House of Lords Select Committee on Science and Technology: Regenerative Medicine

Response by the Wellcome Trust

September 2012

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.[1] 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.

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.[2] 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 iPS cell collection with the MRC, to be publicly announced in October.

[1] http://www.wellcome.ac.uk/News/2012/News/WTVM056287.htm
[2] http://www.pigsbladderfootball.com/about.html

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.[3] This statement has garnered support from a large range of UK and European organisations.[4]

Application of the science

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.

[3] http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/EU-funding-for-stem-cell-research/Full-statement/index.htm
[4] http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/EU-funding-for-stem-cell-research/Signatories/index.htm

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.[5] And recent research holds promising signs for Alzheimer's patients over the longer-term.[6]

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.

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.[7]

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

[5] Ahmad S et al., 2010 Stem Cell therapies for ocular surface disease Drug Discovery Today volume 15 2010 306-313
[6] http://alzheimers.org.uk/site/scripts/news_article.php?newsID=922
[7] http://www.wellcome.ac.uk/News/2012/News/WTVM056288.htm

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'[8] 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
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

[8] http://www.acmedsci.ac.uk/index.php?pid=47&prid=88

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.[9] 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

[9] http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/WTX058237.PDF

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 Captapult to deliver on its potential for stem cell therapies. Whilst there has been much national support for the Catalpult, it is important to build on this. It will be important going forward to clarify the role of Catalpult 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 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 country[15].

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 1 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.[10] 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.

[10] http://www.nature.com/news/stem-cell-pioneer-banks-on-future-therapies-1.11129