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Innovation & Skills

OFFICE FOR LIFE SCIENCES

Taking Stock of Regenerative
Medicine in the United Kingdom

JULY 2011



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Ministerial Foreword

Regenerative medicine has the potential to play an increasingly vital role in delivering the next generation of healthcare, offering treatments or possible cures for areas of unmet medical need such as Parkinson's, diabetes, stroke and heart disease. There is also a real possibility for us here in the UK to gain economic benefit from commercially exploiting this exciting area of technology.

The United Kingdom is already in a strong position, with world-class research, key infrastructure, an active commercial sector, and a single payer healthcare regime in the form of the National Health Service.

However, this report highlights that, as with many emerging technologies, there are steep technological, regulatory and strategic barriers to realising regenerative medicine's significant potential. This Government is investing strongly in the field to fund basic and translational research, but we need to ensure that this is appropriately coordinated, and that we understand where the key challenges lie.

With exciting developments such as the Cell Therapy Technology and Innovation Centre, we believe that there are huge opportunities for us to become a hub for research and investment. This report has built a comprehensive evidence base from which the Government, and the sector, can go forwards.

We look forward to following the development of this field, and working closely with experts to accelerate the translation of our world-class science, into effective therapies, and world-beating companies. Finally, we would like to thank all the individuals and organisations that provided the review team with excellent and thought-provoking evidence for this report.

David Willetts
Minister of State for
Universities and Science

Anne Milton
Parliamentary Under Secretary
of State for Public Health

Executive Summary

This report establishes that the United Kingdom retains a leading position, in Europe and globally, in the science and commercial translation of regenerative medicine. The quality of our work, in research and academia, is of a world class, supported by a strict but permissive legislative, and regulatory, framework that is helping innovation to flourish. The UK is at the forefront of this rapidly evolving technology and is in a good position to take advantage of its promise.

However, despite the huge potential to deliver new treatments and commercial successes, regenerative medicine also faces some key challenges. In particular by using living cells rather than the drug or traditional biologic based capabilities of major multi-nationals, there are associated difficulties for the manufacture, transport and delivery of therapies. Initial treatments are also likely to be expensive, and could challenge existing models of funding, reimbursement and commissioning. It is critical therefore that the field demonstrates safety and efficacy, which in turn is likely to leverage vital future investment.

In the context of these challenges, and significant investment by Government, this report takes stock of developments across the development pathway.

Informed by a series of workshops in London, Edinburgh and Leeds, as well as a call for evidence open to regenerative medicine stakeholders, and supported by key quantitative data, the report:

- Assesses the state of the regenerative medicine field internationally and analyses the UK's strengths, weaknesses and areas of opportunity.
- Identifies key barriers to the therapeutic and commercial use of regenerative medicines and sets out how Government will work to overcome them.
- Provides the UK Government with a strong evidence base on the basis of which it can coordinate funding decisions, and lays the ground-work for an agreed strategy for regenerative medicine that builds on the strengths of the research, the NHS and UK industry.

In addition to the Government's commitment to funding basic science and translational research, this report sets out a series of ten actions that the Government will take to support the sector going forwards. These mark a step-change in support, highlighting a commitment to tackling the field's strategic challenges through greater coordination and focussed support.

The Government will take action to:

Better co-ordinate public investment and leverage funding from private sources:

1. To ensure that future funding has impact in areas of key strategic importance, the Research Councils and Technology Strategy Board will assess barriers to progress by the end of 2011 and further coordinate their investments in the future
2. In recognition of the importance of pharmaceutical companies and other large corporations to the development of regenerative medicine, the Research Councils and Technology Strategy Board will conduct a thorough consultation with the major players by the end of 2011.
3. The Office of Life Sciences will work with partners to investigate creative funding mechanisms from a broad range of sources, including working with UK Trade and Investment to promote international investment in UK regenerative medicine.

Ensure the regulatory framework is facilitating and supported by a strong intellectual property regime, and appropriate standards:

4. The Department of Health will review the UK Stem Cell Toolkit on an ongoing basis to ensure that it accurately reflects the regulatory pathway in the UK, and continues to support research and product development.
5. Regulators will continue to engage with the regenerative medicine community to ensure the regulatory process functions in a way that is easily accessible and engage with new organisations such as the UK's Cell Therapy Technology and Innovation Centre to help build regulatory expertise and share knowledge.
6. In recognition of the value of standards in emerging technology areas, BSI is revising and will re-publish the two existing publicly available specifications in regenerative medicine (PAS 83 and 84), and will also publish the new PAS 93.
7. Recognising the importance of protecting innovation to the development of regenerative therapies in the UK, BIS and the Intellectual Property Office will keep the intellectual property regime in the UK under review.

Provide more clarity and help to get these highly innovative products to patients:

8. The Department of Health will work with the NHS Blood and Transplant Authority to investigate how their involvement in regenerative medicine supply and delivery chains might be extended and developed.
9. NICE, through its technology evaluation and scientific advice programmes, will continue to facilitate useful dialogue with companies developing regenerative therapies on the development of data for comparative effectiveness and health economic analysis.

Support the sector in the long-term, staying ahead of developments:

10. In recognition of its potential as a driver for the UK economy and future healthcare, the Government will work towards an integrated, national strategy for regenerative medicine that builds on the strengths of the country's science, industry and healthcare sectors.

1. Introduction

A definition of regenerative medicine

- 1.1 Regenerative medicine is not one discipline, but covers a number of emerging and sometimes related fields. At its simplest it can be defined as a therapeutic intervention which “replaces or regenerates human cells, tissues or organs, to restore or establish normal function”¹.
- 1.2 Regenerative medicine deploys small molecule drugs, biologics, medical devices and cell-based therapies. However, the term is more colloquially used to mean advanced therapies based on cells, tissue engineering, developmental and stem cell biology, gene therapy, cellular therapeutics and new biomaterials (scaffolds and matrices).
- 1.3 Although not “regenerative”, there are also promising associated cell-based technologies such as the use of cells for non-regenerative therapies, stem cells for drug discovery and toxicity testing and other associated tools and technologies. This report will take into account the impact that these related technologies could have.

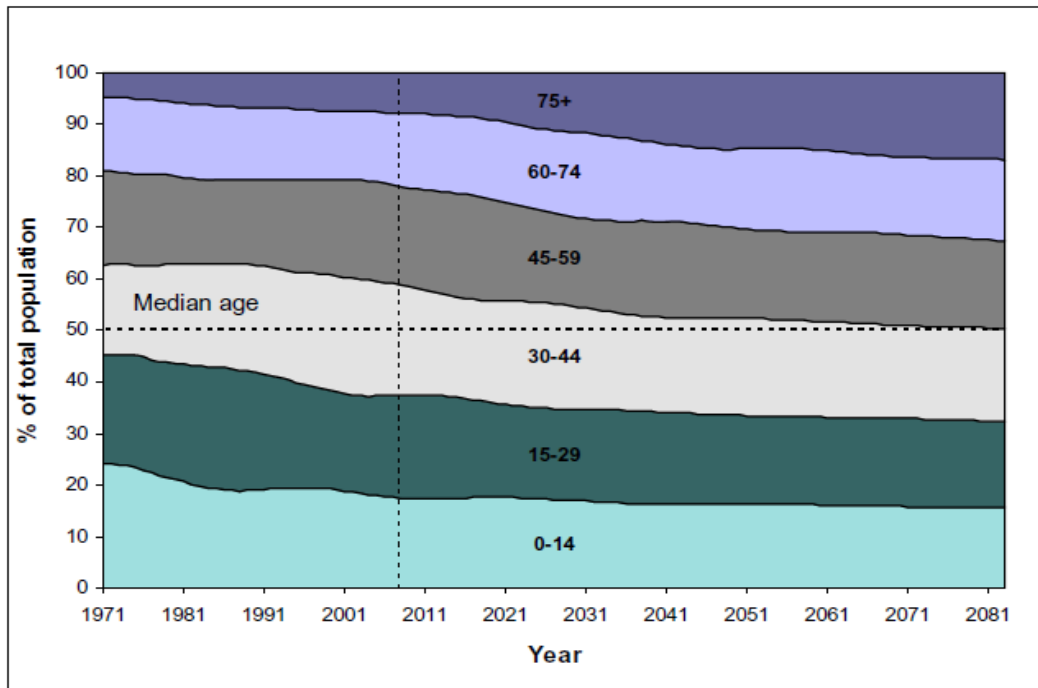
The healthcare context

- 1.4 There are a number of key trends in healthcare today that will impact on the development of regenerative medicine, and provide an indication of the significant role the field could play in the future of healthcare:
 - There are **strong pricing pressures from public healthcare payers** globally as Governments try to reduce budget deficits. Regenerative medicine could potentially save public health bodies money by reducing the need for long-term care and reducing associated disorders, with potential benefits for the UK economy as a whole.
 - Much of the pharmaceutical sector is facing declining **revenue and growth** due to a combination of the so called “Patent Cliff” effect peaking in 2011-2012, (the co-occurrence of drugs losing market exclusivity), inefficiencies in the drug development process leading to growing development costs and high product failure rates leading to fewer product launches. At the same time there is an increasing need to demonstrate the cost effectiveness of individual products to healthcare payers and to show what clinical value new medicines offer over existing medicines. While pharma companies remain attracted to the “blockbuster model” where products are developed to work across the broad patient population they are also beginning to develop medicines for much smaller groups of patients (e.g. stratified medicines and targeted therapies) where their genetic predisposition makes it highly likely that the medicine will be effective.

¹ Mason C, Dunnill P. A brief definition of regenerative medicine. *Regen Med*, 2008; 3:1-5.

- The expected **ageing of the UK's population** (figure 1) will continue to boost market opportunities for regenerative medicine products as well as increase cost pressures on healthcare providers. There are also large and growing unmet medical needs for example neurodegenerative diseases (including Parkinson's disease), stroke and heart failure that currently have no significant therapeutic options and are therefore only managed palliatively.

Figure 1: Projected Age Distribution, United Kingdom, 1971-2083 ²



- The **increase in obesity** and the accompanying rise in type 2 diabetes means that there are growing markets in related products such as advanced wound-care for diabetic ulcers and cardiovascular devices.

Historical Overview of Regenerative Medicine in the UK

1.5 Regenerative medicine isn't new; researchers have been investigating **adult stem cells** since the 1940's and **bone marrow transplants** have been successfully conducted for over 50 years. However it is only recently that **embryonic stem cells** and their unique potential have been discovered. In 1981 Sir Martin Evans became the first researcher to isolate and characterise embryonic stem cells in mice, and it was not until 1998 that Professor James Thomson isolated human embryonic stem cells.

1.6 These developments promised huge potential, but also challenged the existing regulatory framework. A Committee of Inquiry into Human Fertilisation and Embryology was established in 1982, culminating with the much cited "Warnock Report" which was published in 1984. The Committee afforded the human embryo

² Office for National Statistics

with a “special” status and laid the groundwork for the eventual passing of the *Human Fertilisation and Embryology Act* by Parliament in 1990.

- 1.7** This Act was amended after the successful isolation of human embryonic stem cells (human ESC) in 2001 to permit research on human embryonic stem cells for strictly regulated purposes. More recently the Act was revised and updated in 2008, before passing into law in October 2009. In doing so, the UK has developed a strict but facilitating regulatory regime for human ESC-based regenerative medicine.

Regenerative Medicine Dialogue

- 1.8** The Government has encouraged full public debate on all issues around stem cell research and regenerative medicine, including a major stem cell dialogue carried out by the Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council (MRC) in collaboration with the Sciencewise Expert Resource Centre which reported in December 2008. Such schemes have demonstrated the public’s willingness to engage with complex science and helped to increase public confidence in our scientists – and vice versa. This in turn has strengthened the case for investment in research of this kind.
- 1.9** This evidence is supported by recent polls, for example, a recent Eurobarometer poll concluded that 59% of those questioned in the UK supported use of human embryos for the development of new medical treatments.³
- 1.10** It is critical that this dialogue is maintained, and initiatives such as the UK National Stem Cell Network’s Roadshows, and the various regional Stem Cell Network’s public engagement events have made important contributions to this agenda. The Government is committed to maintaining dialogue, as appropriate in the future.

The UK Stem Cell Initiative Report

- 1.11** In 2005 the *UK Government’s Stem Cell Initiative* (UKSCI) report – chaired by Sir John Pattison – set out a long-term vision for UK stem cell research. The report made eleven key recommendations which aimed for the UK to “consolidate its current position of strength in stem cell research and mature, over the next decade, into one of the global leaders in stem cell therapy and technology”.

International Context

- 1.12** With the social and economic implications of ageing populations a concern in many developed countries, a number of Governments have singled out regenerative medicine for significant investment and strategic support. Most famously, California’s Proposition 71 authorised public funding of up to \$3 billion over 10 years for stem cell research.
- 1.13** Indeed the United States as a whole outspends its competitors by several orders of magnitude. In 2010, for example, National Institutes of Healthcare (NIH) spent \$1.2

³ Eurobarometer Report on Biotechnology 2010

billion on stem cell research. It is also notable that federal funding is a small proportion of total US funding, with the Alliance for Regenerative Medicine estimating that the private sector funds ten times as much research as the US government.

- 1.14** However, there has also been uncertainty recently around federal funding for stem cell research in the United States following an injunction by the District Court for the District of Columbia in August 2010. The Chief Judge ruled that the NIH guidelines were in violation of Congress' Dickey-Wicker Amendment (which bans research which injures or destroys an embryo). This came despite an Executive Order issued by President Obama on 9 March 2009, which allowed federal funding of stem cell research on any stem cell line allowed by law.
- 1.15** However, in May 2011 a federal appeals panel voted two to one to overturn the ruling given by Judge Lamberth. Currently this ruling still stands, with Obama's Executive Order allowing federal funding for stem cell research still valid.
- 1.16** Germany is also notable for its significant investment in the field through its cell-based therapies initiative (€30m, 2005-2009) and stem cell initiative (€9m, 2008-2012). Germany has also funded a number of translational centres and research "clusters of excellence", and has a significant number of SMEs involved in the field.
- 1.17** Although the US and Europe have led the research and application of regenerative medicine, Japan has had notable prominence with its production of Induced Pluripotent Stem Cells in mice in 2006 and in humans in 2007.

2. The Science of Regenerative Medicine

Sources of Stem Cells

There are currently four main sources of stem cells, cells with the ability to replicate and differentiate into other more specialised types of cells:

Embryonic Stem Cells

These are cells that are derived from embryos that are a few days old, at a stage lacking any anatomical organisation, and have the potential to differentiate into all 200 cell types of the adult body. Such cells are termed pluripotent.

Foetal Stem Cells

These are derived from aborted human fetuses and have the potential to differentiate into many, but not all, of the adult body's cell types. Such cells are termed multipotent.

Cord Blood and Placental Stem Cells

These are derived from umbilical cord blood and placentas. Although only able to differentiate into a limited number of cell types, such cells offer therapeutic potential and are currently used in bone-marrow replacement therapies to treat a variety of immune and blood related conditions.

Adult Stem Cells

These are already used in a number of therapies, and are found in the vast majority of human tissue and organs. These multipotent cells only have the potential to differentiate into a limited number of cell types and are also known as "somatic stem cells".

Induced Pluripotent Stem Cells

These are stem cells that can be derived from a variety of specialised cell types – for example adult skin cells – using genetic or biochemical manipulation. The resulting cells are pluripotent and have very similar properties to embryonic stem cells.

Science cannot predict at this stage which types of stem cell will prove to be of most benefit and so continued research on all types of stem cells remains necessary to improve our knowledge.

The Parliamentary Office of Science and Technology is currently reviewing scientific developments in stem cell research, and will publish a report of their findings in the Autumn.

Developments in the Science over the last five years

2.1 When Sir John Pattison led the UK's last strategic review of this field, he concentrated on stem cell research. We are taking a broader view of the field, but

there are a number of key developments in stem cell science since 2005 that should be highlighted:

- (i) **Induced Pluripotent Stem Cells:** These were first produced in 2006 from mouse cells and in 2007 from human cells. They are typically derived from adult stem cells and encouraged into a pluripotent state by forcing the expression of certain specific genes. The hope is that they will have the diversity of applications of embryonic stem cells while also reducing the risk of immune rejection, as cells can potentially be taken from an individual, engineered and then re-implanted into the same host. However, more research is required to develop methods of generating iPS cells with a high level of efficiency, without the use of technology that may increase the risk of cancer. Further research is also required to fully understand the nature of the reprogramming process. For this reason, iPS cells are currently thought to be less safe, with higher risks of tumorigenicity, than human embryonic cells. Non-genetic methods of producing iPS cells are constantly being developed but the efficiency of these process is currently very low.
- (ii) **Direct reprogramming of differentiated cells:** in the last few years a number of studies have shown that that a direct route can be taken to convert one differentiated cell to another, without going through an embryonic-like undifferentiated state.
- (iii) **Small Molecule Induced Differentiation** Small molecules can also induce differentiation and have advantages in terms of the ability of the clinician to control dosage. For example small molecules have been used to generate iPS cells by acting as substitutes for genetic reprogramming factors. Such approaches offer the longer term potential to activate dormant stem cells in the adult body, and proof of concept for this has been most recently demonstrated through the use of a small naturally occurring molecule, thymosin beta4, to stimulate cell mediated repair of a damaged mouse heart.⁴

Where is the Science Going?

2.2 Submissions to this report's call for evidence, and consultation with experts established there were seven key areas where progress was expected in regenerative medicine in the next five years:

- (i) **Induced Pluripotent Stem Cells:** In the next five years, the efficiency of generating iPS cells and the understanding of the mechanisms of cell programming and reprogramming is likely to improve. However, there are ongoing concerns over safety presenting a significant hurdle before we will see significant progress towards therapies. In the shorter term the use of iPS cell-technology will have highest impact in establishing models of disease for research into pathological mechanisms and drug development and screening.
- (ii) **Direct reprogramming of differentiated cells** has already been demonstrated, as explained earlier and the ability of certain genetic factors to dominantly specify cell

⁴ Smart et al Nature 2011

fate has been known for some years. However, recent advances have convinced respondents to our call for evidence that this technology is likely to progress significantly over the next five years. Direct reprogramming has a number of major advantages including the potential to produce therapies based on small molecules/biologics for *in vivo* reprogramming. This method would also produce cell therapies without the need to use a pluripotent cell stage, thus greatly reducing the risk of rogue cells leading to uncontrolled cell growth or inappropriate differentiation into an unwanted cell type.

- (iii) **Ongoing trials of adult stem cells** which provide the basis for the majority of current commercial research in stem cell therapies, mostly in the area of bone/cartilage repair and wound healing. Other areas under development include blood-related therapeutic research including T cell immune modulation and cord blood.
- (iv) **Gene therapy and especially genetically modified cells** as therapies (i.e. vehicles for gene therapy delivery) will gain growing prominence – respondents felt that these technologies, that were previously “stalled” due to the state of the science, could now be progressed due to recent advances in other areas. There is also potential to use cells as vehicles to deliver other interventions such as cell-based cancer vaccines.
- (v) **Safety and efficacy data from stem cell derived therapeutics:** in the USA clinical trials using human embryonic stem cells have now started for acute spinal cord injury (Geron), Stargardt’s disease (ACT) and age-related macular degeneration (ACT). Clinical applications using human ES cells will likely be focused on age-related and ‘orphan’ applications initially.
- (vi) **Cord Blood:** traditionally used to supplement the supply of bone marrow, umbilical cord blood is increasingly proving to be as good as, and in some cases better, for unrelated donor transplant. This is mainly due to the fact that research has proven that cord blood units do not have to be identically matched to be transplanted into an individual. This means that a wider range of patients can be treated. The relatively easy access to cord blood and its availability make it a valuable resource for regenerative medicine. Also, in the US especially, it is increasingly seen as route to provide blood stocks as a contingency the increasing threat of emergency situations.
- (vii) **Translational science and technology:** regenerative medicine will require new science and technology to enable successful delivery and application, particularly from physical sciences and engineering. This will include new imaging and diagnostics; regenerative scaffolds for delivery and to support tissue function and cell manipulation; as well as manufacturing monitoring and selection technologies. Related research on translational sciences and technologies is essential if impact and economic benefit is to be realised from stem cell science.

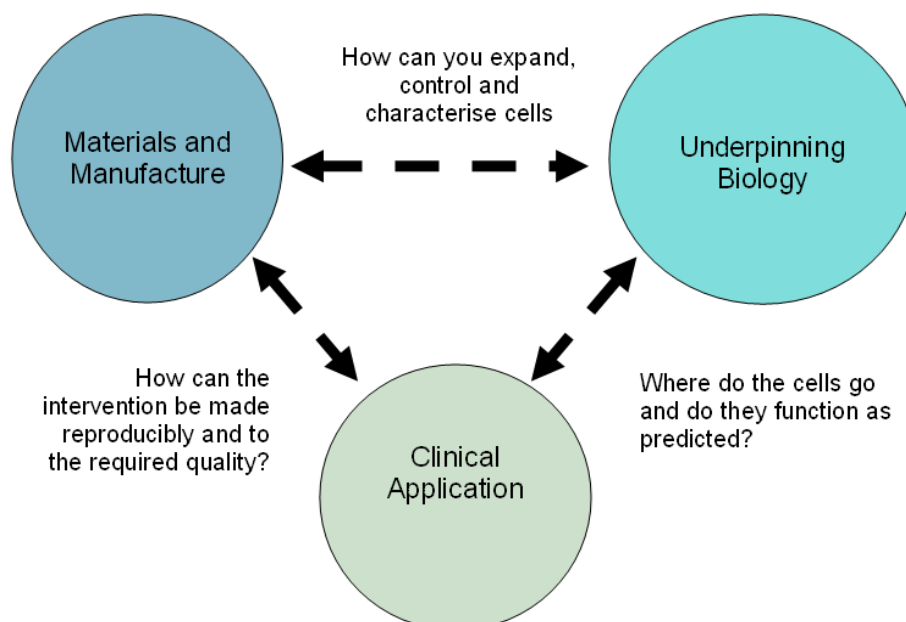
Priorities for achieving widespread therapeutics

2.3 As the first isolation of human embryonic stem cells only took place in 1998, it is not surprising that therapies derived from embryonic stem cell lines (or iPS first discovered in man in 2007) are used in widespread clinical trials yet. Therapies

derived from embryonic, iPS cell lines or from foetal stem cell lines are likely to develop at different rates depending on the specific medical indication, risk-benefit to patients and the technical hurdles that are likely to be encountered in their manufacture and in the clinic.

- 2.4** Although the very first embryonic stem cell trials in patients have commenced (i.e. Geron- spinal cord injury) it is unlikely that stem cell therapies will immediately lead to outright cures. Instead a gradual emergence of efficacy over a few generations of cell-based products is a more realistic expectation. Thus both the discovery science and translational science will be pivotal in making the necessary incremental steps to unlock the full potential of cell therapies.
- 2.5** Many respondents to this report's call for evidence stressed the importance of enabling technologies alongside new therapeutic breakthroughs. Their feeling was that without the ability to manufacture, store, transport and distribute regenerative medicine products, the therapies would never become mainstream clinical practice.
- 2.6** Regenerative medicine interventions will also require advanced diagnostics and stratified approaches, supported by advanced imaging research. Multidisciplinary work on tissue and cell monitoring, labelling, sorting and signalling is also needed, alongside more research into the regenerative repair processes.

Figure 2: Inter-related Challenges for Regenerative Medicine



- 2.7** Researchers and companies certainly need to be encouraged to look at these issues early in the development of a therapy. The field faces challenges in key areas such as:
- (i) **Safety:** It must be established that stem cell derivatives are suitably safe in relation to the risk of tumour formation or production of unwanted cell types in the body. As already mentioned, these concerns are thought to be particularly pertinent for induced pluripotent stem cells, where we need a better understanding of

reprogramming and the epigenetic read-through from the donor cell's chromosomes. We also need to know how to ensure genetic stability as human ES cells and iPS cells undergo multiplication and/or differentiation, along with how different culture methods influence this.

- (ii) **Regulatory Science and standardisation:** respondents felt that scientific methodologies and platforms are needed that assist the community in obtaining the data necessary to meet regulatory requirements and ensure product quality, safety and efficacy. Specifically, regulatory standards need to be developed in an ongoing process alongside, and in communication with, scientific and industrial efforts. It was stressed that this should be an iterative process that would also require a sharing of manufacturing and regulatory expertise.
- (iii) **Imaging and Monitoring:** Dedicated efforts in imaging and other techniques for monitoring cell behaviour is necessary. This was thought to be particularly important given the considerable heterogeneity in the way individual cells respond to behavioural cues. In particular in clinical trials, the variation in cell behaviour must be shown to be within tolerable limits across multiple clinical sites to gain regulatory approval in particular for Phase III trials. For example it will be important to monitor where cells migrate to following administration.
- (iv) **Manufacturing:** the need to manufacture viable (living) cells for regenerative medicine application poses significant challenges. Achieving a controlled and characterised manufacturing process for cell based therapies requires the development of new technologies, tools and techniques.
- (v) **Biomaterials, scaffolds and matrices** Many applications in regenerative medicine require scaffolds and matrices for delivery or to produce a functional regenerative repair, example include organs, tissues which require immediate functionality such as cardiovascular system. Multidisciplinary research which brings together different research communities is needed
- (vi) **Animal Models:** We were told that there had been little research focussed on appropriate animal models, which are necessary for pre-clinical trials and can be predictive of safety and efficacy outcomes. There is a perceived need for improved animal models to allow for the functional assessment of human cells without the risk of rejection. The Academy of Medical Sciences is currently undertaking an expert working group study examining the use of animals containing human material in scientific research. The scope of the study is to examine the scientific, social, ethical, safety and regulatory aspects of research involving animal embryos containing human genetic or cellular material
- (vii) **Scale up/manufacture:** respondents felt we would have to bridge the detail of biological science and bioprocess/biochemical engineering/manufacturing technology to deliver scalable production processes that deliver particular therapeutics that are safe, effective and at an appropriate cost that would facilitate their widespread adoption by healthcare providers including the NHS.
- (viii) **Immunogenicity:** A key issue for some regenerative therapies is the potential for rejection of cell transplants by the patient. This area needs further research with

respect to inducing immune tolerance and developing a new generation of immune-suppression drugs specifically for cell therapies. The length of immune suppression also varies by whether the introduced cells are transient in nature, or become engrafted. The latter would currently require long-term immune suppression.

- (ix) **Cell Viability:** Cell viability, and what constitutes it *in vitro*, was highlighted as another area where we are lacking knowledge. Linked to this is whether we are able to maintain unstressed cells with high therapeutic potential, that will not die, or form un-wanted derivatives. These factors will impact the ability to manufacture, store and distribute potential cell therapies. Workshop respondents felt this was one of the critical “associated issues” for translation and commercialisation.

Action 1

To ensure that future funding has impact in areas of key strategic importance, the Research Councils and Technology Strategy Board will assess barriers to progress and further coordinate their investments in the future by the end of 2011.

An Analysis of Regenerative Medicine Research

- 2.8** As part of this report’s evidence gathering, an analysis of the impact of regenerative medicine research was conducted, to assess the UK’s research strength in the sector in an international context.⁵ As well as considering the total number of publications in the field, this analysis looked at the impact of papers. Publication impact was measured by citations, using normalised citation impact (nci).⁶
- 2.9** The nci values are presented as Impact Profiles® to show how the UK compares with the rest of the world, with, in simplistic terms, a curve further to right indicating greater impact.

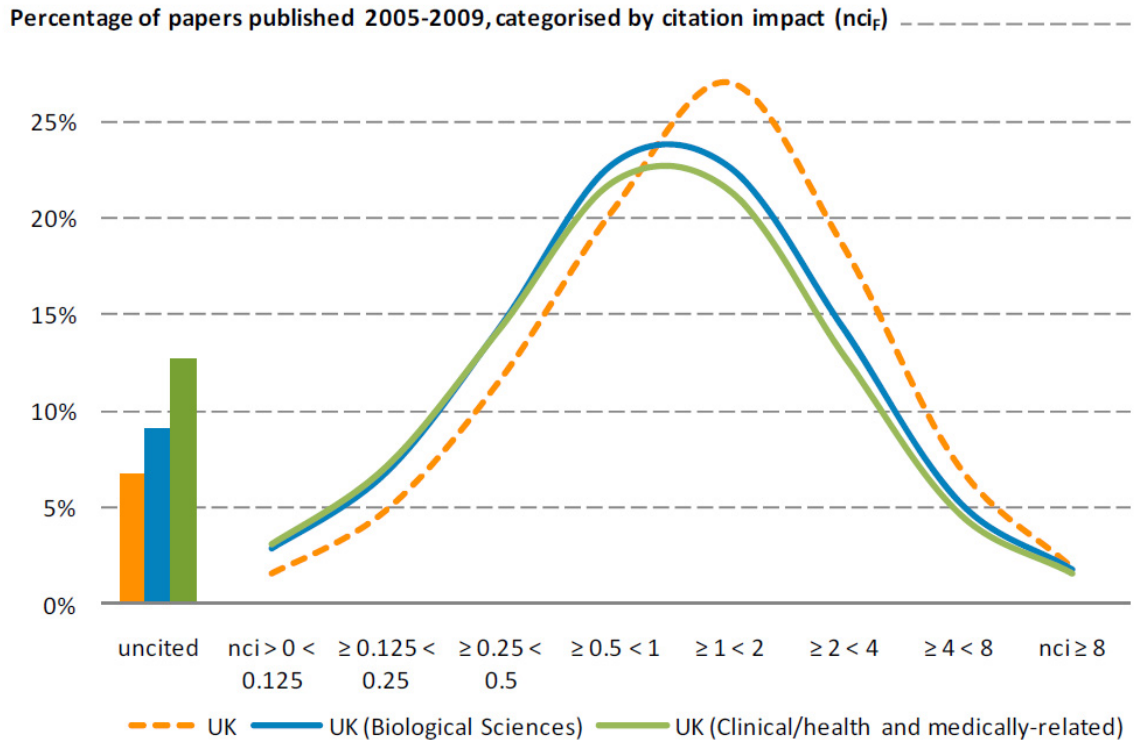
Impact of Regenerative Medicine in the UK

- 2.10** Analysis of the impact of regenerative medicine compared with similar fields such as biological sciences, and clinical/medical related papers, is a useful indicator of comparative strengths in a country.
- 2.11** Analysis of the data set in the UK (see figure 3), shows that regenerative medicine research in the UK, has considerably higher impact than equivalent research in life sciences generally, indicating that this is an area in which the UK has domestic strength. The peak of the regenerative medicine curve is shifted rightwards, to a higher citation impact level, compared with the background curves. There are relatively fewer uncited papers, relatively fewer papers in categories below world average (to the left), the modal peak is above world average, and there are relatively more papers in categories above world average.

⁵ The core ‘regenerative medicine’ data set for this study was drawn from the PubMed database by Evidence, Thomson Reuters, using Medical Subject Heading (MeSH) terms. MeSH terms were agreed in consultation with BIS, Research Councils and the Technology Strategy Board to give the most complete coverage possible of ‘regenerative medicine’.

⁶ May be expressed as nciF for fields and nciJ for journals. Citation count is normalised (or ‘rebased’) for subject (field or journal) and year by comparison with the relevant world average.

Figure 3: The Impact of Regenerative Medicine in the UK compared with the UK Biological Sciences and Clinical/Health Fields⁷



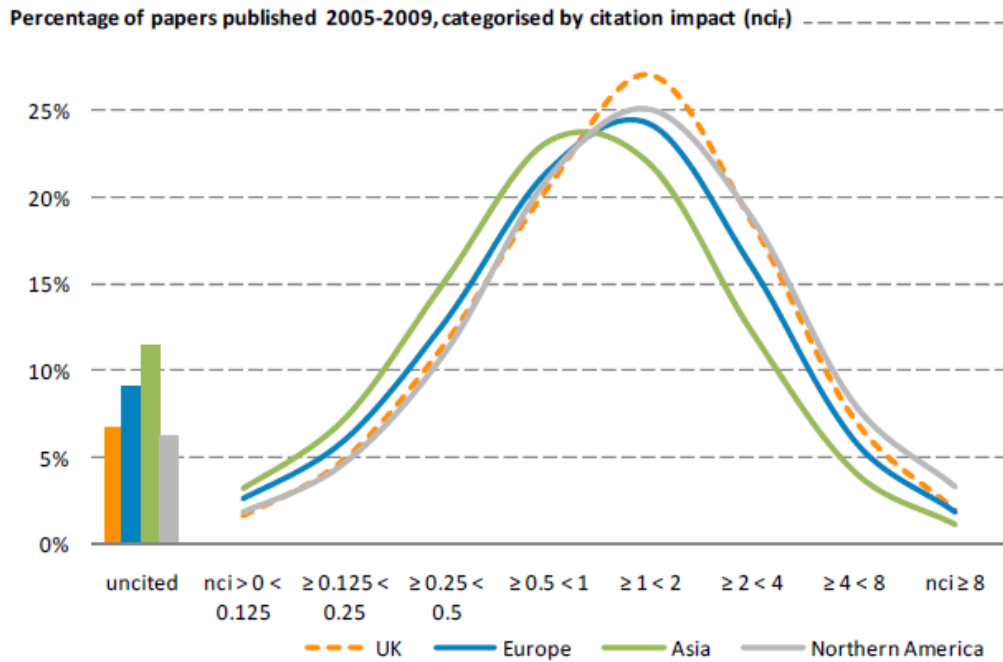
Impact of UK Research Internationally

2.12 Compared with continental averages, analysis shows that the UK is also well placed, with more highly cited research, on average, than the rest of Europe and Asia (figure 4). North America outperforms the UK in terms of its number of very highly cited articles. This is to be expected given the United States' very significant investment in this field. California alone has committed \$3 billion over 10 years to stem cell research.

2.13 It is also notable that high impact research is still predominantly originating from major developed countries, with emerging economies still relatively weak in terms of research impact.

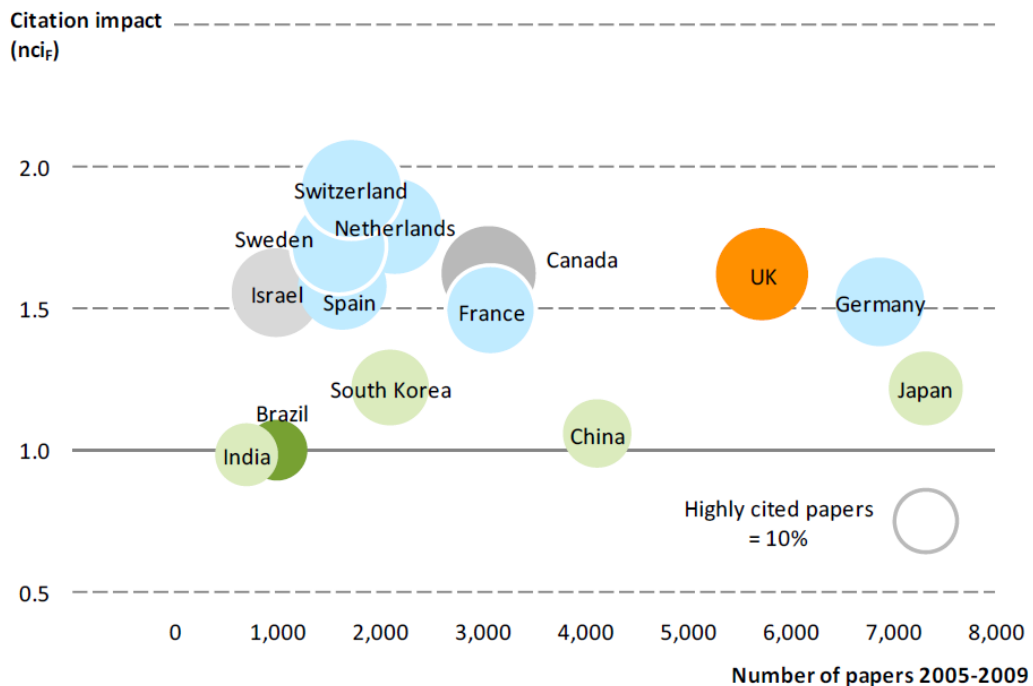
⁷ All graphs in this section (Chapter 2) should be attributed to *Evidence*, Thomson Reuters

Figure 4: The Impact of UK Regenerative Medicine Research Papers Compared with Papers Authored in Major Continents



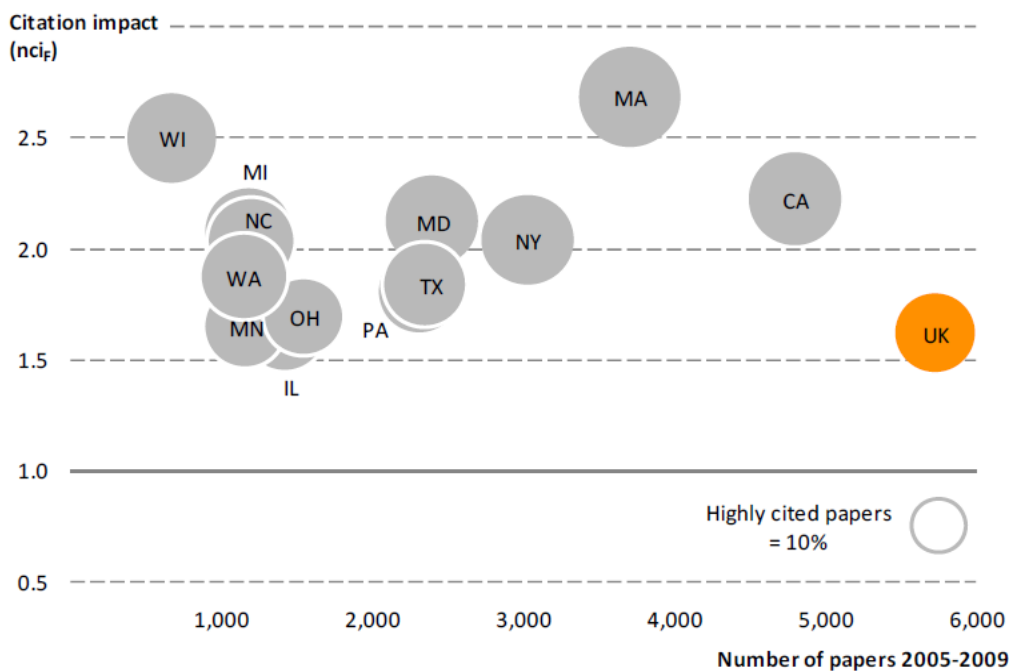
2.14 When compared to other research active countries (Figure 5), the UK while producing higher quality research than its major competitors in Germany and Japan, does not compare as favourably as some smaller European countries (eg Switzerland, Sweden and the Netherlands), who publish a small number of papers which are of a high impact.

Figure 5: Output of Research Papers Compared with Average Normalised Citation Impact for the UK and other research-active countries



- 2.15** The United States has been left off of the analysis in figure 5 as their data skews the results considerably given their very high levels of publication in regenerative medicine. However, comparison can be made with individual US states, where the UK stands out in terms of volume produced, but not citation impact. For example the UK publishes more papers than California but its average impact is no better than most of the smaller states in the analysis (states not included were smaller and had lower impact).
- 2.16** However it should be noted that the relative citation impact of USA research is arguably affected by the large internal volume, which may be self-referential drawing on domestic activity in a rapidly growing field. However, the exceptional performance of research outputs from Massachusetts and, particularly, from Wisconsin are strong indicators of very high quality and widely-regarded activity.

Figure 6: Output of Research Papers Compared with Average Normalised Citation Impact for the UK and other selected US States.



Growth of Research Published Internationally

- 2.17** As discussed, the US out-publishes its competitors significantly, producing 26,744 papers over 2005-2009 period compared with 4,117 papers in China between 2005-2009, 5,725 in the UK, 6,865 in Germany and 7,315 in Japan. The United States' research dominance is unsurprising given the very significant investment that this area has seen over the last five years. China has shown huge growth in terms of number of papers published in the last five years and has come from well behind the UK to an annual output that is now slightly greater than the UK. Over the 2005-2009 period China now only produces slightly fewer than the world leaders.
- 2.18** Japan, by contrast, has had weaker growth at around 25% of its 2005 total though it remains the second largest producer after the USA. Overall, Asia is the region with much the strongest growth trajectory.

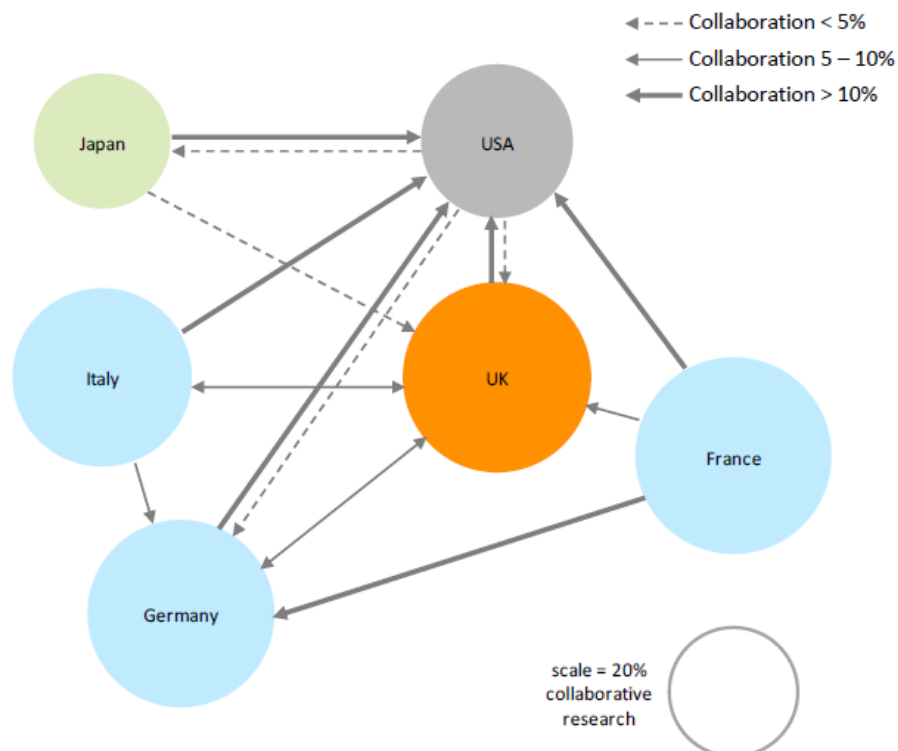
Research Collaboration

2.19 In this analysis, a paper is assigned to a country if one or more author addresses include that country. A paper co-authored by two UK universities and one German laboratory would be assigned once to the UK and once to Germany. There is no fractional counting.

2.20 The USA, UK and Germany are all large research economies, active in this area, so they present a substantial capacity and target for collaboration.

- For all countries in the data-set the USA is one of their top-three locations for collaboration. The US collaborates most with the UK, Germany and Japan.
- At 43% of all published research, the UK publishes significant levels of collaborative research. The UK is a top-three partner for all countries in the data-set with the exception of Brazil, Israel and South Korea.
- The UK's top collaborators are the USA, Germany and Italy.
- Germany is a top-three partner for 11 out of 15 possible partners, but the four not favouring Germany are all in Asia (China, India, Japan and S Korea).

Figure 7: Schematic showing selected collaborations between countries in regenerative medicine research



2.21 Although the USA appears to be highly collaborative this is driven in part by its sheer volume. It is simply a partner of choice for all other countries. However, only 28% of its output in regenerative medicine has an international co-author so in fact most of its papers are entirely domestic. It is assumed that this is probably because

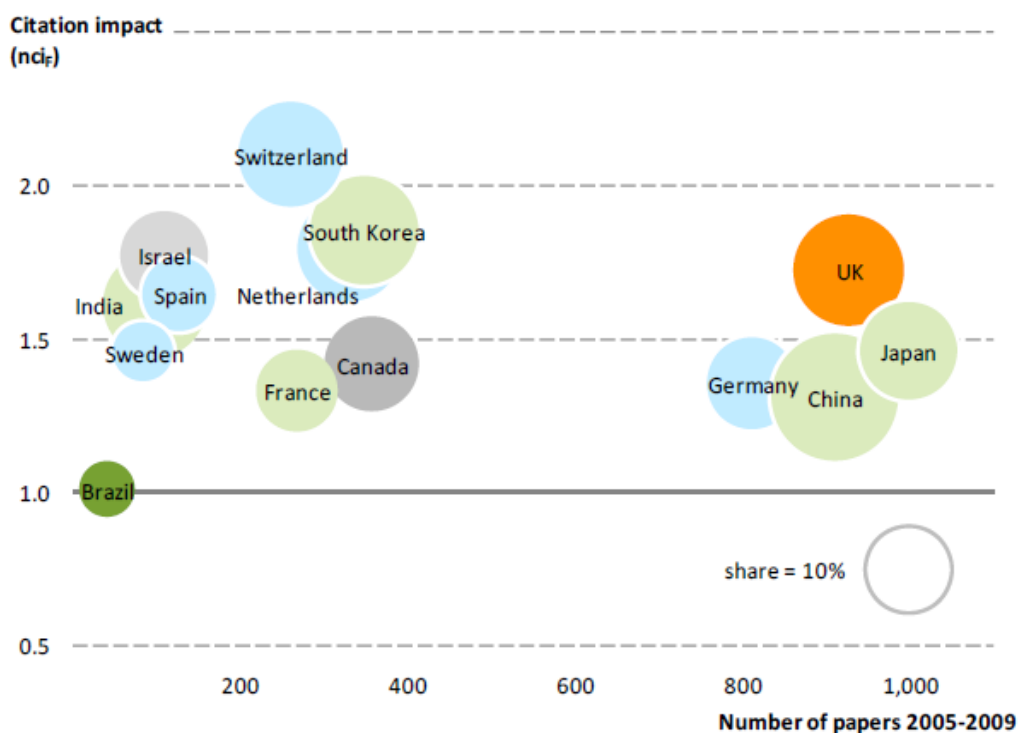
of the opportunities for intra-national collaboration between research groups across States.

- 2.22** Given the relative capacity of different countries, the Germany-Switzerland link is notably intense given the size of Switzerland. Switzerland is highly collaborative in regenerative medicine, a pattern seen for this country in other subject studies, with almost two-thirds of its papers carrying an international co-author.
- 2.23** The general pattern for European research economies is around 40-50% international co-authorship, whereas the Asian countries and Brazil are much less collaborative so far.

Research Specialisation

- 2.24** This report was also interested in whether certain countries were specialising in certain areas of regenerative medicine, and therefore showed particular research strengths.
- 2.25** Figure 8 shows research papers in the area of tissue engineering, a sub-set of the regenerative medicine field. It is notable that the UK produces more high quality research than its major competitors in Japan, Germany, Canada and France, and a significant number of articles overall.
- 2.26** Tissue Engineering output for the UK is greater than Germany and only slightly less than Japan, but growth has plateaued. South Korea has a larger output than all European countries except the UK and Germany and a higher average impact (1.85) than all except Switzerland. India, despite a very small output (46 papers in 2009), also has high impact (1.6).

Figure 8: Output of Research Papers Compared with Average Normalised Citation Impact using the “Tissue Engineering” Medical Subject Heading



Conclusions

Research impact analysis commissioned by this report has shown that the UK has domestic strengths in regenerative medicine, and is producing world class research with significant impact on the field. However, this is an area where competitors are investing strongly, so it is critical that the UK maintains and builds on its existing strengths. In particular, the United States is recognised as the world leader, with other countries specialising in niches within the regenerative medicine field, such as Japan in induced pluripotent stem cell research.

The Government is committed to supporting this field over the long term, enabling business to turn the knowledge generated in our world class science base into new therapies and to create world leading regenerative medicine businesses. For this to happen the sector will need to develop:

- a deeper understanding of fundamental cell mechanisms;
- appropriate processes and techniques for cost-effective scale up and manufacturing
- associated tools and technologies that will help to deliver future therapies
- clinical data demonstrating the safety and efficacy of therapies

The UK has taken the approach of supporting research across the full spectrum of the stem cell and regenerative medicine fields in the belief that this broad approach offers the greatest promise for medical advances. Science cannot predict at present which types of cell will prove to be of most benefit and so continued research on all types remains necessary to improve our knowledge. Indeed, it is unlikely that any one cell type will be a “golden bullet” with all cell types of value in regenerative medicine.

3. The Funding and Investment Landscape

The Commercial Context

- 3.1** Regenerative medicine has seen significant public funding over the last 10 years, and is beginning to receive modest, but increasing, investment from pharmaceutical companies, and private equity. However, as is often the case with emerging technologies, regenerative medicine has predominantly been funded from public and third sector (charity) sources to date. For example, the third sector invested approximately £38m in regenerative medicine research between 2005-2009⁸ and the public sector has invested over £200m in the field since 2003. This balance of public to private investment is broadly typical of an emerging technology, although regenerative medicine also faces some unique challenges, with a route to market that is broadly untested.
- 3.2** In particular, cell therapies and regenerative medicine are dealing with a fundamentally different regulatory environment, development pathway and market to traditional small molecule based drugs and biologics. As well as the need to establish safety and efficacy, cell therapies face the challenge of manufacturing a living 'product' (which in some cases that has to be done at the point of use i.e. in a hospital) alongside associated difficulties in their storage and delivery. Businesses also need to decide whether to focus on a product or service based approach, each of which require significantly different business models. These challenges are likely to extend the time to market for many cell therapy products. A particular concern is funding through the "valley of death" that emerging therapies typically have to tackle⁹.
- 3.3** Once positive clinical data starts to emerge this is likely to trigger more interest from both the pharmaceutical sector and other private sector investors. Indeed, as respondents to our call for evidence told us, the economic potential of regenerative medicine products is huge. The BioIndustry Association, for example, has highlighted that today 80% of healthcare costs go towards treating the late stages of illnesses, such as heart failure, which in the future could be either cured early or better managed using cell therapies.
- 3.4** There is clearly a need to explore the type of business models and value systems that can best support regenerative medicine. Accordingly the Technology Strategy Board has recently funded three projects to investigate this, which will report in 2012 and provide the sector with vital tools and information for commercial development.

⁸ Association of Medical Research Charities

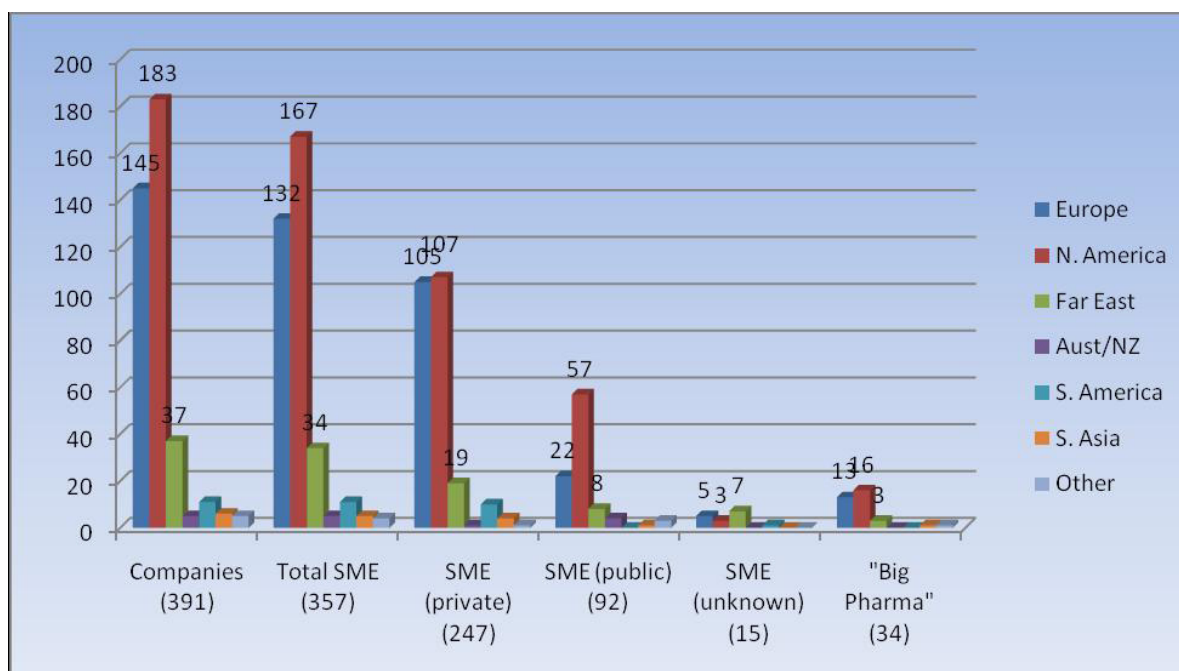
⁹ Sir David Cooksey's review of UK Health Research (2006). The Valley of Death is the period between early pre-clinical proof of concept to successfully completion of Phase II clinical trials.

3.5 In the shorter term, stem cells could see investment to screen candidate drugs and to identify novel targets as well as proprietary soluble factors/drugs. Use of stem cells in this fashion is important because 16% of drugs currently fail in Phase III trials because of adverse effects in man and animal models are expensive. While *in vitro* tests have the potential to improve this success rate there are significant challenges sourcing clinically relevant material e.g. human liver cells for advanced toxicology studies. Stem cells could help to alleviate these problems by potentially providing a source of specialised cells for *in vitro* toxicity testing. This provided the rationale for the establishment of Stem Cells for Safer Medicines, a public-private partnership involving the Research Councils, Department of Health and Technology Strategy Board with big pharma (GlaxoSmithKline, AstraZeneca, UCB and Roche).

Mapping Companies in Europe

3.6 The Regenerative Medicines in Europe Project (REMEDiE) has undertaken an analysis of the emerging needs and challenges for regenerative medicine in a global context. Their analysis has shown that the regenerative medicine landscape in Europe is dominated by SMEs, with a couple of “big pharma/biotech” companies beginning to invest in recent years (eg Pfizer, Genzyme (now Sanofi- Aventis) Smith and Nephew, and Shire). Figure 9 shows this breakdown by organisation type in different continents.

Figure 9- Total Number of Regenerative Medicine Companies by Continent¹⁰



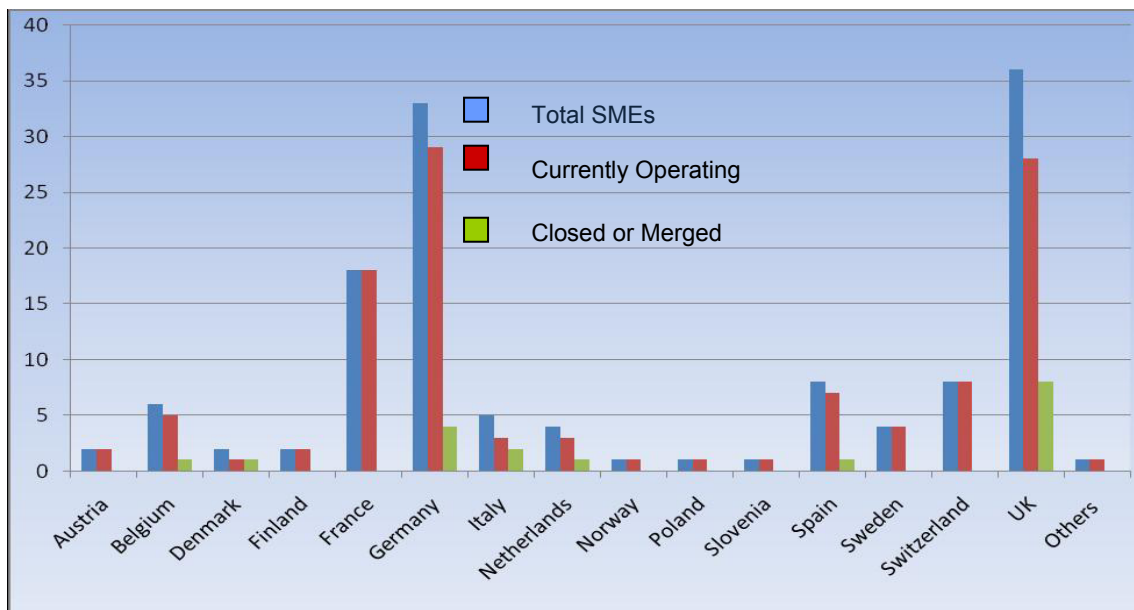
3.7 Europe and N. America are clearly dominant, with Europe slightly behind in terms of the total number of companies operating. Interestingly, there are almost double the number of publicly listed SMEs in North America compared to Europe, perhaps

¹⁰ Regenerative Medicines in Europe Project (REMEDiE), coordinated by the Science and Technology Studies Unit, University of York

indicating a North American preference for listing companies at an earlier stage, or a greater appetite for risk.

- 3.8** As demonstrated by figure 10, regenerative medicine has not seen uniform commercial interest across Europe. There are only 5 or 6 countries with any significant commercial activity in regenerative medicine, with the majority located in either France, Germany or the UK.

Figure 10: Total Number of Regenerative Medicine SME's by European Country¹¹



Business Models: Product or Service?

- 3.9** A key issue for early adopting regenerative medicine companies is developing a compelling business model. One critical aspect of this is the decision on whether to develop a product or service based offering. This distinction is tied up in the choice between sourcing cells from a donor that can be scaled up and universally applied to patients (an allogeneic therapy or “one to many”) or providing a patient with their own cells (an autologous therapy or “one to one”). The choice between the “one to many” and “one to one” routes is proving to be a fundamental one for early adopting companies with significantly different production, infrastructure, logistics, skills and storage requirements for each approach.

The Service Approach

- 3.10** “One to one”, autologous, cell therapies already represent a significant industry that could be embedded in the NHS similar to Assisted Conception Units (IVF), in a service based model. One advantage of one to one procedures is that in these transplants, the body recognizes the cells and therefore does not reject or attack

¹¹ REMEDIÉ

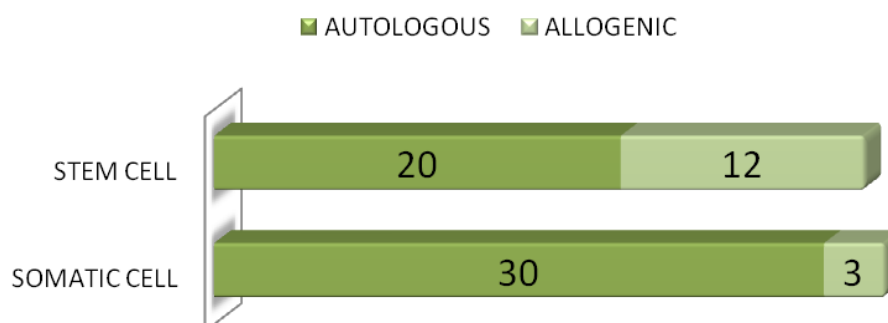
them. For example, bone marrow transplants have been successfully used for many years to restore immune function after chemotherapy, and therapeutic trials using patients' own stem cells to restore other tissues are already underway.

- 3.11** However, one to one cell therapies offer less scope for intellectual property coverage (since a patient's own cells can't be patented) and limited potential to scale up the treatment process since each patient will need their cells expanded *ex vivo* in isolation (i.e. at a discrete workstation) to avoid the risk of cross-contamination. However, one to one therapies typically have a lower capital cost requirement than one to many treatments, as well as possessing safety advantages, and so have historically translated much faster to the clinic.

The Product Approach

- 3.12** "One to many", or allogeneic cell transplants have greater potential for scale up and widespread distribution, thus potentially benefiting from greater economies of scale. This model is closer to the traditional pharmaceutical model, and is a biomanufacturing process that pharma has invested in heavily over the last decade. For this reason a number of prominent companies are currently pursuing this approach such as ReNeuron (UK) and Geron (California). However, "one to many" therapies face a greater risk of immunological rejection, as the cells are not recognised by the host. For these reasons, this model is anticipated to develop more slowly.
- 3.13** As figure 11 shows, there are similar numbers of cell therapy firms involved in developing stem cell, and non stem cell (somatic) therapies. A non-stem cell regenerative medicine might involve taking cells from a healthy site in the body, expanding this cell sample in culture and reapplying it to the damaged area for example. However, there is a strong emphasis in Europe on developing "one to one" rather than one to many therapies, as would be expected given the greater hurdles for "one to many" therapies.

Figure 11: European Cell Therapy SME's by Type and Tissue Source, 2010¹²



¹² REMEDIÉ

Remedi Report on Barriers to Commercialisation & Utilisation of Regenerative Medicine in the UK

Respondents to this report, funded under the EPSRC's Grand Challenge programme, felt that one of the biggest barriers to the development of regenerative medicine was the large gap in funding and investment. Respondents repeatedly argued that regenerative medicine science is an expensive and risky process, from the basic science to the patient-ready product.

They also identified a number of barriers to collaborations such as knowledge boundaries and a lack of shared understanding, and difficulties in establishing and sharing intellectual property (IP) rights. In addition, companies have had, and continued to encounter, difficulties in achieving widespread clinical adoption of their products.

There was agreement that regenerative medicine offered hope for patient improvement in the future, but also concern regarding the lack of credible scientific evidence currently available to support their utility.

*(Interviews were carried out with 54 individuals from the academic, industry and clinical regenerative medicine communities.

Private Sector and Charity Investment

Private Equity

- 3.14** While no venture capital firms responded to this report's call for evidence, the perception of the regenerative medicine community is that the venture model of funding with its 5-10 year period of investment was a difficult fit for regenerative medicine. In particular, the long development timescales, and mixed involvement of large corporates is limiting the potential for trade sales; venture capital's traditional exit strategy.
- 3.15** In contrast with a more positive investment environment in the United States in particular, respondents to this report's call for evidence suggested government support was particularly critical for the field in the United Kingdom. There is some evidence, however, that pharmaceutical venture capital funds are showing increasing interest in regenerative medicine.

Pharmaceutical Companies

- 3.16** The key requirement for pharma is clear evidence that these technologies will deliver safe and efficacious patient therapies that are manufacturable at scale and reimbursable at an appropriate level. Ideally (from pharma's perspective) this would be achieved by using drug-based (small molecule) approaches to modulate endogenous stem cells in situ, a model pharma is traditionally familiar with. The other area appealing to pharma is in drug discovery, where the aim is to make earlier decisions about whether compounds are viable to progress. Ultimately the

goal is to save money in failed Phase III trials through the better use of predictive models for both safety and efficacy.

- 3.17** There have already been a number of examples of commercial interest from pharmaceutical companies in regenerative medicine. Indeed Shire has recently purchased privately-held Advanced BioHealing (ABH) for \$750m. ABH makes an FDA approved tissue-engineered skin substitute (Dermagraft) that is used to treat slow-healing foot ulcers.
- 3.18** But it is expected that big pharma, biotech and medical device companies continue to have a mostly exploratory rather than potentially exploitative interest in the near-term. This will likely remain the position until widespread safety and efficacy can be repeatedly demonstrated for a range of cell-based products. In the meantime pharmaceutical companies have been showing increasing interest in using stem cells for drug screening.
- 3.19** The current uncertainty around future sources of income for big pharma might also be a reason not to expect such companies to step into the funding void in the short-term. On the other hand, regenerative medicine offers a promising diversification of existing business models for pharmaceutical companies, and with a growing market regenerative medicine could provide a persuasive business case in the longer term.

Action 2

In recognition of the importance of pharmaceutical companies and other large corporations to the development of regenerative medicine, the Research Councils and Technology Strategy Board will conduct a thorough consultation with the major players by the end of 2011.

Charity Funding

- 3.20** Charities constitute an integral part of the UK's medical research sector and have invested strongly in regenerative medicine. The Association of Medical Research Charities (AMRC) is a membership organisation of the leading medical and health research charities in the UK. Over the four year period, from 2005-2009, 29 AMRC members invested a combined total of almost £38 million into regenerative medicine. Over this period charitable investment in this area has increased; in 2009-10 when total AMRC investment in UK medical research was just over £1 billion, approximately £13 million of this was directed into research into regenerative medicine.
- 3.21** For example, the British Heart Foundation's latest fundraising campaign for research, Mending Broken Hearts, is focusing on raising £50 million to fund research into regenerative medicine. Their ambition is to be "pioneers in regenerative medicine".
- 3.22** The research activities of the charity sector and those of the Research Councils, TSB and Government departments, are currently coordinated through the UK Stem Cell Funders Forum, chaired by the Medical Research Council. Shared intelligence

of emerging initiatives and opportunities will be important moving forward to ensure the highest level of impact can be achieved through public funding.

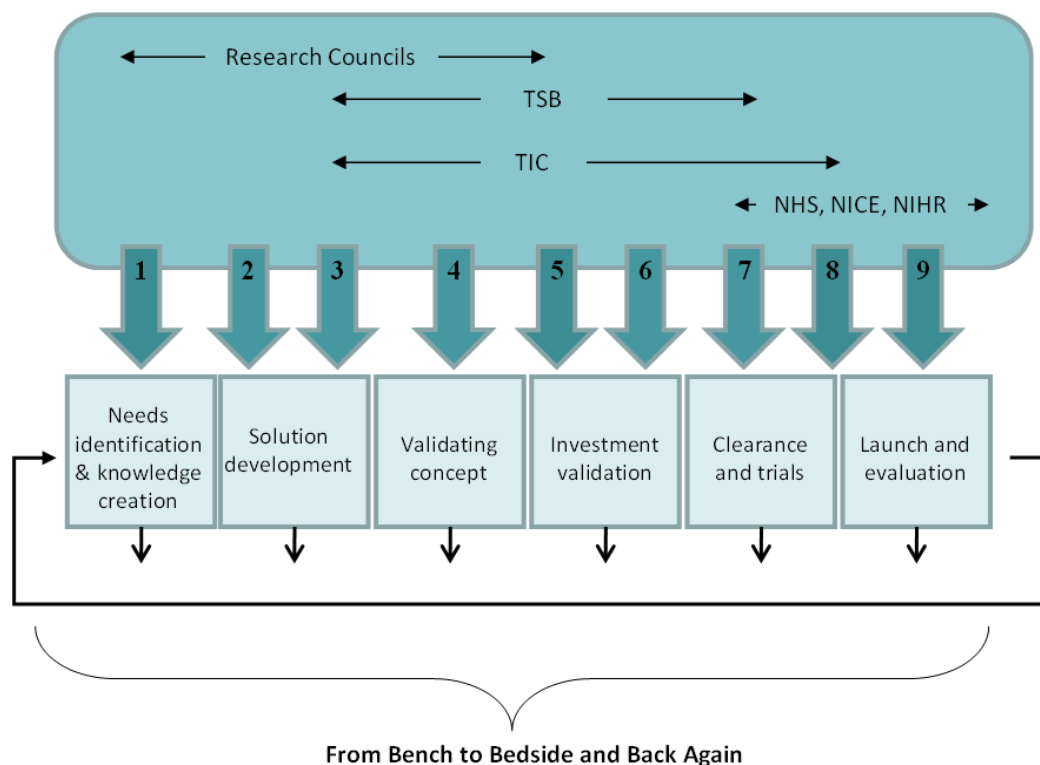
Action 3

The Office of Life Sciences will work with partners to investigate creative funding mechanisms from a broad range of sources, including working with UK Trade and Investment to promote international investment in UK regenerative medicine.

Government Investment and Governance

3.23 Regenerative medicine is typical of an emerging technology area, facing a number of uncertainties; technological, financial, regulatory and strategic. While there has been much recent progress the Government recognises that if the UK is to fulfil its potential in this field, there are a number of developmental challenges which need to be overcome. This is why the Government is supporting the sector through strategic initiatives, infrastructure, regulatory support and funding:

Figure 12: Technology Readiness Levels and Public Funding



The TSB/Research Council Regenerative Medicine Programme

3.24 The Technology Strategy Board is running a £21.5m “RegenMed” programme of investment to support key areas of commercial R&D and the development of R&D partnerships. The programme is being developed in partnership with the Medical Research Council (MRC), Engineering and Physical Sciences Research Council

(EPSRC) and Biotechnology and Biological Sciences Research Council (BBSRC) who have committed up to £4m to the programme.

3.25 The goals of the Technology Strategy Board/Research Council Regenerative Medicine programme are to:

- Underpin and enable the most competitive regenerative medicine businesses to flourish in the UK,
- Build a connected regenerative medicine community through the formation of well-linked programmes of work and activities to develop medicines and technology platforms creating critical mass which is an important element in developing emerging industries.

Cell Therapy Technology and Innovation Centre

3.26 The 2011 Budget announced a competition to form a Cell Therapy Technology and Innovation Centre. The Centre, with a focus on cell therapies and advanced therapeutics, will help support development and commercialisation of therapeutics, as well as the underpinning technologies for manufacturing, quality control and addressing safety/efficacy challenges for these new treatments. Part of this commitment is to fund a centre at a critical level, over 5-10 year period.

Cell Therapy Technology and Innovation Centre

The Cell Therapy Technology Innovation Centre was welcomed by the respondents to this report's call for evidence and hailed as an opportunity to tackle the translation gap both financially and in terms of building expertise, as well as an opportunity to deliver initial clinical data. We were told that sharing knowledge and support on regulatory science will be especially important given that the core regenerative medicine companies are mostly SMEs with little resource to provide this internally.

In addition it was felt that SMEs would benefit from access to professional expertise and supporting infrastructure that minimised their costs and maximised the rate and probability of a company's success. This kind of expertise could come in the form of regulatory assistance, IP strategies, standards, reimbursement, clinical trial design and project management.

UK Stem Cell Strategic Forum: Developing Stem Cell Transplantation Services

3.27 The Department of Health is making £4m available to improve the collection and use of stem cells from bone marrow and cord blood. The work is being taken forward in collaboration with the NHS Blood and Transplant Authority (NHSBT) and Anthony Nolan, the UK's leading bone marrow charity. The work is led by the Department's Health Science and Bioethics Division and is part of its wider programme of work on cell therapy and its potential to innovate and revolutionise the way treatments are developed and applied.

Research Council Funding

3.28 The Medical Research Council is the main UK funder of stem cell research (~1/3 in total), covering basic stem cell biology, translational research and early phase

clinical trials as well as infrastructure and training. MRC spend in this area was £38m in 2009/10. Continued investment in the stem cell and regenerative medicine area has been recognised in the 2009 MRC strategic plan 'Research changes lives' and the MRC Delivery Plan 2011/12 to 2014/15

- 3.29** In 2008/09 MRC established two full MRC Centres focused on stem cell research and regenerative medicine. The Centre awards in Edinburgh (5 year) Cambridge (3 year) represent an investment of £3.4m, and both aim to connect basic stem cell biology with clinical scientists.
- 3.30** The Translational Stem Cell Research Committee (TSCRC) has also been established by the MRC to fund research that will drive stem cells towards application, both clinically and in disease modelling and drug discovery. Since the TSCRC was launched in 2008 the Committee has awarded £21.6m through its response mode funding route and targeted initiatives. Under the TSCRC £3million was awarded in 2008 to establish 20 new clinical grade human embryonic stem cell lines, as well as a £3m investment in 2008 address preclinical barriers that exist towards the therapeutic use of stem cells and £700,000 to pump prime research into induced pluripotent stem cells.
- 3.31** The MRC's Developmental Pathway Funding Scheme (DPFS) and Developmental Clinical Studies (DCS) Programmes complement the work of the TSCRC by supporting the development of non-stem cell based regenerative medicine products. The DPFS supports the pre-clinical development phase and the DCS the clinical phase of a product's development up to proof of concept in man.
- 3.32** The Engineering and Physical Sciences Research Council (EPSRC) has also invested significantly in areas where engineers and physical scientists can make a real contribution towards advancing the regenerative medicine field including manufacturing, underpinning tools and technologies, monitoring, characterisation and manipulation of stem cells and tissue and bioengineering. In particular EPSRC has funded:
- EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, whose aim is to become the "go to place" for manufacturing research for this emerging industry.
 - Innovation and Knowledge Centre in Regenerative Therapies and Devices- University of Leeds, bringing businesses together with world-class experts to accelerate the commercial development of new medical technology products and services.
 - Two Centres of Doctoral Training in University of Leeds and University of Loughborough
- 3.33** The Bioprocessing Research Industry Club (BRIC) is a Biotechnology and Biological Sciences Research Council (BBSRC)-led public-private partnership with the Engineering and Physical Sciences Research Council (EPSRC) and a consortium of 16 industrial partners, ranging from small to medium sized enterprises (SMEs) to major pharmaceutical companies. The Club was launched in 2005 with £13.3M of total funding, and began its second phase with an additional £10M of funding in 2010. The Research Councils provide 90% of the funding and the industrial partners provide the remaining 10%. Together the partners support academic research

projects and the training and development of bioprocessing researchers. The projects support 42 academic researchers, ranging from senior Professors to Post-Doctoral Research Assistants and PhD Students. The researchers are based at 12 different UK Universities.

- 3.34** Most of the Economic and Social Research Council's (ESRC) funding in this area is currently carried out within the ESRC Genomics Network who carry out interdisciplinary research on social, economic, ethical and policy factors that shape developments in the life sciences. Recent investments include the ESRC Social Science Stem Cell Initiative (SCI), which ran from autumn 2005 to June 2009. ESRC have also funded research (and continue to welcome applications in this area) within their responsive mode, Standard Grants scheme, and in partnership with other funders such as the other Research Councils and the Technology Strategy Board.

Stem Cells for Safer Medicines

- 3.35** *Stem Cells for Safer Medicines* is an independent not-for-profit company bringing together Government, academia and industry in a public-private collaboration. Initial research is enabling the use of stem cells in early drug discovery by focusing on key scientific challenges and developing open standards and protocols. This is aimed at providing standardised *in vitro* (i.e. not in animals) testing for toxicity of potential new drugs. SC4SM aims to use a combination of the inventiveness of the academic sector together with the knowhow of its industrial partners.
- 3.36** Public sector funding is coordinated by Technology Strategy Board, with contributions from MRC and BBSRC and small contributions from the Department of Health and the ESRC. The public sector funders have recently committed £1.3 m for the next phase of development.

Stem Cell Bank

- 3.37** In 2002, the MRC with co-funding from BBSRC, established the world's first quality-controlled stem cell bank for the curation and distribution of human embryonic stem cell lines for research purposes. The UK Stem Cell Bank is internationally acknowledged as the leader in stem cell banking and provides a number of human embryonic stem cell lines for research purposes to the researchers around the world. The first clinical grade human ES cell lines have recently been accepted for banking by the UKSCB in readiness for human clinical trials. It is a world recognised source of best practice and regulatory standards, as well as a provider of education and training for the community.

UK National Stem Cell Network

- 3.38** The UK National Stem Cell Network is funded by 4 of the UK's Research Councils, and acts as a "virtual" national coordinating body. The Network's goal is to promote and improve the coordination of research across the sub-disciplines of stem cell science, with a view to enhancing basic research and helping to speed its translation into therapeutic applications.

Stem Cell Toolkit

- 3.39** In 2009, the UK Government's Department of Health and Medical Research Council published an on-line *UK Stem Cells Toolkit* designed to guide human stem cell researchers and translators through the UK's regulatory framework and enable them to develop their own regulatory roadmap specific to their research and/or product needs.
- 3.40** From 1 June 2010 to 1 June 2011 there were a total of 26,603 visits to the Stem Cell Toolkit website, with an average of 72 visits per day. 80% of the traffic was from outside the UK.

Action 4

The Department of Health will review the UK Stem Cell Toolkit on an ongoing basis to ensure that it accurately reflects the regulatory pathway in the UK, and continues to support research and product development

EU Funding

- 3.41** In addition to UK Government grants and funding, UK researchers and companies have successfully bid for European funding in the past through the European Commission's Seventh Framework Programme for Research and Technological Development. With an EU-wide budget of €50b allocated for the period 2007-2013, UK organisations should consider whether their work is eligible for funding.
- 3.42** The Innovative Medicines Initiative Fourth Call for Proposals also launched in June 2011. Research into human induced pluripotent stem cells has been announced as a "Think Big" topic for this call, with an approximate budget of up to €50m.

Monoclonal Antibodies: A Case Study

Monoclonal antibodies (MAb) were discovered in the UK in 1975 but took 20 years to achieve their full potential, during which time the technology matured and associated infrastructure was put in place. Today the MAb market is worth tens of billions of dollars and growing, but the commercial benefits mainly accrued outside the UK. IP has been a hugely important (and controversial) factor. Equally, developing efficient, robust and reproducible biomanufacturing processes has been a huge challenge and one where the industry has had to learn alongside the medicines regulator. Indeed, the industry is still looking for step-change improvements in biomanufacturing to bring down the cost of goods and in the UK, where the BBSRC's Bioprocessing Research Industry Club has had notable success. The parallels between the long history of monoclonal antibodies (a success for both patients and commercially successful products) are strong and present opportunities for lessons to be learnt for regenerative medicine.

Regulation

- 3.43** The regulatory pathway for regenerative medicines in the UK is generally considered to be well established and internationally respected, assisted by initiatives such as the UK Stem Cell Toolkit. In addition, the regulators in this area (HTA¹³, HFEA¹⁴ & MHRA¹⁵) work closely in areas of mutual interest. For example, the HTA and MHRA have undertaken a programme of joint inspections in areas where both the requirements of the Tissues and Cells Directive (2004/23/EC) and the Regulation on advanced therapy medicinal products apply (1394/2007). There is also the Gene Therapy Advisory Committee (GTAC), which is a research ethics committee that considers all proposals for research on human subjects using cells from human stem cell lines. Regulators also hold joint advisory meetings to provide guidance to operators.
- 3.44** However, respondents to our call for evidence highlighted that there was an overarching challenge in this area, where early adopters had to conduct real-time research and development in conjunction with regulators to define data requirements.
- 3.45** Much of this regulatory uncertainty is recognised as being a natural part of organisations new to regulation applying scientific developments in an emerging technology area. The feeling was that many of these issues would get resolved through more research into the science along with technological improvements in biomanufacturing and metrology. However, respondents called for more to be done to provide clear, coordinated guidance for the UK sector, as well as internationally.

Establishing the Health Research Authority

- 3.46** As part of the Government's efforts to streamline the regulatory process, the Government will establish a Health Research Authority this year. The Health Research Authority will work closely with the Medicines and Healthcare products Regulatory Agency (MHRA) to create a unified approval process and with MHRA and others to promote proportionate standards for compliance and inspection. This will reduce regulatory burden on firms and improve the timeliness of decisions on clinical trials and hence the cost-effectiveness of delivery in the UK.

¹³ The Human Tissue Authority (HTA) is the UK's regulator that supports public confidence by licensing organisations that store and use human tissue for purposes such as research, patient treatment, post-mortem examination, teaching and public exhibitions. The HTA also give approval for organ and bone marrow donations from living people.

¹⁴ The Human Fertilisation and Embryology Authority (HFEA) is the UK's independent regulator overseeing the use of gametes and embryos in fertility treatment and research. The HFEA licenses fertility clinics and centres carrying out in vitro fertilisation (IVF), other assisted conception procedures and human embryo research.

¹⁵ The Medicines and Healthcare Regulatory Authority is the supervisory authority for UK manufacturers or importers of centrally authorised Advanced Therapeutic Medicinal Products (including (including gene and cell therapy-based regenerative medicine) as well as the competent authority for ATMPs which are prepared and used under the hospital exemption and made and supplied under the "Specials" scheme., The MHRA is also the competent authority for the assessment of applications for clinical trial authorisations and the associated manufacturer's licence for investigational ATMPs.

- 3.47** Regarding the transfer of functions of the Human Fertilisation and Embryology Authority and the Human Tissue Authority, there is no intention to change any legal requirements, only the regulatory bodies that oversee them. The criteria applicants will have to meet to be authorised to carry out research on human embryos, tissues and cells within the UK will remain the same.
- 3.48** Respondents to this report's call for evidence felt that these changes, and the Academy of Medical Sciences work to capture and detail the significant barriers to conducting medical research in the UK was a step in the right direction.
- 3.49** In particular the community has told us that they welcome a more streamlined approach for clinical trials, saying that this would improve the competitiveness and attractiveness of the UK to companies looking to invest in R&D. In addition respondents felt that the introduction of a national research governance service would streamline NHS R&D permissions, especially for those companies conducting multi-centre trials in small patient populations. The National Institute for Health Research (NIHR) consequently launched the NIHR Research Support Services in May 2011 to standardise and professionalise NHS research management, particularly NHS research governance.
- 3.50** Scotland has already established the NHS Research Scotland Permissions Co-ordination Centre (NRS-PCC), which streamlines the approval process for multi-site clinical studies, and has reduced approval times to a current mean of 16 days. Wales also launches an NHS permissions unit in July 2011 to meet the challenges of the AMS review.
- 3.51** Respondents also stressed that despite the AMS recommendations, SMEs by their nature, would often still not have the necessary resources to invest in technical development and support on regulatory issues. To further assist the sector/SME's the MHRA has published comprehensive guidance on its website and taken the opportunity to engage proactively with stakeholders. For example, in April this year, the Agency co-hosted an event with the London Regenerative Medicine Network. From a European perspective, advice is also available from the European Medicines Agency's Innovation Task Force.
- 3.52** The MHRA is willing to support initiatives from within the sector to further engagement but it is critical that SME's are also supported in developing underpinning expertise and knowledge of regulatory affairs, and encouraged to engage regulators early in their product development. A strategic priority for the sector should be to ensure that expertise is more proactively shared, and where necessary, provided affordably and centrally available to companies. This would put smaller operators in a better position to engage with regulation and the regulators, and vice versa.

Action 5

Regulators will continue to engage with the regenerative medicine community to ensure the regulatory process functions in a way that is easily accessible and engage with new organisations such as the UK's Cell Therapy TIC to help build regulatory expertise and share knowledge.

The Importance of European Regulation

- 3.53** The legislative framework that applies to Advanced Therapy Medicinal Products (ATMPs) is laid down at European level. The European Regulation on ATMPs (1394/2007) came into force on 30 December 2007 and applied from 30 December 2008. Under the Regulation, those medicinal products which come within the scope of Directive 2001/83/EC and are categorised as ATMPs are regulated under the European centralised procedure. Under this procedure, a centralised European marketing authorisation is granted by the European Commission following assessment by the European Medicines Agency (EMA).
- 3.54** Within the Regulation, there is an exemption for ATMPs which are prepared on a non routine basis and used in a hospital in accordance with a medical prescription for an individual patient. In the UK, the MHRA is responsible for the UK's hospital exemption arrangements. The European Commission has committed to review the operation of the Regulation by 30 December 2012. The review will include an assessment of the impact of technical progress on the application of the legislation. The UK will have the opportunity to contribute to this review and it is important that UK regulators and the regulated sector work together to input into this review.

The Importance of Standards

- 3.55** In 2009, the British Standards Institution (BSI) and BIS jointly commissioned Ernst & Young to carry out a review of BSI's "standardization toolkit" in support of the UK innovation agenda. The review concluded there was a significant, though often unrecognised role for standards-related activities in creating and developing emerging technologies. In recognition of the value of standards in emerging technology areas, BSI is revising and will re-publish the two existing publicly available specifications in regenerative medicine (PAS 83 and 84), and will also publish the new PAS 93:

PAS 83 - Guidance on codes of practice, standardized methods and regulations

- 3.56** This document was originally published in 2006 and, for the first time, demonstrated the process steps that a regenerative medicine product goes through and the regulatory framework in place at each stage. The guidance was aimed purely at the UK/European markets. Since 2006, however, some of the legislation has changed, and it has also become apparent that the UK would benefit from information that allows them to access the lucrative US market.
- 3.57** BSI is in the process of revising PAS 83 to give European users knowledge regarding the necessary regulatory steps they need to take to access the US market. Access to the US market is a major goal for most UK regenerative medicine companies.

PAS 93 - Cell therapy characterisation

- 3.58** Companies are currently finding it difficult to gain market authorisation for cell-based products in Europe. BSI has discovered that appropriate and sufficient characterisation of the cells is often lacking, meaning that companies are unable to

provide satisfactory answers to the regulator's essential questions on cell identity, cell viability, cell number and the nature of any cellular impurities. The approach of some companies to establish cellular identity based solely on source tissue and method of culture has not been well received by the regulator. Part of the solution to this is for BSI to publish guidance on characterisation of cell products that helps with market authorisation, and also to reduce the need for further costly clinical trials at a later stage. BSI aims to publish PAS 93 by the end of July 2011.

PAS 84 - Regenerative Medicine – Glossary

- 3.59** BSI had learned that one of the major barriers to development was the lack of a common language and/or vocabulary in this emerging and interdisciplinary field. PAS 84 defines the terms commonly used in the field of regenerative medicine, and provides clear guidance on the meaning of terminology currently used in the UK by industry, regulators, government and academia. It helps the key stakeholders to communicate more effectively and allow the commercialization of the new technology to take place more efficiently and safely. The glossary is currently under revision.
- 3.60** These three specifications are putting BSI and the UK in the lead in the development of terminology, regulatory guidance, and product characterisation guidance as well as ensuring the country has a place in the international standardization arena. By way of illustration, the BSI Regenerative Medicine committee RGM/1 was invited by the European Medicines Agency to be an interested Party to the EMA's Committee for Advanced Therapies (CAT).

Action 6

In recognition of the value of standards in emerging technology areas, BSI is revising and will re-publish the two existing publicly available specifications in regenerative medicine (PAS 83 and 84), and will also publish the new PAS 93.

Analysing Regenerative Medicine Patents

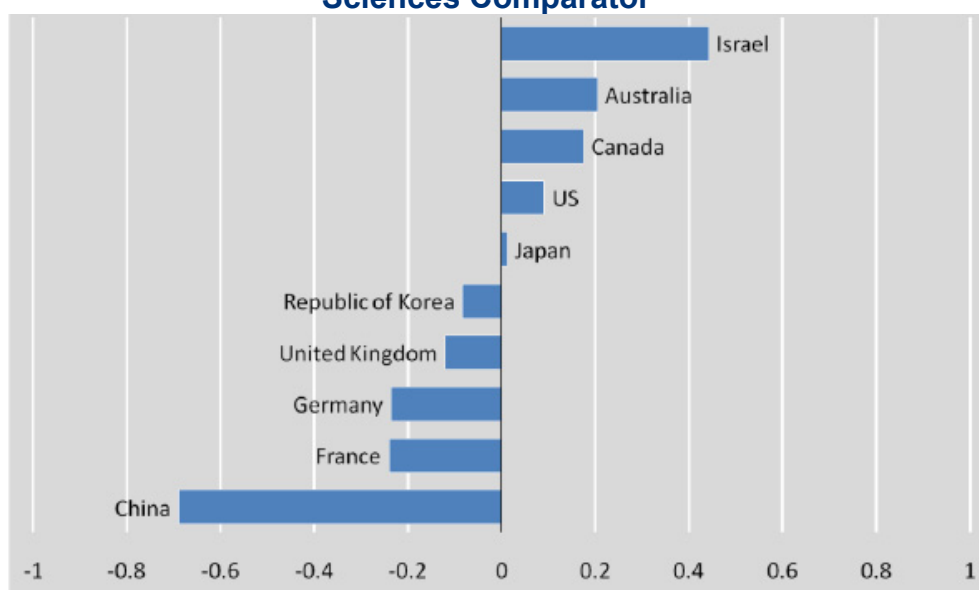
- 3.61** Intellectual property protection can be an indicator of innovation and is a useful measure of the stage of development for a particular technology. Following initial analysis done for the UK National Stem Cell Network this report commissioned an analysis of international patenting trends in the field of regenerative medicine by the UK Intellectual Property Office.¹⁶
- 3.62** This analysis has shown, that as one might expect, regenerative medicine technologies are still at a relatively early stage of development, with most organisations (67%) based anywhere in the world only filing between 1-5 patent applications to date.¹⁷

¹⁶ The full report can be found on the Office for Life Sciences Website

¹⁷ As a sector grows, you would expect organisations to accumulate greater numbers of patent applications.

- 3.63** In terms of the overall number of regenerative medicine patents filed anywhere in the world, the pattern broadly mirrors trends seen in the life sciences field as a whole. US organisations, as with life sciences generally, dominate in terms of total patenting, with Germany and Japan following, with the UK positioned sixth.¹⁸ This is not necessarily surprising given that these countries also publish more research papers than the UK.
- 3.64** Further analysis was undertaken to compare levels of regenerative medicine patent filings by applicants from different countries (see figure 13). This analysis removes country-to-country differences in patent filing behaviour by comparing a field's patenting to the number of patents in a comparator field.

Figure 13: Relative Specialisation Index by Applicant Country Relative to Life Sciences Comparator¹⁹



- 3.65** This “specialisation index” shows that the level of patent filings worldwide for regenerative medicine inventions by UK based applicants falls close to, but just below, the expected level (shown as a negative value in Figure 13). This translates into a shortfall of about ten inventions per year. Considering that UK organisations currently file about 33 regenerative medicine patent applications a year worldwide, this means that UK organisations file roughly 25% less regenerative medicine patents than would be expected, although statistical significance is an issue given the small data set.²⁰
- 3.66** Interestingly this pattern is mirrored by organisations based in other European countries, such as France and Germany, which this report’s bibliometric analysis has shown have domestic strengths in regenerative medicine research. More work would be needed to conclude what factors are affecting these results and whether this is due to European-specific factors.

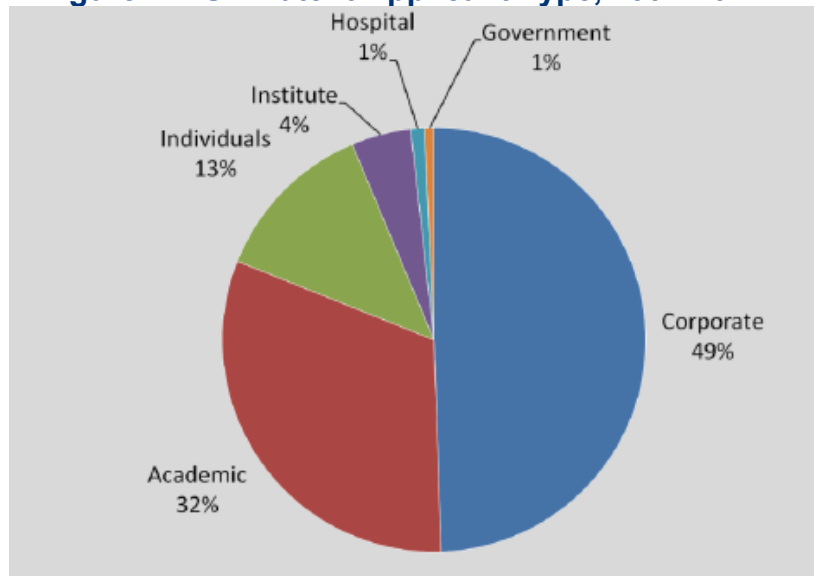
¹⁸ The data does not show any significant differences between the proportion of filed to granted patents for organisations in different countries.

¹⁹ Intellectual Property Office

²⁰ Between 1991-2011 662 applications were made in the UK, compared with the 873 you would expect given patenting levels in the life sciences field

3.67 Unsurprisingly the limited number of active individuals in the UK appears to be conducive to promoting collaboration in patent applications. UK universities appear to collaborate more than found in general worldwide, with all of the leading universities demonstrating strong collaborations, either with other universities or with industry. Several overseas collaborations are also apparent. Greater fragmentation may be expected to occur as the sector grows, and further entrants and competitors appear. It should therefore be a priority for the UK to maintain these strong links in the future.

Figure 14: UK Patent Applicant Type, 1991-2011²¹



3.68 As an emerging field, regenerative medicine also has a greater proportion of academic based patent applicants than other more developed fields. However, the UK has a slightly higher proportion of industry based applicants in regenerative medicine than the world generally (49% vs 46%).

3.69 Previous analysis for the UK National Stem Cell Network (UKNSCN) has shown that in the narrower field of stem cells recent patent applications by UK organisations are focussed on adult (mesenchymal) stem cells, pluripotent cells (e.g. embryonic stem cells) and haematopoietic stem cells/uncommitted or multipotent progenitors.

3.70 For granted patents, the top three areas are pluripotent cells (e.g. embryonic stem cells), stem cells/progenitor cells/precursor cells of the nervous system and haematopoietic stem cells/uncommitted or multipotent progenitors.

The importance of intellectual property

3.71 The Government believes that patents have an important role to play in encouraging innovation. We recognise that the investor community look for a robust patent position when investing and that this is particularly true for products with extended product development times and with a high degree of technical and market uncertainty.

²¹ Intellectual Property Office

- 3.72** The Government supports the current published practice of the Intellectual Property Office in the UK on the patentability of inventions involving stem cells. Embryos themselves are not patentable, but deposited human ESC lines and related technologies are, where there is a demonstrable inventive step in their derivation or use. With its multi-disciplinary nature, complex supply chains and delivery challenges, the importance of trade secrets and “know how”, alongside legal protection, should also not be underestimated for the progress of this field.

Action 7

The Government will keep the intellectual property regime in the UK under review, recognising the importance of protecting innovation to development of regenerative therapies in the UK.

Conclusions

Regenerative medicine is still at the early stages of commercialisation, although there have been significant developments over the last five years. A number of therapies are already being successfully reimbursed, mainly in the United States, and pharmaceutical companies have begun to move from exploration of the field to commercial exploitation. However, the UK and the field in general face a number of challenges before widespread adoption and commercialisation can be seen. As would be expected, funding and regulatory challenges are at the forefront of SME's minds. SME's do not have the expertise or resources available to large corporates.

The lack of engagement from pharmaceutical companies is also limiting the exit strategies of venture capital, which means that engagement and consultation with the large pharmaceutical and biotech companies will be critical going forwards. The Government is also committed to continued strategic investment to support the future development of the field, in particular through the establishment of a Cell Therapy Technology and Innovation Centre, which will have a critical role in providing expertise and infrastructure going forwards. This centre, combined with a critical mass of early adopting companies, key infrastructure and our underlying world-class science base puts the UK in a strong position to commercialise regenerative medicine in the future, reaping economic benefits for the UK as a whole.

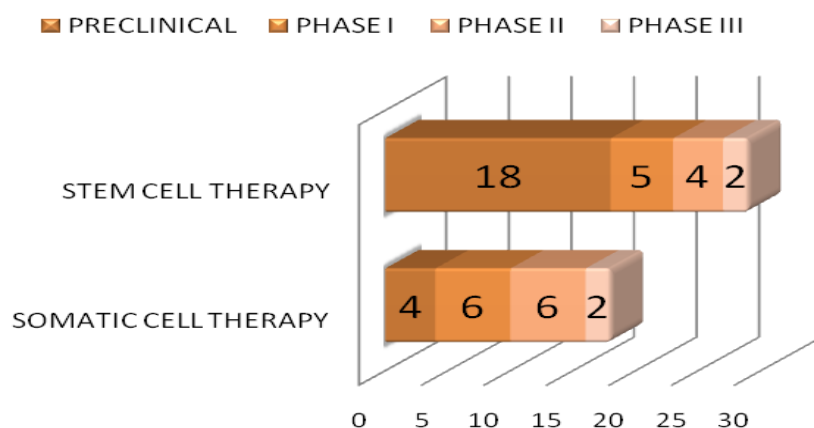
The regulatory landscape for regenerative medicine will also be kept under constant review alongside existing initiatives such as the Stem Cell Toolkit, to ensure that the UK remains a facilitating location for regenerative medicine translation and commercialisation.

4. Translation to the Clinic

Clinical State of Play

- 4.1** Regenerative medicine has already had significant clinical impact for specific patient groups, first through bone marrow transplants, and more recently from tissue engineered skin, where approximately 250,000 patients have now received treatment worldwide. While the patient numbers are still low by the standards of conventional drug-based treatments, a broader range of therapies are fast approaching the clinical trial phase or have recently entered Phase 1 (safety studies). Within the UK these include human ES cell based therapy for age-related macular degeneration (the most common form of blindness in the UK), “one to one”, autologous stem cell therapies for corneal repair, Multiple Sclerosis, Addison’s Disease and to aid hip replacement, a successfully tissue engineered tracheal transplant, and “one to many”, allogeneic therapies for stroke and Parkinson’s Disease.
- 4.2** Much effort is being directed at developing stem cell therapies for common yet intractable clinical indications such as cardiac repair, neuro-regenerative treatments, immunological disorders and cancer. The majority of this activity is currently in the early stages of clinical development (see figure 15) and is unlikely to yield a flood of new therapies in the short term. But the potential is huge, with proof of concept in one area likely to provide a significant boost to investment across the regenerative medicine field. The UK therefore needs to prepare the right infrastructure today, to support the industry tomorrow.

Figure 15: Clinical Development in Europe, 2010²²



- 4.3** With regards to tissues source, almost all the stem cell therapies being developed by European cell therapy firms involve haematopoietic²³ or adult stem cell lineages rather than from human ES cells. Having said that the first clinical-grade human ESC lines have now been deposited in the UK Stem Cell Bank, adding to the human ESC lines only suited to preclinical research.

²² REMEDIÉ

²³ Stem cells that gives rise to all red and white blood cells and platelets

- 4.4** Recognising the technical and regulatory challenges in developing “Good Manufacturing Practice” (GMP)-approved human ESC lines for clinical use, Scottish Enterprise, the Scottish National Blood Transfusion Service (SNBTS) and the University of Edinburgh created the not-for-profit company Roslin Cells, which created the UK’s first GMP-approved human ES cell lines for clinical development.

NHS Barriers and Opportunities

- 4.5** Regenerative medicine shows great potential for treating serious conditions such as diabetes, liver disease, neurodegenerative disorders and injuries such as burns or spinal cord and could also go some way towards combating rising healthcare costs associated with an ageing population.
- 4.6** There could be other benefits of developing expertise in the field. Hospitals might benefit from attracting patients from abroad for example: encouraging people to come to the UK for state-of-the-art treatments. However, care needs to be taken to ensure that “stem cell tourism” does not lead to the exploitation of vulnerable patients. In this regard, the Government supports the work of the International Stem Cell Society to introduce guidelines for those considering paying for private stem cell therapy or enrolling on a private stem cell research trial.
- 4.7** However the unique characteristics of cell therapies need to be tackled today if these cells are to be effectively delivered as part of routine clinical practice to patients. The major challenges include the need for more basic science, translational science and a bespoke infrastructure.
- 4.8** If regenerative medicine is to be utilised in any volume, some respondents to this report’s call for evidence felt that a national system of distribution would be needed.
- 4.9** In this area we are fortunate in the UK in having the well-regarded NHS Blood and Transplant Authority (NHSBT), Scottish National Blood Transfusion Service (SNBTS), Welsh Blood Service and Northern Ireland Blood Transfusion Service which are familiar with these challenges for blood products, stem cells (bone marrow and cord blood) and organs, as well as the necessary tissue typing services. In Scotland, SNBTS is already a key part of the regenerative medicine environment, undertaking clinical development of a pipeline of new therapies, and undertaking a lead role in several multi-partner public and private) projects, for example a Wellcome Trust-funded project to create red blood cells.
- 4.10** Similarly, there is potential for the NHSBT in England to partner with SMEs and other researchers, either as a purchaser of specialised services of infrastructure, or as an incubator for a small number of SMEs in need of GMP production facilities.
- 4.11** While it is vital that NHSBT retain a sharp focus on their blood provision services, it is encouraging that the Authority already provides a diverse range of specialist services in human tissue and cells. The Department of Health believes that NHSBT’s unique position in the UK and international recognition of its expertise in this area would make it a natural partner in any national regenerative medicine

strategy. The Department will ask NHSBT to consider its future role in supporting the development of regenerative medicine technology.

Action 8

The Department of Health will work with the NHS Blood and Transplant Authority to investigate how their involvement in regenerative medicine supply and delivery chains might be extended and developed.

Skills and Collaboration

- 4.12** Regenerative medicine is a multidisciplinary field which must draw on the expertise of a wide range of fields and stakeholders. Collaboration between academia, industry and clinicians is a vital component for the future success of the regenerative medicine field. It was also pointed by respondents to this report's call for evidence that much of the NHS's receptiveness to adopting new therapeutic approaches is dependent on the individual centres and specific clinicians who champion the technology.
- 4.13** It was also pointed out as well as lead clinicians, trained support staff were needed alongside engineers, Good Manufacturing Practice (GMP) production staff and Qualified Persons (QPs) to release finished cell-based products to deliver products effectively. Overall, it was felt that the number of staff (both clinical and non clinical) with the necessary core skills and knowledge to deliver regenerative therapies was limited.
- 4.14** Respondents said that in England the NIHR career development programme was training the next generation of clinical researchers, but said that the number of people entering the different clinical streams was extremely variable. The Medical Research Council has had a funding initiative in place to try to increase the number of clinical fellows entering the field over the past two years.

Support from the National Institute for Health Research (NIHR)

- 4.15** The goal of the National Institute for Health Research (NIHR) is to create a health research system in which the NHS supports outstanding individuals, working in world class facilities, conducting leading edge research focused on the needs of patients and the public. In principle, research in the area of regenerative medicine could certainly come under the remit of NIHR funding, providing the research is of the highest quality. NIHR Biomedical Research Centres (BRC) and Units (BRU) are world-class centres and units which undertake experimental and translational research. There are 12 BRCs and 16 BRUs already established with some 45 trainees in post.
- 4.16** A number of the Centres and Units undertake activities within the area of regenerative medicine, for example at the Moorfields Eye Hospital NHS Foundation Trust which undertake leading edge stem cell studies. More detail about the Biomedical Research Centres and Units can be found at NIHR website (<http://www.nihr.ac.uk>) or via the centres' and units' individual websites.

- 4.17** The NIHR Office for Clinical Research Infrastructure (NOCRI) has been set up to help public, charity and industry research funders work in partnership with NIHR infrastructure. Equally, it ensures that NIHR-supported Centres, Units, Facilities and Networks can work together to help drive innovative research for patient benefit.
- 4.18** NOCRI supports research partners by:
- a. *Research signposting* - help with navigating the clinical research environment and finding expert researchers and world class facilities
 - b. *Research collaboration management* - support for the development of collaborative research partnerships.
- 4.19** A model Industry Collaborative Research Agreement has also been developed to streamline and support the contracting process for research partnerships involving the pharmaceutical and biotechnology industries, universities and NHS organisations.

Biomanufacturing Facilities

- 4.20** Advances in manufacturing techniques and bioprocessing are critical to the development of all cell-based therapies. Current technologies are generally not scalable, and significantly limit the generation of the large number of high-quality cells required either for single patient use, and even more so, for universal “one to many”, allogeneic cell therapies. The challenge is to ultimately develop manufacturing processes that will deliver a product that is efficacious and affordable.
- 4.21** Respondents to this report’s call for evidence claimed that the UK possessed relatively large numbers of manufacturing and bioprocessing facilities, but said that these had been established in an uncoordinated manner over the last 20 years, and were not currently being used effectively. The majority of this infrastructure was also said to be targeted at “one to one”, autologous, therapies, and therefore not necessarily relevant to any future “one to many”, allogeneic therapies.
- 4.22** Respondents stressed that the bioprocessing units were currently struggling to attract and retain trained staff and manage running costs such as the maintenance of the facility and quality management system, regular upgrades, validation and access to a Qualified Person (QP).
- 4.23** Many of the clean rooms and their associated quality systems were also said to be suitable for only Phase I and possibly Phase II clinical trials, with little/no capacity available for Phase III and later commercial manufacture.
- 4.24** Respondents thought that all the facilities should be brought up to a common standard that was fit for purpose with regards to a specific stage of clinical trial development. This could include ensuring the design, qualification, operation and quality systems are consistent across the units and suitable for concurrent multiproduct manufacture.

Adoption of therapies

- 4.25** There is currently no definitive path for the adoption of regenerative medicine products, as each differs by its mode of action, cost and therapeutic application. A tissue engineering product for wound-care is significantly different to an embryonic stem cell therapy for stroke, for example. In each of the English, Scottish, Welsh and Northern Irish National Health Systems, it will be necessary to balance the cost benefit relationship of regenerative medicine products.
- 4.26** Appropriate evaluation procedures will be critical with products likely to have higher upfront costs than current therapies. On the other hand, many regenerative medicines in development are targeting chronic diseases that currently place a significant burden on the UK's healthcare services. For example, within the UK the NHS spends approximately 10% of its annual budget on treating diabetes and its associated complications²⁴ and providing services to patients with heart failure in England costs the NHS an estimated £625 million per year.²⁵
- 4.27** Some respondents claimed that current evaluation systems have difficulties with accepting high up-front costs, even though the long-term cost of a regenerative medicine treatment could be substantially lower than that of the current gold standard, when long-term care costs are taken into account. Despite this claim, there is some existing evidence showing creative reimbursement agreements in the NHS. For example Pfizer agreed to reimburse the NHS for non-responders of its treatment for patients with gastrointestinal stromal tumours, as well as 6 weeks of free treatment and a 5% price cut.²⁶
- 4.28** Examples like this are promising, and should be built on, as appropriate in the future. The NHS is also reviewing how to improve the adoption and spread of innovation, as committed to in this Government's Growth Review, with a view to promoting the uptake of innovative therapies such as regenerative medicine.

Action 9

NICE, through its technology evaluation and scientific advice programmes, will continue to facilitate useful dialogue with companies developing regenerative therapies on the development of data for comparative effectiveness and health economic analysis.

- 4.29** A study is currently being carried out and the findings will inform the response to the Plan for Growth from Sir David Nicholson, Chief Executive of the NHS. The response will address what the NHS National Commissioning Board and other NHS bodies need to do to make the adoption of proven innovation in technology and

²⁴ Diabetes UK Report 2008

²⁵ NHS Information Centre (2010) National Heart Failure Audit 2010: Report for the audit period between April 2009 and March 2010

²⁶ NICE Guidance 2009b, taken from a paper by Dr Cathy Prescott, *The Journal of the Royal Society – Conference Proceedings: What next for stem cells*

practice integrated in healthcare services more rapid. The response is due in November 2011.

Action 10

In recognition of its potential as a driver for the UK economy and future healthcare, the Government will work towards an integrated, national strategy for regenerative medicine that builds on the strengths of the country's science, industry and healthcare sectors.

Conclusions

Regenerative medicine, and in particular cell therapy, has considerable potential to be a UK success, both commercially and in terms of health outcomes. The unique position of the NHS as a national healthcare provider serving 60 million patients should make it a fertile environment for the development and adoption of innovation and scientific advances like regenerative medicine.

It must also not be forgotten that the goal of regenerative medicine of curing or treating (rather than conventional pain control, symptom management and/or palliative treatment) has the potential to provide a step change reduction in healthcare costs, directly and potentially indirectly through impact on social and employment opportunities for both the patient and their carers.

The UK is among the world leaders in the field of regenerative medicine. Our life science industry, academic institutions and research capacity provides us with considerable potential to provide more effective and efficient healthcare with proven better patient outcomes. The NHS, working even more closely with these institutions could prove a considerable driving force in the translation of world-class technology and innovation into an improved patient diagnostic and treatment pathway.

There is significant potential to use the NHS Blood and Transport Service's expertise and infrastructure to manufacture and supply cell based therapies nationally. The Government has taken action on many of the issues but there remain challenges. More and stronger strategic links between NHS research and industry R&D could balance previous strategies focussed on research and provide major benefits for UK plc and the NHS.

The findings of this report highlight, once more, a number of issues that are hampering the adoption of cell therapy in the NHS. An integrated, national strategy will focus on improving the delivery, infrastructure, regulation and uptake of cell therapy and regenerative medicine. It will also provide a focus to tackle the second stage translational gap and develop appropriate partnerships to ensure the supply of safe and effective products or patient services that are affordable, routine and scalable.

Appendix A: Selected Country Briefings

United States of America

National Strategy

- 5.1** The United States does not have a national strategy for regenerative medicine. The NIH however is taking a lead in the area of strategy and is in the process of establishing a NIH Center for Regenerative Medicine (NCRM).

Public Funding

- 5.2** There has been uncertainty around federal funding in recent years due to legal challenges, the most recent of which was dismissed in May 2011.
- 5.3** Federal funding for regenerative medicine was around \$950 million in FY 2009 including one-off stimulus funding. A further \$1.2 billion of funds were made available for stem cell research in FY 2009 (again including stimulus funds). By comparison, FY 2008 levels for Regenerative medicine and Stem Cell Research (before ARRA) were at \$723 million and \$938 million respectively. In 2010 \$1.286 billion was given by the NIH solely for stem cell research. However, federal funding is a small proportion of total US funding, with the Alliance for Regenerative Medicine estimating that the private sector funds ten times as much research as the US government.
- 5.4** Whatever the uncertainties over federal funding of stem cell research, US States are not restricted in funding stem cell and regenerative medicine research with state funds. Each state has its own funding levels and laws' restricting those funds – but the best example of funding at a state level is in California. Proposition 71 authorized public funding of up to \$3 billion over the next 10 years for stem cell research in California. CIRM provides funds stem cell research at non-profit institutions and companies throughout California as well as funding for training and facilities. To date, the CIRM governing board has approved 434 research, training, and facility grants totaling more than \$1 billion, making CIRM the largest source of funding for human embryonic stem cell research in the world.

Private Investment

- 5.5** Given the situation between federal and state funding as well as the large philanthropic activity in this area funding for this sector is fragmented. There is essentially no large scale industry funding at the moment, and companies that are active or have VC funding are almost exclusively in adult stem cells. The main funding streams are philanthropic funding and private (match) funding tied to state funding, and then there is some of VC/industry funding.
- 5.6** Venture capital funds for stem cell related projects have been comparatively small by American standards. One published estimate (Moneytree) places venture capital investment in stem cell companies of all types at \$1.1 billion between 1995 and 2007, a modest amount by venture capital standards. These investments are almost

entirely focused on products developed from adult stem cells (Note: compare OH company list below which shows a similar trend).

- 5.7** “Private investments” by institutions (often private academic institutions and foundations), tied to or supplemented to state funding are currently one of the main driving force for spin-out companies in this field. Consequently the funding landscape is very fragmented and inconsistent, however several states have begun to shift the form of support they offer away from research-oriented grants to universities and towards the support of for-profit companies aimed at product development. California has recently awarded its first substantial grants to private companies and is in the process of developing a loan program targeted at companies involved in the development of stem cell therapies.
- 5.8** Private philanthropy is the second major source for human ES cells and other forms of stem cell research. While private support for biomedical research is nothing new, in human ES cells it has been both unusually large relative to the scale of the research enterprise and the level of federal support and has been used for a wider array of activities than has been typical.

Regulation

- 5.9** There is perceived regulatory complexity in the United States with a lack of a harmonized regulatory framework. The definitions of regenerative medicine are varied and not easily identified. There is no standard regulatory framework for regenerative medicine; all applications are reviewed on a case-by-case basis. The US Food and Drug Administration (FDA) proceeds in this way in new areas because it is too difficult to set standards for new and changing areas of science. Only once they receive a critical mass of applications and can see how the landscape is shaping up can they then devise a more predictable set of regulations. This lack of certainty can discourage innovators from the field.

UK Medical Research Council (MRC)- Californian Institute for Regenerative Medicine Collaboration (CIRM)

- 5.10** The MRC committed £5m to fund two projects in collaboration with CIRM funded researchers to progress treatments to the point of filing an Investigational New Drug (IND) application with the FDA within four years (addressing age-related macular degeneration and acute myeloid leukaemia). The UK component of these projects is integral and the projects could not progress to the clinic without the MRC funded research. This collaboration has highlighted the strength the UK has in this area.

Germany

National Strategy

- 5.11** The Federal Government has no published national strategy for regenerative medicine. However, support for RM and stem cell research is encouraged under Germany’s cross-departmental innovation strategy, the High-Tech Strategy (2006-2009) and High-Tech Strategy 2020 (2010-2013). These encourage the development of new products and innovative services. The Federal Government supports several thematic priorities under these strategies, including in the area of biotechnology covering medical, industrial and plant applications.

- 5.12** In 2006 the Federal Ministry of Education and Research (BMBF) carried out a review of regenerative medicine in Germany. This involved an analysis published by Capgemini in 2007. This report - *Regenerationstechnologien für Medizin und Biologie - Beiträge für ein strategisches Förderkonzept* – outlines a more strategic approach to promoting regenerative technologies. It includes a SWOT analysis of regenerative technologies in Germany and makes recommendations.
- 5.13** The review of RM in Germany identified a strong academic research base and a significant number SMEs in this area. It highlighted the need to improve collaboration between clinics, companies, government and regulators. The review recommended the establishment of translational centres for regenerative medicine to overcome barriers to innovation (see below).

Public Funding

- 5.14** National research funding in Germany is based on two pillars: institutional (base) funding and project funding. Base funding for Germany's research organisations (Fraunhofer, Max Planck, Leibniz, Helmholtz, German Research Foundation) is jointly provided by the Federal and Laender Governments Through project funding the funding government departments directly shape the course of research policies. This instrument offers the possibility of prompt and flexible responses to topical issues, new developments and challenges. The implementation of the programs through the ministries is supported by project management organizations.
- 5.15** Public-sector support for regenerative medicine research and clinical development in Germany is mainly channelled through the BMBF and the German Research Foundation (DFG). The key elements of German funding for regenerative medicine include support for public sector research, R&D in SMEs, and collaborative approaches. The key elements of German funding for regenerative medicine include support for public sector research, R&D in SMEs, and collaborative approaches. This includes:
- Translational centres for regenerative medicine (funded by BMBF)
 - DFG Research Centres and Cluster of Excellence (funded by DFG)
 - Support for research in SMEs
 - Promotion of clinical innovation under the Federal Health Research Programme
- 5.16** In addition to the dedicated funding streams for research in the area of regenerative medicine, tissue engineering and stem cells, the DFG funds research under its individual grants programme (Einzelförderung). The DFG provided an estimated €17.9m in 1999-2007 for stem cell research in the form of individual grants. In the same period, some €13.2m was made available for embryonic and tissue specific stem cells under Priority Research Programmes and a further €1.9m in 2001-2007 for clinical research.

Japan

National Strategy

- 5.17** Japan has so far established a multiple area of strengths in developmental biology, although the US leads way ahead in terms of budget and the ability to call researchers from abroad. Japan has gained confidence with the sensational success

in generating the human iPS cells demonstrating that Japan's S&T policy is effective to produce globally competitive scientists.

- 5.18** A report published by JST²⁷ indicates that Japan clearly lacks the strategy based on a long-term vision, and that major interdisciplinary or cross-sectoral collaboration is yet to be seen. The report recommends that Japan needs to collaborate with multiple countries in order to share or secure wider or longer-term views, and recommends that Japan should not see China and Korea as competitors, but should establish a fifty-fifty partnership, similar to that of a relationship established by the EU nations.
- 5.19** The Ministry of Economy Trade and Industry (METI) has been focusing its support for the development of technologies that are relatively close to commercialisation, such as safety verification technologies and measuring devices required for the cell collection and culture, tissue form and treatment processes for bone, cartilage, cornea and cardiac muscle. METI is also promoting developments for enhanced cell sheets and technologies to manufacture bio cardiac muscle capable of supplying oxygen and nutrition, which aims to establish technology fundamentals, measurement and verification methods for larger, three dimensional structure and self-assembly systems.
- 5.20** Ahead of the initiative explained above, the national project funded by Ministry of Education, Culture, Sports, Science and Technology (MEXT) to promote regenerative medicine was initiated in 2003 (~2008) as a part of Japan's R&D projects for activating the economy. The project was led by Japan's flagship research institute RIKEN in collaboration with major academic, industrial and government bodies. Focus was given to the development/maintenance of stem cell banks for research use, the development of stem cell manipulation technology, and the development of stem cell therapy. In November 2007, a major breakthrough of creating the iPS (induced pluripotent stem) cells from human skin cells was achieved by Professor Shinya Yamanaka of Kyoto University.

Public Investment

- 5.21** The Government and funding agencies have been investing largely into R&D and innovation through direct government projects and competitive funds, especially with a strong focus to support iPS cells research. Examples include:
- The iPS cell achievement led MEXT to additionally inject YEN1billion (GBP6.5million) to the second phase of the project (2008-2012) in order to intensively accelerate the iPS cell research to holistically promote innovation in regenerative medicine. The FY2009 budget for the second phase is estimated to be YEN 2.65 billion (GBP17 million).
 - JST, Japan's major funding agency run by MEXT is another major supporter of the iPS cell research. JST has given grants through its strategic innovation programme

²⁷ International comparison of science and technology R&D in life sciences 2009, published by the Center for Research and Development Strategy, JST

to leading researchers including Prof Yamanaka and the total budget for FY2009 is YEN2.35 billion (GBP15million).

- NEDO, a funding agency run by METI launched a major project in 2008 to promote the development of fundamental technologies for the industrial application of stem cells including iPS cells. The total budget for 6 years until 2014 is estimated to be YEN 5.5billion (GBP35million).
- As a part of the economic stimulus package, the government additionally allocated 270 billion yen (GBP1.7billion) in FY2009 to drive innovation in various sectors, and 30 projects were recently selected. Prof Yamanaka's research for the application of iPS cells to regenerative medicine was selected along with another regenerative medicine project. The package allows up to YEN3-15billion (GBP19-96million) over 5 years.

Regulation

5.22 Regulatory issues have also hindered the advance of regenerative medicine research. Until August 2009, researchers engaging in human ES cells research were required to pass two reviews, one by MEXT, followed by the ethics committee of their own institute, which in some cases, the whole process took almost a year. This was clearly disadvantageous for Japanese researchers in view of the increasingly stiff global competition, thus MEXT revised its guidance for human ES cells research in August 2009 by omitting the review by MEXT. It also eased the regulation for transferring cells created from human ES cells amongst research institutions in order to allow cross-institutional collaborations.

5.23 MEXT revised its guidance for human ES cells research in August 2009 to shorten the administrative process. In terms of other regulatory issues that need to be addressed as stated above, the Japanese Society for Regenerative Medicine declared its recommendations in March 2009 to encourage policy makers to revise the regulations concerned in order to accelerate the practical use of regenerative medicine

5.24 In June 2009, MEXT launched the iPS cell research 10-year roadmap, to effectively and holistically promote research for the early translation of research achievements in to clinical practice. 4 major objectives were identified:

- Identification of the iPS initialising mechanisms (basic/fundamental research)
- Creation and distribution of the standardised iPS cells (standardisation)
- Creation and verification of patients-derived iPS cells for drug discovery and clinical research, establishment of the iPS cell bank
- Regenerative medicine (pre-clinical and clinical research for treatment technologies using cells, tissues, tissue transplant differentiated from iPS cells).

5.25 The developments in iPS cell research is expected to be utilised more to support drug discovery rather than clinical research in regenerative medicine. In April 2009, the IPS Academia Japan Inc., a company set up to manage intellectual property rights related to iPS cells created by Prof S Yamanaka of Kyoto University, agreed for the first time to licence the iPS patent to ReproCELL Inc., and Takara Bio Inc. Targeted at pharmaceutical companies, ReproCELL starts contract business to test candidate drugs' side effects by using human iPS cells.

Appendix B: Research Impact Analysis Methodology

- 5.26** The core ‘regenerative medicine’ data set for this study has been drawn from the PubMed database by *Evidence*, Thomson Reuters, using MeSH terms. Page 52 of this document contains a list of the MeSH terms that were agreed by BIS and its relevant partners (DH, MRC, BBSRC, EPSRC, TSB) to give the most complete coverage possible of ‘regenerative medicine’.
- 5.27** Search and collation was carried out by *Evidence*. Each publication record was identified uniquely with the appropriate PubMed ID. *Evidence* then drew the relevant matching data from the Thomson Reuters Web of Knowledge and acquired associated citation data for bibliometric analysis.
- 5.28** Publication records used for this study:
- Include all primary peer-reviewed papers (substantive articles and reviews, which definition excludes letters and conference abstracts) using the agreed definition of ‘regenerative medicine’.
 - Cover 5 years of publications from 2005 to 2009 inclusive. This makes the sample relatively recent while providing sufficient data points for smaller topics and countries.
 - Are linked to citation data through to the end of 2010. This takes account of the relatively low citation counts to most papers in their first year after publication, particularly for papers published late in the year.
 - Draw on bibliometric data collated by *Evidence* from Thomson Reuters databases.

Numbers of publications

- 5.29** Numbers of publications reflect basic research capacity by showing the volume of papers being produced (or contributed to) by researchers in each region. Volume is affected not only by variations in research capacity, however, but also by local research culture and relative funding. 19. Volume by itself is no indicator of quality, but trends in capacity should be seen as important information about investment decisions and resource availability. Growth in quantity often foreshadows improvements in quality as the national research base develops.

Average normalised citation impact

- 5.30** Publication impact (academic impact) is measured using citations, but citation counts grow over time and rates vary by discipline. It is essential to take into account not only ‘time since publication’ but also the journal category to which an article belongs (Annex 2). The most informative way of analysing citation data is to use the normalised citation impact (or nci – this may be expressed as nciF for fields and nciJ for journals), which is the citation count normalised (or ‘rebased’) for subject (field or journal) and year by comparison with the relevant world average. An nci value of 1 is the world average. The average nci for the UK is usually in the range 1.3 to 1.4.

Highly cited papers

- 5.31** A ‘highly-cited’ paper has generally been considered by Thomson Reuters to be one that falls into the top 1% of cited world publications. For the UK this approximates to

papers with an nci of more than 8 times the world average for most subject areas. While this certainly identifies the most exceptional papers, in order to allow meaningful national comparisons a lower cut-off (say, 4 times world average or papers in the top 5% or 10% by field and year) should be used to identify papers that are relatively highly-cited. For the UK approximately 5% of papers achieve a citation rate that is at least four times world average and around 10% exceed three times world average normalised citation impact.

Uncited papers

5.32 Many papers remain uncited in the first year after publication. Some papers never acquire any citations. While ‘uncitedness’ is not a sufficient quality index in itself, comparisons with other indicators and across countries will convey information. If we compare two organisations in the same field, the one with a lower proportion of uncited papers is often also the one with other indicators of relatively good research performance. For the UK research base, approximately 30% of papers in any ten-year sample are usually uncited at that time, but in biomedical fields this falls to 10 -12%. Over the longer term, around 10% of papers authored in major research economies will tend to remain uncited.

Impact Profiles®

5.33 Publication and citation data, like other variables associated with research activity, are skewed. There are many instances of low value and a smaller number of instances of very high value. The ‘average’ in such right-skewed distributions is typically much greater than the central or median value. The average may therefore be considered to be less representative of the distribution as a whole than in a normal distribution (a normal distribution follows a familiar bell-shaped curve). We use a graphical presentation to enable a more transparent picture of the underlying impact distribution. The nci values are presented as Impact Profiles® to address the disparity in interpretation which an average creates. This illustrates the number of papers in each nci interval where the standard intervals are 0 (uncited papers), and a series of cited categories pivoting around the world average: < 0.125, 0.125 > 0.249, 0.25 > 0.499, 0.5 > 0.99, 1 > 1.99, 2 - >3.99, 4 > 7.99 and 8+

5.34 The Impact Profile® of each organisation or country shows the numbers and % of the papers for each categorical interval. From this analysis it is straightforward to determine how the impact of regenerative medicine papers (or any sub-set) being published within the UK compares with the rest of the world.

MeSH Terms for Bibliometric Analysis

Figure 16: MeSH Terms used to define regenerative medicine for bibliometric analysis

1. Hematopoietic Stem Cell Transplantation	36. Regenerative Medicine
2. Hematopoietic Stem Cell Transplantation/ADVERSE EFFECTS	37. Regenerative Medicine/METHODS
3. Hematopoietic Stem Cell Transplantation/IMMUNOLOGY	38. Regenerative Medicine/ORGANIZATION AND ADMINISTRATION
4. Hematopoietic Stem Cell Transplantation/INSTRUMENTATION	39. Stem Cell Transplantation
5. Hematopoietic Stem Cell Transplantation/ISOLATION AND PURIFICATION	40. Stem Cell Transplantation/CLASSIFICATION
6. Hematopoietic Stem Cell Transplantation/LEGISLATION AND JURISPRUDENCE	41. Stem Cell Transplantation/ECONOMICS
7. Hematopoietic Stem Cell Transplantation/METHODS	42. Stem Cell Transplantation/ETHICS
8. Hematopoietic Stem Cell Transplantation/STANDARDS	43. Stem Cell Transplantation/METHODS
9. Hematopoietic Stem Cells	44. Stem Cell Transplantation/STANDARDS
10. Hematopoietic Stem Cells/CYTOLOGY	45. Stem Cells
11. Hematopoietic Stem Cells/DRUG EFFECTS	46. Stem Cells/BLOOD
12. Hematopoietic Stem Cells/ENZYMOLOGY	47. Stem Cells/CHEMISTRY
13. Hematopoietic Stem Cells/GENETICS	48. Stem Cells/CLASSIFICATION
14. Hematopoietic Stem Cells/GROWTH AND DEVELOPMENT	49. Stem Cells/CYTOLOGY
15. Hematopoietic Stem Cells/IMMUNOLOGY	50. Stem Cells/DRUG EFFECTS
16. Hematopoietic Stem Cells/ISOLATION AND PURIFICATION	51. Stem Cells/ENZYMOLOGY
17. Hematopoietic Stem Cells/METABOLISM	52. Stem Cells/GENETICS
18. Hematopoietic Stem Cells/PATHOLOGY	53. Stem Cells/GROWTH AND DEVELOPMENT
19. Hematopoietic Stem Cells/PHYSIOLOGY	54. Stem Cells/IMMUNOLOGY
20. Hematopoietic Stem Cells/RADIATION EFFECTS	55. Stem Cells/ISOLATION AND PURIFICATION
21. Liver Regeneration	56. Stem Cells/METABOLISM
22. Liver Regeneration/PHYSIOLOGY	57. Stem Cells/PATHOLOGY
23. Pluripotent Stem Cells	58. Stem Cells/PHYSIOLOGY
24. Pluripotent Stem Cells/CHEMISTRY	59. Stem Cells/THERAPEUTIC USE
25. Pluripotent Stem Cells/CYTOLOGY	60. Stem Cells/TRANSPLANTATION
26. Pluripotent Stem Cells/IMMUNOLOGY	61. Stem Cells/ULTRASONOGRAPHY
27. Pluripotent Stem Cells/METABOLISM	62. Stem Cells/ULTRASTRUCTURE
28. Pluripotent Stem Cells/PATHOLOGY	63. Stem Cells/VIROLOGY
29. Pluripotent Stem Cells/PHYSIOLOGY	64. Tissue Engineering
30. Pluripotent Stem Cells/TRANSPLANTATION	65. Tissue Engineering/INSTRUMENTATION
31. Pluripotent Stem Cells/VIROLOGY	66. Tissue Engineering/METHODS
32. Regeneration	67. Tumour Stem Cells
33. Regeneration/GENETICS	68. Tumour Stem Cells/ISOLATION AND PURIFICATION
34. Regeneration/IMMUNOLOGY	69. Tumour Stem Cells/PATHOLOGY
	70. Tumour Stem Cells/PHYSIOLOGY
	71. Tumour Stem Cells/PHYSIOPATHOLOGY

Figure 17: Collaboration analysis by country.

The Table is symmetrical, but the orange highlighting should be read down the columns as indicating the three most frequent partners for that country. Across the rows, the highlight indicates where that country is a frequent partner in that column. Summed column values will add to more than the total collaborative papers for that country because of multiple-authorship.

Country Collaborating V	Publishing >																
	UK	Brazil	Canada	China	France	Germany	India	Israel	Italy	Japan	Netherlands	South Korea	Spain	Sweden	Switzerland	USA	
UK		25	159	89	278	484	17	52	308	150	225	27	161	181	171	896	
Brazil	25		29	3	36	37	1	3	44	8	6	5	11	29	5	155	
Canada	159	29		75	110	157	8	25	97	97	43	61	40	39	56	816	
China	89	3	75		55	74	3	3	26	133	43	44	12	22	28	701	
France	278	36	110	55		316	9	44	222	71	118	10	142	93	166	485	
Germany	484	37	157	74	316		13	95	291	127	241	29	153	160	412	1,165	
India	17	1	8	3	9	13		4	5	20	1	10	4	8	2	80	
Israel	52	3	25	3	44	95	4		67	12	30	3	34	17	24	229	
Italy	308	44	59	26	222	291	5	67		54	113	11	131	120	165	668	
Japan	150	8	97	133	71	127	20	12	54		50	103	31	62	40	965	
Netherlands	225	6	43	43	118	241	1	30	113	50		4	55	67	100	383	
South Korea	27	5	61	44	10	29	10	3	11	103	4		6	13	4	348	
Spain	161	11	40	12	142	153	4	34	131	31	55	6		63	54	296	
Sweden	181	29	39	22	93	160	8	17	120	62	67	13	63		66	282	
Switzerland	171	5	56	28	166	412	2	24	165	40	100	4	54	66		340	
USA	896	155	816	701	485	1,165	80	229	668	965	383	348	296	282	340		
Total collaborative	2,482	289	1,399	1,211	1,420	2,896	167	404	1,479	1,619	1,031	556	713	862	1,107	7,531	
% collaborative research	43.4%	29.1%	45.8%	29.4%	46.1%	42.2%	23.9%	41.0%	38.3%	22.1%	48.1%	26.4%	43.6%	54.2%	64.4%	28.2%	
Total output	5,725	992	3,057	4,117	3,082	6,865	699	986	3,860	7,315	2,142	2,104	1,634	1,591	1,718	26,744	

Appendix C: Patent Analysis

Methodology

5.35 For this project the European Patent Office (EPO) database EPODOC was interrogated, which holds bibliographic and abstract data of published patents and patent applications derived from the majority of leading industrialised countries and patent organisations, for example the World Intellectual Property Organisation (WIPO), EPO and the African Regional Industry Property Organisation (ARIPO). It should be noted that patent applications are generally published eighteen months after filing.

Priority Date, Application Date and Publication Date

5.36 There are generally three dates which can be associated with a patent application as follows:

- **Application date:** The date on which an application for a patent was made.
- **Priority date:** The application date of an earlier, related patent application containing the same invention. A patent can claim a priority date from an earlier application which contains the same subject matter. The priority date is the earliest available indication of the date of invention.
- **Publication date:** The date when the patent application was published. This is normally eighteen months after the priority date or the application date, whichever is the earlier.

WO and EP Patent Applications

5.37 International Patent Applications (WO) and European Patent Applications (EP) may be made through the World Intellectual Property Organization (WIPO) and the European Patent Office (EPO) respectively.

5.38 International Patent Applications may designate any signatory states or regions to the Patent Cooperation Treaty (PCT) and will have the same effect as national or regional patent applications in each designated state or region, leading to a granted patent in each state or region.

5.39 European Patent Applications are regional patent applications which may designate any signatory state to the European Patent Convention (EPC), and lead to granted patents having the same effect as a bundle of national patents for the designated states.

Patent Documents Analysed

5.40 The document dataset was identified through European Classification (ECLA) codes and word searching of abstracts in conjunction with patent examiner technology-specific expertise. As far as possible ECLA codes were matched to the MeSH terms used in the bibliometric analysis to ensure consistency between the two data-sets.

5.41 The applicant and inventor data were cleaned as far as practicable to remove duplicate entries arising from spelling errors, initialisation, international variation (Ltd, Pty, GmbH etc.), or equivalence (Ltd., Limited, etc.).

Relative Specialisation Index

5.42 Relative Specialisation Index (RSI) was calculated as a correction to absolute numbers of patent families in order to account for the fact that some countries file more patent applications than others in all fields of technology. In particular, US and Japan inventors are prolific patentees. RSI compares the fraction of Regenerative Medicine patents found in each country to the fraction of patents found in that country overall. A logarithm is applied to scale the fractions more suitably. The formula is given below:

$$\log_{10} \left(\frac{n_i/n_{total}}{N_i/N_{total}} \right)$$

n_i = number of Regenerative Medicine patents in country
 n_{total} = total number of Regenerative Medicine patents in dataset
 N_i = total number of patents in country
 N_{total} = total number of patents in dataset

5.43 The effect of this is to highlight countries which have a greater level of patenting in Regenerative Medicine than expected from their overall level of patenting, and which would otherwise languish much further down in the lists, unnoticed.

Appendix D: Glossary of Abbreviations

AMRC	Association of Medical Research Charities
AMS	Academy of Medical Sciences
ATMP	Advanced Therapy Medicinal Product
BBSRC	Biotechnology and Biological Sciences Research Council
BSI	British Standards Institute
DCS	Developmental Clinical Studies
BRIC	Bioprocessing Research Industry Club
DPFS	Developmental Pathway Funding Scheme
EPSRC	Engineering and Physical Sciences Research Council
ESRC	Economic and Social Research Council
ES	Embryonic Stem (cells)
GMP	Good Manufacturing Practice
HFEA	Human Fertilisation and Embryology Authority
HTA	Human Tissue Authority
iPS	Induced Pluripotent Stem (cells)
MAb	Monoclonal Antibodies
MHRA	Medicines and Healthcare Products Regulatory Authority
MRC	Medical Research Council
NHSBT	National Health Service Blood and Transplant Authority
NIHR	National Institute for Health Research
NOCRI	NIHR Office for Clinical Research Infrastructure
PAS	Publicly Available Specification
QP	Qualified Person
SC4CM	Stem Cells for Safer Medicines
SNBTS	Scottish National Blood Transfusion Service
TIC	Technology and Innovation Centre
TSB	Technology Strategy Board
TSCRC	Translational Stem Cell Research Committee
UKNSCN	UK National Stem Cell Network

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