

Science and Technology Committee

Oral evidence: [Regenerative medicine](#), HC 275

Tuesday 19 July 2016

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Written evidence from witnesses:

- [British Heart Foundation](#)
- [Research Councils UK](#)

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Members present: Dr Tania Mathias (Chair); Victoria Borwick; Jim Dowd; Chris Green; Graham Stringer; Derek Thomas; Matt Warman

Questions 1-91

Witnesses: **Professor Paul Riley**, British Heart Foundation Professor of Regenerative Medicine, University of Oxford, **Professor Stuart Forbes**, Professor of Transplantation and Regenerative Medicine, University of Edinburgh, and **Professor Peter Andrews**, Professor of Biomedical Science, University of Sheffield, gave evidence.

Q1 Chair: Welcome to this afternoon's session, and welcome to our guests. I am the interim Chair and most of our members are present. We have various questions, but could I ask you initially to introduce yourselves and spend a minute on your background in regenerative medicine, starting with Professor Forbes? We have your biographies; it is just for people listening who do not have that in front of them.

Professor Forbes: My name is Stuart Forbes. I am a director of the MRC centre for regenerative medicine in Edinburgh. I am also chair of transplantation and regenerative medicine. I look after people with serious liver disease, often on the verge of requiring transplantation or after transplantation. I work in the area of liver regeneration. I work on pre-clinical animal models through to first-in-human clinical trials.

Professor Riley: My name is Paul Riley. I am from the University of Oxford. I am British Heart Foundation professor of regenerative medicine and I direct the Oxbridge BHF centre for regenerative medicine. My work is primarily in basic science, and I use animal models moving right through to human cell work. My primary interest is in stimulating resident repair of adult tissue, particularly the heart.

Professor Andrews: I am Peter Andrews, professor of biomedical science at the University of Sheffield and director of the centre for stem cell biology in Sheffield. For many years I have worked on embryonic stem cells and, before they came along, their predecessors,

embryonic carcinoma cells, which are tumour equivalents. My interest has been the basic biology of those cells: what controls what they do, how they will differentiate and self-renew, and how that can lead into applications such as regenerative medicine.

Q2 Chair: To be a bit cheeky, let me ask in reverse order: Professor Andrews, in roughly what year did you start this kind of work?

Professor Andrews: I started working on human embryonic carcinoma cells in 1978.

Professor Riley: I started work on heart development in 1996.

Professor Forbes: I started research into liver regeneration in 1995.

Q3 Chair: The only downside today is that we have approximately an hour, which seems crazy because I am sure we could spend many hours on this. Afterwards we might ask questions that we have not managed to ask, or for clarification. If we ask you for written submissions afterwards as well, I hope that will be fine. Can I put the first question to Professor Forbes? What big advances have been made in regenerative medicine? What advances have now been made, and what trends do you see in the next 10 years?

Professor Forbes: The things that have happened recently and are well known are so-called induced pluripotent stem cells. One can take stem cells and form them into stem cell-like cells.

Chair: Can you say that more slowly? It's the sound.

Professor Forbes: One can take skin stem cells and turn them into pluripotent stem cells that can then be differentiated into multiple cell types. That has been fabulous for disease modelling. We can take those cells from people with specific genetic diseases, or other forms of diseases, and begin to model disease in a dish. One can also try to coax the cells into differentiated cells with the potential for cell therapy. Combining that with genome editing technology, which has come along quite recently, has taken things forward a very long way and raised a lot of options.

There are two other things. One is that understanding of adult stem cell biology has progressed very far. We have been able to identify adult stem cells in various organ types, such as the gut and even the liver, and hopefully we can now expand that and have a disease model or develop cell therapies. The other is our understanding of innate regeneration in damaged tissue and how things like scarring, inflammation and the innate regenerative capacity begin to play together. This is a complex environment, but many advances have been made in it in a pre-clinical setting. That has allowed us to go forward with a number of clinical trials. It is not a huge number, but I think it is the tip of an iceberg that is going to come along.

Q4 Chair: For the next 10 years do you see those themes continuing?

Professor Forbes: I think so. We are at the beginning of the end of the basic understanding of this, but the translation of it is really now. It is a convergence of technologies that is making things happen very quickly now.

Q5 Chair: It might have been easier if I had asked what it cannot do. Would you add to that, Professor Riley, or do you have different ideas?

Professor Riley: I agree with that. A key element is the identification of resident stem cells in so-called terminally differentiated or post-mitotic organs, such as the brain and heart. They have also been shown to have cells that can be targeted towards regenerating tissue and lost cells.

Q6 Chair: Explain post-mitotic, as opposed to—

Professor Riley: The thinking is that with such specialised organs there is not much cell turnover, division and inherent repair, so the identification of baseline conditions where there is some turnover and relatively rare populations of cells that could be amplified for processes downstream of tissue repair has been a real breakthrough.

The other emerging technology is direct programming, which is the idea that you can take key developmental factors that would trigger the conversion of a fibroblast cell to a more specialised one, such as a neuron in the brain and a cardiomyocyte, or muscle cell in the heart—

Q7 Chair: The fibroblast is the conversion from a non-thinking to a thinking cell.

Professor Riley: Yes. Effectively, they are the cells that make up the skeleton of the organ in question. They are a little more complicated than that and there is emerging research in that area, but direct programming is quite a major breakthrough.

Q8 Chair: Move over Frankenstein. Professor Andrews.

Professor Andrews: I would add to that the discussion on how embryonic stem cells or induced pluripotent stem cells work. One thing that has evolved over the past several years, which has given rise to a set of clinical trials for the eye, is exploiting the fact that these cells will do specific things by themselves. If you leave an embryonic stem cell in a dish and let it grow to a high density, it will for some reason produce some black cells that turn out to be retinal pigment cells that people have been able to make use of. That is serendipity in a sense. We are in the middle of trying to understand how that happens. How do we control that and make the cells do that when we want them to do it? How do we prevent them doing what we do not want them to do? If you are going to put retinal pigment cells in the eye, for example, you do not want bone cells to go in there, but we are talking about cells that can make everything.

The point is that we have been exploiting the simple things to some extent. We have been exploiting what these cells will do because they happen to do it, and what we are now beginning to get a handle on is understanding the mechanisms that control gene activity

that allow cells to make decisions between different fates. That is still at a very early stage. It relates back to having to understand human development.

One of the major problems in this area is that we are trying to shoehorn a lot of the findings we have into how mouse embryos develop, because those are the mammals that we know best about. It is very clear that human embryos develop somewhat differently. How differently and how fundamentally is unknown, but it is clear that they are different. To try to understand the mechanisms by which embryonic stem cells and IPS cells can be made to turn into things we want requires us to have a better understanding of early human development.

Q9 Chair: To what extent do you think the UK is taking advantage of these opportunities? Can the Government better support the research and innovation?

Professor Andrews: The UK has had a very strong background in the basic biologies that underpin this sort of work. I talk specifically from the pluripotent stem cell angle because that is where I come from, but there are plenty of other areas as well. The UK has a very strong background in developmental biology, which underpins what we are doing.

Q10 Chair: Are we taking advantage of that?

Professor Andrews: We are. The research councils, the Government and various organisations have clearly put in place the mechanisms for translation. Quite a lot of work has been put in place to begin to exploit these opportunities. The real problem is getting the balance between the basic biology that will feed the pipeline into the translation and how to take it forward. One of the areas is getting a handle on the timescales. We are talking about a very complicated exercise. Taking these cells through to make retinal pigment cells, nerve cells or heart cells, whatever it is, in an effective way is going to take a long time.

Q11 Chair: How could the Government better support that?

Professor Andrews: There is good support. There is always need for further funding, but it is important to recognise the whole pipeline from beginning to end.

Q12 Chair: That cannot be influenced particularly by Government, can it?

Professor Andrews: It is important that a lot of this has come from the bottom up. A lot of the ideas that have driven this have come from investigator-led research coming up with ideas of how to do things. It is very difficult from the top down to decide exactly what we should do. That is an important area that must be kept in mind.

Professor Forbes: I would argue that the Government, via research councils, have provided long-term funding for regenerative medicine, starting off with the Medical Research Council but latterly with the UK regenerative medicine platform, which brings together different research councils. This is a critical ethos. It will take different sorts of technology, not just biology, to drive these things forward. We see this very much in the

States. It is stability of approach that people need in the field to feel confident that there will not be continual change. The cell therapy catapult has been an extremely positive thing. That was a significant investment made by Government, and has helped people develop cell therapies from the laboratory through to MHRA approval and into clinical trials.

Q13 Chair: The catapult helps that timeline.

Professor Forbes: It has been a very significant thing, along with other investment by the research councils. Having a stable joined-up platform has been good for us, and, if it continues, that would be the main message from me.

Professor Riley: I would echo that a multidisciplinary approach is required. The UKRMP certainly sets that up by having hubs of activity that address certain bottlenecks we need to understand, such as the niche or environment in which these stem cells find themselves, an understanding of stem cell differentiation and how they become different cell types and thinking about some of the bio-engineering required to make scaffolds and delivery mechanisms for the cells, if we want to go down an engraftment and transplantation route. The multidisciplinary approach is key, and it goes beyond having hubs of activity to try to link together researchers in different fields: the physicist, the chemist, the medicinal chemist and the biologist. This is absolutely critical. There could be more emphasis placed on that.

I also suggest that, while there is obvious pressure, rightly so, to move down a translational pipeline in the context of both RCUK and charities—the British Heart Foundation, Wellcome Trust and other foundations—leaving behind the basic science cannot be allowed to happen. You need something to translate first and foremost; more importantly, you need to understand the mechanisms of what you are actually doing when you go down these therapeutic routes. One of the key things in the cardiovascular arena is that the field moved too rapidly into clinical trials, transplanting various cell types into people with ischaemic heart disease and myocardial infarction in heart attack. Those have been modest at best and very disappointing in terms of clinical outcome. A huge amount of money, effort and time has been spent on that, because we did not understand the basic mechanisms of what was going to happen when those cells were put in place: their survivability, what they might do, what they might contribute and whether or not they were going to be effective. You need the basic science either to run in parallel or certainly to front-load this type of approach.

Q14 Graham Stringer: What are the ethical and political factors that hinder the development of new regenerative medicine therapies or, for that matter, help the development of them?

Professor Andrews: It depends. You could come from several angles. With embryonic stem cells there was always the ethical issue of working with human embryos and so on. The UK was in a very strong position on that, because of a long history of debate going back to the 1980s and then legislation on how to regulate embryonic stem cell research. One of the areas coming to the fore at the minute, which is a problem we will all have to handle, is genome information and the ability to access information about the gene make-

up of particular cell lines and the extent to which that will impinge on personal privacy and so on. Various discussions are going on at European and UK level and worldwide about how that might cause problems. That is an area that will come up.

Professor Forbes: One of the issues is that these are potentially expensive therapies. We have to be able to go forward and deliver therapies that are accessible to a large number of the population with either chronic disease or otherwise untreatable genetic diseases. I would draw some parallels with transplantation. Initially, it can seem a very expensive activity, but over a number of years it becomes very good value, even within a NICE-regulated NHS system. That is something we need to be mindful of in developing translational therapies, but perhaps the second panel will talk more about that.

Q15 Graham Stringer: The clinical trials directive was heavily criticised and has been changed. Are you content with the new regulatory framework for clinical trials? Can you tell us how it is being improved?

Professor Forbes: It is certainly fair to say that it is complex. We have to deal with potentially a large number of individual regulatory bodies when considering regenerative medicines, but this is where the cell therapy catapult, and indeed the MHRA, have been particularly facilitatory, in that they have been able to take somewhat naive researchers, even clinicians, with a regenerative medicine background and show them common entry points for the clinical trials framework, and help them develop a programme of research that will not stumble very early on in those terms. I do not feel that we are unduly troubled, although it is undoubtedly very complicated and it is not for the faint-hearted. You can undertake these programmes only with the help of associated colleagues, such as the national blood transfusion programmes or the regulatory people who are helping you through. We take great advantage from being a very well-regulated area, but it is not for the single person to go off on their own; we have to use the funding bodies that have been put in place to lead us through this.

Q16 Graham Stringer: Does anyone else want to comment on the clinical trials directive?

Professor Andrews: I do not have a lot of experience at that end of the activity.

Q17 Graham Stringer: Will leaving the EU make the regulatory framework easier or more difficult?

Professor Forbes: I have no idea what is going to happen to our regulatory framework in the United Kingdom in this area. Are we going to remain under European directives, or not? I do not know the answer. From a regulatory point of view, I do not know the answer.

Professor Riley: An interesting point is that if you make an application to the EU or ERC for funding in an area you might be exploiting—for example, the use of human embryonic stem cells, or human tissue from developmental biology resources that exist in the UK—you have to be very rigorous in how you justify it currently; you have to show the associated ethical approval and paperwork in great detail to get over that hurdle. Any

application that does not have that information currently will just be bounced back at triage.

Professor Andrews: One of the issues, whether or not we are in the EU, is that science is an international activity. To a large extent, we will in one way or another be collaborating with colleagues in Europe, North America, south-east Asia, or wherever, so whatever we are doing will have to be compatible with views in other parts of the world, not just Europe for that matter.

Q18 Graham Stringer: What are the safety concerns that still exist around stem cell-based therapies?

Professor Forbes: That comes down to appropriate pre-clinical testing. If one is worried about how a cell is going to behave when it is injected into somebody, the key is to understand how it behaves in a very appropriate model. Does it turn into a tumour? Does it regenerate a tissue, or does it form into a scar-forming area? These are key questions. The better we can model that before we do any human transplantation is the key. At the moment it tends to be primarily mouse models. Mouse models are not perfect, but they are pretty good and they are being continually refined. Personally, I have spent time trying to make mouse models model human disease and be more predictive as to what happens when we put cells into humans. It is very hard to short-cut that.

Q19 Graham Stringer: Are there any obvious knowledge gaps that need to be addressed to make this process safer?

Professor Forbes: Do you mean the transplantation of cells?

Graham Stringer: Yes.

Professor Forbes: There is quite a large knowledge gap, in the sense that we do not well understand what happens when you put stem cells into damaged tissue particulate, which is of course where we aim to put it. That is what a lot of the platform funding by the research councils is aimed at. We well understand cells in a dish or in some simple models, but it is the complexity of the damaged tissue situation that could be the big confounder, and the more time we spend to get that right now, the more it will pay dividends in the future.

Professor Riley: This probably gets us to a critical point about the need for combinatorial therapy. Rather than thinking about just putting cells into a damaged tissue, there is a need to modulate the ensuing inflammation that occurs with the injury, disease and fibrosis, because those are competing events for the cell's survival and integration. It is not a simple matter of putting cells into an organ and expecting efficacious repair; it is thinking about the injury environment that Professor Forbes alluded to. That is really critical. It may well be that there is not a one-stop treatment. There has to be thinking around combinatorial strategies. We do not understand the interplay between those transplanted cells, or resident cell activation and the inflammation and injury response that occurs in tissues and inherent response. We do not understand that interplay very well, and that is a huge gap.

Professor Andrews: I would come to it from a slightly different perspective. There are pluripotent stem cells, embryonic stem cells and induced pluripotent stem cells, and there are several areas where you imagine there could be problems, but we are still working out how to deal with them. One obvious thing is that we would not in a therapy anticipate putting undifferentiated stem cells into a person, because they can produce tumours and there will be a problem. One issue is how we make sure that we are not doing that. We can take those cells and differentiate them into, let's say, retinal pigment cells to go into the eye. One of the problems is to make sure that we do not have any undifferentiated cells lurking around. Having turned them into retinal pigment cells to put in the eye, we need to make sure, for example, that there are no bone cells there. How do we assess that? It could be tricky.

The bigger problem is: how do we know that the cells we have made will function long term in the way we expect them to? We can have all sorts of animal models and we can do lots of tests. We can get to a point where we think there is a very good chance this will work, but at the end of the day, until we put them into a person, we will not know the answer. That is why it is important to look at different kinds of conditions. For example, with the eye, you have a very small number of retinal pigment cells going into an organ and you can look to see what is going on, and you are doing that in an old person who has only a few years of life left, compared with something like diabetes where you might be putting cells into a young person for whom there is a treatment available and you wonder what is going on, so it depends on the circumstances.

Q20 Victoria Borwick: Could you repeat a word you used that is not in our glossary? It began "com".

Professor Riley: Combinatorial. It is combined therapy with more than one drug or treatment.

Victoria Borwick: I ask it for the sake of the minutes and everybody watching. Thank you very much.

Q21 Jim Dowd: Can I look at embryonic stem cells? There are all kinds of difficulties around this in terms of social and cultural issues, but if therapies were developed using embryonic stem cells do you think they could be universally applicable, or would there be such opposition in some parts of the world that it would reduce their usefulness?

Professor Andrews: Are you asking whether from a social point of view people would object?

Jim Dowd: Social and ethical.

Professor Andrews: I am sure it is like everything else. There probably still would be opposition, but if you go back to the early days of in vitro fertilisation, there were lots of objections from lots of groups of people. Once it was shown to work and benefit people, the objections dissipated, but not everywhere. I am sure there are people who still object to that work. It will never go away, but it will look very different once one has actually done some of this.

Q22 Jim Dowd: IVF is fairly universal now, isn't it?

Professor Andrews: Pretty much.

Q23 Jim Dowd: In the more advanced countries.

Professor Andrews: You can go to places in the United States that might object.

Q24 Jim Dowd: Given that pluripotent stem cells, if they overcome this difficulty, seem a more productive avenue of research and examination, why is research on embryonic stem cells still required?

Professor Andrews: One needs to realise that in making what we call induced pluripotent stem cells—where one takes a skin cell and converts it into one of these cells—one is trying to convert that into a cell that is, in principle, identical to an embryonic stem cell. You are changing the genome and a lot of aspects of how the cell works, so in different situations you are moving the cells closer and closer to that point. You do not always get there. You can get cells that you think are induced pluripotent stem cells but they are not identical. We are still in the frame of trying to understand exactly how close we get to that point. In trying to understand how those cells behave, we still need to understand how the embryo works. The mechanisms that control what embryonic stem cells do are the mechanisms that control how human embryos develop. Even if we work with induced pluripotent stem cells only, we still need to understand those mechanisms to be able to manipulate them in a more refined way. The big problem at the moment is that in the mouse, on which a lot of work has been done, it is ostensibly different. For example, human embryonic stem cells and induced pluripotent stem cells that are made equivalent to human embryonic stem cells are not the same in some respects as mouse embryonic stem cells. We are trying to understand whether that is a trivial difference or a fundamental one that will affect how we manipulate those cells.

Q25 Jim Dowd: The embryonic stem cell is the standard or yardstick by which you measure the work you have done on pluripotent cells.

Professor Andrews: Absolutely.

Q26 Jim Dowd: What are the challenges in scaling up the delivery of pluripotent cells?

Professor Andrews: There are several. The first is how to grow them and how to maintain them as stem cells. The big problem with growing these cells is that they can do one of three things. They can divide and make another stem cell, so if you want to grow a lot of stem cells, you want that to happen. You can get them to differentiate into various cell types, at which point they are no longer stem cells. The other problem is that they can drop dead, and those of us working with them know that they die frequently.

Q27 Jim Dowd: Is that predictable, or does it just happen?

Professor Andrews: We do not know, but it happens. Understanding the mechanisms that allow cells to do those things is important if you then want to make a lot of them. More importantly, if you want to make a lot of cardiac cells, you particularly do not want them to make bone cells or nerve cells, and understanding how to stop that is a problem. Scaling it up to make a lot of cells means that it is crucial to understand those basic processes. These cells are no different from any other living organism. They will acquire mutations and so on as you keep them, and you want to avoid undesirable mutations appearing in the system.

Q28 Jim Dowd: You want to encourage beneficial ones.

Professor Andrews: You could, but there is always the question of what is beneficial and what is not. That is another area of knowledge we need to gain.

Q29 Jim Dowd: Can we look at the gene and cell therapy catapult? What is their role?

Professor Forbes: I had quite a lot of contact with them, for example on a cell therapy that we hope is efficacious. We are still in early clinical trials and we do not know the answer to that, but basically they have got us to the point where we are doing a trial, along with many other people, such as the Scottish National Blood Transfusion Service and my team. They have helped particularly with the regulatory environment in allowing interaction with the MHRA submission, which is quite a substantial document to be compiled on the safety and efficacy of the potential product.

Another thing that is not well spoken about or well understood is that, if we have discovered a cell therapy in, say, a mouse and taken it into human cells, there is a gap in making it GMP-compatible: in other words, so that it is clean and safe to inject into a human and you have all the regulatory equipment around it to allow that. We need support in that, and the cell therapy catapult has been very useful in that regard as well.

Q30 Jim Dowd: Do you think the catapult serves academic interests as well as it serves the industrial ones?

Professor Forbes: There is a good interface between them and they can see both ways. They have not yet fully developed their cell therapy production centre in Stevenage, which will add greatly to their efforts in this area, if I understand it. At the moment, their help in pushing forward trials into the clinic has been very useful.

Q31 Chris Green: My question is to the panel as a whole. Has research on adult stem cells led to any cures in regenerative medicine to date?

Professor Forbes: Blood transfusion is the obvious one with haematopoietic stem cell transplant. There is a host of haematological conditions where we ablate the bone marrow—a typical example would be cancer—and we do that using irradiation and drugs. Without that people would die. By receiving a haematopoietic stem cell transplant, those cells are able to recolonise the bone marrow and supply all the individual components of the blood.

There is also eyelet cell transplantation, which is probably not as well known. These are groups of cells that live in the pancreas and help make insulin. They are used particularly for people who are unaware when their blood sugars are low and they fall unconscious in the bath or in very dangerous situations. It affects their lives profoundly, and for that it is absolutely transformative. Those are examples of commonly used adult stem cell therapies. There are others.

Professor Riley: That is a good example. I mentioned the discovery of stem cells in organs such as the heart and brain. It is very recent; for this field it is early days.

Q32 Chair: How recent?

Professor Riley: The best study done on the heart, for example, on carbon 14 data from post-mortem samples from cold war nuclear testing is 2010. This is recent in the context of the discoveries beyond that basic science. It is important to link the potential for stimulating adult stem cells and resident repair of an organ with what is being found now through stem cell therapy and cell transplantation with human ES and IPS, because it is clear, from some of the pre-clinical models at least—there is a good example of a clinical trial going forward for human ES-derived cardiac progenitor cells into ischaemic hearts—that these cells, rather than integrating and forming new cardiovascular cell types, are secreting factors that are helpful for the heart in terms of its functional compensation, and perhaps also stimulate some resident repair. They are being used to identify what those factors might be, with the idea downstream of taking drugs from that and stimulating resident repair through perhaps adult stem cells or some other process. It is clear that there is a balance between our understanding of what we are doing with cell transplantation and perhaps moving that into drug discovery, targeting adult stem cells.

Q33 Chris Green: These are very early stages and there is perhaps huge potential in discovering the extent to which stem cells can be applied across the body. To take the drug approach might well be a promising strategy, but there are always knock-on effects and other effects on the body if you start introducing drugs: will you start stimulating stem cells in other parts of the body or that have other effects? There are always knock-on effects that may happen. In that sense, are there any particular advantages in extracting tissues with the stem cells, expanding them outside the body and injecting them back into the patient at a later date?

Professor Riley: At least in cardiovascular the same issues apply with the transplantation of ES and IPS-derived cell types. The problem is the mode of delivery, the survivability of those cells and their ability to integrate and become the cell types you want them to become. You have the same problems if you isolate even the so-called stem cell-like populations. It has been tried in very small, arguably not well controlled, clinical trials for this type of approach, and it has not been very effective.

Q34 Chair: Were those trials in this country?

Professor Riley: No; they were trials in the US with small numbers of patients, isolating resident stem cells from the heart and putting them back in. You mentioned safety and

problems of off-target effects with drug delivery. One strategy is to repurpose known drugs. In terms of screening for drugs that might have an effect on resident stem cells, or on resident repair processes, in animal models, the idea is to take known drug libraries that exist within pharma and beyond that are now commercially available and screen those in the first instance, because they have gone through all the safety and efficacy in another indication that might be applied to regenerative medicine.

Professor Forbes: To go back to your original question, within the organ transplantation programme, where we have ethically sourced organs for clinical use, unfortunately we have to destroy those organs if they are not in good condition—for example, the liver might be too fatty or the time when there is no blood flow is too long. If we can extract stem cells from those organs it is a good source of cells that are ethically characterised and already within an NHS framework where people are used to handling cells and tissues, and are used to transplantation. That may be one very good avenue for us to go down, given what a good network we have of transplantation within the UK.

Q35 Chris Green: That would not require any major piece of legislation.

Professor Forbes: I do not think so. That is translational science.

Professor Andrews: The only thing I would add to all of this is that, in thinking about adult stem cells in tissues, one has to distinguish between stem cells and progenitor cells. Stem cells are, in principle, cells that will be there for the life of the organism to regenerate the tissue. Progenitor cells often have a very limited lifespan and are there to expand the number of cells that will eventually turn into something or other. There are probably more of those in the tissue than the real stem cells. For example, in the bone marrow situation a lot of the cells you take are not stem cells; they are progenitor cells, and it has taken a long time to work out exactly which are the best cells to transplant to give you proper and effective reconstitution, having destroyed someone's immune system. In a lot of these situations, if we are to make use of such cells we have to understand the basic biology of how they are produced, the difference between stem cells and progenitor cells and what controls their ability to turn into the final functional cells of that tissue. It is still early days.

Q36 Chris Green: In terms of extracting tissue stem cells and reintroducing them at a later date, is there sufficient support for this approach in the community for researchers to start doing it on a far larger scale?

Professor Forbes: We have proof of principle with the eyelet cell programme, which is in clinical use. It is a great shot across the water, and it is up to the community of stem cell researchers—clinicians, transplant biologists and so on—to see whether it is applicable in other scenarios, such as the gut. That is being pioneered in Holland and is showing great promise in this arena.

Q37 Chris Green: If you look at the range of options where limited resources could go, would you favour this direction, or would you say there are other areas you would prefer to concentrate on?

Professor Andrews: I think it depends on who has the best ideas, and that is essentially how funding for science has worked effectively over the last many decades, and has brought us to where we are today. It is funding the people who have the best ideas to take something forward. I do not think one can say in the abstract that we should go in this or that area; we should see who is working in it. If someone has some good ideas in that direction, we should do it; if someone has good ideas in this direction, we should do that. That has been the style that has led us to where we are today in our ability to use any stem cells in therapy.

Professor Riley: There is more than one approach. It would be a mistake to exclude any one of them as they currently exist, because for different disease and injury indications one may be more optimal versus another. You have the cell transplantation mode through pluripotent stem cell route derivatives and then putting back, with the issues we have talked about—scale-up, survivability and what they become—and then you have the isolation of stem progenitor cells for reintroduction. You also have the other option, which is taking drugs and trying to stimulate resident stem progenitors in that context. All of these have benefits and disadvantages, particularly as applied to different indications of disease. It would be a mistake to channel effort, funding and resource into one area at the expense of the other, because they are all progressing very well in the basic science context but moving to pre-clinical and beyond.

Q38 Chair: Professor Riley, we get the idea of the UK's basic science, but you mentioned the US. How does regenerative medicine in the UK compare with the US and the EU? Are we hindered by our regulatory regimes?

Professor Riley: I do not think we are necessarily hindered by our regulatory regimes. We are in good shape for the use of human material and research that leads into these trials and so on, and the derivation of human embryonic stem cell lines and use of human tissue. I do not think that is an issue. As ever, it comes down to resource and cultural and taxation issues; in the US, philanthropic and bio-sector investment is perhaps more pronounced than it is in the UK and there is a cultural thing around it that can inject more funds to get it over the line into a trial setting. I think we punch above our weight on the basic science with respect to what they call bang for your buck. We do very well in that arena, but there is clearly a shortfall compared with the US in the large investment that can occur through the private sector in particular that pushes forward the clinical trials.

Chair: We might come back to that.

Q39 Victoria Borwick: We have touched on animal testing several times. We want to know where that fits into the whole picture. I am very conscious that there are a number of regulations, yet many of these advances would not have happened without testing on animals, from fish to mice and further up the chain. Could you tell us how animal testing fits into the research, particularly in this field?

Professor Forbes: The main player has been the mouse recently, because of the ability genetically to manipulate a mouse to create a particular environment in a tissue that you are trying to study, for example. You may be able to ask what happens if you inhibit regeneration in an organ and it becomes damaged. The mouse is particularly good for

doing that. You can make the mouse immuno-deficient so it can receive human cells as well. It has had a great advantage in that respect.

Zebrafish larvae, and young zebrafish, are an area that is growing very rapidly. These are tiny day-old fish that can be assessed particularly for screening small molecules and drugs to target endogenous regeneration. We are making huge advances in what we call chemical library screening—looking for either known approved drugs or molecules that are not yet well understood to see if they stimulate particular regeneration in these settings. Funnily enough, some of the signals translate through. Obviously, some do not, but we continually need to check our biology and what we find against the human situation; for example, by looking at archival samples from human disease tissue where there is injury and regeneration. Those are the two I would comment on.

Professor Riley: I would agree with that entirely. They have been particularly helpful in moving from, say, fish to rodents and pre-clinical large animals to humans where the cell types you are interested in are entirely conserved, and the molecular pathways that we know about that can stimulate these cells, or their activated form, are also conserved. We have individually had great success in looking at the zebrafish and mouse into human cells where the outer layer of the heart can be stimulated to help heart repair. The fish does that inherently. If you injure its heart, it repairs through a normal response, without any other influence. How those cells behave during that process has been important to our fundamental understanding of how to promote that to happen in mouse and human. We would not have got there without the basic underpinning research with these animal models.

Professor Andrews: I can't add a lot. The fundamental point behind all this is the extent to which the control mechanisms operating through all the range of organisms are very similar. We can take advantage of that. The only problem is that we have to watch out for the fact that they are not always the same. A lot of systems that work in the mouse work in humans, and we can learn a lot from the mouse, but every so often there are bits that are not the same, and we have to be aware of the differences as well as the similarities. Nevertheless, they are absolutely important.

Q40 Victoria Borwick: People will be watching this on the web and suchlike. There are obvious concerns that these animals—fish, mice, rodents and moving up to other animals—are well looked after. What sort of regulations are there to reassure people? Are they positive? How should one explain to people what happens to these animals?

Professor Forbes: The UK is fortunate in that we are very well regulated, and we know how to account very carefully for why we do each experiment on each individual animal and why it is necessary; we have to find a justification for that. We cannot just repeat things endlessly or with no point; we have to have a clear indication. Within our research environments, the overwhelming majority of the time animals are carefully observed for adverse effects. Many times in these experimental approaches, there are no adverse effects. That is a point worth making as well.

Q41 Victoria Borwick: Has legislation helped or hindered research? We are talking about life-changing medicine, not fripperies.

Professor Forbes: On one day I look my patients in the eye—often they are dying, to be frank, or very severely ill—and then I have to go back to the mouse experimental procedures. It is certainly not light touch, that's for sure. We work within it and accept it. I think it is appropriate and necessary, but if it was any more complicated it would be difficult. The assessment is very comprehensive.

Q42 Victoria Borwick: Thank you for that reassurance.

Professor Andrews: I echo what Stuart says. It is very well controlled. Anyone I have known who has worked with animals always does it with real consideration for them. I do not think any of us do any experiment lightly. The level of care that I have ever seen has been very high.

Q43 Victoria Borwick: We have talked about fish and rodents. Obviously, there are other animals: pigs, sheep and so forth. What drives the choice of animal? Is it the science? What is the reason? Is it regulation?

Professor Forbes: Cost is one big thing. Mice and fish are small; you can do your experiments quickly and get the results quickly and efficiently, whereas in larger animals, although they are potentially important for specific indications, it is expensive and takes a long time to develop and analyse. The smaller the animal, the quicker the turnover of results, as long as the organism is appropriate and models well with human conditions.

Professor Andrews: The other key issue driving both mice and fish is genetics. It is a history driven by the fact that they are small animals and you can breed a large number of them, which has allowed the genetics to develop. That is crucial for understanding many of these mechanisms. Genetic tools have allowed us to understand and develop the mechanisms that control what cells do.

Victoria Borwick: I welcome that clarification.

Q44 Chair: Is the work on eyelet cells and haematopoietic cells thanks to mice and fish, or is it just in vitro?

Professor Forbes: I think they were pioneering clinical transplant-type experiments in humans.

Q45 Chair: It was not the mice and the fish.

Professor Forbes: The haematopoietic cell work was definitely informed by the mouse, and we now refine our experiments based on that work.

Q46 Jim Dowd: As Victoria said, this is a very contentious area. Many of our constituents are very concerned about issues relating to testing on animals. Given the fact that you are working at the cellular level, why do you need whole animals to do this?

Professor Forbes: What is particularly important is a complex three-dimensional environment, so you do not have just one cell on its own in a tissue or in the body. It is surrounded by its neighbours, which may be the same or different types of cell, and each exquisitely responds to injury and repair processes with a multitude of signals. At the moment we can begin to model that environment using complex co-culture systems, but they are nowhere near good enough to get close to what we would model, for example, in a mouse where we may have one very simple experiment that tells us a multitude of things about how these different cell types interact.

Professor Riley: The minute you take those cells out of that organ and environment and put them into a plastic tissue culture dish they are no longer the same as they were in the original organ system, so in anything you learn you have to be very careful about caveats around the behaviour of those cells. It is important to have both; it can give you real benefits in making early discovery and so on in vitro, in the tissue culture dish, but you must return to the organ to understand the interplay and the primary cell type behaviour, because it is different the minute you isolate and put it into a tissue culture dish.

Chair: I am conscious that we are a bit over time, but Derek still has some questions.

Q47 Derek Thomas: Can you give us some examples of when tissue engineering is used to repair or even replace human organs?

Professor Riley: I can give you an example that is local to Oxford. At the Kennedy Institute of Rheumatology, scaffold engineering and the introduction of cells to reconstitute cartilage and ligament for highly arthritic or osteoporotic patients has been used in surgery. That is used to great effect. The importance of tissue engineering is to maintain the introduced cells that are going to reconstitute the damaged joint so that they are in the right environment. They are given signals through the engineered matrix that ensure that they survive, differentiate and become the cell types of interest. That is a very good example, and it is being used surgically as we speak.

Professor Andrews: Probably Professor Hollander might be better able to talk about that.

Chair: We will be putting that specific question.

Q48 Derek Thomas: What are the challenges of having both a material and a cell component in the final tissue-engineered product? Are the challenges mainly scientific or regulatory?

Professor Forbes: They are both, definitely. Scientifically, you can engineer it. You can have materials that dissolve; they provide a matrix and then disappear, and that is a very good way forward. The more complex the tissue you make, the more it falls straight into a regulatory-type form that is complicated, but they are all doable.

Professor Andrews: I do not have anything to add. They are important. They are both regulatory and scientific issues.

Professor Riley: The material scientists are pushing the boundary on the type of materials we might be able to use based on biological materials that, as Professor Forbes said, can degrade, having given the support network that is needed for the cells to repair.

Derek Thomas: That is very helpful.

Q49 Matt Warman: We hear a lot elsewhere about 3D printing, and obviously bio-printing is becoming more of a thing in this space. Can you talk generally about what you see as the role of bio-printing in this area and what we could do to promote it, if that is a sensible thing for policy makers to think about doing?

Professor Riley: It is related to the previous question. One of the areas of 3D printing and things like electro-spinning of fibres and so on is the construct of matrices and scaffolds that might seed cells more therapeutically and effectively in the context of repair. The 3D printing element and techniques such as electro-spinning have been influential in the very complex design of matrices and scaffolds that will enable tissue engineering and bio-engineering to move forward. It is a really important area.

Professor Forbes: Having biologists and clinicians working with chemists and physicists in the same collaborative space, not in silos, is really fertile. The magic happens when they are working in environments where those things have been funded together.

Q50 Matt Warman: A lot of this is international, but where does the UK stand in this particular area?

Professor Forbes: It is strong, but I acknowledge that in America places like MIT in the Boston area strongly bring together the biologists and physical scientists. We are doing it, but you have to acknowledge that other places are as well. It can also lead to patentable commercialisation very rapidly, and it is a space we need to stay in.

Q51 Matt Warman: What are they doing that we are not doing or we should be doing more of? It sounds like some of this is about joining the dots as much as it is about investment.

Professor Forbes: We have acknowledged in certain places that this needs to happen. We just need to do more of it. There are good examples where it is happening, but people have really seized that opportunity on the east coast of the States, for example.

Professor Riley: There is very strong activity at Imperial College in London, for example. It is important that funding is made available that brings together networks of people and you are encouraged to look beyond your discipline—a multi-disciplinary approach—getting materials scientists, bio-engineers, physicists and mathematicians to work with biologists, chemists and so on, as Stuart alluded to. That can happen under centre-like funding or strategic award. Those sorts of awards or funding streams exist, but perhaps we could think about developing more focused calls around interdisciplinary areas, because that is where the real magic happens and more than incremental advances can be made.

Professor Andrews: One of the hubs funded under the UKRMP is focused on bio-materials, and there is certainly a strong group that links a number of others around the UK, including Nottingham and Imperial.

Q52 Matt Warman: We have talked a lot about 3D printing. Are there other emergent technologies that you think we should be addressing or encouraging that are not yet there?

Professor Forbes: There is the whole of nanotechnology where it interfaces with biology, and the elutriation of medicines in tissue. You can have matrices that release medicines over a controlled period of time and interact with stem cells. That is easy to say, but to do pre-clinical testing and get a regulated device right through to the clinic is a grand challenge. We can do these things, but it requires a joined-up approach from the basic through to regulation, clinical assessment and commercialisation.

Professor Riley: Coming back to the multidisciplinary approach, another area is mathematical modelling that is predictive of some of the outcomes of these therapies. There are some excellent computational and mathematical experts with an interest in biology. Bringing them in to try to predict some of the outcomes, which can then be tested, perhaps in animal models, prior to moving into the clinical phase and trials, would be a really nice area of development.

Chair: I hope lots of students are hearing this basic science and do not drop any of their science subjects. You have been brilliant and very comprehensive. I hope it is acceptable if we write to you to seek further answers. Thank you very much.

Examination of Witnesses

Witnesses: **Dr Rob Buckle**, Director of UK Regenerative Medicine Platform, Research Councils UK, **Professor Jeremy Pearson**, Associate Medical Director, British Heart Foundation, **Professor Neil Hanley**, Professor of Medicine, University of Manchester, and **Professor Anthony Hollander**, Head of Institute of Integrative Biology and Professor of Stem Cell Biology, University of Liverpool, gave evidence.

Q53 Chair: I am sorry to have kept you waiting. You were probably present at the earlier panel. There are some questions we would like to ask you, and we never have enough time, so I hope you will bear with us if after this meeting we write to you with further questions. For the sake of people who do not have your biographies in front of them, perhaps you would briefly tell us your background in regenerative medicine, starting with Professor Pearson.

Professor Pearson: I am representing the British Heart Foundation. We are the major funder of cardiovascular research in the UK, and actually the major funder in Europe, although that is a separate question. My own background is as a basic scientist working on blood vessels—how they work and go wrong—but now I am research director at the British Heart Foundation, so I am in charge of the research funding process by which we decide on the priorities of what we fund, including regenerative medicine.

Professor Hollander: I am a cartilage tissue engineer, not a clinician. I grow cartilage for arthritis, airway disease and so on. I am head of the Institute of Integrative Biology and professor of stem cell biology at the University of Liverpool. I am also associate pro-vice chancellor for enterprise for the university, and I have a spin-out company that has taken a stem cell therapy for torn knee cartilage through to clinic, so I have a particular interest in the commercialisation of stem cell therapies.

Chair: In this country.

Professor Hollander: Absolutely.

Professor Hanley: I am Neil Hanley, professor of medicine. I am a clinician; I am a hormone doctor and endocrinologist. In the hospital, I am also an R and D director for seven hospitals in Manchester. In the laboratory, I study very early steps in how human organs are put together, and that is allied to aspects of stem cell biology in a dish.

Dr Buckle: I am Rob Buckle. I work for the Medical Research Council as a research funder. I was trained as a biomedical researcher but joined MRC in 2000. I am director of science programmes, at the moment looking after strategy and science funding. In this particular context, I am the administrative director of the UK regenerative medicine platform on behalf of three research councils.

Q54 Chair: Beginning with Dr Buckle, where do you see regenerative medicine in the next 10 years? Do you think there is a financial impact on regenerative medicine as a result of us leaving the EU?

Dr Buckle: In terms of development in the next 10 years, we certainly hope that there would be proof of clinical efficacy of regenerative medicine. In truth, the number of

clinical trials in the next 10 years will be fairly limited, but the translational landscape, as you heard from the first panel, has changed significantly in the last few years. There is real opportunity around the interdisciplinary mix that has been brought together, and the tools and technologies are in large part now there. I think we should be optimistic that there will be good progress in the 10-year timeline, but whether that translates to clinical products is an open question.

Q55 Chair: Do you think there will be any financial impact on regenerative medicine as a result of us leaving the EU?

Dr Buckle: Potentially. It remains to be seen how it shakes down, but the EU provides a big funding source for researchers in this area. I looked at the EU consortia that are funded in this space right now. The UK has leadership in eight large consortia on a scale of €5 million or bigger, and we are involved in another eight. That is probably about three quarters of the consortia in this space. We are very successful. We lead two big innovative medicines initiative programmes in this space that involve bio-pharma at European level, with €90 million of investment between the two. These sorts of consortia are of crucial importance in providing capacity and connectivity. That does not mean they will not exist in the post-Brexit landscape, but we have to be worried about making sure that the connections we have do not dissipate in the interim and that the funding currently going into Europe is available for the research that might be undertaken in this country.

Professor Hanley: I have now got to the stage where I have forgotten what the original question was. I will start on the European bit.

Q56 Chair: We are looking 10 years ahead and at whether EU funding will have an impact.

Professor Hanley: We are where we are with the European thing, so I now try to view it as an opportunity. As you have heard repeatedly, people who set up links are not going to stop them suddenly. It will happen. There is an opportunity now to look at some of this outside Europe perhaps more attentively, but it is contingent on Government support—there is no getting away from it—and recognising that this is a sector of UK business and activity that is good and strong and we want to promote it.

Q57 Chair: Would you agree with the 10-year view of clinical trials coming more into play?

Professor Hanley: Yes. As a clinician, there is a risk of giving a glib answer to that. We have done bone marrow transplantation for decades and that is a stem cell therapy, and we are now making inroads into treating retinal and corneal disorders, so I do not think you can put it in a simple 10-year envelope. There have been great advances, there are advances currently and there will be advances. It is a question of making sure that it is at the right time for that particular area in a safe and responsible way.

Professor Hollander: We are at a critical time over the next 10 years in the evolution of this very young area of therapeutics. It feels to me that we are moving beyond the early exciting stage where everyone sees the potential and we know enough to understand how difficult it is to get from the exciting science into the clinic in a scaled-up meaningful way.

There will be a real need on the part of Government, the public and patients while we do the really hard work of making this a very effective area of expansion of therapeutics.

As to the EU, in addition to what has been said, wearing my commercial hat and thinking about a small company like mine with not much money, there is a risk that, if we are going for market authorisation of a product in a few years' time, we will certainly want to enter the EU market. Will we also have the money to enter the UK market? I am not sure. There is a risk that UK plc will invest a lot of money in developing therapies that will not see the light of day in the NHS because we are putting them out in Europe, possibly in America. They may eventually get to the UK when there is enough money in the company to tackle that market as well. I speak for myself, but I see a potential problem.

Professor Pearson: In terms of the 10-year vision, I go along very much with what Rob and the others said. We are at a pivotal stage in the science, which is advancing rapidly, with the potential for real development into clinical efficacy, but, as the first panel made clear, there is a lot more science yet to be learned to enable that transition to work fluidly and across a wide range. My vision, like Rob's, would be that we will get as far as clinical trials in some areas but not in all in the next 10 years. In my own field of cardiovascular biology I think there will be some, but small numbers. The critical thing going forward is to keep the infrastructure we have and improve on it, such as UKRMP and our own centres for cardiovascular regenerative medicine founded at the same time as UKRMP.

Q58 Chair: When was that?

Professor Pearson: Remind me, Rob.

Dr Buckle: It was in 2012-13.

Professor Pearson: We will be renewing those in some form, and I hope the research councils will renew UKRMP in some form, but the key thing, as we heard, is that they are multidisciplinary; they attract all sorts of science to make sure these interactions work to take it towards translation. Those are the things that I think are really important going forward.

In terms of the EU, the BHF raises its money from the British public entirely, so you could say that the EU does not affect us directly, but it will, because all the research we fund is within UK universities. We are free to fund outside the UK, but clearly we do not do it very much because we raise money in the UK. If you look at the number of people we fund, currently 25% are EU citizens working in the UK. A greater number than that collaborate with people in the EU, and that will go on happening regardless, but to make it happen we need the Government to ensure that it can happen as well as it does now.

Q59 Chair: That is a very well made point.

Professor Hanley: I am conscious that one thing was not touched on in the previous panel, and I missed it just now. There is a key aspect of regenerative medicine that is not about cell therapy and putting things into people; it is the allied bit with stem cell biology in a dish. The bit you may not hear about so prominently is that, as we learn to make these cells in a dish, they get adopted for drug screening, drug discovery and toxicity safety

testing all the way through. That is a huge area. In many ways that is almost the first game because it is far safer; it is in a dish and is not going into patients.

Q60 Chair: That point is well made.

Professor Hanley: I am just conscious that we had not mentioned it.

Chair: We had missed that. Thank you.

Q61 Jim Dowd: Before I go to the main thrust of the questions, I understand that you are here to represent yourselves and we selected you to come, but I notice that all the seven witnesses today are men. Is this not an area that attracts women scientists particularly?

Professor Pearson: I suspect you asked Fiona Watt, but she was too busy to come. She is very eminent in this field and undoubtedly would have given you her opinions. I am not sure there is a good answer to your questions. There are not enough women in science, full stop.

Professor Hollander: We have Sian sitting over there.

Q62 Jim Dowd: Yes, but she is on our side.

Professor Pearson: Are there sides in this? I hope not.

Q63 Jim Dowd: No. It is the broader question of getting women into STEM, with WISE and all the rest of it. I suspect there are also differences within the disciplines in science itself, where there are huge disparities. To come to my main point, I asked the previous panel about the gene and cell therapy catapult. How well do you think it facilitates the link between research and innovation in regenerative medicine, or does it not?

Professor Pearson: From the perspective of the BHF, we have not had many practical examples of that linkage for the people we fund, but we have had a lot of conversations and we find them very helpful. We think they are in the right space to assist that translation, as and when it occurs, but it has not quite got there yet. It is a very valuable piece of the ecosystem.

Professor Hollander: The cell and gene therapy catapult is a partner in an Innovate UK-funded project linking my spin-out company with my university and other partners. It is hugely valuable to us on the one hand as an expertise resource. On the other hand, I think that in future it will help us collectively to figure out how we scale up commercially and turn the discoveries into something that can reach large numbers of patients. I am not sure the model is perfect yet. The catapult is still developing its own self-vision, but we are getting there.

Q64 Jim Dowd: The direction of travel is optimal.

Professor Hollander: For me, it is absolutely right and very valuable as the link between fundamental research space and clinical research on the one hand and commercialisation on the other.

Q65 Jim Dowd: Professor Hanley, you mentioned in an earlier reply that you thought Government support was crucial, whatever arrangements there are post-Brexit, if it ever comes to pass. There are large amounts of British industry that believe the same thing. Given Innovate UK's preference or plan to introduce loans instead of grants, what do you think the likely impact of that will be?

Professor Hanley: For the catapult, or more broadly?

Jim Dowd: More broadly.

Professor Hanley: There is a range of funders in the UK and that is one model. As ever, the breadth of the models for how you do things is important and varies according to the stage you are at in the pipeline. When it comes to those sorts of ventures, I do not have a lot of interaction with the catapult, but it is a good thing. We have to try to do the right thing, which is to take basic science and translate it, so we need to do something in that area. The big issue is making sure it is as efficient, streamlined and successful as possible. You could, therefore, make a case for saying that a loan-type agreement may be a way of securing that, so I have no problem with it.

Q66 Jim Dowd: It would have no significant difference.

Professor Hanley: If everything switched to that, yes, but my point is that there is a breadth of options available from different funding agencies, be they Government, the Wellcome Trust or the BHF, so that mixed model is probably the right way.

Q67 Jim Dowd: Can I look briefly at the issues relating to intellectual property? Are there particular difficulties in regenerative medicine regarding intellectual property and the work of individual researchers?

Professor Hanley: There are challenges. It is easy to say from one area that, yes, we have particular challenges, but I suspect that if you had anyone here from any area they would give you fairly similar answers in terms of IP.

Q68 Jim Dowd: For example, would the patents be more complicated, difficult and technical than in other areas?

Professor Hanley: Potentially, but in any area involving IP coming out of the academic sector on an international level, patent lawyers all over will be picking holes in whatever you have put together. There are always complications and difficulties in it. Perhaps that is so, but my personal feeling is probably not.

Q69 Jim Dowd: Professor Hollander, you became rather animated.

Professor Hollander: I had a rather bruising but ultimately successful battle recently with the American Patent Office around some IP. That battle was over a complete misunderstanding of some of the fundamentals of cells and tissues, not the biology but in the translational sense. I will not bore you with the details, but in effect I had to educate the patent examiner on what they were getting wrong. That worked and the American system allows that. You can keep going back and forth until they get it, but the European system does not allow so many iterations. So far it has been okay, but there is an educational process to go along.

Q70 Jim Dowd: Do you mean there is greater difficulty in dealing with people who know what they are talking about?

Professor Hollander: Or at least pretending they do.

Dr Buckle: The sector has different characteristics in terms of patentability and type of commercial investment. As regards patents, there is a lot of know-how in this area that is probably as effective a way forward as individual patents. These are very complex processes when you get to the manufacturing stage and they are probably very difficult to replicate. This emerged when there was discussion around the European Court of Justice decision on the issue of patentability of human embryonic stem cells. We have not seen much impact from that decision in reality. Part of that is because the companies in this space, such as Anthony's, are generally small and medium-sized enterprises. The business model is different; the money will probably be recovered short term in licensing deals rather than returns on patents. Of course, when we get to the loans issue, it is hard to know what the impact of that change will be, but for small and medium-sized enterprises it might be significantly different from big pharma, and we have to watch this through.

To go back to the original question on the catapult, the UK regenerative medicine platform and the catapult were set up at pretty similar times. We set them up to be complementary, and to a large extent they are. I was quite interested in some of the responses to your inquiry saying that maybe the boundaries between the two were not discrete enough. Primarily the catapult's role is to commercialise. It is a company and therefore the demarcation between the academic research and how it crosses over into the catapult is reasonably clear. There are a lot of projects—for example, Stuart Forbes's trial in liver repair and Martin Birchall's vitrogen, which is larynx repair—that were originally MRC-funded projects that are now being picked up and supported by the catapult. There is a way to go, but it is a good pipeline and model.

Q71 Jim Dowd: Finally, can I go back to the IP arrangements? As they currently stand in the UK, are they helping or hindering research into regenerative medicine and progress in the area, or are they broadly satisfactory?

Professor Pearson: I am not an expert, but from talking to people who work in this area I think the effect is neutral; in other words, there is nothing particularly wrong or right in regard to this particular area in the way the law works.

Q72 Chris Green: In inquiries there is always concern about R and D and innovation and getting ideas into products, in this instance getting regenerative medicine to deliver in the hospital or clinic. Professor Hollander, do you think we have the right infrastructure to take regenerative medicine from the laboratory to the hospital or clinic?

Professor Hollander: Clearly, we can do it because we have. My spin-out company has taken through to the clinic a therapy for torn knee cartilage that was trialled in a hospital in Bristol. We went through the usual regulatory process; we engaged with the NHS, and that happened. Has it been straightforward? No. It has been a fairly complicated process and perhaps it is becoming more complicated, but it can be done. Others have done it as well. The area where it will become particularly challenging is NHS adoption of these therapies. A lot is talked about that, but I am not convinced that enough work is being done to understand what cost model would be used in the future to adopt a therapy when it costs a fair amount up front but the benefits may happen over 20 years if it stops people coming back to the clinic year on year with a chronic disease. Those of us doing translational activity are quite happy to move it through the different challenges, but there is a risk, as I mentioned earlier, but now for a different reason, that we will do all this and not get it into the NHS, and it may benefit other countries or just the private sector.

Q73 Chris Green: There are definitely concerns about regulation and uptake, but in terms of the infrastructure and our abilities—the number of people and the laboratories that can do the work—is there a problem at the moment?

Professor Hollander: Not so much with laboratories. Particularly with the catapult's delivery coming on board, laboratories are probably not the road block right now, because we are not scaled up to the point where labs are at capacity. In terms of skills, maybe we will hit a road block in the future, but we are not there at the moment.

Dr Buckle: The majority of research centres are embedded in or very close to hospitals, and there is an NHSBT support network that could be repurposed to allow delivery of therapeutics when they become available. There are different concerns according to the different areas of therapy. If we look at the ophthalmology model, which is a very tractable area in regenerative medicine terms, because Moorfields is a tertiary referral site for a large region, they have the throughput of patients and the clinical support structure to envisage that they could run the trials in that way. In other areas—for example, Parkinson's disease, which is showing some promise now—it will be far harder to bring patients to one place. The trials will be done in very closely defined populations, and there will need to be a cluster of different centres and different standard routines to get the therapies to them. We have to be conscious that there are very different models out there. The signs are that the connection between the Department of Health investments in its research infrastructure and what has been put on the rails as a result of the regenerative medicine expert group activity is going in the right direction, but we do not have the pipeline of studies yet to start testing it out.

Q74 Chris Green: Do we have an adequate facility to cultivate clinical grade stem cell lines?

Dr Buckle: We have certainly made enough clinical grade embryonic stem cell lines to fuel the immediate need in terms of clinical trials. There are efforts under way to make clinical grade induced pluripotent stem cells. The adult stem cells are used largely to develop autologous-type work, where cells are removed from the patient and put back into the patient, and that is done more locally.

Going back to pluripotent stem cells, the supply of those lines to the trialists is potentially in place when that happens. At the moment there is enough capacity in manufacturing facilities, but, as you will be aware, the cell and gene therapy catapult is creating new manufacturing capability with a view to the future, but the current model is that capacity is robust enough to do the necessary small-scale early phase studies.

Professor Pearson: The capacity and the vision of what the capacity might need to be are in place. The critical question as it accelerates will be whether there is enough resource to make it accelerate at the rate it needs to. We just do not know that yet.

Q75 Chris Green: That is one to watch out for in coming years. The Government have supported projects such as the UK stem cell bank. Are these Government-supported facilities fully utilised by UK regenerative medicine researchers?

Dr Buckle: The Medical Research Council is one of the main funders of the UK stem cell bank. It was set up primarily to manage the ethical characterisation and distribution of human embryonic stem cell lines. It does other work around that, but its main focus is on human embryonic stem cell lines. It was the first stem cell bank globally, and internationally it still has one of the highest profiles of a stem cell bank.

In terms of human embryonic stem cell lines, there is a very well-managed process by which the bank's role is to ensure that there are quality-controlled samples that the research community can use. The research community does not have to use the bank; it can source these cells from anywhere else, but it is very important in this area that people are going back to very well-characterised stem cell lines, because if you start to develop research projects at this point that are nothing to do with the clinic, without that quality that is where things go wrong, and there are examples of that.

The more recent activity of the UK stem cell bank has been to bank the clinical grades, or what they would call the EU cell and tissue directive-compliant cell lines, of which there are 38. That is the world's biggest collection of those sorts of lines. Whether they will be used for clinical trials going forward is an unknown at this moment because we do not have the pipeline, but it is pretty clear in terms of the number of lines that go out from the bank that, once they go to a research laboratory, the laboratory does not have to go back to the bank, so they are there. Nearly all the UK labs working in this space have access to lines that are either through the bank or on the bank's registry.

Professor Hanley: There are certain things we can be proud of in how we have dealt with this over about two decades. The way our collection of funders has approached this in the UK has been fantastic. Things like the stem cell bank have been a fantastic force for good in UK science.

Q76 Victoria Borwick: Can I take us back to dealing with Government and the strategic approach? One of the recommendations of the regenerative medicine expert group was the setting up of a ministerial group to take forward a strategy on regenerative medicine. Do you have any views on whether or not that would be a good idea?

Professor Hollander: To go back to my comments in response to an earlier question, we are at a very critical stage. Developing any new area of therapeutics is going to be challenging. There are particular aspects of using cells to treat people that make it an extremely complicated area of science and translation, and we need to keep that on the agenda. If the ministerial group can work with this community in doing that, it will be timely and valuable.

Dr Buckle: The developments since the setting up of the regenerative medicine expert group and the House of Lords report, in terms of there being a one-stop shop for regulation, and the fact that we have early access opportunities for therapeutic delivery and so on, are all good ones and were brought about by ministerial focus. As we move from the research domain into adoption, with the steps that have to be put in place there, there are certainly some benefits in having oversight of that. Whether it is a ministerial group or some other mechanism is an open question.

Professor Hanley: There are two things. I reiterate what Professor Andrews said earlier. We must never allow the bottom-up approach to be hindered, but the flip side is that ministerial, Government or MP involvement in this area is very important, because engagement is key. That is one of our strengths in the UK.

Q77 Victoria Borwick: If you were setting up such a group, who would be providing the strategic leadership?

Professor Hanley: It depends on what you want the strategy to be.

Q78 Victoria Borwick: As you say, if it is communication that is driving the agenda forward, as Professor Hollander said, I suppose it is a slightly different group.

Professor Hanley: It is a mix. This is another example where our funding structure in the UK is very proactive. For example, the MRC talks to the Wellcome Trust and has good relationships. As we move into clinical translation, as we talked about earlier, there are relationships with NIHR, for example. There are well-placed structures and individuals.

Q79 Victoria Borwick: While we are talking about funding, inevitably there is always a debate about further constraint on health budgets and suchlike. How would you see your area being constrained, or not constrained? Where could you find alternative funding? Is there something the Government should be doing to encourage more private investment? We have talked about the 10-year strategy. How do you see the funding for that?

Professor Hollander: It depends on whether you are talking about the fundamental research, which is very well looked after and well served by the research councils and leading charities. Of course, we always want more, but it does what it does. As you go down, up or along the translational pathway, funding issues become more challenging. For

example, there was a question earlier about Innovate UK and loans versus grants. There are pluses and minuses for both from a commercialisation angle. We will potentially lose the SME-friendly European pathways if we do not get a good agreement with Europe on Horizon 2020 and what follows it. At the moment, there are SME-only or SME-led calls, which I do not think have an exact equivalent in the UK, so there are risks at that end of things, moving forward.

Q80 Matt Warman: This question is mostly for Professor Hollander. In the interests of comprehensive disclosure, I should say that my wife's PhD supervisor was Allen Goodship, who I think is on the board of Azellon, but she has recovered now so it is all right. I want to talk about Claudia's trachea, which happened in 2008—in Spain rather than in this country. Can you tell us a little about why that groundbreaking tissue engineering took place abroad, and whether it would be easier now to do something like that in this country?

Professor Hollander: How long have you got? The simple answer is that the initial concept came from Paolo Macchiarini, the Italian surgeon, in Barcelona at that time, who had been developing the concept of tracheal transplants and was in close contact with my colleague Martin Birchall, who is now at UCL but he was at that time in Bristol where I was. It was simply initiated there. It was not research. We did not have a grant to create Claudia's trachea. She was a patient who the clinicians judged was dying. I am not a clinician, but that was their view. A number of us were asked whether we would pool our technologies—two technologies from Italy, my technology and Martin Birchall's at Bristol, along with other technology in Barcelona—and in a matter of three months find a way to create this tissue-engineered trachea. By the way, my first reaction was that we could not possibly do that, but that is another story.

Q81 Matt Warman: Was that a technical rather than an ethical reaction?

Professor Hollander: Ethical is another story. I took some weeks to satisfy myself ethically. No, the answer was technical and regulatory. I had no idea how to get through this from a regulatory perspective, but on the question why it was led from Barcelona, that was where it started, but it became possible because of the stem cell biology and other aspects we were developing in the UK, and that was what we brought to the party.

Q82 Matt Warman: If it were to happen now and it was an English suggestion, do you think it would be easier to do than it was then, or possible or impossible?

Professor Hollander: I suspect it would be impossible. Remember, this was in 2008 and six months before the advanced therapy and medicinal products regulations came in. Under ATMP, the kind of get-out clauses we had on various aspects to create that so quickly would not have happened, even on the basis of saving the patient's life. We can argue whether it was right or wrong. We were allowed to do it then, but I do not think it could happen now.

Q83 Matt Warman: Is that kind of regulation in your view an improvement? Presumably, Claudia would doubt that it was an improvement.

Professor Hollander: Regulation in general is good; it means we know where we stand. There is always tension between protecting the patient from a cavalier attitude, on the one hand, and a long historical tradition of experimental medicine, which is in a sense disappearing because of regulation, on the other. We have to find the right point for that, and I am probably not qualified to say whether it was better before or now. I do not think we could now do the trachea case in the way we did at that time.

Q84 Matt Warman: It does not sound like progress. Does anyone else on the panel have a view on that?

Professor Pearson: I think the regulatory framework around experimental medicine, as you call it—first-in-man studies—has become more and more complicated as time has gone on to a state where we are doing less of it because it is so complicated to do. That is holding back necessary steps in early translation at the expense of people doing larger trials which then fail. I think there are things wrong with the legislation in that regard at the moment, but it is slightly off the main tack of where we are.

Q85 Matt Warman: Yes and no. After Government concerns in this country about red tape, we had IRAS—the integrated research application system. Has that helped or hindered this?

Professor Pearson: Ask a clinician.

Professor Hanley: It is a bit like the earlier conversation about experiments involving animals, and Home Office regulation and licensing. Of course regulation is required, and some of it is a bit like the one-stop shop we talked about earlier in terms of regenerative medicine. Anything that tries to simplify a pathway is good. There are always people behind all of this, and we need continuous scrutiny to make sure that people are acting to make everything as streamlined and joined up as possible. For example, one of the good things we have done in regenerative medicine is that when we recognise an area with potential, which may take some time, we do not wait until we have something we think may be good before we talk to the regulator. That sort of partnership is of critical importance. My personal belief in a number of these areas is that we could streamline things further and strip it back to the fundamentals. I do not think we would lose public support for the work that is done or the treatments we carry out.

Q86 Matt Warman: That last sentence prefaces my next two questions, which is rather awkward. In that sense, do you think that as we come out of the EU we have the opportunity to do the kind of streamlining you are talking about?

Professor Hanley: Yes.

Q87 Matt Warman: Is that a real opportunity? It sounds like something you think we should be seizing.

Professor Hanley: We have been forced to look at it, and we do have to look at it. Clearly, you will be held according to the market you are trying to sell in. If we are looking to sell into a European market, that still exists. It should always be a continual process. It is a

team. It is not them and us; it is not us versus the funders, and it is not us versus the regulators. We are all in it, so we should be continually studying it.

Professor Pearson: I hesitate slightly, in the sense that in lots of areas of medicine, even regenerative medicine, we will need to run trials on a multinational basis to make sure they work. Therefore, we have to have legislation and governance that is compatible with what other people use. If we have something very different we cannot do that any more, so we have to be careful.

Q88 Matt Warman: Are we now able to look more broadly than the European Union, or was that something that was always perfectly possible?

Professor Pearson: That is what we are doing now.

Professor Hanley: It is the same as selling into a market, isn't it? It is a question of working out what we want and then making sure it is fit for purpose, and we have that opportunity.

Q89 Matt Warman: Following on from something you mentioned earlier, all the surveys seem to show that the public support a tightly regulated version of all the kinds of treatments and therapies we have been talking about. Do the Government need to do more to examine those attitudes, or to try to make the case, or do you feel that the work you are doing is adequately understood and accepted in the wider world as well?

Professor Hanley: Both scientifically and clinically, it is pretty good. I do not see there being a big problem about engagement, and I have not seen that in the course of my work over the past 20 years. I always feel that the public have been very supportive. In the UK, it is quite nice that we also have a very strong network of medical research charities that sit on both sides. A lot of public engagement and patient advocacy takes place through AMRC members. It is a really good environment.

Professor Hollander: Absolutely. I do not remember a single negative comment on this area of research from any engagement I have had with the public. Admittedly, I do not personally work with embryonic stem cells and there may be particular issues there, but the whole debate around stem cells that has gone on over the years has created a positive environment.

Q90 Matt Warman: It seems to me that a lot of that public engagement is driven by the fact that it is not Government or people making money out of it; it is people like the British Heart Foundation, or whoever, who are making the case. Is there anything else where we have done particularly well, or should be doing more of, to make sure we keep the public on the track we are likely to be going down?

Professor Pearson: As funders, researchers and Government we have continually to inform the public as to where the success stories and developing stories are, and that the media are reporting them appropriately. We still get mad stories in the media every other week—ears on the back of a mouse or whatever—and we have to try to counteract that and proactively make sure that what we feed in that direction continues to build the public

trust behind us. You are right that on an individual patient level they are all behind it, because they know it might cure them of something, but out there, as informed by the press, that is not necessarily the case. There is an ongoing need for people like the Science Media Centre to make sure this works well.

Dr Buckle: We last looked at public opinion in this area very closely around the time of the 2008 renewal of the Bill, but two events since then at least show that continued dialogue puts us in a good position as developments come. One was the mitochondrial transfer debate, but more recently I have been involved in the gene-editing discussions. They touched the public nerve and journalistic inquiry about the embryonic angle. It has been quite intriguing, in so far as the same arguments that were present before have come back. Being involved in international meetings around this, it has become clear that the level of public dialogue and understanding, and to some extent our forward thinking in legislative terms, is envied around the world. The Nuffield Council is doing a big consultation on that element. Continual dialogue is the key thing. We do a good job, but it is important for parliamentarians to support that as well and make sure debates happen.

Professor Hollander: Can I say a positive word about the Science Media Centre, which Jeremy mentioned? It is a fantastic example of how we can work together to be very effective in communicating with the public.

Q91 Matt Warman: What more could we be doing to try to make sure that the press is as well informed as it possibly can be in this area?

Professor Pearson: From our perspective as a funder, we try to be absolutely open about what we are funding and why, and to explain it to the press on every occasion we can. I think that is the best we can do.

Professor Hanley: For me, it is a long-term thing. In our media, by comparison with others overseas, there are journalists who have learned a bit of science as journalists rather than science graduates who have then gone into journalism. It's back to science in schools and your hope that they're watching.

Chair: Thank you very much indeed. You have been very helpful. The science has been very well explained, and it is exciting to hear how competitive we may still be. The Committee will be returning to this—it is not our only session—because regenerative medicine is incredibly important. If we ask for written submissions, I hope you will be patient with us and answer our questions. Thank you very much on this incredibly hot afternoon.