials – for example, the length of time to get trials approved, difficulty in recruiting for and lack of focus on progressing trials;
- A lack of public sector funding facilitating the translational preparation of putative therapies for entry into clinical trials. This is a specialist area relating

to product development, conversion to appropriate formats, economic assessments and regulatory approval. This genuine roadblock is key to the progress to the patient. UKSCF had originally been created in order to address this unmet funding need.

- A lack of public sector funding dedicated to progress phase I and II clinical trials as there is still a critical funding gap in this area. The focus of research councils has been on funding basic and underpinning research. However there is a need for more funding to be focused on progressing phase I and II clinical trials. The UKSCF currently is trying to raise over £15 million for phase I and II projects, prior to the stage where the private sector is likely to get involved. Fundraising would be far easier and faster if it was able to match-fund against public sector funding. This was the original intention of the Government following its UK Stem Cell Initiative strategy in 2005;
- As a result of the delays in progressing therapies, a growing number of people in the UK who suffer from degenerative illnesses and conditions are risking their health, lives and life-savings for stem cell treatments in overseas clinics in countries that do not have the same robust regulatory, licensing and safety controls as the UK.

***Who are the major funders of research in the field of regenerative medicine?
What funding is available to support this research?***

Public sector funders of regenerative medicine research in the UK have been well documented in *A Strategy for UK Regenerative Medicine (March 2012)*. The Strategy highlighted spend by the MRC, BBSRC, EPSRC, ESRC and TSB on regenerative medicine in 2010 totalling £72.6 million. It also highlighted that they had virtually no spend on phase I, II and III clinical trials. This is the crucial area in which public sector funding is required to enable underpinning and preclinical research to progress to therapies for patients. Without this, and the clinical trial-enabling translational product development capability, the health and economic benefits of this world-class research will not be realised for UK plc.

To date, the focus of the UKSCF's work has been on progressing stem cell projects towards phase I and II clinical trial. As mentioned previously, it currently is trying to raise over £15 million for projects at this stage of development. This ambition would be far easier and faster realised if it was able to match-fund against public sector funding. The Foundation has found that the general public and donors expect the Government to be contributing to work in this area and are much more willing to donate when they know that their contribution will be matched by the public sector.

The Association of Medical Research Charities (AMRC) has identified that the investment of its third sector members into regenerative medicine has been growing over the last five years, with over £51 million being invested in regenerative medicine between 2005 and 2010. In comparison, the public sector since 2003 has invested over £200 million in the field (*source: Taking Stock of Regenerative Medicine in the UK July 2011*). This shows the significance and importance of the contribution made by the third sector in funding the development of regenerative medicine in the UK.

Interestingly, despite the significance of third sector investment in progressing regenerative medicine in the UK, the third sector has not been consulted or included within nationally significant strategies such as *A Strategy for UK Regenerative*

Medicine March 2012. This is a major omission that fails to recognise the importance of the sector.

It is clear that there is a need for greater collaboration and a more joined up strategic approach between the public and third sectors to progressing regenerative medicine to realise the full health and economic benefits in the UK and beyond.

Following the recommendations of the Government-commissioned Pattison review, the UKSCF was set up in 2005 as part of the UK Stem Cell Initiative *to ensure UK plc remained scientifically and commercially productive over the coming decade.* The Initiative recommended that the Government should provide funding for clinical and translational stem cell research over the next decade at a level matching that raised by the UKSCF, up to a maximum of £10 million per annum, and administer it via a UKSCF/Medical Research Council (MRC) collaboration. Despite this promising commitment from the UK Government, the £50 million funding announced by the Treasury in 2005 for translational research did not become available for distribution through a UKSCF/MRC collaboration.

However, since 2007, the UKSCF has raised approximately £15 million in funding for stem cell projects across the UK. It has fundraised and match-funded against public sector funding, undertaken scientific reviews of projects and defrayed funds on the public sector's behalf. It has achieved a minimum match of £1 for £1 against public sector funding, which provides added value for the public purse. Compared with other publicly-funded research agencies, the UKSCF is unique in this regard.

2.2 Application of the Science

Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

What potential does regenerative medicine hold to treat disease in the next 5-10 years?

What is the reality versus the headlines about what the science will deliver?

The UKSCF funds enabling technologies and translational research in stem cells that could ultimately lead to a phase III clinical trial, with the possibility of becoming new treatments within a five-year period. Its focus is on late preclinical, phase I and phase II projects.

The major potential for therapeutic applications in the next 5-10 years is the realisation of current projects in clinical trials. (As it takes >10 years to develop a therapy, basic research being conducted now is highly unlikely to be commercialised in the next 5-10 years). Major areas of application are in line with the projects supported by the UKSCF, which are bone and cartilage repair, hip revision surgery, liver disease, heart attack recovery, spinal cord repair, glaucoma, corneal blindness, tendon repair and multiple sclerosis. Several of these are either in clinical trial or are

attempting to raise sufficient funding to undertake phase II and III clinical trials. Additional areas for therapeutic applications are stroke and peripheral ischemia.

Sight improvement is one of the most promising of all areas.

The earliest successes are likely to be in autologous stem cell transplants followed by adult stem cells then Induced Pluripotent Stem cells.

In addition advances in our understanding of the factors that control cell differentiation should open up new possibilities for therapy beyond the 10-year horizon.

One of the promising bone and cartilage repair projects that the UKSCF co-funded with the private sector (Geron) has been forced to stop as a result of a corporate decision by Geron to withdraw from the stem cell sector at a global level. This has created an opportunity to progress this technology to the clinic in the UK and for use worldwide.

None of the projects supported by the UKSCF are widely available treatments either in the private sector or the NHS at this stage as none of them have completed their phase III clinical trials. However, several of them are very promising and are likely to become treatments once their trials are complete. These include:

- Heart attack recovery project using autologous bone marrow stem cells (currently a phase II clinical trial led by Prof. Anthony Mathur),
- Spinal cord repair project using autologous olfactory stem cells (currently pre-clinical trial led by Prof. Geoff Raisman),
- MS relapse remitting project using autologous mesenchymal stem cells (currently a phase II clinical trial led by Dr. Paolo Muraro,
- Corneal blindness project using limbal stem cells (currently a phase I/II led by Prof. Bal Dhillon).

Projects for which the UKSCF is raising funding for product development and clinical trials include:

- Glaucoma project using autologous olfactory stem cells (phase I/II),
- Spinal cord using olfactory stem cells (phase I/II)
- Tendon repair project using autologous mesenchymal stem cells (phase I)
- Bone and cartilage repair projects using embryonic and adult stem cells (phase I/II),
- Hip revision surgery project using mesenchymal progenitor stem cells (phase II),
- Cord blood project bolt on to phase II clinical trial.

This is where the major translational funding gap still exists.

Currently the UKSCF alone is seeking to raise over £15 million to progress phase I and II stem cell clinical trials. This is a steep challenge given that it is a small charity with very limited resources. Previous attempts to match fund with research councils

have been mixed. For example, the UKSCF originally set up a joint scientific advisory board with the MRC. However the board encountered difficulties in agreement on funding projects due to MRC favouring basic and underpinning research and UKSCF favouring translational/pre-clinical/phase I and II trials. This led to the Foundation setting up its own review panel to enable promising projects to progress more quickly.

When funding by the public sector research councils and TSB is analysed, (ref: *The Strategy for UK Regenerative Medicine March 2012*), only 3% of funding in 2010 was in phase I, II or III clinical trials. This is where the major funding gap exists that medical research charities such as the UKSCF are trying to fill. However, with no or very little public sector funding to match against and a lack of collaboration with the public sector (with a small number of exceptions, such as the Cell Therapy Catapult), there is a barrier to promising research achieving health and economic benefits.

2.3 Barriers to Translation

Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

o What difficulties are encountered when conducting clinical trials and how could these be overcome?

o What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

o What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

The key barriers to translation are:

- A lack of public sector funding for translational stem cell research (product development, phase I and II clinical trials in particular) to progress into treatments;
- A skills gap in which the expertise in the translational science required to produce a new medicine is scarce.
- Regulatory barriers to clinical trials that are slowing up progress of therapies to clinical development. For example, with one phase I/II trial funded by the UKSCF, it took two years to gain MHRA and GTAC approvals. Whilst the UKSCF's key informants feel that the UK Medicines Control Agency is very efficient in its review of clinical trial applications, they feel that the GTAC is a major hurdle to the efficient conduct of trials. They feel that the GTAC Committee is far too academic and shows poor judgment in assessing the "risk : benefit" issues in the context of the diseases under review, especially in rare disorders. They recommend that the

Committee increases the number of its members who are skilled in drug development and clinical trials. They also feel that GTAC's processes should be formulated with clear guideline and methods of consultation and appeal;

- Inefficiencies in the NHS in conducting clinical trials – for example, the length of time to get trials approved, contracts agreed, difficulty in recruiting for and lack of focus on progressing trials. Investigators have very little incentive to participate in clinical trials. There is a lack of understanding of the detailed adherence criteria to protocols. The system of approval, recently centralised, still requires further centre by centre procedures, which slow down start times. Protocol agreement takes an inordinate amount of time and effort. The largest delays take place in agreeing contracts. Even when approvals are finalised, patient recruitment is patchy and slow. This is especially the case for GP trials, but similar bureaucratic delays occur in major teaching hospitals by personnel in the NHS who are not skilled in clinical trial administration. These are major disincentives to conduct trials in the NHS.

2.4 Barriers to Commercialisation

What is the current and potential future, commercial value of the sector to the UK economy? What is its value to society?

Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

Public sector Support for preclinical work would de-risk technologies and enable a more efficient transition to the private sector.

What role does patenting play in the commercial development of regenerative treatments?

What business models are most appropriate to support the development of regenerative treatments?

There will be a large range from autologous small scale production to large scale allogeneic global medicines. Distribution, storage and delivery will all differ between specific therapies.

What are the barriers to securing finance to develop such treatments?

The major barriers will relate to the immaturity of the majority of regenerative technologies and the lack of familiarity of the investor community with both these products and the roadmap to the clinic.

Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

NHS pricing structures rarely take into consideration the longer term cost savings that a regenerative medicine might engender. The higher cost of production has to be viewed in the light of the potential ability to cure and not treat a condition.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

Procedure codes are created around a relatively conservative set of measures. Greater appreciation of the long term cost benefits will be required. Specialist cell holding facilities may be required in clinic as might a more efficient delivery collection and distribution service (in order to allow the timely delivery of frozen or chilled cell based therapies).

Intellectual Property (IPR patents) is a fundamental necessity for stem cell translational R&D. Fortunately the UK has strong IPR legislation and implementation.

However lessons should be learned from initiatives such as ITI Life Sciences in which the public sector sought to retain IPR on some projects, which was a disincentive for the private sector to invest.

2.5 International Comparisons

What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

The US has supplied significant levels of funding and a supportive environment for entrepreneurial biotechnologists. The creation of CIRM and other funding vehicles has had a dramatic effect on progress.

How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

The processes of conducting clinical trials in Scandinavia are more efficient than in the UK. Whilst central (EMA) approval of clinical trials is part of the current EU consultation /revision of the Clinical Trial Directive, it could result in further delays in the UK if the current clinical trial NHS approval systems are not radically changed.

As a result of desperation and delays in progressing therapies, a growing number of people in the UK who suffer from degenerative illnesses and conditions are risking their health, lives and life-savings for stem cell treatments in overseas clinics in countries that do not have the same robust regulatory, licensing and safety controls as the UK. Although the UK's regulatory procedures can be slow and clinical trials expensive in this country, they play an essential role in ensuring that experimental stem cell treatments are as safe and effective as possible.

20 September 2012

University College London (UCL) Institute of Child Health and Women's Health – Written evidence

Authors:

Mr Paolo de Coppi, Senior Lecturer and Consultant in Paediatric Surgery, UCL Institute of Child Health, and Great Ormond Street Hospital

Dr Anna David, Reader and Consultant in Obstetrics and Maternal Fetal Medicine, UCL EGA Institute for Women's Health and EGA and Obstetric Wing, University College London Hospital

Dr Simon Waddington, Reader in Gene Therapy Technologies, UCL EGA Institute for Women's Health

1. Background

Paolo de Coppi is an expert in regenerative medicine for therapeutic structural repair or amelioration of congenital or acquired neonatal disease. He was the first to demonstrate cells with potential for cell therapy in the amniotic fluid. Anna David is an expert in prenatal therapies and their application during pregnancy to treat life-threatening congenital disease and obstetric disorders. Their successful collaboration is working to develop novel prenatal and neonatal therapies using regenerative medicine.

The Research Base

2. How does the UK rank internationally in the scientific field of regenerative medicine?

With regard to fetal and neonatal regenerative therapies, the UK is one of a collection of leaders in this area. Other leading countries in this area of research and translational medicine include the US, Singapore, Sweden, Italy, Taiwan, and Belgium.

3. Where does the UK have strengths and weaknesses in the field?

The UK strengths are:

- Combining gene therapy with stem cell therapy ie genetic manipulation of stem cells for therapeutic advantage
- Autologous transplantation of fetal stem cells
- Isolation, characterization, differentiation, culture of stem cells from the amniotic fluid (and placenta)
- Use of amniotic fluid stem cells to treat Necrotizing Enterocolitis (NEC) a currently untreatable common neonatal complication affecting affects close to 10% of infants who weigh less than 1500 g, with mortality rates of 50% babies per year in the UK
- Hollow organ regenerative medicine (e.g. the first tissue engineered trachea transplanted in 2010 at Great Ormond Street Hospital)
- Large animal models for testing of clinically relevant techniques to deliver stem cell therapy to the fetus eg sheep experiments.
- Development of amniotic fluid stem cell banking.

The UK weaknesses are:

- Difficulties obtaining sufficient funding to maintain the necessary laboratory equipment, animals and expertise

4. Who are the major funders of research in the field of regenerative medicine?

To date we have been funded by a number of agencies, but these tend to be small amounts of money, and some research training fellowships. We have been more successful if securing funds from other countries for this work (Italy and Taiwan) than the UK. We have made a number of unsuccessful applications to UK charities (Action Medical Research, Sparks, Wellbeing of Women, Wellcome Trust, BDF Newlife, MRC, The Royal Society). In the specific area of regenerative medicine applied to fetal and neonatal therapies, successful applications have been limited so far to:

Small UK charities:

Newlife (Birth Defects Foundation): £15,000 which funded a pilot study. Application for a full project grant was unsuccessful.

Local UK hospital charities:

UCLH charities 18 month pilot funding for a clinical PhD student.

Great Ormond Street Hospital Children's Charity funding translational studies for the use of amniotic fluid stem cells in necrotizing enterocolitis

Large UK funding agency:

Wellcome Trust: Research Training Fellowship to clinical PhD student. Postdoctoral Training Fellowship to clinical postdoc.

Overseas philanthropic funding:

Citta' della Speranza, Italy for research fellows.

Overseas hospital and government funding:

Chang Gung Memorial Hospital, Taiwan for a clinical PhD student

Taiwan Ministry of Education for a clinical PhD student

National Science Council Taiwan (UK-Taiwan Research Cooperation Initiative)

5. What funding is available to support this research?

Funding from local hospital charities, small UK national charities is available for short projects. For research that is close to clinical translation there is funding from the MRC Translational Stem Cell Research Committee. We were advised that an application to this funding stream for our work was premature since there was insufficient supportive data. A successful application to the MRC relies on having sufficient background data and so there is a funding gap.

Application of the science

6. Is the science being translated into applications?

We are working hard to translate our findings, but this is being hampered by the lack of funding. Currently we are planning to apply to the US for funding for a collaborative project in a large animal model that is the final step before translation.

In regards to tissue engineering for hollow organ transplantation, achievements have been obtained in older children and adults by others and us. However, some of the applications could be applied early in life during fetal or neonatal period if we could use placenta, umbilical cord, and/or amniotic fluid derived stem cells.

7. What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally?

Currently there are no regenerative therapies available in the UK or internationally for fetal and neonatal congenital and structural disease. There have been two case reports of in utero stem cell transplantation (IUSCT) for a congenital bone disorder (osteogenesis imperfecta, Sweden and Singapore) that showed therapeutic benefit. These units are applying for funding to evaluate the therapy more fully. There have also been 10 case reports of

successful IUSCT for treatment of fetal SCID (severe combined immunodeficiency) around the world over the last 15 years. Attempts to treat other congenital diseases such as thalassaemia have been unsuccessful.

8. Which treatments are available on the NHS or through private healthcare?

None

9. What potential does regenerative medicine hold to treat disease in the next 5-10 years?

There are two areas that regenerative medicine has potential to treat fetal and neonatal congenital and structural disease:

Congenital genetic disease: currently we believe that IUSCT is unsuccessful for most congenital disease because of the development of a maternal and fetal immune response to the injected stem cells. We are working on genetically correcting the individuals own stem cells collected from the amniotic fluid and placenta which we have shown can be delivered back into the donor fetus, can engraft widely and show levels of therapeutic protein production. This technique is similar to that which has been used so successfully to treat neonatal SCID using bone marrow stem cells corrected by gene therapy. The hope is that this technique will provide a targeted method of correcting common congenital diseases such as thalassaemia, sickle cell, haemophilias, and other liver diseases. The advances in non-invasive prenatal diagnosis mean that in the next decade it will be possible to diagnose many congenital diseases early in fetal life.

Congenital and acquired structural neonatal disease: development of high resolution ultrasound and magnetic resonance have allowed precise definition of fetal structural anomalies. Neonatal repair of those malformation often require the use of prosthetic material and multiple operations. We aim to use the amniotic fluid stem cells from fetuses diagnosed with congenital malformation for preparing autologous tissues or organs which could eventually be transplanted at birth. Stem cells from amniotic fluid and placenta could also be banked and used later in life if required.

10. What is the reality versus the headlines about what the science will deliver?

The science is likely to deliver novel therapies for some but not all fetal and neonatal conditions. The conditions we are considering are uncommon and untreatable life-threatening disorders.

Barriers to translation

11. Are the actions outlined in the Government's Strategy for UK Life Sciences their report: Taking Stock of Regenerative Medicine in the UK, and the Research Council and Technology Strategy Board's Strategy for UK Regenerative Medicine sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required?

In particular:

12. What difficulties are encountered when conducting clinical trials and how could these be overcome?

Application of regenerative medicine into the clinical scenario have been mainly conducted by doing single cases (e.g. transplantation of tissue engineering trachea) and it remain difficult to translate stem cell therapy using clinical trials. We believe that clinical trials may be easily

applied to congenital conditions associated to poor outcome, particularly to the ones in which the options available cannot be curative.

13. What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

There are difficulties with banking of stem cells. We are very fortunate that at UCL there is a clinically approved biobank, through which we are setting up a bank for amniotic fluid stem cells. Amniotic fluid will be collected from NHS patients and taken to the biobank for storage and then will be available for clinical use in the future. This will be the first AF stem cell bank in the UK and overseas. Although we have access to the UCL biobank, nevertheless there are a number of hurdles that need to be addressed (patient consent, transport of cells, correct process of storage), however the main one of which is funding.

14. What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

Applications to regulatory bodies to conduct clinical trials are complex and requires dedicated funding.

Barriers to commercialisation

15. What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

Banking of amniotic fluid stem cells (and placental stem cells) and their successful use in therapeutic regenerative medicine could provide significant commercial value for the UK economy (and the NHS). At the moment there is an opportunity to set up such stem cell banks ahead of the commercial sector. The commercial value of cord blood banking can be used as an exemplar of how the sector might look. When using commercial companies, parents typically pay £1500-2000 to bank their baby's cord blood stem cells. There are now 10 NHS cord blood banks in the UK set up to provide the number of stem cells for clinical requirements, and this number is increasing.

16. Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

As far as we are aware there are no incentives or plans by the Government to invest in amniotic fluid or placental stem cell banking.

17. What role does patenting play in the commercial development of regenerative treatments?

Clinical translation of stem cell application is expensive and requires partnership with the industries. Patenting of technologies may help attractive funding and interest from the industries. We have successfully patented the isolation and banking of amniotic fluid stem cells which we hope it may help the translation of these technologies for therapy.

18. What business models are most appropriate to support the development of regenerative treatments?

Patent applications from universities could be used to generate new spin-off companies which could partner with researchers to develop the technologies to the clinic. It is possible that some of these new companies may be taken over by larger biotech and pharmaceutical companies.

19. What are the barriers to securing finance to develop such treatments?

The main barrier to securing finance is a lack of investment in the UK for these therapies. We have been funded for a number of years by overseas funding agencies (eg Italy and Taiwan), who are willing to invest in potentially high risk projects, for long term gain. The problem with only using the academic model of translational medicine is that as academics our success is measured by how much money we bring in, and the number of papers published, rather than a long term translational strategy.

20. Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

Not applicable yet.

21. What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

Not applicable yet.

International comparisons

22. What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

There needs to be some investment in bringing stem cell therapies to the stage of successful translation.

23. How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

Regenerative medicine application in UK are regulated by European regulations which takes into account patient safety.

24. Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

Not sure?

25. What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

Some Countries do not have a clear and standardized regulatory system. In these Countries doctors and companies can offer treatments based on regenerative medicine technologies which have not been validated, and of which security and efficacy has not been proved.

25 September 2012

University of Manchester – Written evidence

Background on the University

The University of Manchester, a member of the Russell Group, is the largest single site university in the UK. It has 22 academic schools and hundreds of specialist research groups undertaking pioneering multi-disciplinary teaching and research of worldwide significance. According to the results of the 2008 Research Assessment Exercise, the University is one of the country's major research universities, rated third in the UK in terms of "research power". The University had an annual income of £808M in 2010/11.

Regenerative medicine is a priority of the University, which has an excellent track record in basic and translational research relevant to regenerative medicine, especially in the biology of tissue formation and repair, in the design/ fabrication/engineering of biomaterials, and in biomedical translation. Our research is also supported by strong links to Biopharma. Our biomedical campus provides, in contiguous new buildings, state-of-the-art basic and translational research facilities in biomedicine and material science, a Clinical Research Facility and a major NHS Trust site incorporating specialist clinical research centres, the Manchester Academic Health Science Centre (MAHSC) and the new Manchester Collaborative Centre for Inflammation Research.

Summary

Regenerating damaged tissues and restoring their function is one of the major goals of biomedicine. Diseases that cause tissue degeneration and injury present a huge and increasing clinical and socio-economic burden, in the UK costing the NHS well over £1 bn/year. Vascular disease causes ~30% of all global deaths, most due to cardiovascular and cerebrovascular disease (stroke); musculoskeletal diseases cause a great burden in pain and disability, and account for 8.8 million working days lost per annum in the UK alone. Diabetes, which affects ~350 million people worldwide, greatly increases the risk of heart disease and stroke, and causes neuropathy and chronic wounds. Approaches to tissue regeneration include stem cells and cell-based therapies, biomaterials design and tissue engineering.

Stem/progenitor cells offer major opportunities for regenerative medicine and the UK has a vibrant stem cell research community, with major international strengths in scientific research on stem cell biology (embryonic stem cells, mesenchymal/adult progenitor cells, induced pluripotent stem cells), in the biology of tissue formation (e.g. cell-extracellular matrix biology, mechanobiology) and in inflammation biology/immunology. However, in the UK and world-wide, it has proved challenging to exploit these strengths to effective translation for clinical and commercial benefit. Outstanding issues include incomplete understanding of how cells make/repair tissues, the need for improvements in the characterisation and expansion of stem cells from different tissue sources, the necessity to control cell differentiation and inflammatory processes, the requirement to direct neovascularisation and nerve regeneration, and the safety of all these approaches. Despite these issues, the concept that adult cells can be reprogrammed to regenerate or repair tissues is now widely accepted, and the mechanisms to achieve these cell-driven reparative changes are increasingly well understood. Thus, it is our view that the time is right for the UK to invest substantially now to achieve a market-leading position in a translational regenerative medicine 'industry'. Specifically, strong investment is needed in the

underpinning biology, in the training of cohorts of basic and clinical scientists in the requisite interdisciplinary skills, and in the translational pipeline from bench to first-in-man. There is a real opportunity now to build on our scientific and translational strengths to develop new strategies for the repair of musculoskeletal, ocular and other tissue defects, in part as a legacy of the recent successful Paralympics.

I. The research base

Areas of major UK strength include:

- basic stem/progenitor cell biology (i.e. in the cellular principles underlying pluripotency and differentiation, including cell signalling, epigenomics, genome stability, control of inflammation; cell expansion; developmental processes);
- understanding how cells make tissues (e.g. cell-extracellular matrix biology which examines how the cellular microenvironment [niche] directs cell phenotype);
- the responses and contributions of cells to inflammation processes that profoundly affect repair processes;
- biocompatible biomaterials chemistry, design and fabrication;
- Good Manufacturing Practise (GMP) expertise and capacity.

Current UK research funders are the Medical Research Council (strategic calls and response-mode), Engineering and Physical Sciences Research Council and Biotechnology and Biological Sciences Research Council (chemistry/ biomaterials), the Wellcome Trust, and smaller charities (e.g. British Heart Foundation, Arthritis Research UK).

Strategic needs include:

The need for better understanding of stem/progenitor cells and their regulation

Many tissues have resident stem/progenitor cells, e.g. mesenchymal stem cells (MSCs) that are obtained from bone marrow and adipose tissue, blood vessels and umbilical cord. These cells can vary in self-renewal and differentiation potential, and are highly sensitive to culture conditions. There is a need for more definitive cell surface markers to identify tissue-specific progenitor cell sub-populations. MSCs have the potential to differentiate into many tissue-specific cell types, which could contribute directly to the regeneration of defective or damaged tissues, or indirectly to repair by secreting growth and anti-inflammatory factors. The *in vivo* cues that direct the differentiation of endogenous progenitor cells, e.g. to myofibroblasts during wound healing, remain poorly understood. Understanding of neural progenitor cells and their contribution to neurogenesis is also limited. A further challenge is that tissue progenitors are heterogeneous populations. Moreover, for MSCs and other pluripotent stem cells, we do not understand how the cell transitions from stem to early committed progenitors are regulated.

The need to understand how the cellular microenvironment regulates repair processes

Pericellular extracellular matrix presents to cells a complex array of signalling molecules which profoundly influence cell fate. By affecting receptor signalling and controlling cytoskeletal organisation and the mechanical environment, ECM controls cell survival, proliferation, migration, shape, differentiation and growth factor bioavailability. We need to understand better how the pericellular ECM-rich niche of progenitor cells (normal and diseased) regulates genetic, transcriptional, epigenetic and signalling network, and thus tissue regeneration/repair processes. This understanding must be extended to regulation of the niche in culture, in order to recapitulate accurately the stem and progenitor niche in a dish (e.g. for controlled *in vitro* expansion).

The need to regulate tissue inflammation

This need is a priority, since pathological inflammation is a major underlying cause of adverse tissue remodelling in most non-communicable diseases including cardiovascular and cerebrovascular disease, diabetes, obesity, musculoskeletal disease and cancer. Here, stem/progenitor cells offer the important prospect of anti-inflammatory therapy. After intravenous delivery or transplantation, they can secrete protective anti-inflammatory molecules which locally and systemically can reduce inflammatory damage. stem/progenitor cells may also influence directly cells of the immune system (e.g. dendritic cells and regulatory T-cells) to suppress inflammation. Stem/progenitor cells exhibit complex inflammatory molecule expression profiles that are tightly controlled by extracellular matrix and cell culture environment, illustrating that it should be possible to direct expression of anti-inflammatory molecules *in vivo* by exploiting niche cues e.g. by engraftment in specific matrix biomaterials. The application of autologous stem/progenitor cells will minimise the need for immunosuppressive regimes. Allogeneic application may (in some cases) be possible, thus extending their therapeutic potential.

The need to direct neovascularisation and nerve regeneration

Effective tissue repair usually requires not only cells and ECM, but also functional blood and nervous supplies. Neovascularisation often occurs via angiogenesis, which involves endothelial sprouting, ECM remodelling and stabilisation of newly formed blood vessels. The ability to promote nerve regeneration following injury or in diabetic neuropathy may be achievable by transplantation of differentiated progenitor cells. The ability of stem/progenitor cells to regulate and contribute to these tissue processes needs to be very much better understood.

The need for capacity building

Developing effective tissue regeneration strategies requires tight (local and national) coordination of multiple approaches spanning molecular and cellular biology, proteomic/glycomic and systems biology research, design of innovative biomaterials, and translation to pre-clinical models and clinical trials, which is possible only with excellent interdisciplinary skill-sets. They also require the capacity to develop and upscale these concepts to clinical translation as viable long-term interventions. With the UK's breadth of biomedical research, superb clinical translational facilities and links to NHS Healthcare Trusts, we are ideally placed to train scientists and clinicians who can translate basic research discoveries through to clinical applications.

The need to determine the true merits and weaknesses of different stem cell types

It is still unclear which stem cell types will have the highest utility for different applications. It is strategically important to produce the comparative data which allows prioritisation of one cell type over another to allow appropriate channelling of funds for different purposes, for instance a particular developmental or disease model, or a specific cell therapy.

The need to develop robust strategies to regulate the mobilisation and control of endogenous tissue stem cells and progenitors

A further area in need of investment is that of mobilising often rare endogenous stem cells to undertake tissue repair. This may involve use of small molecules or manipulating the stem cell niche and is often compromised in disease conditions (e.g. diabetes).

The need to enable stable cell expansion in vitro to allow efficient affordable therapies

Pluripotent stem cells can be greatly expanded outside the body, but in formats that are not conducive to automation making such processes labour intensive and liable to variation. We need to generate new systems for low cost expansion avoiding cell stress leading to differentiation or cell death. Adult stem cells generally have limited expansion capability, meaning that they need to be repeatedly harvested, again requiring labour and expense. Hence new ways to avoid their senescence need to be established.

The need for clinically suitable delivery

A few current therapies need immediate production in the lab and transport to the clinic to be co-ordinated with patient surgery. However these do not generally treat disease in routine NHS procedures (blood transfusion being an exception). The clinician really needs to work with stable patient-compatible materials which can be stored in the clinic for a reasonable time (reasonable shelf-life). Yet the problem of delivery for cell-based therapies has been almost entirely neglected. There is an urgent need to develop formats for delivering cells in gels or scaffolds in which they can be stored frozen/refrigerated for later use while retaining viability and function. This requires research and funding.

2. Application of the science

One important proviso when considering the various applications in this area is that there is a current of opinion which claims that we have now done the majority of the research and that the major push should now be to get regenerative medicine translated to the clinic and the lab for patient/commercial use. However, actually there is still a considerable amount of basic science that needs to be achieved before many therapeutic applications will be ready for patients. Thus there is a grave danger of forcing applications into the clinic which are still not fit for purpose, but could become fit for purpose by further careful research.

Cell therapy

Clearly, if cells of high viability and function can be generated which retain function and integrate in the host target organ, stem cell therapies will become an attractive and desirable part of the routine clinical armoury. However, it is essential to note that translation to regenerate tissue function will not just be about cells into patients; indeed the generation of models that can be used to produce safer traditional medicines and for the development of new drugs should not be ignored.

Developmental models

We lack valid *in vitro* cellular models of different aspects of human development. Since animal development often diverges from human, such models are critical to our understanding of human developmental processes beyond the purely anatomical. Such models can be provided by stem cells, particularly pluripotent (embryonic, induced-pluripotent) stem cells which retain the capacity to differentiate to all body cells.

Disease models

In the same vein if things go wrong in development (congenital defects) or in mature cell function (genetic disease), we rely on animal (transgenic etc) models to explore the biology of that disease. With increasing awareness of the pitfalls of, and a wish to avoid, animal experimentation and the understanding that mouse/rat development is not identical to human, it is of fundamental importance to produce improved cellular, tissue and whole organ models that can recapitulate at least aspects of human disease processes. Such models allow development of new therapeutic and sometimes preventative approaches.

In vitro models for predictive toxicology

Once we have good human models of tissue formation *in vitro*, these will be of great benefit to biopharma for testing current and emerging drugs for toxicity and off-target effects. Use of such models from diverse genetic backgrounds may start to predict adverse reactions to generally safe medicines found in minorities of the population or specific racial groups.

In vitro models for drug discovery

Our ability to induce stem cell differentiation to particular desired cell types at high efficiency, together with production of iPS cells from patient somatic tissues will allow valid human disease models which can be used to test new drugs for their amelioration of disease processes.

3. Barriers to translation

Efficacy in vivo and in vitro: we still cannot reliably differentiate many stem cell types to a desired differentiated cell type reproducibly and at high efficiency. In many cases, we do not have sufficiently robust *in vitro* assays to establish whether we have functional cells. Animal models are useful but do not necessarily reflect full integration and function in the human organ.

Safety

There is still much concern about possible retention of embryonic stem cells after differentiation which might then go on to form tumours in the body. Although a number of studies have been done in animals to suggest this does not occur in properly conducted research in the short term (months), this is still considered an issue for the long term and needs to be addressed further. Adult stem cells do not always stay where they are put, or all reach their targeted site and research is needed to investigate whether cells lodged off target will interfere with the off-target organ functions or cause illness by continuing to move. Methods of destroying off-target cells or cells which do not differentiate appropriately or retain their differentiated phenotype are required.

Immune rejection and immune reaction

The degree of tissue matching for allogeneic therapies is still unclear particularly as this will be site-specific. However in some cases, the need for large amounts of immune suppression may be a barrier to translation of allogeneic therapies. MSCs have immune-suppressive properties and are thus seen to have potential as allogeneic therapies, but their *in vivo* stability and immunogenic effects are unknown.

Delivery

As indicated above, appropriate means of stable delivery have often not been developed or optimised. This may completely block translation, if not successfully overcome.

Affordability

Personalised medicine is a great idea but it is extremely doubtful that personal cell-based therapy will ever be affordable on the NHS for most diseases. Thus it will be important to use research to develop cheaper but efficacious processes for generating cell therapies which can be made available to large numbers of people. This may occur through banking, allogeneic use and careful tissue matching with conventional immunosuppression, or co-application of immunosuppressive cells together with the cells for therapy in the short term. Further cheaper ways of culturing the cells and applying costly regulatory factors more efficiently for differentiation protocols are required.

Clinical engagement

One major barrier is the lack of engagement with potential new treatments by clinicians who have little time and reduced budgets and who are already challenged by NHS changes. This is a definite barrier to the development of clinical trials.

4. Barriers to commercialisation

Risk

For cell therapies, the cells themselves are the product making therapy production extremely complicated and difficult to control compared to generation of small molecules drugs. Together with the complex delivery and safety, this makes the production of such therapies high risk.

Expense

Companies balance the chances of producing a successful therapeutic format which will be taken up by clinical providers and earn them sufficient financial rewards (including a profit margin), with the vast accrued expense of developing a therapy for patient use. The balance is still not considered in the patient's favour because of some of the other barriers that are not yet near solution and the problem is exacerbated by the inappropriate drug discovery model (below). Moreover, these commercial risks face companies during a global recession.

Commercial squeamishness

Commercial organisations have been convinced that the general public will not accept certain therapies (e.g. ES cells) and that to participate may generate reputational risk. Public engagement activities question that this extreme view is a reality in the UK. It has been argued by a number of individuals that not utilising IVF-derived spare embryos, which would not and could not ever be used to create a child, for ES generation and potential therapy is the more unethical stance.

Inability of cell therapies to fit the drug discovery model

Pharmaceutical companies are not used to generating cells for use in the clinic and the pharmaceutical model for drug discovery and development does not fit cell therapies (including reimbursement). However companies have been slow to develop an alternative model although this has often been discussed at the academic/clinical/commercial interface. Patenting is probably not the major issue sometimes considered, since some major products (Coca Cola, for instance) have been commercialised successfully without patents. Thus, many consider the EU directive forbidding patenting of ES derived products is not an issue. Commercial secrets can be maintained in these cases.

5. International comparisons

We have a forward looking and well regulated translational climate compared to the US and Europe. We are world leaders in regulation and already have a well respected research base. Thus UK plc should be in prime position to take research in regenerative medicine forward and, given the clinical input, will translate it into mainstream therapies. Patients travelling abroad in desperation to less developed countries may face unsafe therapies with little information and poor post-operative care, since regulatory systems are frequently rudimentary or lacking. Moreover these dangers of receiving completely unproven products come with a hefty bill.

Harmonisation between European countries has improved since the European Tissue Directive. However, in terms of production of a therapy, different standard regulatory rules are still applied in different countries. Since the UK is a small market, this means there is still a significant barrier to developing a therapy acceptable across Europe.

Authors:

Professor S. Kimber, Professor of Stem Cells and Development

Professor C. M. Kielty, Professor of Medical Biochemistry

12 September 2012

Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, Professor Michael Linden, King's College London and Professor Charles Ffrench-Constant, University of Edinburgh - Oral evidence (QQ 1-20)

Dr Ludovic Vallier, University of Cambridge, Professor Steven Sacks, King's College London, Professor Michael Linden, King's College London and Professor Charles Ffrench-Constant, University of Edinburgh - Oral evidence (QQ 1-20)

[Transcript to be found under Professor Charles Ffrench-Constant, University of Edinburgh](#)

Professor Andrew Webster, Science and Technology Studies Unit (SATSU), University of York – Written evidence

The public perceptions of regenerative medicine

1. The term 'regenerative medicine' is not one that is familiar to many members of the public, unlike the more established 'stem cells'. The latter has had much greater media coverage and so engagement with diverse publics through the wide-ranging debates over embryonic stem cells, the 2008 MRC/BBSRC 'Stem Cell Dialogue', and the variety of public engagement activities that were associated with the former UK National Stem Cell Network (2008-11) linked to the Research Councils' 'festivals of science', or bespoke road-show events run by the same network and UK Stem Cell Bank within the UK during 2011. Other regional activities have complemented this.

2. In contrast, 'regenerative medicine' (referring to the wider domain of tissue engineering, gene therapy, cell therapies etc) has had relatively little prominence in public debates. Moreover, though there has been quite extensive social science research on regenerative medicine in regard for example to clinical trials (Webster *et al* 2011), regulation (Gottweis *et al*, 2009; Salter and Salter, 2010;), the comparative analysis of the field at a global level (Webster, 2013), and the tissue economy (Waldby and Mitchell, 2006; Plagnol *et al* 2009; Faulkner 2012), public perception as such has been little studied by those working in this field. While public engagement with science in the broadest terms is now the focus of a major new research project at the University of Nottingham, funded by the Leverhulme Trust (2012-15) entitled 'Making Science Public', it is still the case that the empirical work does not include regenerative medicine. Finally, there has also been very little by way of a sustained programme of public engagement with respect to regenerative medicine by government, similar to the early days of stem cells developments, when it was then noted by the House of Lords Science and Technology Committee (in 2000 and 2002) that public engagement practices were 'ad hoc, passive and disconnected from the policy making process'.

3. There is then a need for more sustained research and policy engagement in regard to public engagement and the cultural attitudes found therein. It is, even so, possible to make some tentative extrapolation from the earlier work on stem cells (such as the MRC/BBSRC 'Dialogue'), as well as from the few studies that have touched on this in the US and elsewhere. Recent doctoral work by Richard Elliott (2012) provides a useful overview of some of the core issues here: these include the publics' reliance on media news stories for their information on regenerative medicine, though these often are treated with caution and skepticism; patient groups acting as key drivers of the regenerative medicine promise through their own support (including financial – such as the BHF) for the field; diverse and complex views about the field that reflect their experiences of disease, judgements about alternative, readily available treatment, and issues surrounding ethical questions over the use of human tissue, allied to socio-economic considerations related to health equity and effective use of limited health resources.

4. Extrapolation from the MRC/BBSRC 'Stem Cell Dialogue' report provides some indicators regarding public perception of the field since in some of the data gathering exercises reference was made to 'regenerative medicine'. Members of the public from

across the UK (n=200) gave their broad support for research which related to serious diseases (and drew some clear boundaries around what the latter might be – degenerative disorders, cancer etc in contrast to more ‘cosmetic’ needs). In regard to the clustering of ethical values in the area, three groups were identified, ‘confident supporters’, ‘selective acceptors’, and ‘pro-life critics’. More generally, there were concerns over commercial exploitation by firms and the long-term affordability of treatments. These views led the authors of the report to suggest that in order to encourage productive public engagement, future developments in the area need to be characterised by greater investment and coordination between public and private sectors, clearer indication from the private sector of the social value of their investment, and much greater transparency over the sourcing and use of donated tissue (such as foetal tissue, IVF-derived oocytes and so on).

5. Work led by SATSU (see evidence from the REMEDiE project: www.york.ac.uk/remedie) has included examination of the governance of regenerative medicine, an important issue which can have a significant impact on public perception. Governance of regenerative medicine is highly fragmented across Europe because of differences among Member States and the multiple agencies involved. There is considerable variation in contexts for clinical trials and the social role they play beyond trials. As interaction between states, international bodies and networks become more complex, so new forms of multi-level governance, (transnational, public/private, global) become more pressing while the recruitment of patients/tissue donors is an important route for accessing core material but issues of informed consent among different public groups and the impact of cultural and religious differences are still being debated within these different governance settings.

6. The REMEDiE project work on the procurement of oocytes for research by regenerative medicine labs exemplifies this complex public landscape. We can see a trend towards different forms of commercialization of oocytes for research in recent years, and closer links between IVF clinics, research labs and companies that results from this. At the same time, managing such processes in such a way as to secure public legitimacy has to be understood in a context where most countries in Europe and elsewhere are seeking competitive advantage in the emerging regenerative medicine sector. Germany, the UK and Spain are prioritising regenerative medicine within their national research strategies, providing funding for major research centres, shared infrastructure such as cell banks, support for commercialisation and developing regulatory frameworks which facilitate research with human embryonic stem cells. At the EU level support for RM research has facilitated the development of scientific collaborations between scientists in member states, facilitated standardisation (for instance through the human embryonic stem cell registry) and has also benefited industry. The development of a harmonised regulatory framework for RM products is seen as a major advance on the previous patchwork of divergent national frameworks.

7. These various risks have led the International Society of Stem Cell Research to stress the need for oversight of clinical experimentation and trials. Within the regulatory context other issues arise: whereas in the US the system for regulating clinical trials via the IND procedure is a federally harmonized procedure, in Europe, clinical trials registration and approval – although sought to be harmonized on the supra-national level via the Clinical Trials Directive (CTD) and subsequent policies -- still is in the hand of National Competent Authorities. However, the CTD – often heavily criticised by stakeholders in the field – has been opened up for renegotiation in December 2012. It is still unclear in which direction the policy process will go, and a new draft is to be elaborated soon. The impact on clinical trials

in Europe, and regenerative medicine clinical research more specifically, has to be assessed in the course of the ongoing policy making process, and in particular how patient groups and thereby the wider public's expectations about these trials, their involvement in them, and expectations of them, will be managed in an open way.

8. Public perception has an especially strong focus on patient safety so there will be a need for new models of monitoring of clinical trials as scale-up occurs, that go beyond conventional forms, such as found in regard to pharmacovigilance. Moreover, the prospective take-up of new products will depend on firms addressing more effectively matters of clinical utility and relevance against existing therapies or products, if they are to persuade patients, clinicians and the wider public of the relative merits of regenerative medicine. At the same time, this requirement appears to be one that is at least to be met within a favourable political climate in terms of public receptivity to regenerative medicine. The most recent report from the Eurobarometer that examined the field shows broad support for it. As the report itself observed: 'Developments in regenerative medicine attract considerable support across Europe. 68 per cent of respondents approve of stem cell research and 63 per cent approve of embryonic stem cell research', though it does go on to note that 'Approval is contingent upon perceptions of adequate oversight and control' (2011, p.8).

9. In conclusion, public perception has to be seen against the backdrop of evidence summarised above of a complex regulatory and research landscape that is on the cusp of developing its first products, but which as such will need to do so with a public engagement (through patient groups especially) that works with rather than hides the uncertainties ahead, and that develops more transparency in respect to the public/corporate relationships especially if, as seems likely, the NHS becomes a more explicit resource (in terms of access to patient records, tissue and new forms of trialing) for the field.

10 November 2012

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Wellcome Trust – Written evidence

Key Points

- The UK needs to maintain support for basic research in all avenues of regenerative medicine research, as well as applied and translational research.
- To facilitate translation of regenerative medicine, a culture of research should be embedded within the NHS. The system of obtaining research approval from NHS R&D departments needs to be overhauled, something the Government is currently looking at. Healthcare professionals should be encouraged to engage in research and should be educated in new applications and technologies.
- The UK must maintain a facilitative regulatory regime for the translation of research into healthcare benefits.
- The UK government needs to take a proactive lead in discussions in Europe on Horizon 2020 funding programme, which could affect the outlook for stem cell research.
- It is critical that industry, academic and clinical partnerships are developed to facilitate and accelerate the translation of research in regenerative medicine for clinical therapies.
- Researchers should be cautious not to ‘over-hype’ the potential healthcare benefits of regenerative medicine research, especially stem cell research, in communications with the public. Although some therapies may undergo clinical trials over the next five years for particular conditions, many more may take longer to develop.

Introduction

1. The Wellcome Trust is pleased to have this opportunity to respond to the call for evidence issued by the House of Lords Select Committee on Science and Technology. We have consulted with experts internally and externally in the field of regenerative medicine to inform our response.
2. The inquiry uses a broad working definition of ‘regenerative medicine’, which is taken to refer to any methods that replace or regenerate human cells, tissues or organs in order to restore or establish normal function. This definition includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques. We have included examples that cover this broad definition and do consider the field as a whole but the main focus of our response is on stem cell based regenerative medicine, this is primarily because this is where the majority of our funding lies. However, we do agree that it is sensible to consider a broad definition and look at the regenerative medicine field in its entirety as many of the issues encountered in the field are cross-cutting.

Funding and the research base

3. **Research Funding:** The Wellcome Trust funds regenerative medicine, as defined broadly by this inquiry, through a number of routes. Our overall funding totals over £70 million and covers a full spectrum, from basic science research to translating regenerative medicine technology and public engagement and from stem cells to medical engineering.
4. In the last five years, the Wellcome Trust has spent approximately £40 million on basic stem cell research. A recent award includes £5.6 million to the newly established Wellcome Trust-MRC Cambridge Stem Cell Institute, the amalgamation of two stem cell centres at the University, which draws together basic and clinical stem cell scientists from across Cambridge to generate new knowledge about the biology of stem cells and provide the foundation for new medical treatment. In addition, and reflecting the potential opportunities presented by induced pluripotent stem (iPS) cells, the Trust and MRC are to fund a joint project that aims to establish a human iPS cell collection from normal and patient groups, allowing the exploration of the impact of genetic variation on cell phenotype and ultimately providing new insights into disease mechanisms. This programme will be announced publicly in October and is embargoed until then.
5. The Technology Transfer Division (TTD) at the Wellcome Trust invests in translational research projects across a broad spectrum of technologies via Programme Related Investments (PRIs) that are governed by U.K charity law. TTD has funded 16 awards in the field of Regenerative Medicine worth £30.8m. Of the total seven awards have been made to academic institutions, seven awards have been made to biotechnology companies and we have also jointly funded two Medical Engineering Centres of Excellence with the Engineering and Physical Science Research Council (EPSRC). The work of these centres comes under a broad definition of regenerative medicine, for example at Imperial College ('A centre for medical engineering solutions in the management of Osteoarthritis') and Leeds University ('Engineering solutions for an ageing population with musculoskeletal and cardiovascular disease - 50 more years after 50').

Four of the total sixteen awards have been made via the Health Innovation Challenge Fund, which is a parallel funding partnership between Technology Transfer and the Department of Health. The aim of the scheme is to stimulate the creation of innovative healthcare products, technologies and interventions and to facilitate their development for the benefit of patients in the NHS and beyond. One example of this funding is Professor Robert MacLaren's project at the University of Oxford which is a Phase I clinical trial of gene therapy for blindness caused by choroideraemia.

TTD has just announced the new Translation Fund, which is a merger of two previous funding schemes.³⁴⁴ In recent years, huge advances have been made in translating stem cell research and other areas of regenerative medicine such as developing novel medical devices that can replace the function of an organ. These areas of medicine are examples of themes TTD will consider as part of 'Restoring the Body', the first strategic highlight for the scheme. 'Restoring the body' will encourage research proposals aiming to restore function to the body and enable people to lead full and independent lives.

³⁴⁴ <http://www.wellcome.ac.uk/News/2012/News/WTVM056287.htm>

6. We also fund public engagement activities to encourage discussion about stem cell research. For example, a recent project funded by a Wellcome Trust Small Arts Awards saw artist John O'Shea spend time in the Clinical Engineering Research Unit at Liverpool University with scientists Professor John Hunt and Theun Van Veen. The artist sculpted a football made from pig stem cells, replicating the same techniques used to create artificial human organs and encouraging viewers of the sculpture to consider the role stem cells will have in daily life in the future.³⁴⁵ This kind of public engagement work asks the public to think laterally about regenerative medicine technologies and to engage with such technology in different ways.
7. **Basic and applied research must be supported:** It is crucial that regenerative medicine research, particularly for stem cells, is supported across all parts of the innovation chain, from basic research through to clinical use. It is critical to ensure the government's current focus on treatment outputs as key indicators of success does not lead to a reduction in funding for basic research. For example, it is not clear which types of stem cells hold the most promise for therapies. Therefore, it is vital to continue advancing our understanding of all types of stem cells over the next five years. Fundamental research needs to continue in embryonic stem cells (eSC), adult stem cells, cord blood stem cells and induced pluripotent stem cells (iPSC - when adult somatic cells are forced to become pluripotent). Understanding the similarities and differences between the different stem cell types is crucial to determine their potential for use in different applications, for example in cell replacement therapies, in models of disease or for drug screening.
8. There continues to be a strong case for investment in stem cell research; while research in this area continues to develop rapidly and promisingly, the research infrastructure must keep pace. A recent development is the rapidly growing potential of iPSCs. There is an identified need for investment in banking and distribution facilities for cell lines in order to increase their availability to researchers and maximise potential benefits for patients. The Trust recently committed £8.75 million to part-fund the establishment of a UK human iPSC cell collection with the MRC, to be publicly announced in October.
9. In the current EU discussions regarding Horizon 2020, the future funding programme for science in the EU, it will be important to maintain a hospitable climate for stem cell medicine research. This may also provide an opportunity for opponents of stem cell research to open up wider discussions about changing the regulatory climate for stem cell research as well as discussions about funding such research. It will be important for the UK government and scientific community to advocate for stem cell research should the need arise. The Trust alongside a coalition of leading funders of biomedical research and patient groups has issued a joint statement calling on the European Parliament to continue funding human embryonic stem cell research.³⁴⁶ This statement has garnered support from a large range of UK and European organisations.³⁴⁷

Application of the science

³⁴⁵ <http://www.pigsbladderfootball.com/about.html>

³⁴⁶ <http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/EU-funding-for-stem-cell-research/Full-statement/index.htm>

³⁴⁷ <http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/EU-funding-for-stem-cell-research/Signatories/index.htm>

10. We are funding translation projects as detailed above in paragraph 5. We would reiterate our concern that basic research should not be ignored at a time where it might appear attractive to focus more resources on translation.

Focussing on stem cells, in the next five years we anticipate advances in:

11. ***Direct re-programming of somatic cells:*** In the next five years direct re-programming may provide an alternative to stem cells in some applications. Direct reprogramming is a process in which one type of differentiated cell is transformed into another, without going through a stem cell stage.
12. ***Cell models:*** Importantly, stem cells provide the opportunity to produce cell models, useful for research on specific diseases and also large scale pharmaceutical screening. The advantage of human stem cell based models, is that they can possess specific mutations of polymorphisms associated with human disease. The Trust expects to see the development of these models in the near future which will allow for the large scale screening of drugs in a predictable and reproducible format.
13. ***Cord blood stem cells:*** In the next five years we also anticipate advances in the use of cord blood stem cells. Within the European Union there are moves towards advancing this area of medicine and making these cells more readily available for research. For example, the European Union is funding EUROCORD-ED to educate scientists and healthcare professionals in umbilical cord blood biology; disseminate best practice; and increase understanding of regulatory issues and to accelerate translation. There are two public cord blood banks in the UK, the NHS cord blood bank and the Antony Nolan Trust cord blood bank. The Antony Nolan Trust cord blood bank is combined with a research facility and aims to store 50,000 donations by 2013, 20,000 of which are suitable for transplantation and 30,000 for use in research.
14. ***Endogenous stem cells:*** Researchers ultimately wish to move away from cell-based replacement therapies toward harnessing the capacities of endogenous stem cells. This would minimise the issues involved in generating cells for implantation, risks of surgery, and could decrease the associated risks of developing cancer. The timeframe in which this can be achieved is uncertain. For this change in strategy, further advances in the understanding of endogenous stem cells and their environment, the stem cell niche, are required. Multiple Sclerosis is a condition which is more readily amenable to therapies using this approach because the resident population of oligodendrocyte precursor cells (OPCs) is relatively well characterised when compared to other progenitor populations. Already, several pathways that regulate their differentiation have been identified, and are possible targets for endogenous stem cell therapies.
15. ***Neural stem cell therapy*** Research into neural stem cell therapy holds promise for the treatment of many conditions, including early spinal cord injury, neurodegenerative disorders and brain cancer. There remain challenges to the safe and successful development of neural stem cell therapy, notably: detailed characterisation of the cell types; scalable methods for exact cell production; and immunological compatibility. Researchers at the Wellcome Trust Sanger Institute in Cambridge working with neural stem cells include David Ryan, a Wellcome Trust-funded Clinical Research Fellow looking at neural stem cells in glioma therapy. Given safety concerns about cell compatibility and tumour-forming propensity, they are currently focusing on autografts

of cells generated through induced pluripotent stem cell (iPSC) technology, which allows genetic matching of cells to the diseased or damaged tissue.

Current gaps in scientific knowledge on stem cells

16. Currently, there is a lack of appropriate disease models in which to test the efficacies of many stem cell therapies. For example, in Multiple Sclerosis research, the most widely used animal models are those involving pharmacologically-induced demyelination injuries. These models of acute demyelination may differ critically from the human disease, which is characterised by progressive and episodic demyelination. It is a common goal throughout the scientific community to develop models that more closely mirror human diseases.
17. As outlined above in paragraph 12, stem cells also provide the opportunity to develop human cell-based models from affected individuals that could be useful in testing therapeutics. A resource that would be of particular use in this area would be the creation of a public national stem cell bank, including cells isolated from individuals affected by monogenic diseases. This would provide the opportunity for researchers to access stem cells associated with particular conditions which could be used to make a variety of differentiated cell-based models in the laboratory. These could be used to study pathological processes and potential interventions.
18. More basic research on stem cells is required to understand how to scale up the process of growing and maintaining stem cells *in vitro*. This will be necessary both if cells are to be used in large screening protocols, or in cell-based therapies. Additionally, more research is required to investigate the ability of these cells to differentiate *in vivo*, as well as their long-term stability.
19. Progress is needed in the development of outcome measures with which to evaluate the success of interventions and therapies. Two areas that may hold particular promise in determining where regeneration has taken place are improved imaging techniques and the use of biomarkers.

Current and future therapies

20. Stem cell research is already finding its way into therapeutics in the UK. For example, many people with Limbal stem cell deficiency have been treated with cultured Limbal stem cells to restore their sight.³⁴⁸ And recent research holds promising signs for Alzheimer's patients over the longer-term.³⁴⁹
21. In the UK, we understand that the early therapeutic use of stem cells holds most promise in organs/tissues with the most simple cellular architecture, for example cell replacement therapies for retina, cartilage and skin. Proof-of-concept clinical trials (Phase 1-2) are anticipated in cardiovascular disease and peripheral vascular disease in the next five to ten years in the UK. Harnessing endogenous stem cells through pharmacological approaches may also have clinical impact in certain conditions, such as Multiple Sclerosis, in the near future.

³⁴⁸ Ahmad S et al., 2010 Stem Cell therapies for ocular surface disease Drug Discovery Today volume 15 2010 306-313.

³⁴⁹ http://alzheimers.org.uk/site/scripts/news_article.php?newsID=922

22. In the longer term (up to 15 years), there are possibilities for stem cell-based therapies for diabetes (beta-islet cell replacement), Parkinson's disease and a stem cell-based therapy for a common form of hearing loss in humans (auditory neuropathy) based on research in gerbils.³⁵⁰
23. However, we would urge that the communication of potential therapies to the public needs to be realistic and not 'over-hyped'.

Barriers to translation

Research in NHS

24. The UK's reputation as a competitive location for world-class research has been built on our world-leading universities and research institutes, the quality of our research infrastructure, and the perception that the UK government and public are strongly supportive of science. Specifically in the field of stem cells, the UK is considered to be a world leader in basic stem cell research and the field received both public and political support during the debate surrounding the passing of the Human Fertilisation and Embryology Act 2008 and subsequent amendments.
25. However barriers to research have a knock on effect to translating regenerative medicine in wider sense too. These barriers include R&D approvals for clinical trials. This applies to stem cells but also other areas such as medical engineering and medical devices. We are aware of, and welcome, initiatives underway to address concerns around barriers to research such as the NIHR Research Support Services Framework.
26. Currently the NHS does not capitalise enough on the UK's strengths in research. The NHS Innovation review recognised the need to increase the uptake of innovative activities in the NHS. The NHS should build on our strong research base, to be the catalyst for uptake of research into clinical practice. We support on-going efforts to embed research as a core function across the NHS. The NHS lacks the capacity and capabilities necessary to facilitate adoption of new technologies and the regulatory environment presents barriers to the efficient translation of research into healthcare practice. Furthermore, educating healthcare professionals on the importance of research in general, as well as the potential of new technologies such as stem cell-based therapies, is vital to increase participation in clinical trials and to promote translation.
27. A major issue for researchers has been obtaining research permission from the NHS to carry out their work. We support the findings of the Academy of Medical Sciences (AMS) report 'A new pathway for the regulation and governance of health research'³⁵¹ which found that NHS Research and Development (NHS R&D) permissions are perceived to be by far the single greatest barrier to clinical studies in the UK within the regulation and governance framework. In England there is no set timescale for this process and the AMS report found that the NHS R&D permission process is duplicative and inconsistent. R&D offices were widely seen as being inefficient, inconsistent and risk averse

³⁵⁰ <http://www.wellcome.ac.uk/News/2012/News/WTVM056288.htm>

³⁵¹ <http://www.acmedsci.ac.uk/index.php?pid=47&pid=88>

28. The Government has set out measures intended to address these issues in the Plan for Growth. These measures include the NIHR Research Support Services Framework and greater accountability through a 70 day benchmark to recruit first patients for trials, which is tied to NIHR funding. We look forward to seeing how these developments progress.
29. We would suggest that regenerative medicine should be led from within the NHS, with active involvement from clinicians and medical schools from the outset. This would ensure that new treatments and their R&D would be driven and undertaken by the potential end users and that the scope of the research and the resultant technology would be fit for purpose, providing benefits above and beyond existing standard of care.

Cost of research

30. Another cross cutting issue, wider than stem cells, is the high cost of developing regenerative medicine therapies, particularly stem cell therapies due to initial trials being based on individual patients. This has raised the problem of who should provide funding; the public purse, industry, venture capital firms or a collection of partners? To assess the affordability of regenerative medicine in clinical care pathways it will be necessary to take a lifetime perspective. For example, stem cell therapies that replace diseased cells with healthy cells have the potential to permanently eradicate a disease. Long-term follow-up studies on the efficacy of these treatments will be required to determine the cost and benefit of these therapies to compare with conventional ones. Unlike drug treatment, the benefits of stem cell therapy could be life-long. This may require the development of new methods to assess benefit.
31. The limited access to risk capital in the UK has been described as a contributing factor to the UK's lack of recent global success stories compared to the US where companies, for example Genentech, have taken a global lead. We therefore encourage the UK's leading researchers to engage globally to access the risk capital required to translate these therapies. Furthermore, the development of more academic, clinical and industrial partnerships, similar to the Stevenage life sciences cluster, may create an environment with better understanding of risks that could stimulate investment in the future.

Regulation

32. Collaborations between industry, academia and the NHS are required for the efficient translation of regenerative medicine technologies, again an issue that applies more widely than just for stem cells. Uncertainties in the regulatory and R&D environment may discourage investment from venture capitalists and pharmaceuticals. The recommendations outlined in this response to improve the culture of research in the NHS and to decrease the regulatory burden (see paragraphs 24- 29) should decrease the uncertainties and risks involved in taking regenerative medicine therapies to clinic and could increase industry participation.
33. We welcome the establishment of the Health Research Authority (HRA) as a move that will reform and streamline the regulatory system around much health related research, including regenerative medicine. We also think that the HRA has an important role to play in creating a clearer and more certain environment. We are pleased that the HRA appears to be taking a proactive approach to streamlining the regulatory process and we look forward to seeing how these positive changes affect regenerative medicine.

34. The Trust has concerns about the negative impacts of the current European Union Clinical Trials Directive (EU-CTD). We have suggested a number of improvements to the Directive, for example to introduce more proportionate regulation and to streamline the authorisation process for clinical trials.³⁵² The Commission's proposal for a Regulation to replace the current Directive attempts to address a number of our key concerns and we look forward to working with European legislators and the Medicines and Healthcare products Regulatory Agency to ensure the Regulation meets these goals.
35. Any discussion about the future of the HFEA and HTA will clearly have an impact on the regulation of stem cell therapies and possibly other regenerative medicine technologies. The Trust is responding to the current Department of Health consultation.
36. In any debates on regulation and regenerative medicine, it is important that on-going public dialogue continues so that public concerns and expectations can be addressed and managed. A recent example, albeit on a different area of medicine, is the HFEA consultation on MID which is engaging the public on a breakthrough area of medicine.

Barriers to commercialisation

37. Patenting

Patenting is becoming an increasingly controversial issue, in particular with stem cells. The outcome of the European Court of Justice (ECJ) case of *Brüstle v Greenpeace* is likely to have ramifications for the translation and commercialisation of therapies stemming from embryonic stem cells in Europe and for research in this field. The ECJ ruled that a process involving removal of a stem cell from a human embryo at the blastocyst stage, entailing the destruction of that embryo, cannot be patented. However the full impact of this judgement is not yet clear.

38. Technology Strategy Board (TSB) Catapult

We look forward to seeing the development of TSB's Cell Therapy Catapult and for the Catapult to deliver on its potential for stem cell therapies. Whilst there has been much national support for the Catapult, it is important to build on this. It will be important going forward to clarify the role of Catapult for the research community.

39. Affordability

The practical implementation of some regenerative medicines may potentially be beyond the capacity of the NHS, as the treatments may need to be personalised. This applies to stem cells but also more widely to regenerative medicine technologies. The health economics may only balance if the treatments are for niche / orphan indications or where the long-term patient costs are taken into account. Future clinical technologies may require that NHS pricing structures look at long-term costs e.g. if the cost of patient re-admission off-set by the cost of a long-term treatment. If a treatment costs thousands of pounds per patient, as maybe the case with a personalised regenerative medicine, NICE may find this difficult to approve.

40. The route to market and the delivery of living tissue to patients is an infrastructure challenge or perhaps an opportunity for institutions which already deliver some living

³⁵²http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/WTX058237.PDF

products -such as the National Blood Transfusion Service- to take the lead in developing a pathway when the time comes.

International comparisons

41. In stem cell research, the UK is a world leader. The most common collaborations in the community are within the UK. We understand that researchers in the UK also collaborate with academic and industry partners in North America and Europe, while collaborations with Asia are less frequent at the present time. However, Asia is seen as an area of potential growth, particularly because researchers perceive there being less of a regulatory burden in Asia than in the UK, which could make it an attractive destination for further research. In early 2011 the Chinese Academy of Sciences launched Innovation 2020, which made stem cell research one of seven research priorities for the country¹⁵.
42. We acknowledge that the location of future collaborations is hard to predict and will largely depend on the funding environment. It will be important for the UK government and research community to engage in international discussions around the regulation and funding of regenerative medicine from an early stage.
43. The US has strengthened its position in regenerative medicine due to stronger federal support for stem cell research. There is a perception amongst researchers that the United States Food and Drug Administration (FDA), is more willing than the MHRA to engage with scientists at early stages of research. We would encourage the UK to adopt an approach which facilitates dialogue between researchers and regulatory agencies at all stages of the approvals process. Currently communication with regulatory agencies is often restricted to formal applications, which are not well suited to iterative processes of development. Forums that allow earlier engagement of researchers with regulators could streamline this process. Regulators of regenerative medicine should be encouraged to understand the importance of iterative development and flexibility in the production techniques for complex Advanced Therapy Medicinal Products (ATMPs), such as cell-therapies during phase I trials.
44. Japan is preparing for translation on a large scale should iPS stem cell technology be shown to be successful in humans. Professor Shinya Yamanaka of Kyoto University has established a cell bank for the production of stem cells.³⁵³ This is something the UK government and funders should examine for the future. As mentioned in paragraphs 4 and 8, the Trust will announce in October joint initiative with the MRC to increase understanding of iPSC technology.
45. The Trust is aware of the importance of this consultation to help the UK maintain UK its competitive position as a leader in regenerative medicine, both for societal benefits and as a driver for the UK economy. We await the outcome of this consultation with interest. We would be very happy to discuss our response in more detail.

28 September 2012

³⁵³ <http://www.nature.com/news/stem-cell-pioneer-banks-on-future-therapies-1.11129>

Wellcome Trust, British Heart Foundation (BHF) and Government–Department of Health (DH) and Medical Research Council (MRC) – Oral evidence (QQ 42-63)

Wellcome Trust, British Heart Foundation (BHF) and Government–Department of Health (DH) and Medical Research Council (MRC) – Oral evidence (QQ 42-63)

[Transcript to be found under Government–Department of Health](#)

Wellcome Trust Sanger Institute (WTSI) – Written evidence

The Wellcome Trust Sanger Institute (WTSI) is pleased to have the opportunity to contribute to the Select Committee on Science and Technology call for evidence on regenerative medicine.

1. We believe that the UK is well placed to contribute to and benefit from the translation of knowledge from world-leading research to regenerative medicine treatments. It has the expertise, particularly strengths in mammalian cell biology and genomics, and a number of centres of excellence. However, this task will require a very large and long-term investment in the research needed to refine current strategies for regenerative medicine and to develop new ones. The USA is currently leading the field of regenerative medicine, in large part due to the amount of funding it has accessed, and Asia, especially Japan, has great potential.
2. Stem cells offer incredible opportunities as a research tool and the ground-breaking achievement of generating induced pluripotent stem cells (iPSCs) has led to an array of possibilities for systematic studies of human gene function. Their use is particularly valuable to study cells that cannot easily be isolated or expanded in culture and to observe cellular processes that may have occurred in diseases that lead to the destruction of certain cell-types.
3. Next generation sequencing (NGS) technologies are now allowing researchers to develop comprehensive catalogues of genomic variation and regulation and to investigate differences between organisms and cells, over the course of their development as well as in response to treatment and environmental exposures. The ability to apply NGS technologies to study stem cells will advance our understanding of cell biology and how it may be affected in a wide range of medical conditions, from cancer to rare diseases, thereby creating opportunities for the development of regenerative therapies.
4. There are many technical challenges that need to be resolved to produce stem cells in a consistent and robust manner and there are currently only a handful of cell-types into which scientists know how to differentiate stem cells *in vitro*. Research progress has been hindered by a lack of general consensus on how stem cells should be assayed and selected, which is key to enabling comparison between research groups. WTSI researchers have devoted considerable efforts to establishing standards for iPSC methods.³⁵⁴ Further efforts to develop authoritative guidance on definitions of different stem cell types will be very important.
5. Comprehensive genome-wide studies of genetic variation in stem cells and their characterisation will require large-scale programmes and high-throughput facilities as many genetic and phenotypic assays require large quantities of cells (e.g., 1 billion cells for mass spectrometry analysis). In addition to generating a wealth of knowledge that can benefit medicine, this research is likely to contribute to developments in methods for cell production.

³⁵⁴ Wang et al., Rapid and efficient reprogramming of somatic cells to induced pluripotent stem cells by retinoic acid receptor gamma and liver receptor homolog 1, PNAS 108(45):18283-8, Nov 2011.

6. Genetic engineering technologies have considerably evolved, notably with a major breakthrough led by WTSI scientists,³⁵⁵ and they are likely to be key to success in several areas of regenerative medicine. In a proof-of-principle study, WTSI researchers and their collaborators have demonstrated that a point mutation gene deficiency affecting liver metabolism can be functionally corrected in human iPSCs.³⁵⁶ WTSI researchers have also recently shown that changing the genetics of immune cells may be a way to destroy cancer cells,³⁵⁷ and they are investigating the use of iPSC-based neural stem cells in glioma treatment. Translating novel techniques such as these into healthcare benefits requires long-term commitment and funding support.
7. WTSI has particularly focused on developing genetic resources that enable scientists to study disease, uncover underlying molecular and cellular mechanisms, and experiment with therapeutic approaches. The opportunities and challenges described above have led the Institute to considerably expand its stem cell and cellular phenotyping activities to study the impact of genetic variation at the cellular level. Current plans include the production, analysis and sharing of human iPSC from thousands of healthy individuals and individuals from specific patient cohorts, and of human iPSC and mouse ESCs engineered to be homozygously null for ultimately all protein coding genes. Widespread research use of stem cells has been limited by the expertise required to prepare them to analyse gene function and such a resource is therefore greatly needed. This initiative has attracted experts from organisations around the UK with whom WTSI is collaborating closely to maximise the platform's utility. A particular feature of WTSI phenotyping that will be extended in the future is to study response to a controlled series of pathogen challenges. The platform will also provide opportunities for the screening of small molecules and drugs. The latter capability is of particular interest to the pharmaceutical industry.
8. The value to the UK of successful developments is potentially very large as significant areas of unmet clinical need may be addressed (e.g., organ failure). The UK needs to be world-leading to attract commercial investment and a net inward flow of potential related spending. This will require continued and substantial investment in research and secure technology. Patents have been important to protect innovators' freedom-to-operate. Realistic timeframes must also be set. Rushing the development of therapies in particular has the potential to cause serious setbacks. A robust regulatory system will guarantee that only safe and trusted products are developed.

Author: Stephanie Dyke, WTSI Policy Adviser

20 September 2012

³⁵⁵ Yusa et al., Generation of transgene-free induced pluripotent mouse stem cells by the piggyback transposon, *Nature Methods*, 6(5):363-9, May 2009.

³⁵⁶ Yusa et al., Targeted gene correction of α_1 -antitrypsin deficiency in induced pluripotent stem cells, *Nature*, 478:391-6, Oct 2011.

³⁵⁷ Li et al., Reprogramming of T Cells to Natural Killer-Like Cells upon Bcl11b Deletion, *Science*, 329:85-9, Jul 2010.

Welsh Government and the National Institute for Social Care and Health Research (NISCHR) – Written evidence

Letter from Lesley Griffiths AC/AM, Minister for Health and Social Services

The Welsh Government welcomes the opportunity to respond to the House of Lords Select Committee on Science and Technology call for evidence on regenerative medicine. Please find the Welsh Government response, which has been prepared by officials from the National Institute for Social Care and Health Research (NISCHR), following.

- 1) The National Institute for Social Care and Health Research (NISCHR) and the Welsh Government welcome the opportunity to respond to the House of Lords Select Committee on Science and Technology call for evidence on regenerative medicine.

Regenerative medicine research and funding landscape in Wales

- 2) In Wales, health and social care research is supported by the Welsh Government through NISCHR, the Higher Education Funding Council for Wales (HEFCW) and the Department for Business, Enterprise, Technology and Science (BETS).
- 3) NISCHR is the Welsh Government body that develops, in consultation with partners, strategy and policy for research in the NHS and social care in Wales. To support its policies, NISCHR invests strategically in funding schemes and initiatives and funds a national research infrastructure for Welsh researchers. In addition, NISCHR commissions services and works in partnership with other funding bodies to provide further support to health and social care researchers in Wales.
- 4) NISCHR recognises the importance of regenerative medicine research and NISCHR response-mode funding calls are open to researchers working in this field. In recent years, NISCHR has invested in grants to support studies investigating the potential of stem cell / progenitor transplantation and the stimulation of endogenous repair mechanisms.
- 5) HEFCW provides core funding for research through its Quality Research (QR) funding stream with allocations to institutions based on the quality and volume of research submitted to the UK-wide Research Excellence Framework. In 2011/12, HEFCW, provided £14.8m of Quality Research funding to support research in clinical medicine, dentistry and subjects allied to medicine.
- 6) In Wales, there are several active research groups working in the field of regenerative medicine and stem cell research, including The Cardiff Institute of Tissue Engineering and Repair (CITER) which is based at Cardiff University. CITER conducts interdisciplinary research into mechanisms of tissue repair, regeneration and rehabilitation. Furthermore, the European Cancer Stem Cell Research Institute, also based at Cardiff University, is investigating the role of cancer stem cells in tumour formation.
- 7) We would like to make the following comments in response to the questions and issues highlighted in the call for evidence.

Barriers to translation

What difficulties are encountered when conducting clinical trials and how could these be overcome?

- 8) The state of transplanted cells is often unknown in pre-clinical and clinical trials of cell-based therapies; unlike trials of drugs, the dosage and survival of cells is difficult to determine due to the ability of cells to multiply and the variability of immune responses in hosts. The situation is further complicated as cell batches often vary over the course of the trial. Therefore, there is a need for further work to generate quality controlled, 'clinical-grade' cell lines. Supporting ongoing work at the UK Stem Cell Bank to develop 'clinical-grade' human embryonic stem cell lines will be an important step to overcome these hurdles.
- 9) Regenerative medicine treatments often target super-orphan and chronic conditions. It will be important to determine measures of success for chronic illnesses; for example, would success be defined as maintaining the current status of the illness or delaying the onset of serious adverse events?
- 10) There is considerable variability in disease type for many illnesses treated by regenerative medicine therapies. This complicates clinical trials as it becomes more difficult to obtain clear demonstrations that treatments work. It will be important for funders to support research to develop suitable biomarkers to enable a stratified approach to regenerative medicine therapies. Clinical trials in regenerative medicine are also complicated by the need for long-term assessment of both positive and negative outcomes and the need to back-correlate to frozen donor samples. Supporting researchers in improving the design of clinical trials will be essential for the generation of future therapies. In Wales, support and advice on trial design and methodology is provided by 4 UKCRC-registered clinical trials units, 3 of which are funded by NISCHR (a fifth unit with haematological expertise has recently received provisional UKCRC registration).
- 11) There are significant hurdles facing basic scientists who wish to progress their research beyond the bench. In particular, researchers often lack the expertise, knowledge and confidence to expand their work into preclinical / clinical trials. The regulatory workshops proposed in 'A UK Strategy for Regenerative Medicine' and the UK Stem Cell Tool Kit will certainly help to address these issues. Moreover, embedding specialist staff with QA/QC expertise within universities and research institutions to provide advice on setting up preclinical / clinical trials would further help to overcome this hurdle.

What other difficulties are encountered conducting translational research within the NHS and how can these be overcome?

- 12) The translation of lab-based research to effective therapies requires strong collaboration between basic researchers and clinicians. For the field of regenerative medicine, it will be even more important for funders to provide incentives to encourage cross-disciplinary research involving biologists, clinicians and engineers. CITER brings together researchers from a range of disciplines in one research institution, and this is an approach that has often proved successful in forging strong multi-disciplinary

collaborations. Therefore, the UK Regenerative Medicine Platform call, which aims to establish interdisciplinary research hubs, should help to overcome the difficulties encountered in conducting translational research.

- 13) To efficiently capitalise on knowledge gained through basic science it is crucial to engage clinicians in research, and NISCHR funds a Clinical Research Time scheme to provide protected research and training time for clinicians. It will also be important to ensure that research methodology and training are included at the very early stages of clinical training to encourage a greater proportion of clinicians to become research-active.
- 14) Building on this, the formation of a specific UK research network in regenerative medicine would help to improve the co-ordination of clinical research, help to scale up activity in the field and drive collaboration with industry partners.
- 15) Funders need to ensure that there are incentives for scientists to consider the impact of their research at all stages of a project, and tools such as the ESRC Pathways to Impact toolkit help to realise the maximum impact of research. The Research Excellence Framework 2014 will encourage researchers to reflect on the impact of their recent research and this could help to underpin the translation of basic research into the clinic. Funders could also consider mechanisms in which funding is released in a step-wise manner upon the achievement of specific milestones. This helps to drive research towards an eventual patient benefit, and has proven to be successful within the Severnside Alliance for Translational Research (SARTRE).

Barriers to commercialisation

What role does patenting play in the commercial development of regenerative treatments?

- 16) Our research community has not drawn to our attention any particular issues or examples in relation to patenting acting as a barrier to innovation in regenerative medicine. We consider that IP rights should be managed proportionately in the context of the overall objectives of research and innovation so that they can help facilitate research, particularly collaborative research, and not hinder it. In this vein NISCHR is developing a set of IP principles to accompany our research funding terms and conditions which aim to ensure that the outputs of research achieve maximum benefit for patients. These principles will apply to funding associated with regenerative medicine.

What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

- 17) One barrier to commercialisation is the length of time taken to recruit patients for large-scale, late phase clinical trials. The development of secure, anonymised databases of pre-consented patients with illnesses requiring regenerative medicine interventions will help to make the UK more competitive in attracting investment from major pharmaceutical companies.
- 18) Given the complexities of conducting regenerative medicine clinical trials, it is even more crucial that NHS commissioning bodies take an active role at an early stage in the development of new therapies. This will help to ensure that costly trials are avoided for therapies that are not suitable for uptake by the NHS.

Summary

- 19) Clearly, more research is needed in the field of regenerative medicine to harness its potential. Whilst the actions outlined in 'Taking Stock of Regenerative Medicine in the UK' and the 'Strategy for UK Regenerative Medicine' will help to overcome many of the barriers facing researchers, innovative approaches will need to be taken if progress is to keep up with the pace of developments in other countries. NISCHR will continue to provide funding opportunities which are open to researchers conducting translational research in regenerative medicine.

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Dr Robert Westwood, Independent Consultant, Dr Graham M. Wynne, University of Oxford, Dr Angela J. Russell, University of Oxford, Professor Stephen G. Davies, University of Oxford and Professor Dame Kay E. Davies, University of Oxford – Written evidence

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[Submission to be found under Dr Angela J. Russell, University of Oxford](#)

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