A Strategy for UK Regenerative Medicine
Regenerative medicine is an emerging discipline that holds the promise of revolutionising patient care in the 21st century. The UK is a leading player globally in the science that underpins regenerative medicine, as established by the UK Government’s 2011 *Taking Stock of Regenerative Medicine in the United Kingdom*, and is well positioned to translate this knowledge to achieve clinical and economic impact. However, while the UK is at the forefront of this rapidly evolving field, we cannot be complacent, given increasing global investment and competition.

In order to identify opportunities and challenges faced by the UK regenerative medicine community, spanning discovery, translational science and clinical delivery, four UK research councils (BBSRC, EPSRC, ESRC and MRC) and the Technology Strategy Board (TSB) have undertaken a review of the field. This identified eight key UK strategic objectives that will need to be addressed if the UK is to make the most of its current position. To be of greatest impact, advances in the field will need to be made in parallel within a framework that brings balance and coherence to the UK effort.

To this end, the sponsor group has developed a coordinated and overlapping set of delivery mechanisms, spanning its area of responsibility, to meet the identified objectives.

### Underpinning Research

A range of biological, engineering and socioeconomic drivers of regenerative medicine were identified that merit further investigation. These include a need to increase our understanding of cellular reprogramming, differentiation and ageing, disease and reparative mechanisms, stem cell niches, the extracellular environment, genetic instability, of how we harness the immune response, advanced bioprocessing, and undertake predictive modelling of innovation and value systems. Support for such investigations will be provided through response mode funding, and continued strategic investment in centres of excellence and partnerships with industry.

### Therapeutic Options

A number of approaches are being pursued, spanning cell transplantation, the stimulation of the body’s own repair systems, and the use of acellular products. The UK’s legislative and regulatory framework has helped build and maintain broad public support for investigations of the full spectrum of regenerative medicine interventions. Given uncertainties regarding the efficacy and safety of these different approaches, it will be important to maintain studies of all. Going forward, this translational science will be supported through the MRC/TSB Biomedical Catalyst Fund, complemented by EPSRC response mode funding.

### Product Development

It is important that early stage regenerative medicine product development be closely linked to the establishment of manufacturing, transportation and delivery solutions. Meeting this challenge will require engagement between translational scientists, the process development and clinical communities, and the regulatory agencies. To help foster this engagement, enhance connectivity and drive innovation, MRC, BBSRC and EPSRC will establish a UK Regenerative Medicine Platform (UKRMP). This initiative will build on existing investments in centres of excellence, and will operate in close partnership with the TSB Cell Therapy Catapult Centre.

### Clinical Delivery and Evaluation

The UK specialist hospitals, academic health science centres and NIHR Biomedical Research Centres provide a world-class environment for clinical research and trials. The clinical testing of regenerative medicine technologies, however, poses particular challenges. The MRC and ESRC will co-sponsor workshops with field participants, design experts and regulators, to explore clinical trial challenges in order to establish the most effective trial designs and improve the transparency of the regulatory framework.
Innovation and Value Systems

Sustainable business models will be required if regenerative medicine products are to have broad impact. To generate necessary revenues, companies will need to secure reimbursement for their products, drive adoption and be able to protect their positions from competition. ESRC response mode funding can support investigations addressing issues such as the evolution of new business models, product development mechanisms (including reimbursement and adoption), and open innovation.

International

Given the global nature of the field, and the increasing investment being made around the world, it will be necessary for the UK to remain alert to international activity if it is to maintain its leading position in the field. The sponsors will work with overseas partners through established long-term relationships and new partnerships to capitalise upon emerging opportunities and provide access to complementary expertise that will benefit UK science. To help provide insights into overseas opportunities and threats, ESRC will sponsor a workshop on “International developments and future global challenges”.

Focus

By addressing a common goal, focused programmes of research could help bring the field’s expertise together in collaborative efforts that could attain the critical mass required to achieve key goals, such as the establishment of clinical proof of concept. The UKRMP, by establishing a national cluster of activity, will provide one such foundation for driving focused therapeutic efforts. Accordingly, the sponsors will work, in a second phase of the UKRMP initiative, to identify key disease areas/therapy types meriting concerted investment, and will work with other interested funders to develop mechanisms to capture these opportunities.

Interdisciplinary Collaboration

This field requires the bringing together of strong complementary skills, expertise and infrastructure across disciplines. Effective interdisciplinary research is built upon shared and valued goals. Developing such goals requires individual-to-individual contact and communication. The sponsors’ review has highlighted the need for a unifying but needs-driven network to provide a platform for such interaction. Together, the sponsors will develop appropriate mechanisms to achieve a needs-focused networking activity.

The strategic objectives and delivery mechanisms described within this strategy aim to provide a coherent framework for UK research and development activity in this area over the next five years to ensure that current UK strength is effectively built upon. Taken together, it is hoped that the sponsors’ initiatives will ensure that the UK retains its leadership position in regenerative medicine worldwide and delivers on the great promise of regenerative medicine to the benefit of both patients and the UK economy.
Lung endothelial cells
1. Introduction

1.1 Background

A strategic review of regenerative medicine has been jointly undertaken by four UK research councils (RCs) (the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC), Economic and Social Research Council (ESRC) and Medical Research Council (MRC)) and the Technology Strategy Board (TSB). This has sought to identify the opportunities and challenges faced by the UK regenerative medicine community, spanning discovery and translational science and the needs for clinical delivery. The findings of this review have been used to develop a comprehensive UK strategy and route map for future investment for regenerative medicine, and while focused on the research and development agenda where the sponsor group has greatest influence, this strategy has also considered barriers to application in areas beyond the immediate research domain.

For the purposes of this strategy, regenerative medicine has been defined as an interdisciplinary approach spanning tissue engineering, developmental and stem cell biology, gene therapy, cellular therapeutics, biomaterials (scaffolds and matrices), nanoscience, bioengineering and chemical biology that seeks to repair or replace damaged or diseased human cells or tissues to restore normal function. It may involve:

- transplantation of stem cells, progenitors or tissue
- stimulation of endogenous repair processes
- the use of cells as delivery vehicles for genes, cytokines and small molecules
- cell engineering/synthetic biology

1.2 Review Process

The methodology used for the sponsors’ review of the UK regenerative medicine field was developed in consultation with a cross-RC/TSB Regenerative Medicine Advisory Group, with membership drawn from across the academic and industrial spectrum

The review considered the findings of:

- the 2011 UK Government report: Taking Stock of Regenerative Medicine in the United Kingdom
- the outputs of a Key Opinion Leaders Workshop, held in September 2011
- an analysis of the portfolio of sponsor investments in the field (the 2010 Regenerative Medicine Portfolio), complemented by an overview of other UK funder activity; and
- an international perspective, based on the comments of overseas Key Opinion Leaders and an assessment of current overseas initiatives

Key Opinion Leaders Forward Look Workshop

A Key Opinion Leaders Workshop, involving 30 research experts from academia and industry, was held in September 2011 to provide an opportunity for the sponsors to hear the community’s views on the status and future priorities for regenerative medicine research and development in the UK. The Forward Look workshop used a road-mapping approach to gather participant views on the key objectives for the field and the drivers shaping them, the field’s current position, perceived barriers to progress, and the enabling mechanisms required to meet the identified goals. A copy of the Workshop Report is available on the MRC website and the list of participants is provided in Annex I.

2010 Regenerative Medicine Portfolio

A review of sponsor investments in the regenerative medicine domain, live on 19 November 2010, was undertaken to map the current distribution of investment and to enable a comparison to be made with the 2007 UK stem cell portfolio. This was done to help identify investment trends and assist gap analysis. Portfolio highlights are provided in section 3 and the portfolio analysis is provided in Annex II.
The Taking Stock of Regenerative Medicine in the United Kingdom report established that the UK retains a leading position, in Europe and globally, in the science and commercial translation of regenerative medicine. UK research in this domain is internationally competitive and of high impact, and is supported by a strict but permissive legislative and regulatory framework that is helping innovation to flourish. However, although the UK is at the forefront of this rapidly evolving field, it is clear that we cannot be complacent, given increasing global investment in this field. Accordingly, the review has identified eight key UK strategic objectives (described in section 4 below), which will need to be addressed if it is to make the most of its current position. Before turning to these future objectives, it is helpful to understand the field’s current position.
2. Current Research and Development Position

Regenerative medicine is not a new discipline; the use of bone marrow transplantation to regenerate the blood cell compartment became clinically established in the 1970s. Currently, a range of treatments and approved products are available (see 2.2), spanning the full spectrum of regenerative strategies from acellular matrices through to stimulators of endogenous repair mechanisms. Furthermore, recent developments in the field, including advances in our understanding of stem cell pluripotency and in biomaterials research and nanoscience, mean that the field is now poised to move beyond its historic focus on blood, bone, cartilage and skin repair, to help address the broader needs of an ageing population.

2.1 Understanding the Science of Regeneration

All regenerative medicine strategies depend upon the harnessing, stimulation or guidance of endogenous developmental or repair processes. Insights into these underpinning processes as exemplified by, for instance, the identification of regulators of precursor cell differentiation within specific cell lineages, or the characterisation of the three-dimensional structure of the stem cell microenvironment or “niche” for appropriate function, provide the basis for the development of more rational interventions.

The development of methods able to tune the surface properties of scaffold materials combined with the recognition of the critical importance of the cellular environment, including the extracellular matrix, in maintaining and directing cellular differentiation provides an opportunity to transform scaffolds from passive mechanical supports to active components of regenerative medicine manufacturing processes and therapy.

The recent description of methods to derive pluripotent stem cells from adult donors, induced pluripotent stem cell (iPSC) technology, provides the opportunity not only to develop therapies matched to a patient’s own cells but also to establish more accurate cellular models of diverse human diseases based upon the genotype of affected individuals. The continuing refinement of methodologies to achieve cell reprogramming, as exemplified by the recent description of approaches to reprogramme cell identity directly from one differentiated type to another without going via a stem cell intermediary (trans-differentiation), opens up further applications and therapeutic options.

2.2 Therapeutic Developments

Regenerative medicine products seek to replace or repair damaged or diseased cells or tissues or to stimulate endogenous repair mechanisms. They cover a broad spectrum of product types including: acellular products, which in the UK fall under a medical device regulatory regime; cell-based products, which may or may not incorporate a biomaterial component; and exogenous stimulators of repair that, when alone, fall under the pharmaceutical regulatory regime. Representative examples of currently approved versions in clinical use for each of these categories include:

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Examples</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acellular scaffolds</td>
<td>Tissue based: Alloderm (Lifecell)</td>
<td>Donated human skin tissue depleted of epidermis and cells; for hernia repair and breast reconstruction.</td>
</tr>
<tr>
<td></td>
<td>Synthetic: Actifuse (Baxter)</td>
<td>Synthetic silicate-substituted calcium phosphate scaffold; used as a bone void filler.</td>
</tr>
<tr>
<td>Cellular</td>
<td>Bone marrow transplant</td>
<td>Stem cell therapy; to reconstitute the blood and immune systems of certain cancer patients.</td>
</tr>
<tr>
<td>Cellular scaffolds</td>
<td>Dermagraft (Shire)</td>
<td>Human fibroblast cells seeded onto a polyglactin scaffold; to treat full-thickness diabetic foot ulcers.</td>
</tr>
<tr>
<td>Stimulators of endogenous repair</td>
<td>Erythropoietin (Amgen, Johnson &amp; Johnson)</td>
<td>Recombinant hormone; used to manage anaemia in chronic kidney disease and cancer patients.</td>
</tr>
<tr>
<td></td>
<td>Plus scaffold: Infuse (Medtronic)</td>
<td>Recombinant human bone morphogenetic protein soaked into collagen sponge; to treat lower leg fractures.</td>
</tr>
</tbody>
</table>
The therapeutic areas with the most marketed regenerative medicine products are for skin (including the ocular surface), bone, adipose, cartilage and blood disorders. Of the marketed cell therapies about 80% are for cartilage and skin repair. Other areas that have attracted major research interest are liver disease, retinal degeneration, diabetes, cardiovascular disorders, neurodegeneration and stroke. However, these are all currently some way from clinical application.

A key UK advantage over other global regions is that investigators are able to explore the full spectrum of potential regenerative medicine interventions, including both adult and embryonic stem cell (ESC) based approaches, which as well as offering distinctive options for therapeutic development according to disease area, provide important cross-fertilisation of biological understanding. The UK’s well developed legislative and regulatory framework has helped build and maintain broad public support for this position, which, given the high level of uncertainty around the efficacy and safety of the different available options, is likely to be of continuing benefit.

2.2.1 Acellular Products

The increasing clinical evidence-base for the more established acellular matrices indicates that, as with other therapeutic interventions, patient response is heterogeneous. Some patients appear to benefit well from the intervention with others only responding marginally or not at all. Such differences point to the need for a deeper understanding of the repair processes underpinning such strategies that might in turn help target (stratify) the intervention to those most likely to respond as well as help to refine it further or identify new interventional approaches.

2.2.2 Cell-based Products

Cell-based therapies fall into two broad classes, i) those derived from a patient’s own cells (autologous) and ii) those derived from a donor’s cells (allogeneic). The former have the advantage of being immunologically matched to the patient but, being a one-to-one treatment, are bespoke in nature. As such, the costs of these interventions can be very high, potentially limiting their uptake in financially constrained healthcare systems. Allogeneic treatments offer the opportunity of providing a one-to-many treatment and, if scalable, may be better able to address the needs of large patient populations. However, in order to meet these needs, allogeneic treatments will need to avoid immune rejection.

i) Autologous

Autologous products are at a relatively advanced stage of development and in some cases are already in clinical use or in late stage trials (worldwide there were 15 late phase trials registered in 2011). Examples of autologous interventions include the use of:

- adipose-derived stem cells for reconstructive breast surgery (eg Celution from Cytori)
- chondrocytes (eg Carticel from Genzyme) and mesenchymal stem cells for cartilage repair
- haematopoietic stem cell transplants as the standard second line treatment for lymphoma
- keratinocytes for burns
- satellite cells for skeletal muscle regeneration; and
- bone marrow stem cells applied to denuded donated trachea for airway replacement

ii) Allogeneic

Allogeneic haematopoietic stem cells, from bone marrow, have been widely used in the management of leukaemia and acute myeloid leukaemia. In these cases, a combination of human leukocyte antigen (HLA) matching between the donor and host and the use of immunosuppressive drugs is required to enable the stem cells to avoid immune rejection. Allogeneic cells have also been used with limited success in beta islet cell transplantation for diabetes, while the first clinical trials have recently commenced in the US and UK for interventions based on both human ESC and neural progenitor cell lines. However, the deployment of this approach is currently constrained by the availability and difficulty of expanding donor material. In general, the immunological challenges faced by allogeneic products, due to potential donor and host incompatibilities, means that their development currently lags behind that of autologous products.

The recent development of IPSC technology appears to offer an attractive route for the exploitation of the therapeutic potential of pluripotent stem cells. However, much uncertainty remains around the safety and efficacy of production of specific, functional therapeutic cell populations from IPSCs and currently this is seen as an area of promise rather than delivery. IPSCs could in principle be used in either an autologous or an allogeneic form. In the former case, the cost of generating patient-specific cells for transplantation may be prohibitive given that this would require bespoke cell manipulation and manufacture for each or HLA-matched groups of individuals. For allogeneic therapy, it is as yet unclear whether IPSC-derived cells offer advantages over ESC-derived cells; the different routes to derivation give rise to subtle biological differences between the two forms with IPSCs exhibiting some variability in epigenetic status that underlies concerns over their tumourigenic potential.

2.2.3 Stimulation of Endogenous Repair

Biopharmaceutical stimulators of endogenous replacement and repair processes are already in the clinic. Examples include granulocyte-colony stimulating factor, a potent mobiliser of haematopoietic stem cells used clinically to accelerate recovery from neutropenia after chemotherapy, and erythropoietin, used to manage anaemia in chronic kidney disease and cancer patients through the stimulation of red blood cell production. In the preclinical arena a number of promising approaches are emerging, for example in the use of growth factors to repair heart muscle, cytokine and small molecule approaches to stimulate remyelination in the nervous system, and the use of nitric oxide to stimulate muscle stem cells. An improved understanding of the natural stem cell microenvironment or “niche” to be targeted by exogenous stimulators will be critical for our ability to predict responses of endogenous cells to drugs or biologicals.
2.2.4 Modelling Mechanisms, Efficacy and Safety

The availability of human ESCs and IPSCs provides new avenues for investigating disease mechanisms and for assessing the potential efficacy and safety of therapeutic interventions. Although such studies may not directly lead to new regenerative medicine products, the insights gained could help inform new strategies, perhaps based on an understanding of underlying developmental biology and repair mechanisms. In addition, the processes developed in such investigations, such as the reproducible expansion and differentiation of cells to a defined target cell type, could have direct application in the regenerative medicine field.

An early application of IPSCs and trans-differentiated cells may be in generating patient-specific disease models and cells, for probing disease mechanisms, and for testing the efficacy and toxicity of drugs. Such approaches have the potential to recapitulate the genetic background to complex disorders, as well as the ability to model diseased tissue that is currently unavailable through biopsies, for example in disorders of the brain. Late stage attrition of drugs in development remains a significant problem to the pharmaceutical sector, and human ESC- or IPSC-derived cells, such as hepatocytes and cardiomyocytes, offer the potential of more predictive safety screens.
To help identify the potential gaps and imbalances in current research activity, the sponsor group’s research portfolio in regenerative medicine was mapped. This analysis, which also took stock of research funding provided by the National Institute of Health Research (NIHR), recorded all research awards live on 19 November 2010. An analysis of the 2010 Regenerative Medicine Portfolio can be found in Annex II, with key headlines presented below.

3.1 Total Spend by Sponsor

The 2010 Regenerative Medicine Portfolio includes 353 awards with a total annualised spend of £72.6 million. The split per sponsor was as follows:

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Number</th>
<th>Value (£m)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBSRC</td>
<td>97</td>
<td>12.8</td>
<td>27%</td>
</tr>
<tr>
<td>EPSRC</td>
<td>58</td>
<td>11.3</td>
<td>23%</td>
</tr>
<tr>
<td>ESRC</td>
<td>6</td>
<td>0.9</td>
<td>2%</td>
</tr>
<tr>
<td>MRC</td>
<td>137</td>
<td>37.7</td>
<td>39%</td>
</tr>
<tr>
<td>NIHR</td>
<td>9</td>
<td>1.1</td>
<td>3%</td>
</tr>
<tr>
<td>TSB</td>
<td>46</td>
<td>8.8</td>
<td>13%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>353</td>
<td>72.6</td>
<td>100%</td>
</tr>
</tbody>
</table>

Value is the annualised award value = total award/duration of award in years and this, rather than number of awards, has been used as the means of assessing investment intensity.

3.2 Spend by Stage

The developmental stage of each award has also been classified using the Technology Readiness Level (TRL) system (definitions in Annex II), which at the lower end (TRL1) covers hypothesis-driven exploratory research and moves towards application as the stage numbers increase.

In line with the relative immaturity of the field, it can be seen that the majority of sponsor funding is focused on the earliest TRLs, supporting investigations probing the field’s underlying science, with levels reducing as projects move further down their developmental path.

3.3 Spend by Health Category

Each award has been classified by health category using the UK Clinical Research Collaboration (UKCRC) Health Research Classification System. For those awards targeting or supporting therapy development, the spread of investments can also be shown by developmental stage.

The prominence of musculoskeletal awards and their relative higher proportion of late stage projects reflect the fact that this area has been an early and significant focus of regenerative medicine activity. The significant preclinical development in Eye likely reflects the emergent understanding of the tractability of this application area.

3. www.hrcsonline.net
3.4 Infrastructure

Regenerative medicine in the UK can draw upon a range of infrastructural investments that include:

**RC/TSB centres of excellence**
The RCs and TSB have established several national centres of excellence. These include the EPSRC, TSB and BBSRC jointly funded Innovation and Knowledge Centre in Regenerative Therapies and Devices in Leeds, and the EPSRC Centre for Innovative Manufacturing in Loughborough. The MRC supports investigations spanning basic stem cell biology and its application through a number of its institutes, units and dedicated centres: MRC Clinical Sciences Centre and National Institute for Medical Research both in London, MRC Molecular Haematology Unit in Oxford, MRC Centre for Stem Cell Biology and Regenerative Medicine in Cambridge and MRC Centre for Regenerative Medicine in Edinburgh. In addition, EPSRC has established Doctoral Training Centre awards in Tissue Engineering and Regenerative Medicine across Leeds, Sheffield and York and in Regenerative Medicine spanning Loughborough, Nottingham and Keele.

**Stem Cells for Safer Medicines (SC4SM)**
SC4SM is a UK public-private partnership founded via a consortium of major international pharmaceutical companies and public sector funders, including TSB, MRC and BBSRC, to utilise human ESCs to establish differentiated cell-based assays, for example using hepatocytes for predictive drug toxicology screening.

**UK Stem Cell Bank**
The UK Stem Cell Bank was established with funding from the MRC and BBSRC to provide a repository of human embryonic stem cell lines as part of the UK’s governance arrangements for the use of human embryos for research. Its role is to provide quality controlled stocks of these cells that researchers worldwide can rely on to facilitate high quality and standardised research. The Bank also supplies a number of fetal and adult stem cell lines.

**Production facilities**
NHS Blood and Transplant (NHSBT) currently provides around 2,000 bone marrow stem cell therapies annually and has 32 Advanced Therapy Medicinal Product (ATMP) clean rooms. These facilities are located throughout England and are supported by a national quality system and Good Manufacturing Practice (GMP) trained staff. This infrastructure is complemented by the facilities of the Scottish National Blood Transfusion Service and the Scottish Centre for Regenerative Medicine in Edinburgh, which includes GMP facilities and an academic cell therapy unit.

**Biomedical research centres and units**
The NIHR and Welsh Government have established comprehensive biomedical research centres (BRCs) and smaller more specialised units (BRUs) in leading NHS and university partnerships to drive progress on innovation and translational research in biomedicine into NHS practise. A number of these host activities support regenerative medicine. These include the Cambridge BRC, which has established a GMP resource for stem cells and regenerative medicine, the BRUs in Birmingham, Bristol and the Imperial College BRC, who are pursuing stem cell therapies in liver and cardiovascular disease, and the Musculoskeletal Disease BRUs in Leeds and Oxford.
Retina blood vessel and nerve cells
4. Strategic Objectives and Implementation

The research and development strategic objectives and initiatives described in this section provide a comprehensive response to the field’s needs and opportunities, as identified through the sponsors’ review. One of the field’s key challenges arises from its breadth and intra-dependencies. This field, more than most, requires the bringing together of strong complementary skills, expertise and infrastructure across a range of disciplines in order to achieve its goals. To be of greatest impact, advances in the field will need to be made in parallel. For example, therapeutic developments should be matched both with growing fundamental and clinical insight, helping to ensure product safety and efficacy, and with developments in manufacture, helping to ensure product reproducibility, volumes and cost. This will require appropriately balanced investment across the field, to be provided within a framework that brings coherence to the UK effort. Accordingly, the sponsor group has developed an overlapping set of delivery mechanisms spanning its area of responsibility that seeks to address the identified needs and opportunities in a coordinated effort, as detailed below:

4.1 Underpinning Research

In this area, a range of underpinning research opportunities warrant investigation, including:

- Understanding cellular differentiation, and how it might be controlled to benefit the development of cell-based therapies and/or in the development of small-molecule/biopharmaceuticals targeting endogenous repair mechanisms
- Routes to reprogramming, including directed (trans) differentiation and use of chemical biology
- Understanding disease mechanisms, drawing upon the emerging importance of iPSCs in probing disease processes
- The biology of stem cell niches; the importance of 3d-structure and co-culture of different cell types for accurate recapitulation of function
- Cell ageing and maturation; an emerging feature of current differentiation protocols is that cellular derivatives are embryonic-like, rather than adult-like, in function
- Genetic instability during cell propagation and expansion
- Extracellular surface modifications to direct cellular development; the role of external factors in guiding cellular propagation and differentiation
- Biomaterials development, both for structural support and the direction of propagation and differentiation
- Immune response, encompassing immune suppression, immunological tolerance, and immune privilege
- Mechanism of action of therapeutic products; addressing how cell-based therapies exert their effects, utilising back-translation from clinical subjects as this is not always through expected routes
- Bioprocessing and scale-up methodologies underpinning cellular product characterisation and manufacture
- Predictive modelling of value systems, regulatory systems and stakeholder perspectives to facilitate commercial development of stem cell-related products across all the niches described above

Support for underpinning research need not, of course, be justified solely on the potential to deliver against predetermined goals and opportunities, such as those listed above. Investment in basic research can also reveal unanticipated insights, such as the breakthrough in IPSC technology in 2006, which can be of broad value both within and beyond the field of enquiry.

Implementation

The sponsors will use established response-mode funding to provide support for underpinning investigations, although it will be necessary to ensure that these schemes are open to and able to evaluate cross-disciplinary research, and that where appropriate these investments are connected to the translational agenda. The sponsors will continue to provide support for and, where appropriate, lever existing strategic investments in partnerships with industry, such as the BBSRC and EPSRC funded Bioprocessing Research Industry Club (BRIC), which underpins the bioprocessing of cellular therapies, and RC centres, to help provide critical mass focused on stem cell biology, phenotyping and early-stage translation. Specific support will be provided to capture emerging opportunities, such as the use of iPSCs and associated methodologies for disease modelling. In those areas where collaboration between UK and complementary overseas strengths might better enable the field to meet its goals, the RCs will work with relevant UK and international partners to develop platforms for targeted collaboration. One such area is chemical biology, which provides an opportunity to probe biological processes and might provide a springboard to therapeutic development. To further this area of research, the MRC is establishing a centre for chemical and
synthetic biology at the MRC Laboratory of Molecular Biology. Connections might also be made to US groups with a leadership position in this area to complement the strengths in UK cell and developmental biology.

It is likely that the areas of study highlighted above would benefit from advances being made in bioinformatics and systems biology/medicine. It will therefore be important that these activities are appropriately linked and include the participation of mathematicians and computer scientists able to connect biological data to produce predictive mathematical models of biological behaviour. To address identified priorities, researchers will likely need to draw upon both technical resources, for example proteomic platforms, and biological resources, with support and direction to ensure appropriate quality control and access to data and material. As these may derive from materials such as embryos and fetal tissue, their establishment and curation will need to be sensitive to the particular ethical and moral issues pertinent to this area. Understanding these challenges and the potential links between researchers and these material data resources might also inform approaches to coordinate biobanking at the international level and the provision of access to commercial parties.

**Cross-disciplinary research:** To engender collaboration in the area of chemical biology, BBSRC, EPSRC and the MRC intend to host a meeting to bring together relevant US and UK research groups to discuss collaborative opportunities, including connectivity to aligned investments in bioinformatics and systems biology.

### 4.2 Therapeutic Options

A range of therapeutic options exist for regenerative medicine, including:

- **Autologous products** (eg those involving cell isolation and reinfusion of unmodified or relatively short-term cultures of mature cell populations)
- **Stimulation of endogenous repair** (by biologics or small molecules, assessed as pharmaceuticals)
- **The use of purified, differentiated cells for drug safety and efficacy testing** (using human ESCs or IPSC-based in vitro platforms)
- **Acellular products** (eg scaffolds and matrices, products assessed as medical devices)
- **Allogeneic products for use in large-scale markets** (in the near-term based on human ESCs or derived progenitors)
- **IPSC-based products** (albeit some way off clinical application at present due to concerns over the clinical transfer of current derivation protocols)

The above list is ranked in order of where the field perceives focus might be applied to achieve best impact, as established by the Forward Look workshop. This prioritisation reflects both the scale of the needs that each class of product might address and their likely timescale to deployment.

When considering the options for cell-based therapies, autologous products are deemed the most desirable from a safety and patient acceptability point of view and for these reasons may well continue to be the earliest products to come into clinical trial. However, they are the least desirable from a commercial perspective, due to the requirement of producing a batch of one each time, while the inherent complex nature of the product also raises challenges at the scientific level for determining the active component and mechanism of action and thereby how to improve efficacy going forward. From a regulatory perspective, those autologous products requiring minimal manipulation and no expansion provide the least challenges, and such products are already being developed. However, there is a risk that efficacy could be compromised through such an approach, which requires the use of starting material relatively abundant in stem cells, and which might miss the possibility that rarer, more potent stem cells could provide better therapeutic potential, even if this would require expansion in a clean room.

Allogeneic product development, on the other hand, will require a strong focus on addressing the immune response. Whether ESC-derived allogeneic products for wide scale use will require HLA-matching remains to be determined. This may in part depend on whether it is necessary for allogeneic cells to participate in tissue regeneration processes and remain within the repaired tissue, or whether strategies for using allogeneic cells for their short-term trophic effects, recruiting host cells to complete the repair, might be more effective. Another factor will be the site of cell transplantation, given that certain sites in the body, such as the eye and parts of the central nervous system, are more immune-privileged than others. Lastly, strategies might be engaged to encapsulate the donor cells to hide them from the host immune systems in scenarios where the cells provide a paracrine effect, as for example is currently being commercially pursued in the US for the development of a human ESC-based therapy for diabetes.

### Implementation

Given uncertainties regarding potential safety and efficacy, it will be important to continue to support the investigation of all available options. The development of therapies beyond the preclinical stage will in most cases require the development of multidisciplinary teams, and linkage across the academic and industrial sectors. The MRC/TSB Biomedical Catalyst Fund, recently announced as part of the Government’s Strategy for UK Life Sciences4, will support the development of individual interventions, of all types, as they traverse their own critical developmental steps and as they transition from the academic to the industrial base. Through providing seamless support across these boundaries, it is hoped that the Biomedical Catalyst Fund will improve the efficiency of product development, ultimately resulting in benefits to patients and the UK economy. The Biomedical Catalyst Fund will include the MRC Translational Stem Cell Research Programme and Developmental Pathway Funding Schemes, both focused on early translation and with an existing

4. www.bis.gov.uk/ols
portfolio of regenerative medicine awards. The Fund will be complemented by EPSRC response-mode funding that will continue to provide support for the early stage development of products incorporating or made of biomaterials, including tissue engineered products.

An analysis of the 2010 Regenerative Medicine Portfolio (Annex II) suggests that endogenous repair solutions are underrepresented compared to their perceived potential. Such interventions, if identified, are likely to face an easier developmental path than cell-based products, as they will likely be either small molecule or biologic products, whose routes of development are well characterised and understood by biopharma, regulators and investors alike. In recognition of this underrepresentation, BBSRC and the MRC will highlight the endogenous repair field of enquiry to stimulate the research community to address this area.

4.3 Product Development

Developing and producing safe, effective and reproducible regenerative medicine interventions at the desired volume and cost will require a range of capabilities, including suitable safety and efficacy models, manufacturing processes, transportation and delivery solutions. There is an important role for the social sciences here in modelling innovation and regulatory potential to optimise the translation process from basic scientific discovery to practical application.

Although the developmental requirements of regenerative medicine products are not unique, their nature, particularly those of cell-based interventions, pose particular challenges. For safety and efficacy studies it will be necessary to develop cell modification/reporting tools to track cell distribution/mobility (involving novel cell imaging/labelling technologies) and possibly routes to programmed destruction for cells escaping the site of action or not fully differentiated. Greater investment is required in the development of translational models to accelerate clinical application, with current clinical trials being based on minimal proof of concept data. It may be necessary, given the risks of incompatibility and rejection as well as differences in target organ physiology across the species barrier, to develop humanised animal models. Alternatively, equivalent animal cells may need to be tested in same-species models. As animal models can be poor predictors of human outcome, non-animal based models such as tissue-equivalent assays should also be evaluated. Alongside this, effort is needed to establish new approaches for cell/product targeting and therapeutic delivery (for example gene therapy, biological vectors or cell encapsulation) as well as devices for site-specific transplantation. The establishment of new tools, standards and approaches to assess efficacy and safety will require regulatory sciences studies, which may include a social sciences dimension. Such studies were not well represented in the 2010 Regenerative Medicine Portfolio, and may be an area worthy of further development.

Unlike in the case of small molecule drugs, where questions of manufacturability can be largely divorced from early development, it is important that early stage regenerative medicine product development be closely linked to the establishment of manufacturing processes. In the case of cell-based products, these processes must be able to reproducibly propagate, expand and differentiate cells such that they are able to meet the ATMP requirements of potency, purity and safety. Such processes can provide regulatory compliance and cost benefits, particularly at scale, from undertaking process checks rather than checks on individual products. However, the development, accreditation and standardisation of large-scale automated cell culture for clinical grade applications remains a work in progress, and may continue to present significant technical and regulatory challenges for allogeneic products in the medium term.

Meeting the product development challenge will require close and parallel engagement between the process development community and:

- “Early stage” basic researchers, to inform, for instance, the characterisation of cell lines, gene vectors or biomaterials, and the nature of required drivers
- Patient groups and the clinical community, to help define efficacy parameters, based on an understanding of the intervention’s mechanism of action
- The regulatory agencies, who will need to be satisfied that the products meet appropriate efficacy and safety standards

In addition to overcoming manufacturing challenges, it will be necessary to establish storage, transportation and distribution solutions if regenerative medicine therapies are to become mainstream clinical practise. The manufacturing capacity and UK-wide distribution capability of the NHSBT service might provide a platform by which UK-based product developers could reach a wide clinical population, to their potential competitive advantage.

Implementation

The UK’s recognised strengths in basic stem cell and developmental biology, its established biopharmaceutical manufacturing capability (which has addressed similar challenges in the biologics sector), the recent publication of British Standards Institution PAS

5. www.mhra.gov.uk
ensure that the UK operates as a single, globally competitive
help the hubs define priority areas and help the CTCC to retain a
build links to relevant dispersed national activity. This linkage will
in four or five hubs with appropriate critical mass, incentivised to
engineering and manufacturing science, with investment focused
disciplines such as stem cell biology, medical imaging, tissue
more development is needed to underpin the delivery of new
impetus for strengthening such links. The UKRMP will be challenge­
with the TSB, to support the translational agenda and to provide
participation of the different RCs in the existing centres is relatively
than regenerative medicine, will assist in meeting the field’s later
therapy Catapult Centre (CTCC), whose remit, although larger
established a series of national centres of excellence
the RCs have established a series of national centres of excellence
in the field and TSB has recently announced the creation of a Cell
Therapy Catapult Centre (CTCC), whose remit, although larger
than regenerative medicine, will assist in meeting the field’s later
stage developmental needs. The portfolio review suggests that co­
participation of the different RCs in the existing centres is relatively
limited, and improving the links between them and the new CTCC
would provide a major opportunity to stimulate further interdisciplinary activity informed by real world application.
Accordingly, MRC, BBSRC and EPSRC will establish a £25 million
UK Regenerative Medicine Platform (UKRMP), in close cooperation
with the TSB, to support the translational agenda and to provide
impetus for strengthening such links. The UKRMP will be challenge­
ged in order to address the knowledge gaps and obstacles where
more development is needed to underpin the delivery of new therapeutic approaches. This will build on existing excellence in
disciplines such as stem cell biology, medical imaging, tissue
engineering and manufacturing science, with investment focused
in four or five hubs with appropriate critical mass, incentivised to
build links to relevant dispersed national activity. This linkage will
help the hubs define priority areas and help the CTCC to retain a
state-of-the-art position in later stage product development, and
ensure that the UK operates as a single, globally competitive
cluster.

MRC/EPSRC/BBSRC UK Regenerative Medicine Platform: £25m joint investment as a managed national programme to address key early translational knowledge gaps. The goal of the UKRMP will be to establish an interdisciplinary and systems-based programme to address i) generic issues, for example safety science (eg cell stability, tracking, immobilation), immunomodulation, engineering challenges and technology platforms, as well as ii) areas such as cell functionality, acellular technologies, delivery systems, diagnostics, manufacturing and screening technologies, where a more tailored approach is needed according to the physiological focus. The Science and Technology Facilities Council (STFC) will contribute up to £0.2 million per annum to support the UKRMP through providing access to technology and expertise including the ability to build demonstrators or equipment to support researchers.

TSB Cell Therapy Catapult Centre (CTCC): The TSB is establishing a Catapult Centre in cell therapy as part of its strategic long-term investment in the UK’s innovation capability. The centre will be one of a network of technology and innovation centres in sectors that will drive economic activity for years to come and significantly increase wealth

creation by building a bridge between our world-leading research base and business. The CTCC will be based in London and open in late summer 2012. The objective of the CTCC is to enable the creation of a new industry for the UK that both grows to substantial economic levels and retains a very significant part of the value generated in the UK. The centre will support the development and commercialisation of cell therapies addressing challenges in the preclinical, manufacturing and clinical areas.

ESRC Responsive Mode: Alongside the above developments, ESRC is pleased to receive responsive mode or partnered applications in the social sciences addressing issues such as “anticipatory sustainable value system development”.

4.4 Clinical Delivery and Evaluation

The clinical testing of regenerative medicine technologies will rely on the careful selection of the clinical indication to be pursued (reflecting the likely risk–benefit ratio for the patient), as well as insights into patient selection and stratification to target those patients who might respond most favourably to such interventions. Consideration will also be required as to donor selection, screening and procurement (whether for tailored, immunological matched or allogeneic approaches), as well as how the regenerative medicine product will be stored and delivered to the clinic (requiring research into cryopreservation/cell hibernation and transportation).

Of the various approaches to regenerative medicine, clinical trials of cell therapies pose unique challenges, which include the difficulty of predicting potency in an intrinsically polypharmic product and dose (cells unlike drugs have the ability to multiply). Indeed, the very regenerative potential that makes stem cell treatments appear so promising is also the quality that makes them risky: securing stable implantation can be difficult, cell batches can vary over the course of a trial and endpoints might be difficult to determine where patients carry a range of comorbidities. Given such difficulties, there is a need to develop biomarkers to track cell integration and therapeutic effect, amongst others. In addition, it is not clear that classic drug trial designs are appropriate for regenerative medicine products, given their higher levels of uncertainty and their likely focus on ultra-orphan conditions. New trial designs may therefore be required, perhaps more adaptive in nature. Such methodological changes could affect trial governance and ethics, for instance if products were to be evaluated in a non-patient group, which would need to be further considered.

Trials should consider patient selection and follow-up, where long-term assessment of both positive and negative outcomes will be needed, potentially across studies. For example, the ability to back correlate to frozen product samples could provide valuable safety information. If the correlation identified a donor-specific issue, this might raise questions about whether and how this information should be fed back to the donor.
The UK specialist hospitals, academic health science centres and NIHR Biomedical Research Centres provide a world-class environment for clinical trials. The sponsors’ review however identified a need for much greater engagement with the clinical community, which was generally regarded as being underrepresented in the field. This engagement will be critical for ensuring that new products target real world needs, and for the planning and execution of clinical trials.

In addition to improved trial design, the field would likely benefit from improved transparency of regulatory pathways and for the regulatory system to be optimally aligned in support of innovation. Uncertainty regarding regulatory paths is a disincentive to researchers and importantly is seen by the venture capital community as an impediment to investment. Recently, the UK Stem Cell Tool kit has been established by the MRC and Department of Health (DH) to provide a one-stop-shop to orientate researchers to the regulatory needs in the stem cell area. Meanwhile, regulatory coverage of somatic cell therapies has been in place since 2003 and this was added to in 2007 with the ATMP regulation, since when the committees and guidance that this regulation called for have been put in place within the medicines regulatory framework. Nevertheless, there is likely to be continued benefit from engagement between regulators and those working in the field to ensure the sharing of informed guidance at an early stage.

Implementation

The clinical testing of regenerative medicine technologies poses particular and potentially unanticipated challenges that will require close coordination between investigators and regulators along with social insights into appropriate risk governance mechanisms for innovative technologies. A dialogue with the regulators could help to clarify the regulatory path and address, for example, the appropriateness of product testing in animal models and whether classic drug trial designs are suited to regenerative medicine products. If new trial designs are required, changes will need to account for trial facilitation and governance, studies of which fall within the remit of ESRC response mode funding. The sponsors will work with the UK’s Departments of Health to ensure that the UK’s strong clinical trials base is supportive of regenerative medicine product development. In order to meet regulatory requirements, investigators will need access to clinical grade cell lines; support for the UK Stem Cell Bank will be ongoing to help meet this demand, and opportunities to ensure the supply of clinical-grade IPSC or trans-differentiated cell lines will be kept under review as this technology matures.

Regulatory workshops: MRC and ESRC will co-sponsor workshops with field participants, design experts and regulators such as the MHRA, to explore clinical trial challenges to improve transparency of the regulatory framework and improve trial design. These workshops, which should include overseas representation (eg the US Food and Drug Administration), would likely benefit from the experience of gene therapy clinical trialists who have faced similar issues (eg ultra-orphan indications, unpredictable potency and novel safety risks). Outputs will inform the further development of the MRC/DH Stem Cell Tool Kit to embrace the full spectrum of regenerative medicine.

ESRC Responsive Mode: ESRC is pleased to receive responsive mode or partnered applications in the social sciences addressing issues such as trial facilitation and governance.

Cell supply: The UK Stem Cell Bank, under its current funding cycle, is focusing on generating clinical-grade human ESC lines to supply potential phase 1 clinical studies. The MRC has to date invested £3 million in three derivation centres with the aim of providing 25 such lines to the Bank, and the world’s first xeno-free human ESC lines have now been deposited. The Bank also leads an international initiative aiming to standardise global approaches to clinical-grade human ESC validation and distribution.

4.5 Innovation and Value Systems

Sustainable business models will be required if regenerative medicine products are to have broad impact. To generate the revenues required to reach a sustainable position, a company needs to secure reimbursement for its product, drive adoption and be able to protect its position from competition.

Demonstrating cost effectiveness and gaining positive decisions from Health Technology Assessment (HTA) bodies is a significant challenge for industry. There is a concern that HTA bodies have not begun to address the question of how to evaluate regenerative medicine products and services, which, as they seek to intervene in whole-life process, may not be appropriately assessed by short-term outcome measurements. In addition, as many of the cost savings that these products and services might offer could fall outside the healthcare budget, new methods of assessment may be required to capture these benefits appropriately. The challenge of capturing the benefits of regenerative medicine products may be more straightforward in the UK, given the unique position of the NHS as a sole national healthcare provider, than in countries with more fragmented healthcare delivery models.

Reimbursement alone does not guarantee revenues, the latter being dependent on adoption. If the field is to succeed, it needs to consider both the development of its products and its future customer base. Unless the customer base is attuned to the opportunity offered by regenerative medicine products and organisationally prepared for their introduction, significant delays in building revenues could occur. Assessment of how best to adapt the healthcare system to support adoption could help address questions such as whether it would be better to organise delivery around healthcare specialties with cell-therapy included as one of the treatment options or via a central cell-based therapy centre.

6. See www.sc-toolkit.ac.uk
7. www.ukstemcellbank.org.uk/international_initiatives.aspx
covering multiple healthcare specialities. In addition, it may be worth comparing models of the public delivery of currently available regenerative medicine products, such as blood products and bone marrow transplants compared to commercial delivery models for medical devices and pharmaceuticals.

Having established a market, commercial groups will wish to protect their position. Uncertainty over patenting in the field is regarded by the venture capital community as a further hurdle to investment. The recent decision by the Court of Justice of the European Union regarding the patentability of human ESCs was not seen as a positive development. However, the enormous complexity of stem cell technologies, which makes them inherently more difficult to reproduce than more traditional therapeutic agents, provides an opportunity to use scientific “know how” as a means of staving off competition, even in the absence of underlying patent protection.

Lessons from Gene Therapy

Gene therapy products, like regenerative medicine products, often target super-orphan diseases and have required the development of complex bio-manufacturing processes, in order to deliver effective treatments. A review of developments in this field is perhaps salutary, as it exemplifies the long maturation cycle of new product interventions such as these, which typically take 20 to 30 years to meet their early promise, having to overcome both technical and commercial challenges along the way.

The gene therapy field grew rapidly in 1990s. Many trials were started before vector technology had matured, resulting in most trials yielding very little in terms of efficacy but nonetheless providing useful safety data. From this start, which is nearly 20 years ago, it is now clear that the technology has matured, and is supported by many robust proof of concept studies in animal models.

Over the last few years, clinical benefit has been established in trials covering at least six conditions (one ocular, three blood, one skin and one liver) all of which are rare diseases. One of these products is now close to filling the efficacy requirements for market authorisation. Success has come from academia rather than industry and primarily from those with disease expertise not those with just vector expertise. The prospects for clinical application are now very good. It is perhaps ironic therefore that now that gene therapy is working, there is less commercial interest than ever before. Investors appear reluctant because of past losses, the time it takes to develop a product, and complex cross-licensing issues.

Clinical trial costs are large. It is now very difficult to proceed into clinical gene therapy trials without industry participation. However, success requires close collaboration between academic and industrial partners. Biotechnology firms focusing on gene therapy are struggling (many have disappeared). Companies may rush/be driven prematurely into clinical trials and then fail to raise investment when trials do not meet expectations. Large pharmaceutical firms appear to struggle with the small market size of rare diseases, a complex product with risks that are difficult to quantify, and with manufacture and scalability problems.

Implementation

A potential UK challenge is illustrated by the example of reimbursement for autologous chondrocyte therapy, which has yet to be achieved in the UK but is possible in other European Union (EU) countries and in the US, where some healthcare providers will reimburse. The challenging UK reimbursement environment, which is not restricted to such autologous therapies, may drive regenerative medicine product development outside the UK if this situation continues. One option to consider would be to grant conditional regulatory approval upon the successful attainment of phase II goals, with reimbursement meeting product costs in late stage trials. Such an approach, while outside the sponsors’ remit, could significantly change the position of the UK potentially helping to retain and attract companies here, thereby assisting the development of the UK regenerative medicine field.

In the past two years, TSB, working with ESRC and the Scottish Government, has funded three projects examining value systems and business models associated with different types of regenerative medicine products. These projects are completing their investigations and their generic findings will soon be disseminated to help the UK community make more informed decisions regarding the challenges of bringing products to market.

Delivering products and processes that meet societal needs will require effective contributions from all relevant scientific disciplines and could benefit from additional contributions from the social sciences, including: (i) company innovation strategies and development of support systems for commercialisation of cell therapies; (ii) incorporation of new approaches to regulatory science and the development of “smart” regulatory systems to support affordable innovation strategies; (iii) future mapping/foresight of new scientific developments, and associated business, regulatory and market environments. Social science research could thus support decision making by scientists undertaking basic research, by companies developing the technology, and by policy makers and regulators seeking to optimise the operating environment for businesses in this area. Investigations addressing how best to adapt the healthcare system to support adoption may be beneficial, as might a comparison of related biopharmaceutical and medical technology business, which could stimulate the evolution of models suited to regenerative medicine. The experience of the gene-therapy field, which is perceived to have been held back by a thicket of patents, and the potential impact of the recent European Court of Justice’s ruling on the patentability of products and processes using human ESCs, suggest that studies of open innovation systems and patenting issues may also be timely.

ESRC Responsive Mode: ESRC is pleased to receive responsive mode or partnered applications in the social sciences addressing issues such as the evolution of new
4.6 International

The Taking Stock of Regenerative Medicine in the United Kingdom report found that the UK research base is well placed, with more highly cited research, on average, than the rest of Europe and Asia. North America outperforms the UK in terms of its number of very highly cited articles, which may be expected given the significant investment in the US in this field. Given the global nature of the field, and the associated and increasing investment being made around the world, it will be necessary for the UK to remain alert to international activity if it is to maintain its leading position. Opportunities might also emerge that can be capitalised on to provide the UK research community with access to strong complementary skills and expertise, for example in the emerging area of stem cell systems biology as well as preclinical development where multidisciplinary teams of significant critical mass may be needed.

Implementation

The sponsors remain committed to supporting the full spectrum of regenerative medicine interventions and the underpinning science behind these. This position combined with the UK’s strict but permissive legislative and regulatory framework should continue to attract world-leading scientists, collaborations and inward investment.

To retain its leading position, the UK will need to track, influence and address overseas opportunities and threats. The sponsors will work with overseas partners through established long-term relationships (eg California Institute of Regenerative Medicine (CIRM), the International Stem Cell Forum, National Natural Science Foundation of China®), engage with relevant consortia funded through the EU Framework Programmes (FP7 and Horizon 2020 / FP8), and look to capitalise on emerging opportunities through these routes and new partnerships. For example, the ongoing relationship with CIRM could provide UK access to complementary clinical and regulatory expertise and thereby facilitate access to the world’s largest therapeutics market, while the National Institutes of Health (NIH) is making significant and potentially complementary investments in the IPS field (a new NIH Regenerative Medicine Center was established in 2010). Influencing the remit of EU Horizon 2020, to ensure it appropriately reflects the full breadth of the field, including a focus on the development of preclinical tools and technologies, could help lever UK investments and infrastructure.

The emerging economies, including India and China, are investing heavily in this area as well as exploring governance structures that sometimes differ from the dominant paradigms that have thus far prevailed. How those structures are being redefined and the implications of this will need to be analysed and interpreted.

International Workshop: ESRC will sponsor a workshop on International developments and future global challenges.

Responsive Mode: The RCs will respond to international collaborative opportunities through existing schemes. ESRC is pleased to receive responsive mode or partnered applications in the social sciences addressing issues such as the understanding of international markets and competitiveness relevant to regenerative medicine.

4.7 Focus

The sponsors’ review highlighted the need for the UK effort to achieve greater focus, if it was to achieve impact in the light of increasing global competition, be this in the area of fundamental research, the choice of clinical targets, or approaches to therapy. This requirement, which is born, in part, of necessity, given resource limitations, was regarded as being vital for the attainment of the critical mass required to achieve key goals, such as the establishment of clinical proof of concept.

By providing a common goal, focused programmes of research could be established to help bring the field’s complementary expertise together in a truly collaborative and synergistic effort. The formation of such collaborations would benefit from the availability of practitioners conversant in more than one of the field’s sub-domains. This agenda can be supported by promoting appropriate training programmes to build capacity and provide the skills-base needed for the field to flourish. Stem cell biology is now very much a mainstream topic area, which together with regenerative medicine represents an attractive area for graduates to enter. Currently 7% of the RC research portfolio is directed towards training (see Annex II), and the established studentships and fellowship schemes appear to be meeting current needs. However, this pipeline needs to be kept under review, with a particular emphasis on the promotion of interdisciplinary research. It may be that training programmes for clinical students and research that crosses the field’s many boundaries could be of benefit.

Implementation

The UKRMP, by establishing a national cluster of activity, could provide the basis for focused therapeutic efforts. The sponsors will work, in a second phase of the UKRMP initiative, to identify, in consultation with the community, key disease areas/therapy types meriting concerted investment and will work with other interested funders to develop mechanisms to capture these opportunities. This investment will need to be of a sufficient scale to generate the critical mass necessary to obtain clinical proof of concept, and be aligned with regulatory and end-user needs. This focused investment should, however, be part of a broader portfolio of support that includes support for individual projects.
In terms of capacity building, consideration will be given as to how best to promote interdisciplinary training programmes within research environments such as centres which are able to provide the necessary concentration of expertise to support this agenda.

**UK Regenerative Medicine Platform – Phase II:**
Under a second phase of the managed programme, MRC and EPSRC will seek to further their goals by assembling research clusters to address disease-focused needs where critical mass is required for preclinical development. These activities will integrate and exploit the more generic core of the UKRMP hubs funded through phase I, and will seek to build on existing partnerships with stakeholders such as UK research charities and CIRM.

### 4.8 Interdisciplinary Collaboration

As identified in the previous section, this field, perhaps more than most, requires the bringing together of strong complementary skills, expertise and infrastructure across disciplines in order to achieve its goals. Interdisciplinary working and approaches for its support were seen as critical by the community. Although desired, there exist community-based hurdles to its formation, including the challenge of establishing a common language between disciplines and defining shared and valued goals. Unless individuals within the field perceive that working in collaboration will better enable them to meet their own goals, the promotion of interdisciplinary research is unlikely to succeed.

Developing shared goals requires individual-to-individual contact and communication. The sponsors’ review has highlighted the need for a unifying but needs-driven network to provide a platform for such interaction. Such a network should be inclusive and garner the respect of all potential members, and have the capacity to reach out to conjoint disciplines.

**Implementation**

The sponsors agree that a regenerative medicine network, able to provide a platform for the initiation of interdisciplinary collaborations and for the sharing of knowledge and experience, is critical. Such a network will need to span the academic research base – fundamental, developmental and clinical – and the commercial – regulatory, business development, finance. The sponsors are firmly of the view that the network must be responsive to the community that it serves, and consider that a key challenge will be how such an activity engages and retains the commitment of the clinical community.

**Network:** The RCs and TSB will together develop appropriate mechanisms to achieve a needs-focused networking activity, leveraging current and future capacity investments.
Hyaline cartilage
The implementation mechanisms described above provide, within the sponsors’ areas of responsibility, a comprehensive response to the UK’s regenerative medicine research and development needs and opportunities (figure below). The described mechanisms will not however be the sole response to the identified challenges. The objectives laid out above provide a framework for the development of future initiatives, which will need to account for emergent scientific and clinical opportunities in this fast moving domain.

It is hoped that within five years, the sponsors’ initiatives will provide the following benefits to UK science, patients and economy:

- An advancement in the basic understanding of the biological, engineering and socioeconomic drivers of regenerative medicine
- A platform for coordinated translational activity, moving underpinning science towards application
- A growing therapeutic pipeline and evidence base of clinical efficacy and potential patient benefit
- A smooth iterative path from academia to a growing industrial base

To assist the sponsors to monitor progress towards these goals and to make recommendations on potential new initiatives, the sponsors will establish an overview group, drawn from both the scientific and commercial bases.
6. Concluding Remarks

This joint strategy takes account of the current state-of-play of the science relating to regenerative medicine, and the emerging opportunities as well as barriers to progress. The strategic objectives and delivery mechanisms described aim to provide a coherent framework for UK research activity in this area over the next five years, aligning the respective interests of the sponsor group to ensure that current UK strength is appropriately built upon to ensure that the UK retains a leadership position in regenerative medicine worldwide. A mixture of top-down and bottom-up approaches are envisaged that together will seek to provide the critical mass of activity required to address the challenges of this dynamic and multidisciplinary scientific field. Taken together, it is hoped that these initiatives will help deliver the great promise of regenerative medicine to the benefit of both patients and the UK economy.
Brain astrocytes
# Annex I

## 2011 Forward Look Workshop Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Dr Tim Allsopp</td>
<td>Pfizer</td>
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<td>Professor Peter Andrews</td>
<td>University of Sheffield</td>
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<td>Professor Martin Birchall</td>
<td>University College London</td>
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<td>Dr Drew Burdon</td>
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<td>Dr Nigel Burns</td>
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<td>Professor Steve Dunnett</td>
<td>Cardiff University</td>
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<td>Dr Raj Chopra</td>
<td>AstraZeneca</td>
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<td>Professor Pete Coffey</td>
<td>University College London</td>
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<td>Professor Tariq Enver</td>
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<td>Professor Paul Fairchild</td>
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<td>Professor Neil Hanley</td>
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<td>Professor Anthony Hollander</td>
<td>University of Bristol</td>
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<tr>
<td>Mr Michael Hunt</td>
<td>ReNeuron</td>
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<td>Dr Paul Kemp</td>
<td>Intercytex</td>
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<td>Dr Alastair MacKinnon</td>
<td>Phase4 Ventures</td>
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<td>Professor Chris Mason</td>
<td>University College London</td>
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<td>Professor Roger Pedersen</td>
<td>University of Cambridge</td>
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<td>Dr Ian Rees</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>Professor Michael Schneider</td>
<td>Imperial College London</td>
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<td>Professor Kevin Shakesheff</td>
<td>University of Nottingham</td>
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<td>Dr Glyn Stacey</td>
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<td>Professor Joyce Tait</td>
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<td>Professor Fiona Watt</td>
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<td>Professor Andrew Webster</td>
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<td>Professor Paul Whiting</td>
<td>Pfizer</td>
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<tr>
<td>Professor David Williams</td>
<td>University of Loughborough</td>
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Annex II
2010 Regenerative Medicine Portfolio

Background

On behalf of the sponsors (BBSRC, EPSRC, ESRC, MRC and TSB), MRC has compiled a detailed analysis of the sponsors’ regenerative medicine funding portfolio.

The sponsors and NIHR research funding programmes supplied the MRC with data for regenerative medicine awards from each of their portfolios that were live on 19 November 2010. The MRC then coded the projects by the following criteria:

- Type of award – Research, Resource and Training
- Application area – Therapy, Platform and Socioeconomic
- Application type – Acellular, Cell-based (ESC, Adult Stem/Progenitor Cell, iPSC, Cell type not specified), Endogenous repair
- Platform type – Disease/Safety Modelling, Imaging, Biomarkers, Cell Control and Differentiation, Cell Culture (Small Scale), Bioprocess (Large Scale), Cell Sorting, Formulation, Transportation, Delivery, Manufacturing QC/Metrology
- UKCRC Health Category (Source: www.hrcsonline.net)
- Technology Readiness Level (Source: US Department of Defense, Technology Readiness Assessment Guidance April 2011 and Deskbook July 2009)
- Geographical Location of Award

What the analysis shows:

- A total of 353 grants were included in the analysis
- The total annualised sponsor spend on regenerative medicine was £72.6 million for grants that were live on 19 November 2010.
- 89% (£64.9m) of funding goes on research grants, 7% (£5.3m) on training and 3% (£2.4m) on resources. However, as these figures do not include RC studentships because grant details were not available, the training proportion is likely underrepresented.
- The majority of funding 78% (£56.8m) may inform therapeutic development or be actual therapy developments, 19% (£13.5m) is directed towards platform development and 3% (£2.3m) contributes to socioeconomic understanding. It is worth noting that underpinning therapeutic studies may also have platform applications.
- 85% (£62.1m) of funding goes on call-based approaches, 8% (£5.1m) on acellular approaches and 6% (£4.7m) on endogenous repair strategies.
- Awards cover a variety of categories of health relevance. The largest fraction (36%, £26.3m) is for generic health relevance. Musculoskeletal and neurological research receives the second (14%, £10.3m) and third (12%, £8.9m) largest amounts of funding respectively.
- More than half of the funding (59%, £43.9m) was spent on underpinning research (TRLs 1 and 2).
- The region with the largest spend is Greater London (30%, £21.9m), followed by the East of England (15%, £10.9m).

2010 Regenerative Medicine Portfolio Analysis

1. Total Spend by Funding Organisation
2. Breakdown of Spend by Award Type
3. Breakdown of Spend by Application Area
4. Breakdown of Spend by Application Type
5. Breakdown of Spend by Platform Type
6. Breakdown of Spend by UKCRC Health Category
7. Breakdown of Spend by Stage
8. Breakdown of Therapy Spend by UKCRC Health Category and Stage
9. Geographical Distribution of Spend
10. Technology Readiness Level Definitions

1. Total Spend by Funding Organisation

The 2010 Regenerative Medicine Portfolio includes 353 awards with a total annualised spend of £72.6m. The split per sponsor was as follows:

<table>
<thead>
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<th>Funding Organisation</th>
<th>Number</th>
<th>Value (£m)</th>
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<tr>
<td>BBSRC</td>
<td>97</td>
<td>12.8</td>
</tr>
<tr>
<td>EPSRC</td>
<td>58</td>
<td>11.3</td>
</tr>
<tr>
<td>ESRC</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>MRC</td>
<td>137</td>
<td>37.7</td>
</tr>
<tr>
<td>NIHR</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>TSB</td>
<td>46</td>
<td>8.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>353</td>
<td>72.6</td>
</tr>
</tbody>
</table>

Value is the annualised award value = total award/duration of award in years
2. Breakdown of Spend by Award Type

Awards were categorised for the type of funding. These figures do not include RC studentships, as grant details were not available.

3. Breakdown of Spend by Application Area

Each award was categorised by whether it falls within a Therapy, Platform or Socioeconomic application area. Therapy awards cover underpinning investigations that may inform therapy developments (examples include stem cell biology, studies of endogenous repair mechanisms) and the development of specific therapies. Platform awards support the development of therapies but are not embodied within the end therapy (examples include the development of a safety/efficacy model or a new manufacturing process). Socioeconomic awards include, for instance, studies on the patient acceptance of regenerative medicine therapies and cost effectiveness. It is worth noting that underpinning therapeutic studies may also have platform applications.

4. Breakdown of Spend by Application Type

Awards were classified by the type of intervention based on potential outputs. For example, studies developing biomaterials for use without cellular components were classified as application type acellular, studies investigating the differentiation of ESCs were classified as application type ESC, studies developing cell isolation techniques for adult stem cells were classified as application type adult stem cell, and studies investigating wound repair were classified as application type endogenous repair.
5. Breakdown of Spend by Platform Type

All Platform Awards were further classified by the type of platform they were seeking to develop.

6. Breakdown of Spend by UKCRC Health Category

All awards were coded for disease relevance using UKCRC Health Categories.
7. Breakdown of Spend by Stage

The developmental stage of each award has also been classified using the Technology Readiness Level (TRL) system, which at the lower end (TRL1) covers hypothesis-driven exploratory research and moves towards application as the stage numbers increase.

This shows that the majority of sponsors’ funding is focused on the earliest TRLs, supporting investigations probing the field’s underpinning science, with levels reducing as projects move further down their developmental path.

Spend by stage can be broken down further by examining the distribution of spend for the therapy and platform application types.

Given the field’s overall stage of development and sponsor focus, the distribution by stage is perhaps not surprising. However, there may be a need to provide continued support into the clinic, given a paucity of commercial funding in this field.

Platform TRL1 and TRL2 investments may be underrepresented due to the challenge of identifying awards at this phase, as these may not yet be linked to an application in regenerative medicine.
8. Breakdown of Therapy Spend by UKCRC Health Category and Stage

The coding of the portfolio enables additional analysis to be undertaken including an investigation of spending on therapy awards by UKCRC Health Category and Stage. The prominence of musculoskeletal awards and their relative higher proportion of late stage projects reflect the fact that this area has been an early and significant focus of regenerative medicine activity. The significant preclinical development in Eye likely reflects the emergent understanding of the tractability of this application area.

Therapy Spend by UKCRC Health Category and Stage

The prominence of musculoskeletal awards and their relative higher proportion of late stage projects reflect the fact that this area has been an early and significant focus of regenerative medicine activity. The significant preclinical development in Eye likely reflects the emergent understanding of the tractability of this application area.
9. Geographical Distribution of Spend

The regional location of the lead organisation on each award has been classified to examine the geographical distribution of spend. Percentage of total spend by region is shown below.

![Geographical Distribution of Spend Map]

- Scotland: 11%
- Northern Ireland: 0%
- North: 1%
- North East: 1%
- North West: 5%
- Northern: 2%
- Yorkshire and The Humber: 9%
- East Midlands: 2%
- East: 15%
- London: 30%
- South East: 12%
- South East: 2%
- South: 12%
- South West: 2%
- West: 3%
- West Midlands: 2%
- Wales: 2%
- East: 3%
- Midland: 9%
- South West: 2%
<table>
<thead>
<tr>
<th>TRL</th>
<th>Definition</th>
<th>Generic Product Description</th>
<th>Therapeutic Product Description</th>
<th>Therapeutic Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basic principles observed and reported.</td>
<td>Lowest level of technology readiness. Examples might include paper studies of a technology's basic properties.</td>
<td>Maintenance of scientific awareness and generation of scientific and bioengineering knowledge base.</td>
<td>Underpinning</td>
</tr>
<tr>
<td>2</td>
<td>Technology concept and/or application formulated.</td>
<td>Invention begins. Applications are speculative, and there may be no proof or detailed analysis to support the assumptions.</td>
<td>Intense intellectual focus on the problem, with generation of scientific 'paper studies' that review and generate research ideas, hypotheses and experimental designs.</td>
<td>Early Preclinical</td>
</tr>
<tr>
<td>3</td>
<td>Analytical and experimental critical function and/or characteristic proof of concept.</td>
<td>Active R&amp;D is initiated. This includes analytical studies and laboratory studies to physically validate the analytical predictions of separate elements of the technology.</td>
<td>Basic research, data collection and analysis begin in order to test the hypothesis, explore alternative concepts, and identify and evaluate technologies supporting drug development. Initial synthesis of candidate(s), identification of their sites and mechanisms of action and characterisation in preclinical studies.</td>
<td>Late Preclinical</td>
</tr>
<tr>
<td>4</td>
<td>Component and/or breadboard validation in a laboratory environment.</td>
<td>Basic technological components are integrated to establish that they will work together. Examples include integration of ad hoc hardware in the laboratory.</td>
<td>Non-Good Laboratory Practice (GLP) laboratory research to refine hypothesis and identify relevant parametric data. Exploratory study of candidate drugs (eg formulation, route(s) of administration). Candidate drugs are evaluated in animal model(s).</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>5</td>
<td>Component and/or breadboard validation in a relevant environment.</td>
<td>Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so they can be tested in a simulated environment.</td>
<td>Research with pilot lots provide basis for a manufacturing process amenable to current Good Manufacturing Practice (cGMP) compliant pilot lot production. Conduct GLP safety and toxicity studies in animal model systems. Stability studies initiated.</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>6</td>
<td>System/subsystem model or prototype demonstration in a relevant environment.</td>
<td>Representative model or prototype system, which is well beyond that of TRL 5, is tested in a relevant environment. Represents a major step up in a technology's demonstrated readiness.</td>
<td>Phase I clinical trials are conducted to demonstrate safety of candidate in a small number of humans under carefully controlled and intensely monitored clinical conditions.</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>7</td>
<td>System prototype demonstration in an operational environment.</td>
<td>Prototype near or at planned operational system. Represents a major step up from TRL 6 by requiring demonstration of an actual system prototype in an operational environment.</td>
<td>Phase II clinical trials are conducted to demonstrate initial efficacy and capture further safety and toxicity data.</td>
<td>Phase III</td>
</tr>
<tr>
<td>8</td>
<td>Actual system completed and qualified through test and demonstration.</td>
<td>Technology has been proven to work in its final form and under expected conditions. In almost all cases, this TRL represents the end of true system development.</td>
<td>Implementation of expanded phase III clinical trials or surrogate tests to gather information relative to the safety and effectiveness of the candidate drug. Process validation is completed and followed by lot consistency/reproducibility studies.</td>
<td>User Adoption</td>
</tr>
<tr>
<td>9</td>
<td>Actual system proven through successful mission operations.</td>
<td>Actual application of the technology in its final form and under mission conditions, such as those encountered in operational test and evaluation.</td>
<td>The pharmaceutical (ie drug) or medical device can be distributed/marketed. Post-marketing studies (non-clinical or clinical) may be required.</td>
<td>User Adoption</td>
</tr>
</tbody>
</table>