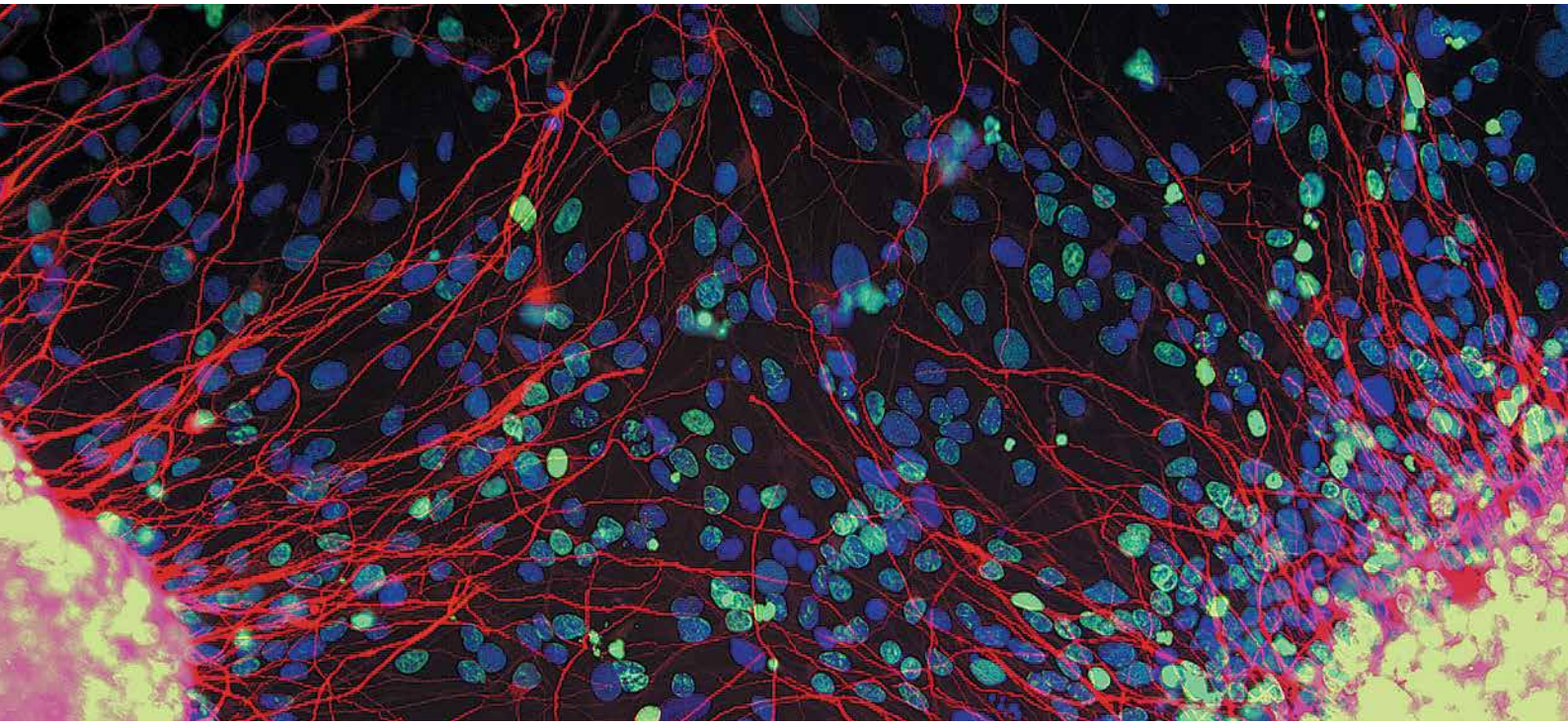
UK Regenerative Medicine Platform



FIRST ANNUAL REPORT

2014

BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

Contents

1. Foreword

Regenerative medicine promises to revolutionise healthcare over the coming decades, through providing a spectrum of approaches to repair, restore or replace damaged or diseased tissues and organs. It offers the hope of being able to cure previously untreatable injuries and diseases, and of addressing the medical needs of an ageing population. In addition, the underlying science and technological developments are likely to offer non-clinical application, for example by providing artificial tissue to aid drug development and toxicity testing, or as biosensors to detect environmental threats.

However, as with any emerging sector, there are steep technological and strategic barriers that must be overcome before this potential can be realised. Advances will be needed to improve our understanding of how the body's regenerative processes can be controlled, manipulated and targeted, while new engineering strategies will be needed to harness this emerging science and support the commercial activity required to bring these new therapies to patients.

Success in this area will be dependent upon nurturing a truly interdisciplinary approach, and we are fortunate in the UK in having a vibrant and world-leading research base, a collaborative ethos, and a well organised translational and clinical environment that will enable us to drive forward the development of regenerative medicine to the benefit of both patients and the UK economy. It is in this context that the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council (MRC) are very pleased to have joined forces in funding the £25M UK Regenerative Medicine Platform (UKRMP) which will help realise these goals and ambitions.

Professor Jackie Hunter

Chief Executive, BBSRC

Professor Philip Nelson

Chief Executive, EPSRC

Professor Sir John Savill

Chief Executive, MRC

BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

2. Introduction

The UK Regenerative Medicine Platform (UKRMP) has been established to address the technical and scientific challenges associated with translating promising scientific discoveries in regenerative medicine towards clinical impact. It is funded as a single joint programme, through the BBSRC, EPSRC and MRC. Collectively the three Councils are investing £25M over four years (2013-17) to support this activity.

Regenerative medicine is a fast-moving interdisciplinary area of science that seeks to repair, replace and/or regenerate damaged cells, tissues and organs. It encompasses a multidisciplinary approach including discovery, translational and clinical science, and requires the interplay of developmental and stem cell biology, chemical biology, tissue engineering, nanotechnology, biomaterial development, bioprocessing and manufacturing, transplantation science and gene and cellular therapeutics.

While rapid scientific progress is being made on a number of fronts, it is apparent that a number of significant developmental challenges need to be overcome in order to successfully translate promising discoveries into the clinical setting, and for regenerative medicine to deliver its anticipated benefits for patients and the UK economy. These challenges include ensuring the timely translation of science, accompanied by the necessary knowledge to validate and refine experimental approaches, and having the necessary infrastructure in place to support promising scientific developments. These issues are elaborated upon in the Research Council/TSB Strategy for UK Regenerative Medicine[1], published in 2012.

The aim of the UKRMP is to ensure that research addressing regenerative medicine connects seamlessly from discovery science through to clinical and commercial application. The Platform provides a cornerstone to support the overall strategy and has been progressed through two stages.

£20M has been invested under Stage I to establish five interdisciplinary and cross-institutional research Hubs, with the first becoming functional in autumn 2013. Each Hub has the critical mass and expertise to address key knowledge gaps in the translation of stem cell and regenerative biology towards clinical application. Together they will provide the new tools, platform technologies, engineering solutions and knowledge-base needed to promote therapeutic development.

Each Hub focuses on a distinct but interlinked core theme:

- **Cell behaviour, differentiation and manufacturing**
- **Engineering and exploiting the stem cell niche**
- **Safety and efficacy, focussing on imaging technologies**
- **Acellular approaches for therapeutic delivery**
- **Immunomodulation**

These are described more fully in the next section.

1 www.mrc.ac.uk/documents/pdf/a-strategy-for-uk-regenerative-medicine/

Stage II of the Platform aims to provide a more disease or systems-based approach, through which focused projects can be pursued that link to or exploit aspects of the science being progressed through the Hubs. The Research Council sponsors provided £5M in support of this, which has led to the recent award of five cutting-edge research consortia in areas ripe for clinical intervention. Three of these are being progressed in partnership with Arthritis Research UK and Reumafonds, an allied Dutch funding agency, who between them provided an additional £2.1M of funding to this part of the UKRMP programme.

The five Stage II research projects address:

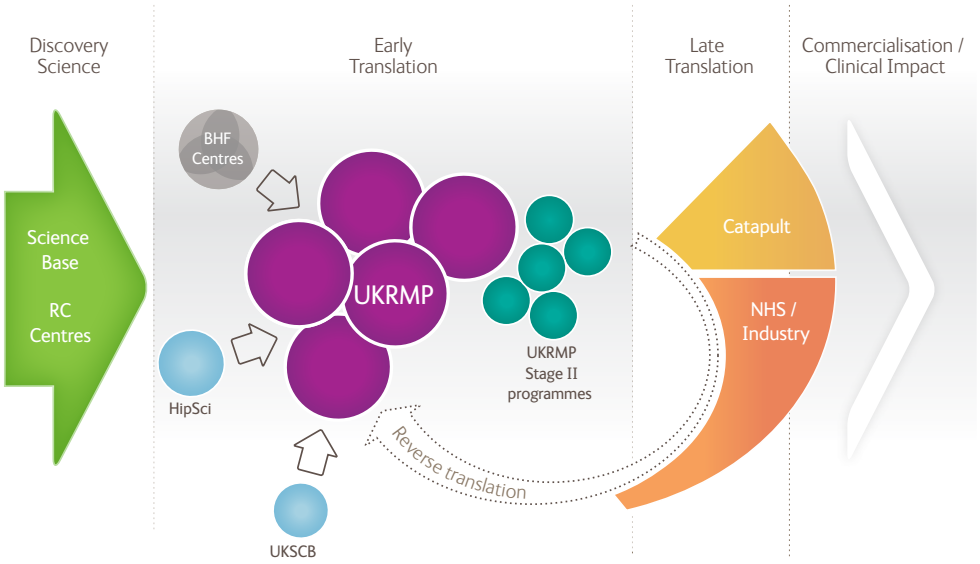
- Repair of cartilage defects using tissue-specific adult stem cells
- Cell replacement in dry age-related macular degeneration, using an autologous iPSC-based approach
- 3-dimensional liver organoids for the treatment of human liver disease
- A smart material cell therapy programme focused on osteoarthritis
- Increasing regeneration and healing capacity in non-union bone defects.

These awards are described more fully in Section 4. Each project has linkages to one or more Hubs, providing the research teams with access to a broad range of technological support, expertise and advice to advance their goals.

Taken together, the UKRMP provides a broad-based but goal oriented programme that connects and integrates expertise and capability across a number of key disciplines. The Platform is proactively managed through an independent Programme Board which has overall responsibility for guiding the initiative and monitoring delivery of the component Hubs (see Annex 1).

Importantly, the UKRMP is outward facing and is building links to other key national investments and infrastructures, for example the Cell Therapy Catapult, the UK Stem Cell Bank (UKSCB), the Wellcome Trust/MRC Human IPSC Initiative (HipSci) and the British Heart Foundation's (BHF) cardiovascular regenerative medicine centres. A further goal of the Platform is to promote 'reverse translation' through such a network. This is the process by which appropriately designed clinical studies can provide data and samples for lab-based research that will help increase our understanding of the body's regenerative processes, thereby allowing the refinement and improvement of therapeutic approaches and products in an iterative manner.

The UKRMP therefore provides the core of a world-leading and fully connected national programme that is seeking to pull through excellent discovery science to support the commercial development and clinical delivery of regenerative medicine products.



3. Stage I – Hub Awards

3.1 Cell behaviour, differentiation and manufacturing Hub

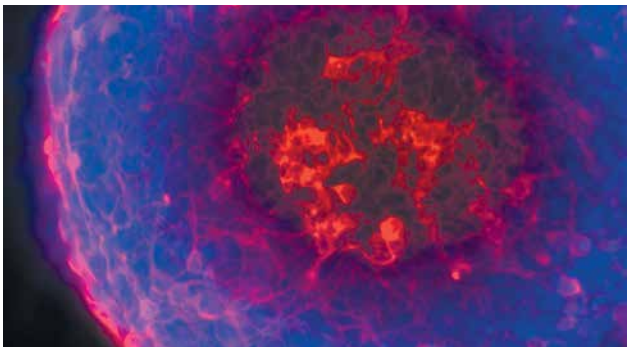
(Pluripotent Stem Cell Platform – PSCP)
Director: Professor Peter Andrews, University of Sheffield

Who:

- **University of Sheffield**
  Peter Andrews, Harry Moore and Marcelo Rivolta
- **Wellcome Trust/MRC Stem Cell Institute, University of Cambridge**
  Austin Smith, Roger Barker, Robin Franklin and Ludovic Vallier (Phil Driver – Project Manager)
- **EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, Loughborough University**
  David Williams, Nicholas Medcalf and Rob Thomas
- **UK Stem Cell Bank, NIBSC**
  Glyn Stacey
- **Wellcome Trust Sanger Institute**
  Mike Stratton and Kosuke Yusa
- **Babraham Institute**
  Wolf Reik

Why:

The cell behaviour, differentiation and manufacturing Hub, known as the Pluripotent Stem Cell Platform (PSCP), is building upon emerging pluripotent stem cell (PSC) technologies to establish optimised processes for consistent and scalable cell manufacturing, which meet the requirements of clinicians, regulatory authorities and industry, for cell therapy applications in regenerative medicine.



Neurospheres derived from iPSCs

What:

The PSCP is a translational alliance, combining experts in PSC biology, genetic analysis and clinical cell therapy with leaders in cell manufacturing, safety and regulatory science. We are addressing critical translational bottlenecks by focusing on four key objectives, to:

- Establish protocols for transgene-free, EUTCD-compliant production, expansion and safety qualification of PSC (both embryonic and induced)
- Develop methods to minimise the occurrence of functionally significant genetic or epigenetic variants during PSC manufacturing
- Standardise PSC differentiation protocols for deriving, manufacturing and banking therapeutically relevant lineage-specific intermediate stem or progenitor cells
- Provide qualified processes for manufacturing regulatory compliant PSC products suitable for clinical use.

The outputs from the PSCP will have broad applicability. However, our research will focus initially on a few therapeutic areas where proof of concept has been established to indicate clinical potential - the production of dopaminergic and optic neurons aimed at treatments for Parkinson's Disease and neuropathic deafness, the production of pancreatic and hepatic cells for addressing diabetes and liver failure, and the production of blood products for transfusion.

Bioreactor system to assess cell metabolites

"Pluripotent stem cells offer huge opportunity for regenerative medicine, but one of the challenges is to generate sufficient quantities of cells that you can put into patients which are both safe and are going to work. Our Hub will provide core information on cells' behaviour and safety in order to inform both the manufacture of suitable cells and regulations governing their large-scale use in the clinic." – *Peter Andrews*

How:

Our strategy relies on interdisciplinary operation, and requires close interaction and integration between each of the research centres and external partners within three clear themes:

- **Cell characterisation and stability** provides a platform to operate within the necessary regulatory directives and guidelines, enabling derivation and validation of iPSC lines, developing quality acceptance criteria and protocols for the scale-up of PSCs, and to enable standardisation and transition to automated platforms. Tools for monitoring genetic and epigenetic changes in PSC (both hESC and iPSC), methods to minimise deleterious variants and an assessment of potential risks posed by these variants for regenerative medicine will be provided. These factors will inform the development of quality indicators (viability, genetic integrity and pluripotency) to allow for the scaled production of defined differentiated phenotypes.

Clean-room for automated cell-culture

- **Understanding routes to differentiation** will provide protocols for the expansion of PSC-derived neural and endodermal progenitors with stable potential for onward differentiation. It will also address the integration of biology with process engineering and manufacture, including manufacturing and supply requirements, identification of preferred production system and technology configurations with associated risk assessments and mitigation strategies.
- **Quality control, safety and reproducibility** will optimise the detection of adventitious agents that may compromise the safety of PSC-derived clinical materials and provide appropriate reference standards. In addition, this theme will determine the barriers to operational GMP for our chosen clinical exemplars by establishing a measurement system capable of comparability at three sites and a scalable manufacturing process. Ultimately, this could herald wide-ranging benefit across cell therapies and would place the UK ahead of the curve in terms of forward thinking on ATMP safety.

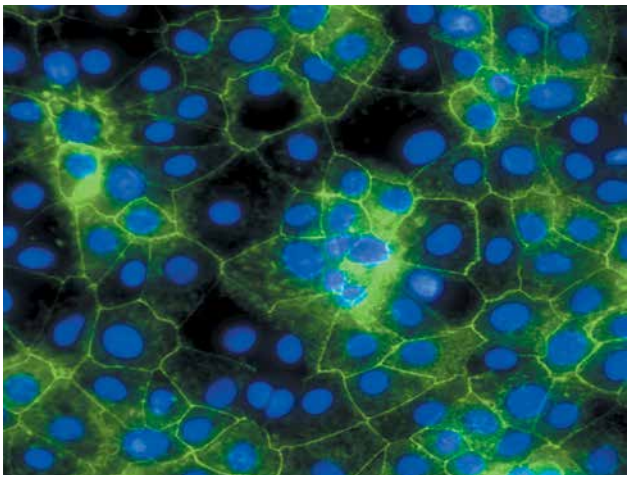
Through the PSCP we will organise workshops on 'regulatory science' that aim to develop a consensus on 'principles of best practice' for manufacturing, risk assessment and safety testing pertaining to candidate cell therapies. We will adopt an open innovation model for pre-competitive research with bio-industry, with the intent of engagement. In addition, we will seek to engage new partners where these offer future opportunities for complementary work that builds on that of the existing partners.

3.2 Engineering and exploiting the stem cell niche Hub

Director: Professor Stuart Forbes, University of Edinburgh

Who:

- **MRC Centre for Regenerative Medicine, University of Edinburgh**
  Stuart J Forbes, Mark Bradley, Charles ffrench-Constant, David Hay, Bruno Peault and Anna Williams (Peter Freeman – Project Manager)
- **University of Liverpool**
  Anthony Hollander
- **Wellcome Trust/MRC Stem Cell Institute, University of Cambridge**
  Robin Franklin, Ludovic Vallier
- **Imperial College London**
  Molly Stevens
- **Keele University**
  Alicia El Haj
- **King's College London**
  Anil Dhawan, Fiona Watt
- **University of Manchester**
  Cay Kielty, Sue Kimber
- **University of Strathclyde**
  Nick Tomkinson



Layer of liver cells

Why:

Over the last decade there have been rapid advances in stem cell biology and the understanding of the cellular and molecular controls of tissue damage and repair. However, few regenerative therapies have yet to emerge from this knowledge. To develop a stem cell based regenerative cell therapy it is necessary to understand how a stem cell or its derivative would behave over time in a damaged tissue. An alternative approach is to promote endogenous tissue repair, by targeting the stem cells and their niches in damaged tissues with small molecules or biological agents.

What:

To achieve this safely will require an understanding of the correct signals to stimulate tissue repair, but also the real-time analysis of the regenerating tissue. Through a greater understanding of the stem cell niche our collaborative network aims to target tissue repair by targeting the stem cell niche directly in damaged tissues ("the soil") and improving the function of transplanted cells within damaged tissues ("the seeds"). Likewise, to produce better stem cells and derivatives for transplantation or drug testing we aim to use knowledge of stem cell niche biology to produce high quality stem cells in the laboratory.

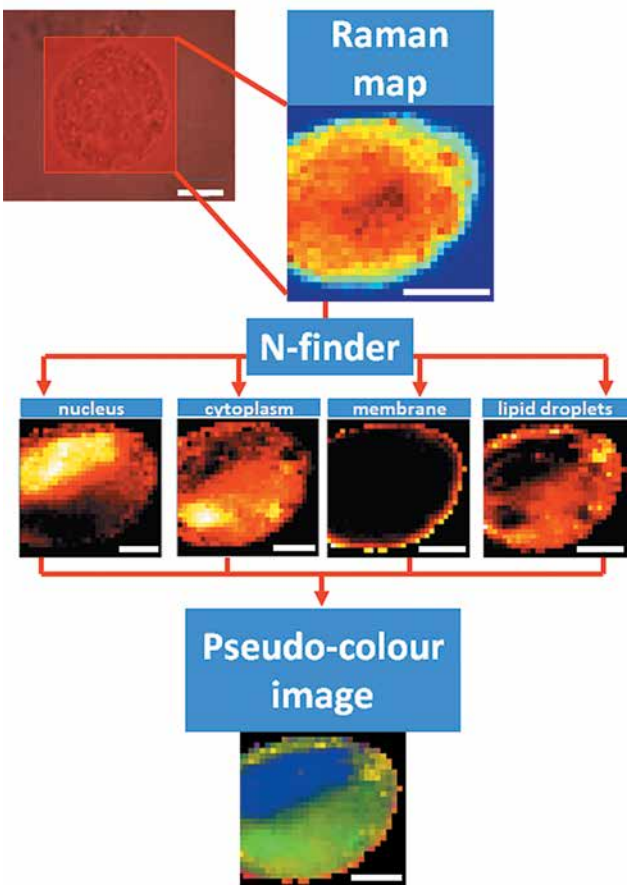
"Stem cells are only useful to patients if they can survive in, and regenerate, damaged tissue. This means that in order to provide a clinical benefit to patients, we need to improve our understanding of how stem cells interact with their host environment. Our Hub is exploring this `stem cell niche' by bringing together scientists and clinicians with a wide range of expertise." – Stuart Forbes

How:

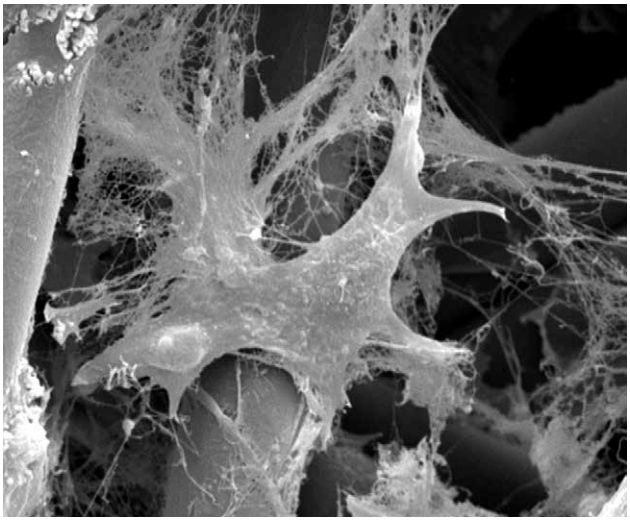
We have brought together scientists and clinicians with experience in stem cell niche biology, tissue repair and stem cell matrix biology. Their expertise spans neuronal, liver, skin and mesenchymal repair. Collaborative programmes of research are underway that cross both disciplinary and organ boundaries. *In vitro* approaches include high content screening platforms to analyse the effect of various niche signals upon stem cell behaviour in a non-biased manner. We will reconstruct the normal niche microenvironment to enable expansion and accurate differentiation of stem cells, and optimize small molecule and drug development strategies using adult, mesenchymal and pluripotent cells.

Pre-clinical *in vivo* approaches are underway that are seeking to enhance the function of both transplanted and endogenous stem cells within damaged tissues. The niche signals that control proliferation and differentiation of endogenous cells will be directly targeted using biological agents, drugs/small molecules or synthetic materials to promote healthy regeneration. For example, in the liver repair program human hepatocytes derived from stem cells of various sources are being studied both in artificial niches to stabilise their *in vitro* function and then following transplantation. The translational direction of the Hub is exemplified by the neural repair program where the signals that control remyelination are being analysed in a non-biased manner, through *in vitro* studies and then in pre-clinical *in vivo* models of remyelination. We are utilising real-time imaging of stem cell niches and regenerating tissue through the use of Raman Spectroscopy and other approaches. Wherever possible, human stem cell systems are being utilised with direct translational potential, including GMP compatible human stem cells.

The niche Hub is highly collaborative; internally, with other Hubs and with external research partners, all of which reinforce the translational drive of the Hub and Platform as a whole.



Raman imaging analysis of human embryonic stem cell



Artificial liver engineering using stem cell-derived hepatocytes

3.3 Safety and efficacy, focussing on imaging technologies Hub

Director: Professor Kevin Park, University of Liverpool

Who:

- **University of Liverpool**
  Kevin Park, Dan Antoine, Chris Goldring, Neil Kitteringham and Dean Naisbitt **(MRC Centre for Drug Safety Science)**; and Dave Adams, Mathias Brust, Marta Garcia-Finana, Raphael Levy, Patricia Murray, Lorenzo Ressel, Matt Rosseinsky and Bettina Wilm (Claire Hutchinson – Project Manager)
- **University of Manchester**
  Marie-Claude Asselin, Sue Kimber, Rachel Lennon, Stephen Williams and Adrian Woolf
- **University College London**
  Mark Lythgoe, Paul Beard and Martin Pule
- **MRC Centre for Regenerative Medicine, University of Edinburgh**
  Stuart Forbes and David Hay

Why:

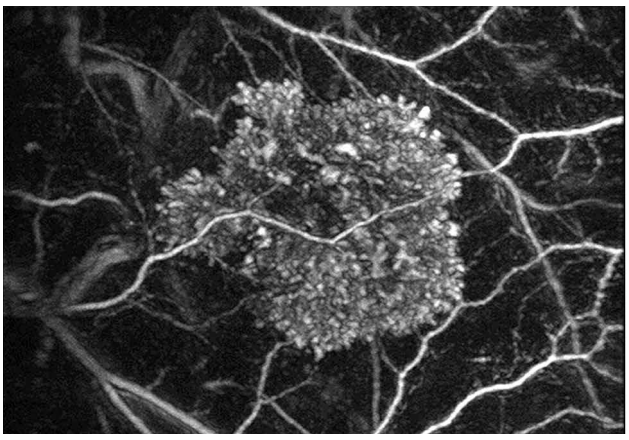
Our focus is to provide a clearer understanding of the potential hazards (and associated risks) of Regenerative Medicine Therapies (RMTs), so that scientific stakeholders are able to accelerate these new medicines into the human population with full confidence.

What:

The major challenge is to expedite clinical translation by developing technologies that enable the distribution and behaviour of transplanted cells to be monitored in relevant pre-clinical models to evaluate the safety and efficacy of RMTs. To address this, we are developing novel imaging probes, state-of-the-art multimodal imaging platforms, and cutting-edge quantitative bioanalysis technologies to identify the tissues that cells populate, in order that such tissues can be subjected to thorough efficacy and safety assessment in animal models.

How:

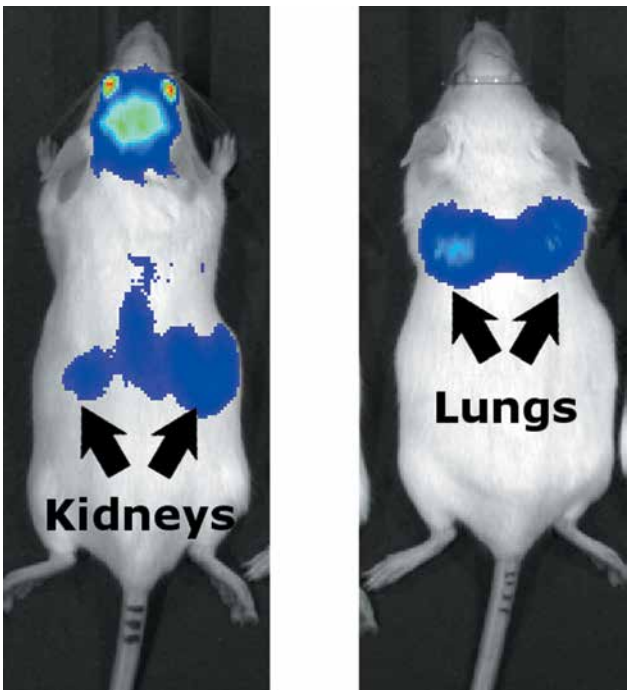
Certain types of labels that show promise in tracking RMTs are nanoparticles which act as contrast agents for different imaging techniques. A number of these nanoparticles have been approved for clinical use. However, they do not currently display the necessary characteristics for the sensitivity that is required to track transplanted cells. We are combining the use of these direct labelling strategies with genetic reporters, providing a powerful tool for whole body cell tracking using multimodal imaging. Liverpool, with MRC support, is establishing a Centre for Pre-clinical Imaging to facilitate multimodal imaging, housing photoacoustic, bioluminescence, fluorescence, and magnetic resonance imaging equipment. With complementary imaging facilities at Manchester and UCL this will allow the development of joint molecular imaging strategies that permit transplanted cells to be monitored in a single animal over time, with a range of imaging modalities.



Photoacoustic image of transfected cells

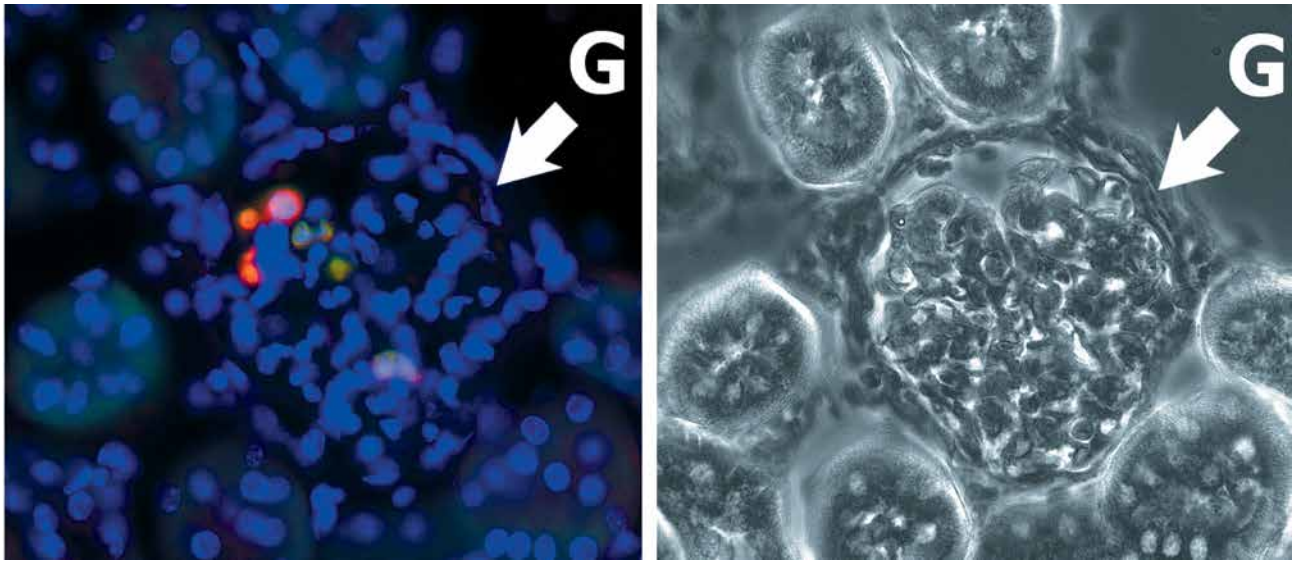
"In order to take forward regenerative medicine therapies into the clinic, we need to understand the potential hazards and risks associated with them. To address this we are using cutting-edge imaging techniques, tracking agents and clinical methodologies to monitor the movement and behaviour of stem cells transplanted into the body." – Kevin Park

The Safety Hub brings together world-leading nanoparticle chemistry expertise, stem cell biology, and cutting-edge imaging from four UK universities. To monitor the bio-distribution and behaviour of administered stem cells we are using well-characterised kidney and liver disease models to relate the disposition of these cells to the physiological, pharmacological and pathological responses of the host tissues that the cells populate. A suite of organ-selective, translational, mechanism-based biomarkers of toxicity for liver and kidney, available through the MRC Centre for Drug Safety Science, allows a seamless link between pre-clinical studies and subsequent clinical application of RMTs. Liver disease is a target for macrophage-based RMT, where injury is ameliorated by stimulating endogenous repair. This therapy, pioneered at Edinburgh, is likely to progress to a first-in-man study; non-invasive MRI cell-tracking methodology developed by our Hub will facilitate this considerably.



IVIS Spectrum image of mice injected with kidney stem cells

The technologies and methodologies we are developing in the kidney and liver models will be broadly applicable to quantitative assessments of the efficacy and safety of RMTs across a wide range of tissues and organs. The Safety Hub will, for the first time, provide a clear framework for the most appropriate label and imaging technology to use for robust safety assessment of RMTs. The benefits will be felt by those involved in the development of novel RMTs, ultimately leading to the acceleration of these therapies into a clinical setting.



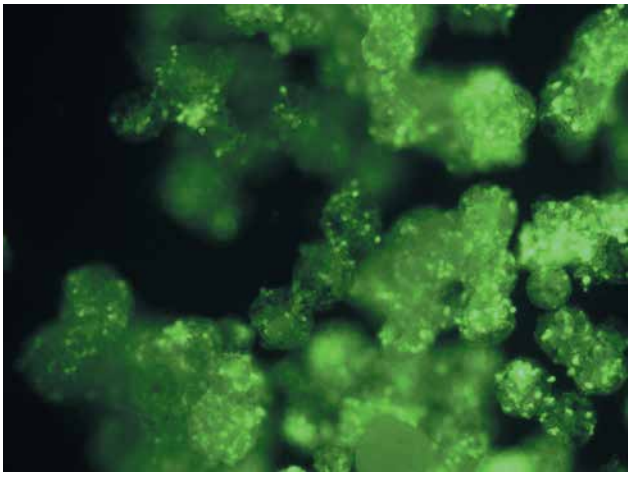
Histological validation of stem cells in renal glomeruli

3.4 Acellular approaches for therapeutic delivery Hub

Director: Professor Kevin Shakesheff, University of Nottingham

Who:

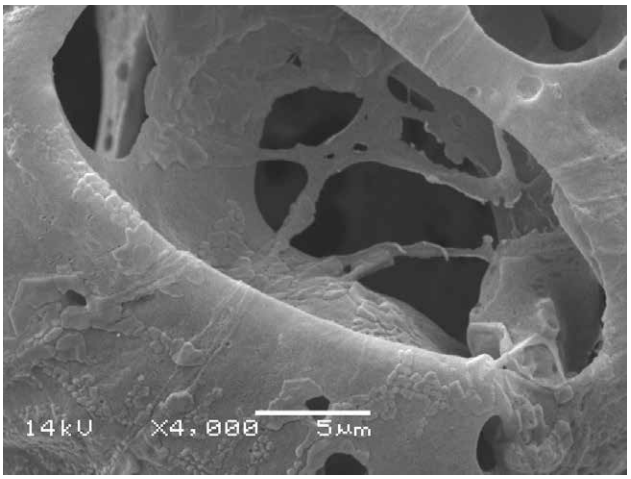
- **University of Nottingham**
  Kevin Shakesheff, (Sharon Crouch– Project Manager)
- **Imperial College London**
  Molly Stevens
- **University of Southampton**
  Richard Oreffo
- **Keele University**
  Alicia El Haj
- **University of Manchester**
  Julie Gough
- **Clinical Spokes include**
  James Fawcett (Cambridge), Philip Newsome (Birmingham), Sheila MacNeil (Sheffield), Charlie Archer (Swansea), Rachel Oldershaw (Liverpool), David Deehan (Newcastle) and Krish Raganuth (Nottingham)



Cell delivery system

Why:

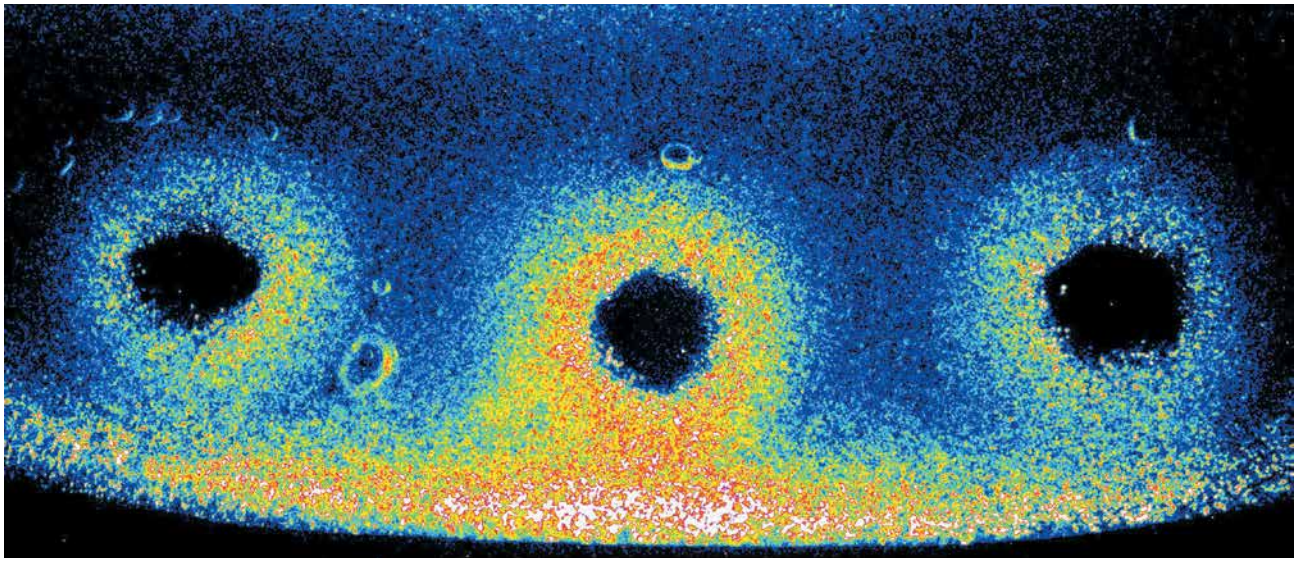
Regenerative medicines promise to be highly effective cures for untreatable diseases and injuries. However, the delivery of therapeutic cells or drugs to sites requiring regeneration is a major bottleneck for clinical and commercial translation; the site of action of the cell or drug is often a hostile environment due to the body's response to injury, a lack of blood supply or inappropriate mechanical stresses.



Neural cells attached to an engineered particle

What:

Our Hub aims to create new advanced materials and technologies that protect and nurture cells from the final steps of manufacturing through to tissue formation within the patient. Materials can redefine the local environment of cells post-administration and can protect cells from damaging conditions throughout the product lifecycle. These technologies also provide control over the response of local tissues, such as promoting stem cell migration into defects. Our technologies also allow regenerative drugs to be presented within the body with kinetics that maximise repair and minimise side effects.



3D printed biomaterial containing vascular structures

How:

The core of the Hub is a group of five materials and tissue engineering groups, with a wider collaborative network that covers most classes of materials and processing techniques used in regenerative medicine. We have three key milestones that will create platform technologies for cell injection, drug delivery and using materials to force tissue architecture to form during repair. Specific examples of the range of technologies that will be developed include:

- novel injectors with low shear for delivery of cells and viscous solutions into the body without significant loss of viability
- injectable and self-assembling biomaterial matrices to promote self-repair and help target transplanted cell therapies
- new intracellular delivery systems providing sustained release (and thereby decrease dose required) of transcription factors and signalling molecules to induce a change in cell differentiation of mesenchymal stem cells
- functional, transplantable devices, for example mimicking a structure such as the oesophagus, through the 3D patterning of smooth muscle cells in 2 separate layers of a tubular construct that generate more contraction in the direction of the cells than at a perpendicular angle.

In addition, we have eight clinical spokes that are setting the clinical problems that our technologies must address. Currently this includes Parkinson's Disease, liver damage, bone fractures, non-healing skin wounds, cartilage repair, oesophageal replacement and anterior cruciate ligament replacement.

Our approach is highly collaborative and new teams are joining our network to ensure we have the best platform technologies available for clinical and commercial partners.

Industrial links are extensive with our core groups. Acellular technologies offer excellent opportunities for intellectual property protection and we are committed to the translation of our platforms to accelerate the industrial development of regenerative medicine and to enhance the efficacy and safety of cell and drug therapies.

"Delivering therapeutic cells or drugs to patients is challenging because regeneration sites are often hostile environments which can stop the cells from working. We're looking to develop industry applicable materials and technologies that interact with the transplanted cells. By cushioning the cells' transition into the patient and making them "think" that they are in a natural environment, these therapies are more likely to work." – *Kevin Shakesheff*

3.5 Immunomodulation Hub

Director: Professor Fiona Watt, King's College London

Who:

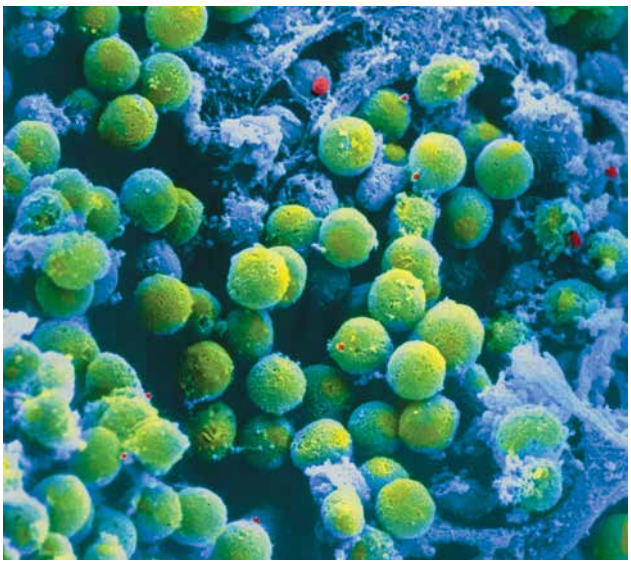
- **King's College London**
  Fiona Watt, Francesco Dazzi, Frederic Geissmann; and from the **MRC Centre for Transplantation**, Giovanna Lombardi and Steven Sacks
- **University College London**
  Robin Ali
- **Cancer Research UK London Research Institute**
  Caetano Reis e Sousa
- **University of Oxford**
  Paul Fairchild and Fiona Powrie
- **University of Birmingham**
  Philip Newsome
- **Newcastle University**
  James Shaw
- **Imperial College London**
  Sian Harding

Why:

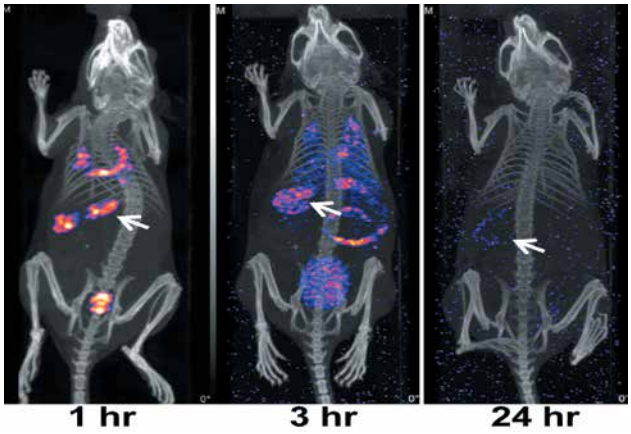
The central goal of regenerative medicine is to replace damaged or diseased tissue. This can potentially be achieved by stimulating endogenous tissue repair or by transplanting autologous or allogeneic cells. Regardless of which strategy is taken, host immune responses can represent a formidable obstacle to success. Unless autologous cells are used, transplanted cells will have different degrees of major histocompatibility antigen (MHC) mismatch with the recipient and will therefore be at risk of rejection by the adaptive immune system. Even when donor and recipient are matched for the MHC, antigen-independent inflammatory pathways (the innate immune system) modulate endogenous repair and can hinder donor cell engraftment. By modulating different aspects of the immune system we intend to improve the efficacy of regenerative medicine therapies.

What:

We have assembled a team of investigators to form the immunomodulation Hub. We come from diverse clinical and non-clinical research backgrounds. Collectively, we provide expertise in tissues for which there is an unmet clinical need for regenerative treatments, in innate and adaptive immunity, and in whole organ transplantation. We have brought together researchers already involved in clinical trials of cell therapies and researchers with relevant models of endogenous tissue repair. Our expertise spans both adult tissue and pluripotent stem cells. We have also included partners with a background in cancer research due to the potential insights into regenerative medicine that can emerge from tumour immunobiology.



SEM of lymphocytes in cortex of thymus



Treg cell infusion in mice

"The immune system can represent a significant obstacle to the survival of transplanted cells. The partners in our Hub are working together to modulate the innate and adaptive immune systems in order to ensure that cell-based therapies are able to survive in the patient after transplantation." – *Fiona Watt*

We are pooling our collective knowledge and sharing experimental tools to answer three key questions:

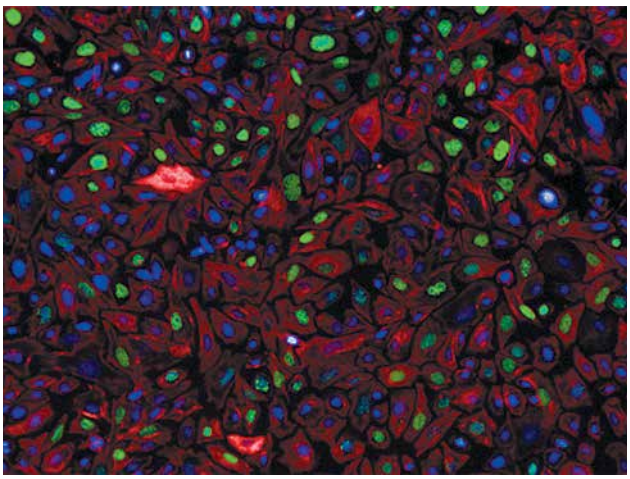
1. How do differentiated cells signal to the host innate and adaptive immune system?
2. How do transplanted cells provoke adaptive immune responses?
3. How does the inflammatory niche contribute to endogenous repair and influence the fate of transplanted cells?

How:

Innovative features of our Hub are the comprehensive assessment of immunomodulatory signals produced by different types of donor cells of adult and pluripotent stem cell origin, the evaluation and modulation of adaptive responses to transplanted cells in humanised mice, and the simultaneous assessment of novel parenchymal cell subsets in multiple tissues.

We will use *in vitro* assays to compare how differentiated human cells isolated from the relevant tissue or induced from iPSC signal to the immune system under steady state and hypoxic conditions. The key findings will be validated *in vivo* using humanised mice. The use of iPS cell-derived dendritic cells to modulate immune tolerance and enhance T regulatory cell (Treg) therapy, alone or in combination with complement inhibitory peptides, will be explored as a means of improving the survival and function of transplanted cells. Finally, we will examine the contribution of recently discovered subsets of macrophages, fibroblasts and dendritic cells to the inflammatory niche in the context of cell transplantation, chronic inflammation and endogenous repair.

Our vision is that by working together to answer these questions in a laboratory setting we will make a substantial contribution to long-term clinical deliverables that include improved efficacy of photoreceptor cell therapy to treat blindness, improved repair of damaged heart tissue, and improved survival and functionality of transplanted hepatocytes as an alternative to liver transplantation.

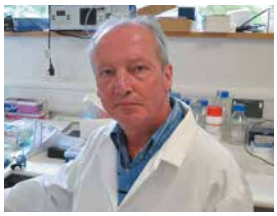


Proliferating epidermal cells

4. Stage II – Disease/ Systems Awards

The second stage of the Platform provides a disease-focused approach through the support of five cutting-edge research consortia. These consortia are all undertaking cross-discipline translational programmes in regenerative medicine, where a specific disease- or tissue-focused programme of research is ripe for clinical intervention.

The projects address osteoarthritis, blindness, liver disease, and bone fractures, as detailed below.



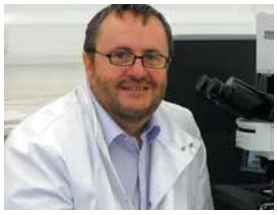
4.1 Professor Charlie Archer (Swansea University)

Generating durable and resilient repair of cartilage defects using tissue-specific adult stem cells – a systematic, therapeutic approach.

"Production of functional implantable articular cartilage, able to withstand compression and tension, will be a major clinical advance."

Cartilage surface

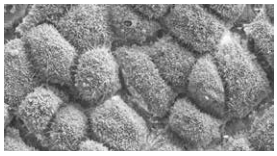
Osteoarthritis is the single largest cause of physical disability in the world, and yet, there are no clinically validated and effective treatments to restore normal, pain-free movement of affected joints. In general, osteoarthritic lesions begin as small isolated cartilage defects that spread across the joint. If these defects can be repaired, an excellent opportunity exists to restore function and prevent further disease. Our solution to this problem encompasses the full developmental pathway for repair; from using articular cartilage-derived stem cells where we will evaluate retention of chondrogenic phenotype, chromosomal stability and factors affecting cell proliferation, to inducing maturation of bioprinted tissues constructs to rapidly restore normal cartilage function. In addition, we will be using 3D bioprinting techniques to fabricate topologically defined and functional osteochondral constructs on a large scale to address current unmet clinical needs.



4.2 Professor Pete Coffey (University College London)

Scalable production of RPE cells from induced pluripotent stem cells under GMP conditions for cellular replacement therapy of the dry form of age-related macular degeneration.

"We expect this to lead on to the first European trial using induced pluripotent stem cell technology, which will provide a personalised therapy as a way of overcoming immunological issues."



Microvilli of RPE monolayer

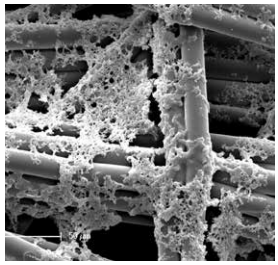
The aim of the study is to select patients with a common and currently incurable eye disease – dry age-related macular degeneration (AMD) – and characterise the disease using state-of-the-art novel imaging. We will create pluripotent stem cells from skin biopsies taken from these patients, and from these derive retinal pigment epithelial (RPE) cells in the laboratory which have the ability to replenish the damaged retina. We will then evaluate the safety and efficacy of these cells in preclinical models to provide the evidence base to undertake a clinical trial. Our goal is to produce a cell replacement therapy from stem cells derived from patients themselves, which is effective in replacing those cells that deteriorate and die in AMD. By using a patient's own cells as the basis for this approach, we hope to overcome potential problems of transplant rejection. If successful, this will lead to a surgical therapy capable of stabilising and restoring vision in the vast majority of patients.

4.3 Dr David Hay (MRC Centre for Regenerative Medicine, University of Edinburgh)

The development of 3-dimensional implantable liver organoids.

"The project will deliver novel templates for human tissue engineering as a basis for treating human liver disease"

Liver disease is the fifth most common cause of death in the UK. The only curative option for end-stage disease is liver transplantation; however, organ availability cannot meet demand. There is a clear imperative to identify alternatives to liver transplantation. We will use human pluripotent stem cells co-cultured with mesenchymal stem cells and endothelial cells to generate primitive liver organoids. These will then be further developed into a clinically relevant form, for example with a functional biliary system, using an interdisciplinary approach incorporating tissue engineering and materials chemistry. Our team has complementary expertise in the production of stem cell derived hepatocyte and cholangiocyte-like cells, tissue niche construction and *in vivo* modelling, and includes scientists and clinicians with experience in GMP cell production and clinical cell therapy for liver disease. It is therefore ideally placed to translate these pre-clinical observations into a therapy for patients.

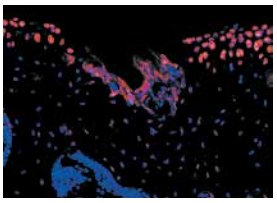


Liver matrix

4.4 Professor Andrew McCaskie (University of Cambridge)

SMART STEP - Stepwise Translational Pathway for Smart Material Cell Therapy.

"Cartilage repair by targeting the patient's own cells to bring about the repair, using a combination of materials and molecules in a cell-free therapy"

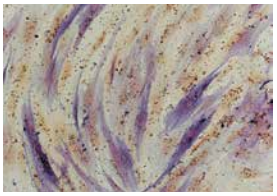


Damaged cartilage cells (red)

Osteoarthritis is a disease that can ultimately destroy the surfaces of joints causing severe pain and reduced function. Current surgical treatments such as joint replacement are targeted to end stage disease. We will focus on repair and regeneration of cartilage at an earlier stage in order to reduce the progression of joint damage. Our approach is to target the patient's own cells to bring about repair using novel smart material technology together with the incorporation and controlled presentation of signalling molecules. Our aim is to modulate cell signalling pathways to affect recruitment, proliferation and chondrogenic differentiation of endogenous mesenchymal stem cells. Our clinical goal is to make such treatments affordable, easy to apply and deliverable as a day case. The SmartStep Pipeline will establish a stepwise translational pathway from "bench to bedside" to facilitate core stakeholders beyond the consortium.

4.5 Professor Manuel Salmeron-Sanchez (University of Glasgow)

Synergistic microenvironments for non-union bone defects.



Osteogenic cells

Long bone fractures involve damage to the surrounding tissues and vascular networks. As a result, the natural bone healing capacity is lost and non-union defects are formed. We present a therapeutic solution to address unmet clinical needs in bone regeneration and vascularisation in non-union bone defects. Our novel approach is based on the use of synthetic functional materials polymerised on the surface of 3D structural scaffolds. This simple, robust and translational material-based platform will be used to fine tune the presentation of safe but effective doses of human growth factors (BMP-2) to cell surface receptors, at much lower doses than is currently possible which should mitigate the problems observed with this therapeutic approach to date. This approach will lead to the recruitment of stem cells and will create synergistic microenvironments to enhance bone regeneration and vascularisation.

"We will develop a novel therapeutic approach for bone regeneration and vascularisation in critical size defects, which are unmet major problems after trauma or cancer."

5. UKRMP Director's Report

5.1 Progress over the first year – Dr Rob Buckle, Director

Since the publication of A Strategy for UK Regenerative Medicine in 2012, a number of UK funding agencies in both the public and charity sectors have provided substantial new investment in support of this emerging field. Over £140M strategic funding has been provided since 2012 over and above normal response-mode mechanisms, demonstrating both the support of the UK Government and public in pursuing the promise offered by regenerative medicine, as well as the willingness of UK research organisations to work collaboratively to align this effort in the most productive way. Central to this has been the establishment of the UKRMP, which is focused on bringing together sometimes disperse expertise into a number of themes of primary importance for the translation of regenerative science towards clinical application.

The building blocks of the UKRMP are now in place. The first Hubs became functional in September 2013, with the final Hub awarded in March of this year. In the interim it has been heartening to see productive links being built across the various thematic groupings. Indeed the longer gestation period for the Immunotolerance Hub has allowed it to incorporate a broader base than seemed likely at the outset of the process, and in a format that adds significant opportunities to the other Hubs. The exciting challenge over the next year is to ensure these promising beginnings are built upon and that connections continue to grow with other important elements and activities across the UK, both in the academic and commercial sectors.

The funding of five Hub-linked projects with specific therapeutic goals under Stage II demonstrates how added value can be provided, with the expectation that these will provide pathfinder-type activities of value to the wider field as a whole. Connectivity with grants to be awarded through standard funding routes also offers the prospect of building a supportive network of activity that can provide the shared experiences, tools and technologies to drive forward the translational agenda. In this respect it is worth noting the recent translational investments made in this area through the individual sponsor Research Councils, where for example the MRC's Biomedical Catalyst programme has in the last year made ten awards to progress the clinical development of cell and gene therapies. Two notable awards from this list include a laryngeal reconstruction clinical trial at UCL using stem cell based tissue engineered laryngeal implants, and a potential treatment for liver cirrhosis where scientists in Edinburgh are to undertake a clinical trial using bone marrow derived macrophages to promote liver regeneration. In both cases the research teams behind these studies are collaborating with the emerging UKRMP programme. Alongside this clinical focus BBSRC is currently supporting six programmes in biomanufacturing for regenerative medicine through its Bioprocessing Research Industry Club (BRIC2) initiative, while EPSRC has made a number of grant awards in the last year that build capacity in the application of next generation or 'smart' materials and nanoscience to advance stem-cell based therapeutics.

More broadly, the UKRMP is working closely with the Cell Therapy Catapult as it supports the commercial development of validated approaches in cell therapy, with productive links established at both the executive and scientific levels. The shared technology platforms needed to exploit the rapid progress in our understanding of stem cell biology and differentiation have also driven connectivity with the UK's developing iPSC agenda, for example through HipSci and UK-led IMI programmes (see 6.3), ensuring that there is strong cross-fertilisation of the resources and expertise being applied to these challenges. It is

expected that interaction between the Platform and the Catapult will become stronger as each initiative develops, and the opportunities to align and enhance projects and capabilities emerge.

Lastly it is encouraging to see how the interconnected network that has been established through the UKRMP is providing a basis to train the next generation of multidisciplinary scientists in this field. £11M has recently been awarded to three new Centres for Doctoral Training in Regenerative Medicine led from Leeds (EPSRC-funded), and Loughborough and Manchester (joint EPSRC/MRC funded), all of which have links to the UKRMP Hubs.

In summary this progress and outreach over the past 12 months has helped to firmly establish the UKRMP on the UK landscape, and it is to be hoped that the programme will continue to grow productively through the partnerships and commitment provided by the scientists and research teams involved.

5.2 The road to collaboration – Dr David Pan, Programme Manager

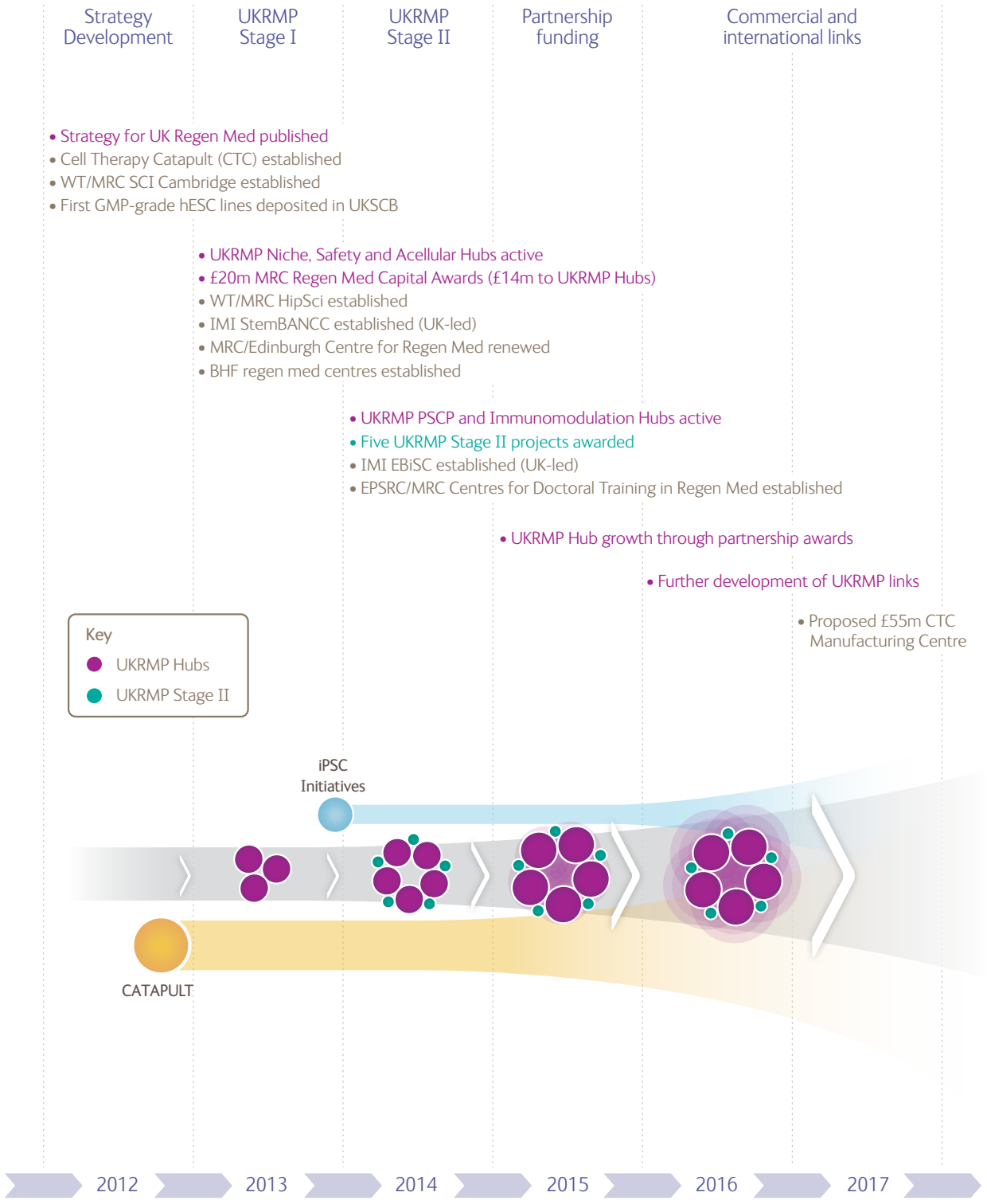
The exciting feature of the Hubs is that they are not locked into a rigid structure or composition but are expected to be dynamic and responsive to new opportunities and a changing scientific landscape. During the course of the award the Hubs will use some of their funding to establish complementary research activities with each other and bring in new research partners and stakeholders, both academic and commercial. The use of such 'partnership funding' is intended to strengthen the Hub's research and technological capabilities, as well as engage external groups to help address the identified challenges.

Moreover, the Hubs will develop networking activities to address key needs relevant to each Hub's theme. In doing so the outputs are expected to have value to the interests of the wider research community. It is anticipated that the networking process will involve researchers and stakeholders beyond the Hubs, drawing on the best available expertise, and provide outputs of interest and benefit to the wider UK regenerative medicine sector. These might for example entail the provision of protocols and guidelines, or position papers in emerging and uncharted areas of scientific opportunity.

Details of this partnership and networking activity will emerge over the coming 12 months. Together these mechanisms will help build connectivity and coherence in delivering the goals of the UKRMP, and increase the likelihood that solutions will be found to many of the translational barriers that are currently inhibiting the progress of regenerative medicine, and ultimately allow its potential to be fully realised.

The Platform has been designed to promote alignment of effort across the UK, and as a vehicle to consolidate interdisciplinary and collaborative approaches. While still early days for the Platform, the coalescence of activity that is emerging through linkage with the Cell Therapy Catapult, the BHF centres and new strategic iPSC programmes, demonstrates the growing momentum of the UK regenerative medicine effort. As the Hubs get fully up to speed over the coming year, the UKRMP will seek to forge new partnerships where opportunities can be found, whether nationally or internationally, in order to grow its capability and drive forward the regenerative medicine agenda.

5.3 UKRMP timeline



6. The UKRMP Environment

6.1 Industry partnerships

A key objective of the UKRMP is that new tools, protocols and resources generated by the Hubs should be utilised by other UK research groups in academia and industry. Where relevant, early stage substrates and pre-clinically validated therapeutic opportunities generated by the Hubs will be taken on by the Cell Therapy Catapult (see below) and/or industry. In addition, innovative technological solutions relevant to the Hub activities may be developed in partnership with commercial providers or provide new opportunities for exploitation.

It is early days in the establishment of the Platform, however all of the Hub programmes include strong plans and engagement with bio-industry and end-users outside of the Hub. For example;

- the PSCP Hub has interactions with Neusentis, GSK, Astra Zeneca, Plasticell and BetaLogics for demonstration projects addressing pre-competitive generic issues in stem cell manufacturing

- the Niche Hub is developing links with GSK and BioAscent in relation to providing tools for manipulation of the stem cell microenvironment

- the Safety Hub has links to iThera for Multispectral Optoacoustic Tomography (as a reference site) in the UK, GE Healthcare around stem cell tracking and imaging applications, and a co-organisational role with GSK for Innovative Medicines Initiative Safety of Stem Cells training programme

- the Acellular Hub has interactions with both leading international companies and innovative SMEs (GE Healthcare, Intercytex, Mica Technologies, Neusentis, Haemostatix, RegenTec, Smith and Nephew, Neotherix, NCTS, PA consulting and Oval Medical) through interests focused around the therapeutic delivery component of its research programme.

It is anticipated that as the Hubs progress and increase their output and visibility, additional interactions will flourish. This may include attracting companies outside of the UK who may be looking at prospective global sites to expand their activity in regenerative medicine, offering an inward investment opportunity.

The UKRMP has also formed a productive relationship with the Cell Therapy Catapult, established in 2012, whose focus is on later stage translational development, and in particular the delivery and commercialisation of cell therapies. The parallel and aligned development of the Platform and the Catapult over the coming years should therefore be pivotal in reinforcing and expanding the developing academic-industry network in UK regenerative medicine.

6.2 Capital awards to support regenerative medicine

In 2013 the MRC was able to inject £20M of capital funding to provide state-of-the-art facilities and equipment to support the work of the UKRMP and the wider regenerative medicine research community. This capital funding supports 12 projects at UK research institutions, many of which are linked to the existing UKRMP Hubs. For example;

- £3.1M to the PSCP for equipment for high throughput cell observation, characterisation and manufacture. A key element of this investment is to establish comparability between protocols and assays at multiple sites in Sheffield, Cambridge and Loughborough

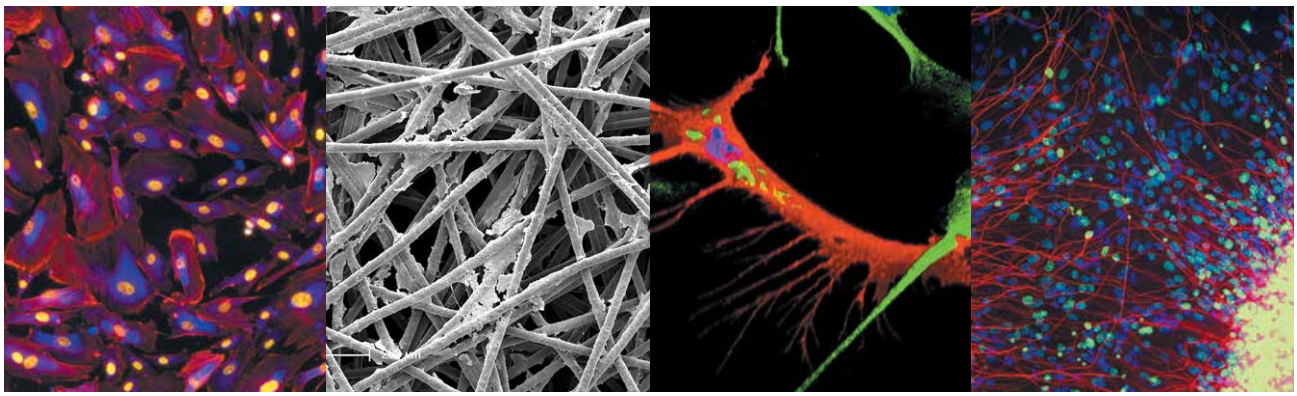
- £5M investment (matched by £5M from the University of Edinburgh) to establish a new "Centre for the Computational and Chemical Biology of the Stem Cell Niche" to enable experts in stem cell biology/ regenerative medicine to work alongside chemists and bioinformaticians to create niche-based biomaterial and phenotyping technology platforms to help develop artificial niches to support therapeutic development

- £3.3M to provide preclinical safety imaging technologies for the Safety Hub, to support cutting-edge approaches to monitoring cell biodistribution and efficacy following transplantation into animal models

- three awards, totalling £3.1M, to support the activity of the Acellular Hub for fabrication, 3D printing and analysis of advanced biomaterials (Stevens, MacNeil) and to establish a nanoscale imaging facility (Oreffo).

Five awards were made to research teams outside of the UKRMP, providing further national capability. Three of these awards have application in developing regenerative therapies in ophthalmology and cardiovascular medicine. In the latter case, the awards (to Imperial College London and Bristol) support two of the three BHF Centres in Cardiovascular Regenerative Medicine, all of which have established links to the UKRMP since their establishment in 2013.

A full listing of these 12 awards is provided in Annex 2.



6.3 Stem cell supply

The UKRMP Hubs have strong linkages with other initiatives that support the UK regenerative medicine effort, which together provide a fully integrated community and conduit to commercialisation and clinical application. Fundamental to regenerative medicine approaches are stem cells, and several key strategic initiatives are in place to characterise and provide high quality and ethically sourced cell lines to the community, including an increasing number of 'clinical grade' stem cell lines. Brief details of each of the initiatives with, type and number of cells that can be provided, are listed below:

UK Stem Cell Bank (UKSCB)

www.nibsc.org/science_and_research/advanced_therapies/uk_stem_cell_bank.aspx

The UKSCB was established to provide a repository of human embryonic, foetal and adult stem cell lines as part of the UK governance for the use of human embryos for research. Its primary role is to provide quality controlled stocks of human embryonic stem cells (hESC) that researchers worldwide can rely on to facilitate high quality and standardised research. It also prepares stocks of EUTCD-grade cell lines for use as starting materials for the development of cellular therapies.

There are currently 217 approved hESC lines on the UK registry [www.mrc.ac.uk/documents/pdf/uk-stem-cell-line-registry/]; 184 research grade and 33 EUTCD (clinical) grade. For the research grade lines, 24 are available on request through the UKSCB, while the 33 clinical grade cell lines have been approved for deposit and are undergoing banking and characterisation before being made more widely available. The Bank's capacity allows the banking of 10 research and clinical grade cell banks per year. The current phase of funding for the UK Stem Cell Bank will see increased emphasis on the characterisation of cell lines held by the bank and qualification and implementation of new methods for culture, preservation and analysis of cells intended for therapy. The Bank will utilise its growing expertise in this area to support those involved in early stage translational research, particularly on aspects of safety and standardisation.

Human Induced Pluripotent Stem Cell Initiative (HipSci)

www.hipsci.org

HipSci is a £13M initiative funded by the Wellcome Trust and MRC which brings together expertise in genomics, proteomics, cell biology and clinical genetics to create a national iPS cell resource which will be used to support cellular genetic studies. HipSci's overall aim is to generate iPS cells from over 500 healthy individuals and 500 individuals with monogenetic disease, and to use these cells to discover how genomic variation impacts on cellular phenotype and to identify new disease mechanisms.

A total of 146 lines have been generated to date, with approximately 400 anticipated by the end of 2014. QC data is available on 120 of the lines with 42 of these expanded and banked for downstream experimental assays. All lines are to be fully characterised and made widely available to the research community. It should be noted that the consent under which these cells have been obtained precludes them from therapeutic use in humans.

Phase two of the project includes the derivation and characterisation of 500 iPS cell lines from patients with monogenic diseases, with the first two collections being established in Bardet-Biedl Syndrome and maturity-onset diabetes of the young (MODY).

Stem cells for biological assays of novel drugs and predictive toxicology (IMI StemBANCC)

www.stembancc.org

StemBANCC is a €56M EC-funded Innovative Medicine Initiative (IMI) programme that aims to provide well characterised patient derived induced pluripotent stem cell lines and associated biomaterials in an accessible and sustainable bio-bank. StemBANCC is led from the University of Oxford and coordinated by Roche. The programme aims to demonstrate proof-of-concept for the utility of iPSCs in drug discovery for hard-to-treat disorders. The overall goal is to generate 1500 iPSC lines from 500 individuals, with iPSCs from a total of 100 subjects (300 lines) to be released by December 2015. The cell lines will be comprised of healthy controls, monogenic forms of Alzheimer's disease, monogenic forms of Parkinson's disease, hereditary neuropathy, familial migraine and monogenic diabetes.

European Bank for induced pluripotent Stem Cells (IMI EBiSC)

www.ebisc.org

EBiSC is a €35M EC-funded IMI programme that is aiming to provide researchers with a single point of access for iPSCs from multiple sources across Europe. Conceptualized and coordinated by Pfizer in Cambridge, UK and managed by Roslin Cells in Edinburgh, the iPS cell bank will act as a central storage and distribution facility for human iPS cells. It is adopting a phased strategy for development of its iPSC Catalogue, which will have an eventual capacity to store up to 10,000 cell lines. In the initial 'Hot Start' phase, the project is validating important standard procedures for cell line processing and distribution, using over 50 lines sourced from across Europe. Samples will be distributed to a limited set of organisations external to the project from late 2014 onwards.

Cell Therapy Catapult / Roslin Cells

www.ct.catapult.org.uk / www.roslincells.com

The Cell Therapy Catapult and Roslin Cells recently announced a partnership to establish a source of 'clinical grade' induced pluripotent stem cells banked according to Good Manufacturing Practice (GMP) in the UK. An initial six iPS cell lines are expected to be available for clinical research in both academia and industry by the end of 2014.

Annex 1

UKRMP Governance

Executive Group

- **Dr Rob Buckle,** Director of Science Programmes, MRC, Director UKRMP
- **Professor Ian Greer,** Pro-Vice-Chancellor (Health and Life Sciences), University of Liverpool, Chair UKRMP Programme Board
- **Dr Ruth McKernan,** Snr Vice President Pfizer, CSO Neusentis, Cambridge UK
- **Dr Declan Mulkeen,** Chief Science Officer, MRC
- **Dr Lesley Thompson,** Director, Research Base, EPSRC
- **Professor Melanie Welham,** Director of Science, BBSRC

Programme Board

- **Professor Ian Greer** (Chair), University of Liverpool, UK
- **Professor Nissim Benvenisty,** The Hebrew University of Jerusalem, Israel
- **Professor Kenneth Boheler,** University of Hong Kong, China
- **Dr Drew Burdon,** Smith and Nephew, UK
- **Dr Nigel Burns,** Cell Medica, UK
- **Professor Alan Clarke,** Cardiff University, UK
- **Professor Jöns Hilborn,** Uppsala University, Sweden
- **Dr Trevor Howe,** Janssen R&D, Belgium
- **Dr Andrew Lynn,** University of Cambridge, UK
- **Professor Marc Peschanski,** I-STEM Paris, France
- **Professor Paul Whiting,** Pfizer Regenerative Medicine, Cambridge UK
- **Professor Peter Zandstra,** University of Toronto, Canada

Annex 2

UKRMP Stage I - Hub awards

- Professor Peter Andrews, University of Sheffield
  Cell behaviour, differentiation and manufacturing Hub. £4.6M

- Professor Stuart Forbes, MRC Centre for Regenerative Medicine, University of Edinburgh
  Engineering and exploiting the stem cell niche Hub. £4.6M

- Professor Kevin Park, MRC Centre for Drug Safety Science, University of Liverpool
  Safety and efficacy, focussing on imaging technologies Hub. £4.6M

- Professor Kevin Shakesheff, University of Nottingham
  Acellular approaches for therapeutic delivery Hub. £3.8M

- Professor Fiona Watt, King's College London
  Immunomodulation Hub. £2.3M

UKRMP Stage II – Disease/Systems awards

- Professor Charles Archer, Swansea University
  Generating durable and resilient repair of cartilage defects using tissue-specific adult stem cells – a systematic, therapeutic approach. £1M * (£0.29M RC, £0.2M ARUK, £0.51M Reumafonds)

- Professor Pete Coffey, University College London
  Scalable production of RPE cells from induced pluripotent stem cell under GMP conditions for cellular replacement therapy of the dry form of age-related macular degeneration (AMD). £1.6M

- Dr David Hay, MRC Centre for Regenerative Medicine, University of Edinburgh
  The development of 3-dimensional implantable liver organoids. £1.6M

- Professor Andrew McCaskie, University of Cambridge
  (SMART STEP) Stepwise translational pathway for smart material cell therapy.
  £1.6M * (£0.64M RC, £0.53M ARUK, £0.43M Reumafonds)

- Professor Manuel Salmeron-Sanchez, University of Glasgow
  Synergistic microenvironments for non-union bone defects. £1.0M # (£0.54M RC, £0.46M ARUK)

  * partnered with Arthritis Research UK and Reumafonds
  # partnered with Arthritis Research UK

MRC regenerative medicine capital awards

UKRMP-linked

- Professor Peter Andrews, University of Sheffield
  Pluripotent Stem Cell Platform - capital investment. £3.1M

- Professor Cay Kielty, University of Manchester
  Regenerative medicine: instrumentation for flow cytometry and cell printing. £0.7M

- Professor Stuart Forbes, University of Edinburgh
  The computational and chemical biology of the stem cell niche. £5.0M

- Professor Sheila MacNeil, University of Sheffield
  Open-access biomaterials microfabrication and non-invasive imaging facilities for regenerative medicine. £0.7M

- Professor Richard Oreffo, University of Southampton
  Southampton Imaging: 3D imaging at millimetre to nanometre scales for regenerative medicine using multiple complimentary modalities. £1.2M

- Professor Brian Park, University of Liverpool
  In vivo imaging technologies to assess the efficacy and safety of regenerative medicine therapies. £3.3M

- Professor Molly Stevens, Imperial College London
  State of the art biomaterials development and characterization of the cell-biomaterial interface. £1.2M

Capital awards outwith the UKRMP Hubs

- Professor Robin Ali, University College London
  A flow cytometry facility for ocular regenerative medicine. £0.7M

- Professor Raimondo Ascione, University of Bristol
  Pre-clinical in-vivo functional imaging for translational regenerative medicine. £2.8M

- Professor Anne Dickinson, Newcastle University
  Clinical grade cell separation technologies in the Newcastle Cellular Therapies Facility. £0.2M

- Professor Sian Harding, Imperial College London
  BHF Imperial Cardiovascular Regenerative Medicine Centre. £0.7M

- Dr Charles Hunt, UK Stem Cell Bank (NIBSC)
  Automation of cell banking & characterisation pathways at the UKSCB: underpinning delivery of a core component of the UK infrastructure for regen med. £0.3M

Annex 3

Image annotations

Cover Image
Human neural stem cells. *Dan Webber, MRC Centre for Regenerative Medicine*

"Neurospheres derived from iPSCs" on page 6
Neuron specific marker (Map2) in neurospheres derived from equine iPSCs. *PSCP Hub*

"Bioreactor system to assess cell metabolites" on page 7
DASGip bioreactor system used to asses cell metabolites under varying conditions which aids the comparability of processes across multiple cultures. *PSCP Hub*

"Clean-room for automated cell-culture" on page 7
Researcher working on the automated cell culture platform the GMP Compact Select. *PSCP Hub*

"Layer of liver cells" on page 8
Layer of human embryonic stem cell derived hepatocytes expressing E-Cadherin. *Niche Hub*

"Raman imaging analysis of human embryonic stem cell" on page 9
Raman component analysis of a human embryonic stem cell. Different components can be extracted by interpreting Raman spectra from a high resolution mapping. *Niche Hub*

"Artificial liver engineering using stem cell-derived hepatocytes" on page 9
Human stem cell derived hepatocytes replated on a bio-artificial liver scaffold and grown in a dish. *Niche Hub*

"Photoacoustic image of transfected cells" on page 10
Photoacoustic image showing cells transfected with tyrosinase, and surrounding vasculature following injection under the skin of a mouse. *Safety Hub*

"IVIS Spectrum image of mice injected with kidney stem cells" on page 11
IVIS Spectrum imaging of normal CD1 mice after injection into either the tail vein or left ventricle with fluorecence labelled mouse kidney stem cells demonstrates that the route of administration affects localisation. *Safety Hub*

"Histological validation of stem cells in renal glomeruli" on page 11
Kidney section analysis confirms the presence of kidney stem cells in the renal glomeruli (G) of animals that received left ventricle injection. *Safety Hub*

"Neural cells attached to an engineered particle" on page 12
Neural cells interacting with a surface engineered particle. Neurites are formed during the manufacturing process and retained after in vivo administration. *Acellular Hub*

"Cell delivery system" on page 12
A cell delivery system in which the cells adhere to biodegradable particles. The system aims to enhance the retention and function of the cell therapy at the site of repair. *Acellular Hub*

"3D printed biomaterial containing vascular structures" on page 13
3D printed vascular structures in materials promote fibroblast cell survival. The architecture of the material assists tissue formation by enhancing transport in and out if the regenerating structure. *Acellular Hub*

"SEM of lymphocytes in cortex of thymus" on page 14
False-colour scanning electron micrograph of the cortex of a thymus. The spheres are T-lymphocytes, white blood cells vital to the cell mediated response of the immune system. *CNRI/Science Photo Library*

"Treg cell infusion in mice" on page 15
NanoSPECT/CT image showing the biodistribution of infused Tregs. *Greg Mullen, King's College London*

"Proliferating epidermal cells" on page 15
Cultured human epidermal cells proliferating in response to factor produced by macrophages. *Immunomodulation Hub*

"Panel of images" on page 16
Osteoarthritis of the knee. *Thinkstock*; Image of the macular region of a healthy eye. *Pete Coffey, University College London*; Male liver. *Thinkstock*: Fractured femur. *Thinkstock*.

"Cartilage surface" on page 16
Scanning electron microscopy image of human articular cartilage. *Archer award*

"Microvilli of RPE monolayer" on page 17
Electron microscope image of the apical microvilli of a retinal pigment epithelium (RPE) monolayer. *Coffey award*

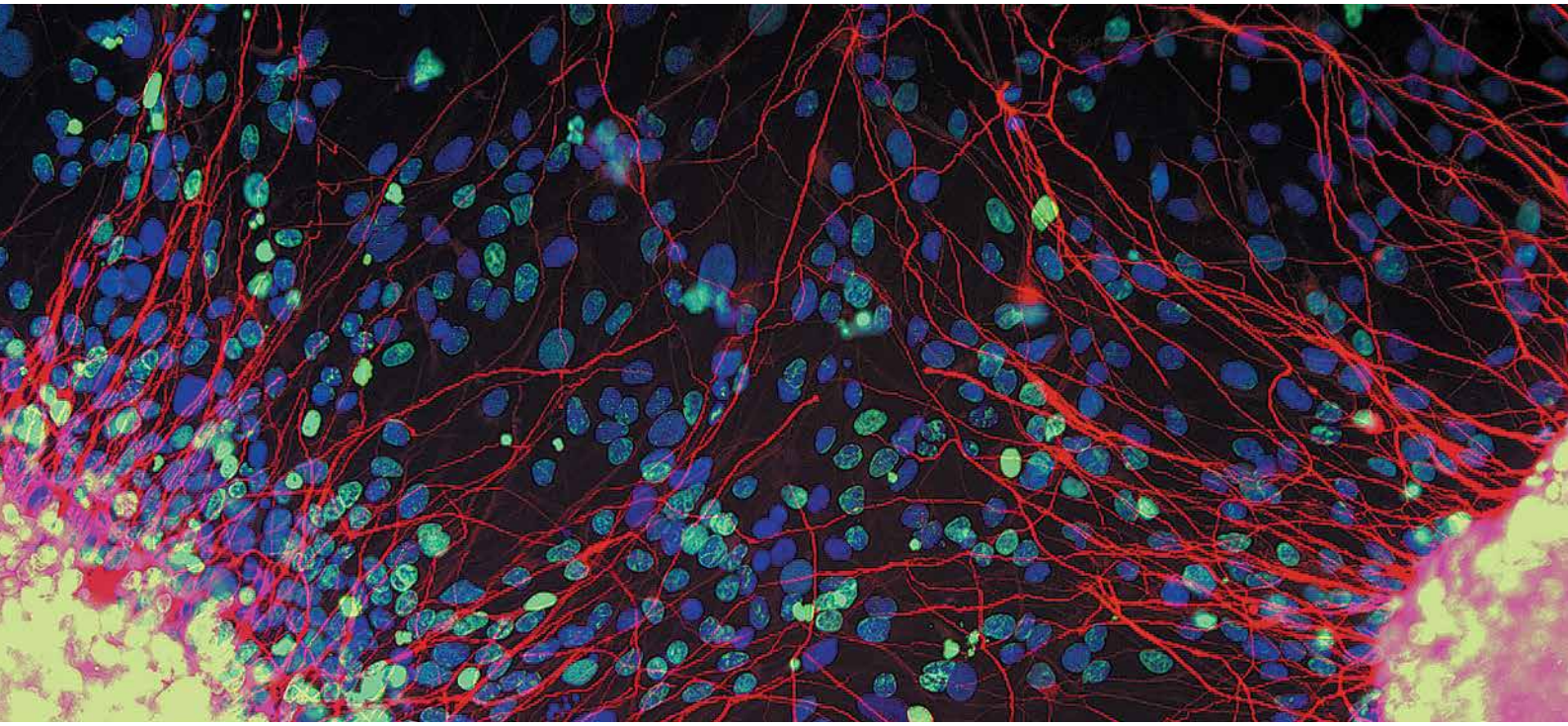
"Liver matrix" on page 17
Synthetic polymer coated liver matrix. *Hay award*

"Damaged cartilage cells (red)" on page 18
Fluorescent labelling technology allows the study of different cells that contribute to cartilage repair after injury e.g. red fluorescent cells in this image are present at an area of damaged cartilage. *McCaskie award*

"Osteogenic cells" on page 18
Osteogenic differentiation of human bone marrow mesenchymal stem cells on materials surfaces shown by alkaline phosphatase staining. *Salmeron-Sanchez award*

"Panel of images" on page 23
Osteoblasts on biomaterial; stem cell derived hepatocytes on a bio-artificial liver matrix; stem cells attached to infected macrophages; human neural stem cells. *MRC Centre for Regenerative Medicine*

UK Regenerative
Medicine Platform



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