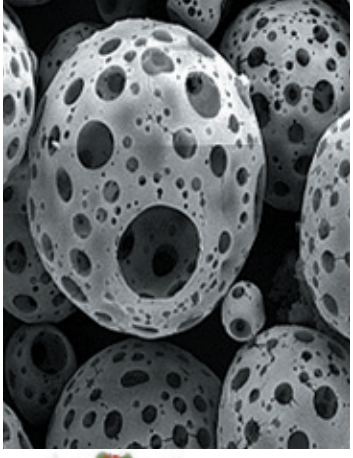
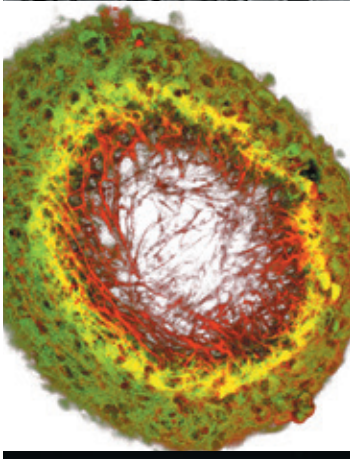
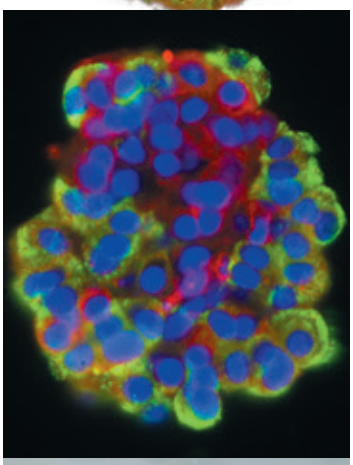
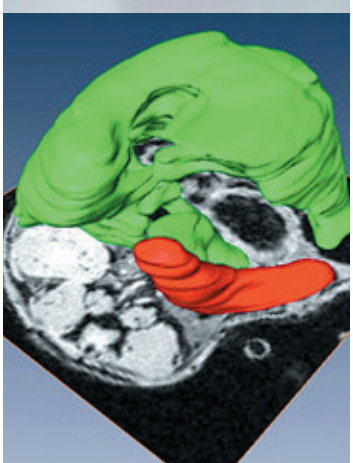








UK Regenerative Medicine Platform

ANNUAL REPORT

2015

BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

Cover Images:

Top to bottom: Microparticles - Acellular Hub; Immunostained human bone marrow derived MSC 3D spheroids - Niche Hub; Human islets stained for insulin (green) and HLA class I (red) - Immunomodulation Hub; Researcher culturing cells under GMP conditions - PSCP Hub; 3D rendering of mouse liver and spleen - Safety Hub.

Contents

1. Introduction

UKRMP Director : Dr Rob Buckle

1.1 Background

The UK Regenerative Medicine Platform (UKRMP) was established in 2013 to tackle the technical and scientific challenges that need to be surmounted if we are to ensure that regenerative medicine - which seeks to repair, replace and/or regenerate damaged cells, tissues and organs – can benefit patients across a wide range of chronic and debilitating diseases.

This initiative has brought together the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Science Research Council (EPSRC) and Medical Research Council (MRC) under a shared vision to build a translational and interdisciplinary programme capable of attracting the best UK scientists and developing fruitful commercial partnerships. The Councils have jointly invested £25M over four years to support this activity, targeted at specific bottlenecks that are slowing progress towards the clinic. Addressing these barriers will also help de-risk future commercial investment, which at this point in time remains cautious relative to other areas of biomedicine where the business models are more certain.

The UKRMP funding has established five interdisciplinary and cross-institutional research Hubs, and five aligned disease-focused projects. These bring together leading research teams from 17 different universities and from different areas of science spanning biology, medicine and engineering. The Hubs are designed to bridge the conceptual gap between scientific discovery and efforts to bring therapeutic products to the clinical market, and collectively will provide the new tools, engineering solutions and knowledge base needed to support the wider regenerative medicine community. These activities are described in more detail in the following pages of the report.

The work of the UKRMP is guided by a Strategy for UK Regenerative Medicine[1] which sets out the opportunities and challenges faced by the field. The Platform operates in close partnership with the Cell Therapy Catapult, which was established to a similar timeline and aims to promote the late-stage development and commercialisation of regenerative medicine products. It is also aligned with other national strategic investments in the area, such as MRC, EPSRC and British Heart Foundation research centres, and the UK Stem Cell Bank and the WT/MRC Human IPSC Initiative which underpin the supply of high quality cell lines.

1.2 Progress

As we reach the end of the second year, the Platform has moved from its establishment phase to being fully operational, with the first fruits of this effort now beginning to emerge. The Hubs are at various stages of maturity, with the Pluripotent Stem Cell and Immunomodulation Hubs being the youngest at 18 months and 12 months old respectively. Nevertheless, all

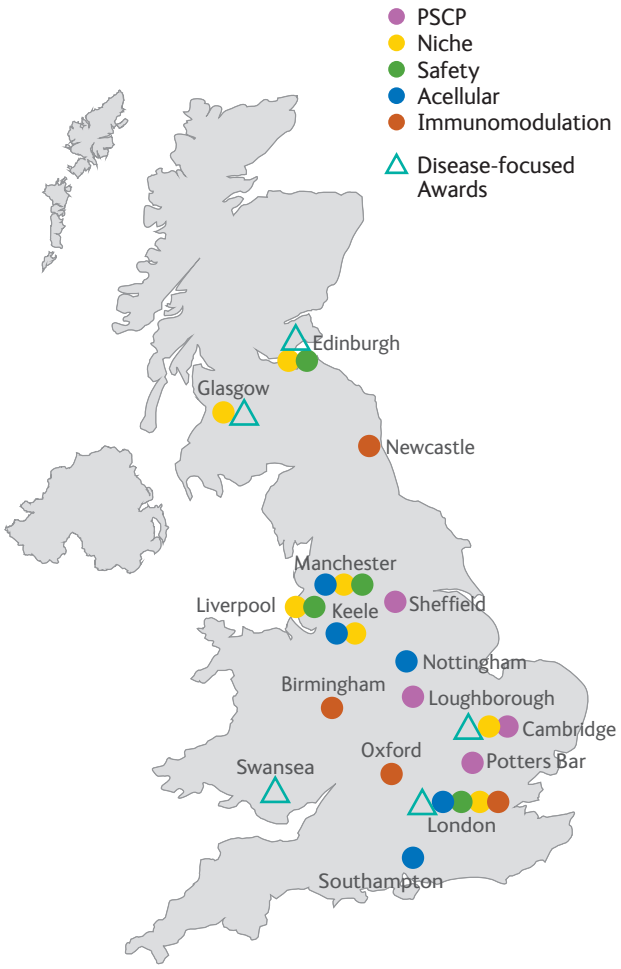
1 www.ukrmp.org.uk/wp-content/uploads/2014/06/A-Strategy-for-UK-Regenerative-Medicine.pdf

are producing a variety of tools, reagents and protocols, a number of which are now being made available for wider use – for example to support cell characterisation, tracking and delivery, and molecular screening and high-end microscopy.

The most mature Hubs have been able to grow their activity through the activation of earmarked partnership funding, which to date has initiated 16 new projects across the Platform. This has allowed new links to be forged with national and international research groups, and with commercial partners. The development of stronger inter-Hub relationships has also added to the overall coherence of the Platform. In many cases this has consolidated effort around specific clinical challenges, with initial focus in the areas of liver regeneration, cartilage and ligament repair, wound healing, and Parkinson's disease. Indeed, several of these efforts link to separately funded research programmes involving Hub principle investigators and to the Cell Therapy Catapult, and a pipeline of further projects is expected to evolve out of the Hubs as we move forward.

The expertise that has been brought together through the Hubs is ideally placed to undertake horizon-scanning activities and assess critical needs in areas of technological challenge. With this in mind the Hubs have established a programme of networking activities that seek to address end-user and stakeholder needs, from which the first white papers will be published in the coming months.

UKRMP Hubs and Awards



Developing a strong relationship with industry partners remains a goal for the UKRMP, and to date over 20 companies have been engaged. This upward trajectory should continue with the more active promotion of Hub outputs in 2016. The UKRMP's strategic approach is also gaining commercial recognition overseas, as highlighted by the recent establishment of an open innovation platform to develop automated scale-up and manufacturing solutions for stem cell-based products. The core technology for this is provided by a Japanese company, that has established its European research base in the UK to support this development as part of an MRC/BBSRC-funded consortium involving academic groups with links to the Platform.

Lastly, the Platform provides an important network to support the development of the next generation of regenerative medicine researchers, complimenting separate but aligned capacity building activities such as the three EPSRC/MRC Centres for Doctoral Training established in 2014. Through its support for scientific excellence and a truly interdisciplinary agenda, the UKRMP is well placed to help nurture the cadre of postdoctoral researchers that will emerge through such training investments, something that the Platform is committed to progressing over the coming years.

2. UKRMP Hubs

2.1 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 (Zoe Hewitt – Project Manager)
- **Wellcome Trust/MRC Stem Cell Institute, University of Cambridge**
  Austin Smith, Roger Barker, Robin Franklin and Ludovic Vallier
- **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, Cambridge**
  Mike Stratton and Kosuke Yusa
- **Babraham Institute, Cambridge**
  Wolf Reik

What

The UKRMP Pluripotent Stem Cell (PSC) Platform 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:

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

Scientific Developments

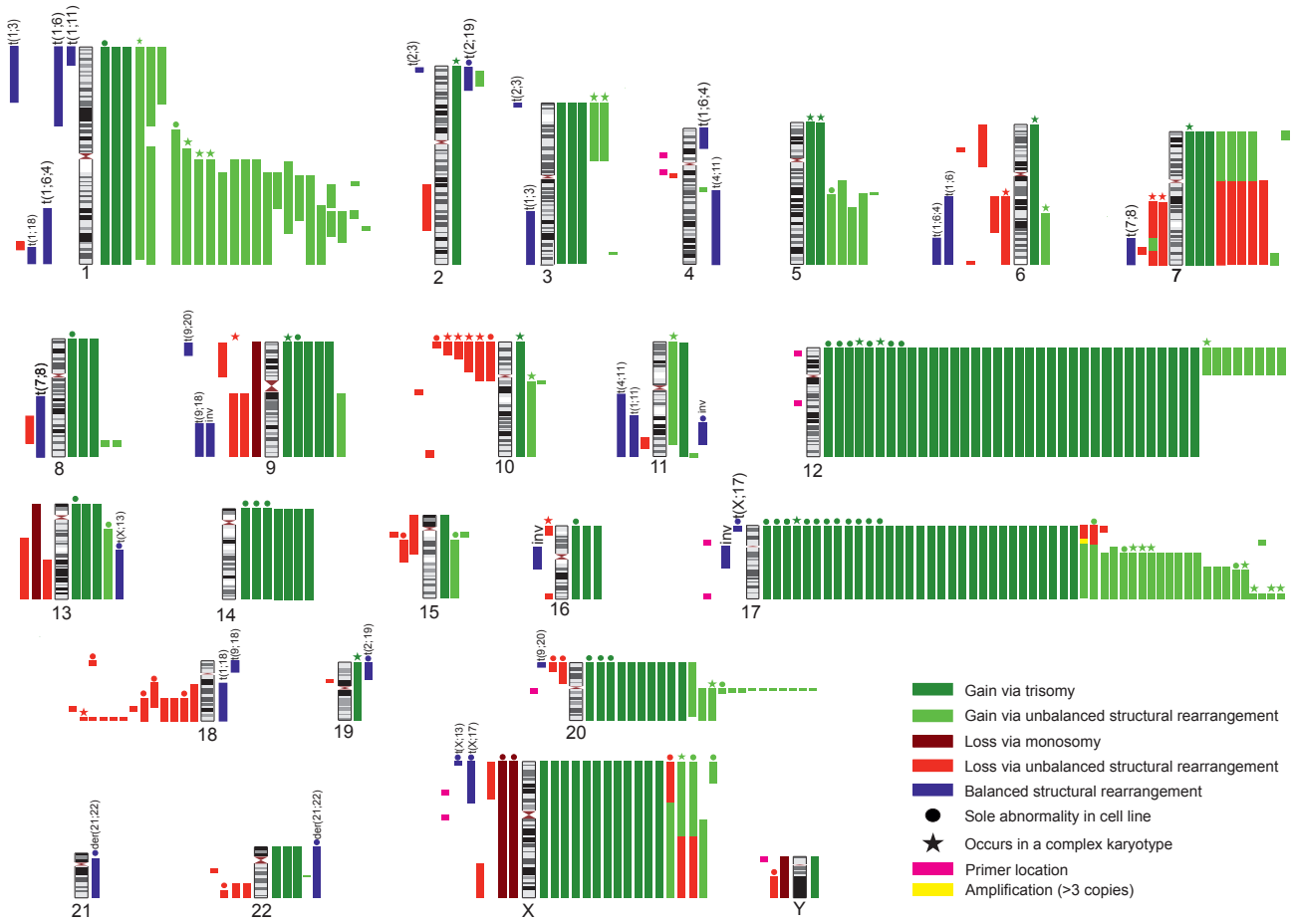
To fully exploit the potential of human PSC (hPSC) there are several bottlenecks to overcome: our research focuses on three clear themes to address these issues:

Cell characterisation and stability

Human PSC are susceptible to acquiring genetic mutations in vitro; we term this 'genetic instability'. This phenomenon is poorly understood but genetic instability results in extra copies of entire chromosomes, partial duplications in smaller regions of DNA, or sometimes partial or complete loss of chromosomes, which could compromise safety and efficacy of any therapeutic products derived from hPSC.

Chromosomes 1, 12 and 17 are often duplicated in hPSC and cells with these extra chromosomes have a proliferative advantage and 'out-compete' their normal counterparts. This means that a small number of mutant cells amongst a normal population will quickly take over the culture. The same is true for a less obvious, but equally as common mutation: a small region of chromosome 20. This mutation conveys a cell survival advantage over their normal counterparts, resulting once again, in mutant cells taking over the entire population.

Our work, and the focus of post-doctoral researcher **Oliver Thompson** at Sheffield, seeks to understand why and how genetic instability occurs in hPSC. We are looking at the biological reasons that render hPSC susceptible to



Common karyotypic abnormalities occuring in hPSC

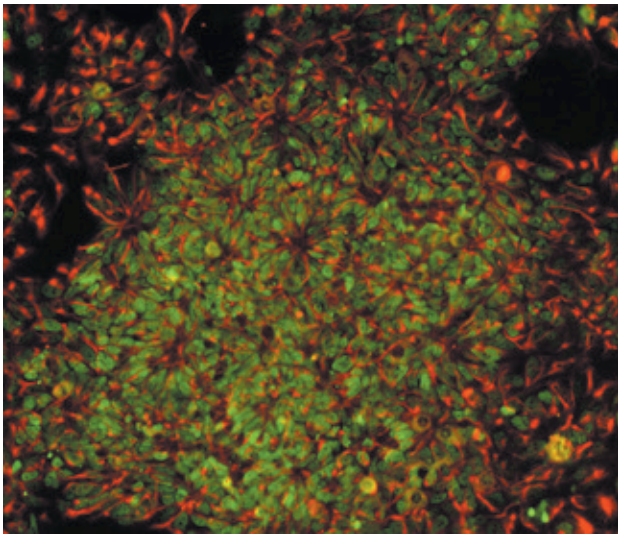
mutation, and we are seeking ways to prevent or minimise these changes. So far we have identified agents that help to suppress the growth advantage of mutant cells carrying the common gain of chrosomosome and we are determining if these conditions are effective at suppressing other common hPSC variants, for example gains of chromosomes 12 and 17.

Understanding routes to differentiation

Our research, driven by Post-doctoral researcher **Loriana Vitillo** at Cambridge, focuses 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.

Initially we have concentrated on 14 clinical-grade human embryonic stem cells derived in Sheffield (the MasterShef lines) which we have adapted to GMP-compatible culture conditions suitable for a broad spectrum of differentiation protocols and for automated manufacture. After screening their differentiation potential for endoderm and neural lineages, several MasterShef lines have been used to develop standardised protocols for the generation of intermediate neural and foregut progenitors. We will now concentrate on the characterisation and further differentiation of the intermediate progenitors, leading to standard differentiation programmes as the foundation for GMP manufacturing.

"In our first year we have exploited our complementary expertise in the biology of pluripotent stem cells, their derivation and maintenance under GMP conditions, and in cell manufacture to begin to establish a strong translational platform for the production of derivative cells for safe and effective applications in regenerative medicine." – *Peter Andrews*



MShef7 neural differentiation - NES7 p1 Nestin DACH1 merge 20x

Quality control, safety and reproducibility

Next generation sequencing (NGS) is extremely valuable for the detection of unexpected viral contaminants in bio-therapeutics and vaccines derived from cells (Dupinay et al., 2012). However, the veracity of the results can be influenced by the method of preparing test samples, the amplification protocols used, the algorithms employed to analyse the data and the quality of the databases used to analyse positive signals. This raises the possibility that NGS analysis without appropriate reference materials to control the technical variables could miss a significant and potentially lethal contamination. Furthermore, it could identify false positive signals which could prevent or delay delivery of treatment to patients.

To avoid the problems to which such false positive and negative results give rise, the PSCP through **Ross Hawkins** at UKSCB has been working to develop optimised sample extraction methods to promote sensitivity for detection of all virus groups. We are also developing novel reference materials which can be used to assure the sensitivity and accuracy of NGS analysis for adventitious agents in cell therapeutic and products. These reference materials are intended to qualify NGS test results to give continuous assurance for the absence of agents from all animal virus groups.

Hub Growth

There have been no changes to the principle contributors to the PSCP, with the exception of a new Project Manager based at the University of Sheffield (Zoe Hewitt). However, it is anticipated that in the forthcoming months new partners will be brought on board and thereby expanding the capabilities of the Hub.

Industry collaborations

Members of the PSCP are actively working with international and national developers of therapeutics including Reneuron and the Cell Therapy Catapult. This is by provision of services in-process and facility design particularly for the scale out of the production of therapeutics using automated expansion and differentiation platforms

Networking Activities

PSCP will deliver a series of four scientific workshops in areas relevant to its work. The aim of the workshops are to engage a broad range of academic scientists with relevant stakeholders from industry, including product manufacturers and developers and their supply chain, clinical users and regulators. Workshop topics chosen are of key translational concern for the field. In a two day format, they review latest developments and promote discussion to identify the perspective of the attendees on core issues both to inform the work of the community and the PSCP programme itself.

In conjunction with the Safety Hub, the first workshop was held in Sheffield in January 2015. The Science-based Assessment of Source Materials for Cell Based Medicines was its topic and it brought together leaders in hPSC biology, clinical translation, bio-manufacturing and regulatory issues to define requirements for source materials for the production of hPSC-derived therapies particularly from the perspective of product safety. A summary of the workshop content and conclusions will be published later this year.

Our second workshop on Comparability: Manufacturing, Characterisation and Controls was held in Cambridge, 14th–15th September 2015. The workshop focused on tractable approaches to addressing the challenge of demonstrating a product's equivalence after a process change.

"In the coming year we will continue our series of workshops with stakeholders, regulators and companies to inform future decision making for pluripotent stem cell-based regenerative medicine and to engage others outside PSCP and UKRMP. We also look forward to evaluating cells for the treatment of Parkinson's disease." – *Peter Andrews*

Future Directions

To assist with generating protocols for reproducible manufacture of therapeutic cells, PSCP will be engaging with clinical expertise; in the first instance in the field of Parkinson's disease (PD) through an EU funded project TRANSEURO (www.transeuro.org.uk). PD has as part of its core pathology the loss of a specific set of nerve cells (called nigral neurons) that secrete a unique chemical transmitter called dopamine. Treatment for this aspect of PD has involved grafting dopamine cells into the brain to replace the ones lost in the disease process and this was first undertaken many years ago using human foetal dopamine cells. Although it helped some patients in a dramatic and sustained way, it did not work in all cases. TRANSEURO has sought to better define which patients will do best with this approach using the dopamine cells collected from aborted foetuses, and how these cells can be best delivered and protected in the PD brain.

The first patients from this study were grafted in May 2015. However, each patient requires dopamine cells from 3 or more foetuses, and this material cannot be stored for any length of time prior to grafting, which poses major logistical problems with using foetal material for treatments. TRANSEURO has been investigating the use of stem cells as an alternative donor source and found that human PSCs (and in particular hESC) look most promising. Although there is still much work to be done, there is every expectation that a collaboration with PSCP will progress this approach with a view to undertaking human clinical trials in PD in the next 2-3 years.

Outputs

- Tools and resources
    - Cytogenetics services for stem cell work through Duncan Baker at the Clinical Cytogenetics Group in Sheffield;
    - MasterShef clinical grade hPSCs[2];

For further information or access to the tools and resources, contact the PSCP Hub project manager Zoe Hewitt:
z.hewitt@sheffield.ac.uk

2. Available through the UK Stem Cell Bank. Application forms: www.nibsc.org/science_and_research/advanced_therapies/uk_stem_cell_bank/application_forms.aspx

2.2 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 French-Constant, David Hay, Bruno Peault and Anna Williams (Jenny Cusiter/Marieke Hoeve – 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

New partners over the past 12 months

- **Keele University**
  Ying Yang
- **King's College London**
  Shukry Habib
- **University of Edinburgh**
  Pierre Bagnaninchi, James Dear
- **University of Nottingham**
  Kevin Shakesheff (Acellular Hub)
- **University of Liverpool**
  Kevin Park (Safety Hub)

What

The UKRMP Niche Hub research is focused on understanding the signals to stimulate cartilage, liver, and neural tissue repair and on developing tools and technologies for real-time analysis of the regenerating tissue. The Hub's main objectives are:

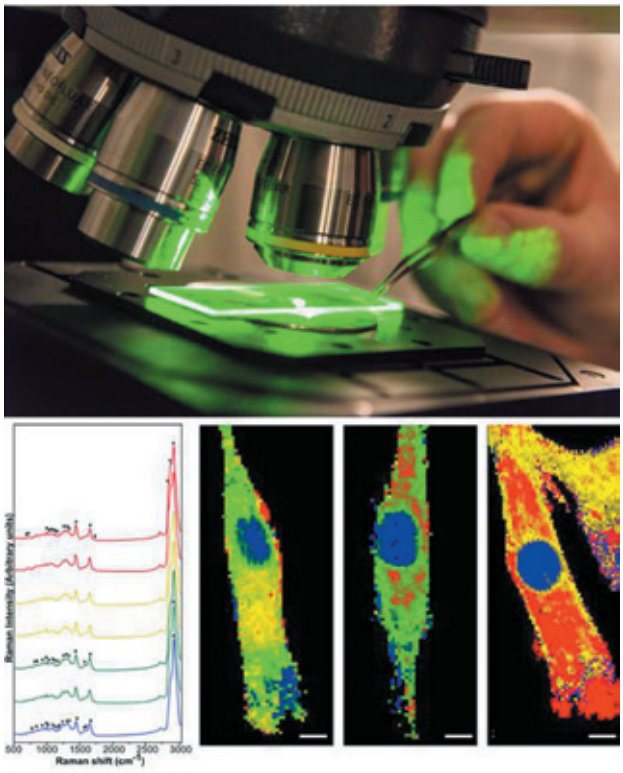
1. Identification of key factors from the study of niche biology that can promote adult and pluripotent stem cell differentiation.
2. Identification of molecular targets to direct stem cells to promote endogenous repair and thereby promote healthy regeneration of organs and tissues.
3. Identification of factors influencing the engraftment and function of transplanted cells in diseased tissues. We aim to manipulate the abnormal niche created by disease-induced inflammation and damage to improve the longevity and the function of the transplanted cells.

Scientific Developments

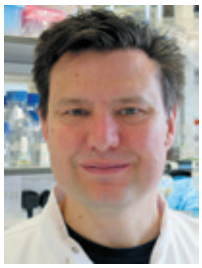
The Niche Hub has made significant scientific and translational progress over the past year.

Identification of key stem cell niche factors that promote cell differentiation

Niche Hub research is focused on defining the niche and identifying key components to influence cell differentiation across cartilage, neural and liver repair. Important developments include using spectroscopic and optical assessments of the niche using non-invasive monitoring instruments which ultimately will be translatable to the clinic, e.g. Raman spectroscopy and optical imaging. Notable outputs are the identification of Raman spectra that can successfully distinguish unlabelled myelinated, demyelinated and remyelinated brain in real-time, identification of key Extracellular Matrix (ECM) molecules that can influence stem cell chondrogenesis, and the identification of a distinct cell population with unique regenerative properties. Using proteomic analyses of the cell-matrix interface of human mesenchymal progenitor cells the Niche Hub has identified novel markers and their cell-regulatory functions (Holley et al, Stem Cell Reports 2015). We have established a supply of ECM molecules which can be used by members of the Hubs for research.



Raman microspectroscopy. Representative images of characteristic spectra within human MSCs (scale bar = 10μm); adapted from Autefage et al, PNAS 2015;112(14):4280-4285.



A key achievement is the development of a two cell-type 3D 'spheroid' culture system to study mesenchymal stromal/stem cell (MSC) differentiation and extracellular matrix deposition in different stem cell niches. This 3D model has been developed by **Stuart Cain**, a senior postdoctoral fellow in the Kielty Group who is analysing the effect of modulating selected genes upon the phenotypic behaviour of MSCs. Stuart is exploiting his model to analyse matrix organisation within a range of spheroid cultures using confocal Raman spectroscopy in collaboration with the Stevens Group. In collaboration with the Kimber Group, Stuart is developing lentiviral-based cell tagging for tracking in vivo using bioluminescence and infra-red fluorescence.

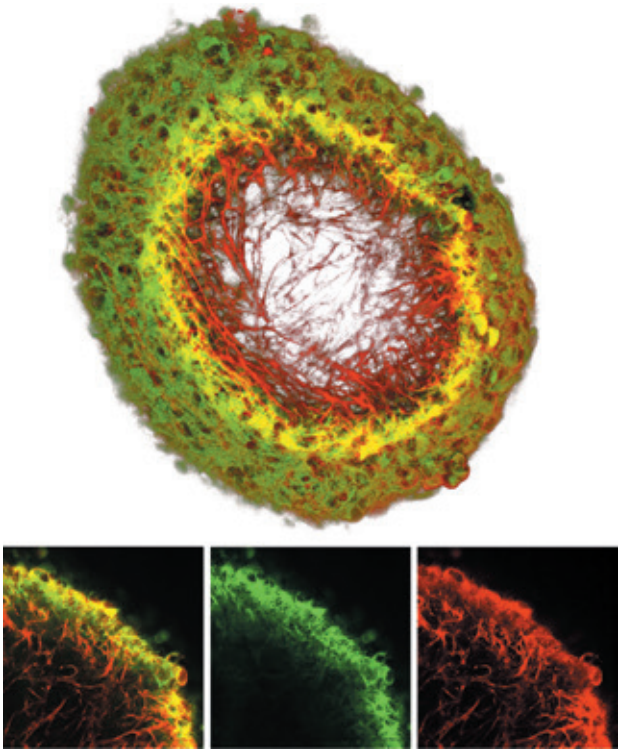
Identification of molecular targets to promote healthy regeneration of organs and tissues

Using various approaches the Hub has identified novel target molecules that influence tissue regeneration. For example, the Dear group has performed the largest profiling study of circulating microRNA in humans with acute liver injury. This has provided the team with a new tool to stratify patients with liver injury at the hospital "front door" and help select the most effective therapy. (Dear et al, Nature Science Reports 2015; in press).

The Niche Hub has developed various in vivo models to test candidate regenerative targets. Hub research has enabled novel platforms for the translation of clinically relevant signal molecules for clinical application. Highlights include: (i) the development of a high throughput and content screening platform for studies on neuronal cells, (ii) the design of a multi-modal optical imaging system for monitoring tissue engineered implant growth and maturation, and (iii) the establishment of a 3D model of the bone periosteal niche.

Identification of factors influencing the engraftment and function of transplanted cells in diseased tissues

Wei-Yu Lu, a postdoctoral fellow from the Forbes group, has characterised a population of stem cells that reside in the biliary system that can regenerate the severely damaged liver. These cells can be expanded in the laboratory prior to transplantation and can restore near normal liver architecture and function to severely damaged



Immunofluorescence microscopy of human bone marrow-derived MSCs cultured as 3D spheroids, showing differential patterns of deposition of extracellular matrix (fibronectin green, fibrillin-1 red).

liver (Lu et al. Nature Cell Biology 2015). Future work aims to define the transplantability of such cells isolated from human livers that are unsuitable for whole organ liver transplantation. In collaboration with Nick Tomkinson and team, the Forbes Group will identify small molecules that can directly activate the liver stem cells to improve liver regeneration.

"A challenge for the regenerative medicine field is to have real-time point of care assessment of the form and function of regenerating tissue. In the Niche Hub we have formed extensive collaborations between experts in tissue regeneration and RAMAN spectroscopy to develop much needed expertise in this area." – *Stuart Forbes*

Hub Growth

Partnership funding

Pierre Bagnaninchi, Ying Yang and Shukry Habib are collaborating with Alicia El Haj on the project "Defining a translational niche for tissue engineered products" that will generate dynamic tissue bioreactor designs, tunable targeted nanomaterials and extend real time imaging capacities.

Tamir Rashid has expertise in the production of iPSC-derived hepatocytes and is collaborating with Anil Dhawan, Fiona Watt and Shukry on the ECM interactions of human iPSC-derived hepatocytes, with the goal of improving the transplantation of encapsulated hepatocytes to treat acute paediatric liver failure.

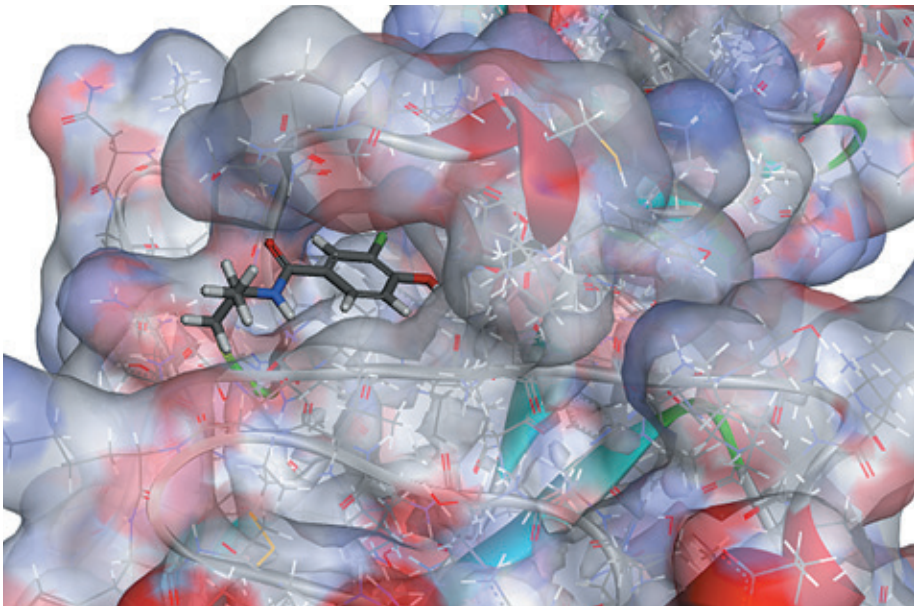
Industrial collaborations

Various new industry partnerships have developed over the past year, including:

- Development of a point of care platform for measurement of lead microRNAs, in collaboration with Applied Enzyme Technology (Dear, Edinburgh).
- CNS slice cultures as a tool for remyelination research, in collaboration with GSK (Williams, Edinburgh).
- Identification of inhibitors of the Semaphorin 3A Receptor Neuropilin-1 interaction on oligodendrocyte precursor cells to promote remyelination in Multiple Sclerosis, in collaboration with Sanofi-Genzyme (Williams, Edinburgh).

Networking Activities

The UKRMP Niche Hub is planning various networking activities for the coming 12 months, including workshops covering the topics 'Cell Therapies: Preclinical to Clinical Translation', and 'Small Molecules for Regenerative Medicine'.



Schematic of a docked hit molecule from virtual screenings that will be progressed for in vitro biological evaluation.

"A major focus of the Niche Hub is the production of cells that are potentially suitable for development as a clinical therapy. I am pleased that the Cell Therapy Catapult is engaged in this regard, to identify potential projects at an early stage and help develop their translational pathway." – *Stuart Forbes*

Future Directions

The Niche Hub aims to drive its research towards clinical therapies through direct cell therapies and by targeting and improving the "endogenous repair" of damaged tissue. The collaborations that have developed both within the Niche Hub and with other UKRMP Hubs will accelerate the progress of regenerative medicine from the laboratory to the clinic.

Cartilage regeneration. The Hub aims to generate stable stem cell derived chondrogenic cells in 3D environments capable of providing high quality hyaline cartilage repair for joint defects in acute sports injury and osteoarthritis. The Hub's non-destructive tissue- and cell imaging tools are a critical component of this effort.

Liver therapy and repair. Exploiting its expertise in the production of human hepatocyte-like cells from various stem cell sources, the Hub will collaborate with the Safety and Efficacy Hub and the Cell behaviour, Differentiation and Manufacturing Hub to facilitate their use as a clinical cell therapy.

Neuronal repair. The aim is to develop drugs that improve CNS remyelination in diseases such as Multiple Sclerosis and spinal cord injury. This involves the identification of potential small molecule targets using newly developed high content screening assays and validation in in vivo model systems.

The targeting of therapeutic cells to diseased tissues constitutes a key Hub-Hub collaborative research programme, aiming to develop and test 'GMP usable' particles to enhance cell delivery to various organs, including the liver.

Outputs

- Publications as a direct result of Hub activity (see Annex 4)
- Tools and resources
    - Biological/cell handling and assessment equipment, providing screening platforms for studies on cells in high throughput and high content format;
    - Protocols and advice on an ex vivo murine CNS slice culture system that allows investigation of myelination, demyelination and remyelination, which can be used as an initial reliable screen to select the most promising remyelination strategies (reference PMID:21515259)

For further information or access to the tools and resources, contact the Niche Hub project manager Marieke Hoeve:
m.hoeve@ed.ac.uk

2.3 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

New partners over the past 12 months

- **University of Liverpool**
  Harish Poptani
- **University of Glasgow**
  Marc Clancy
- **University of Manchester**
  Kostas Kostarelos
- **University College London**
  Quentin Pankhurst
- **University of Illinois, Chicago**
  Natalia Nieto

What

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.

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 methods to monitor the biodistribution and behaviour of transplanted cells in well-characterised disease models using novel imaging probes, state-of-the-art multimodal imaging platforms, and cutting-edge quantitative bioanalysis technologies, to relate the disposition of administered cells to the physiological, pharmacological and pathological responses of the host tissues that the cells populate.

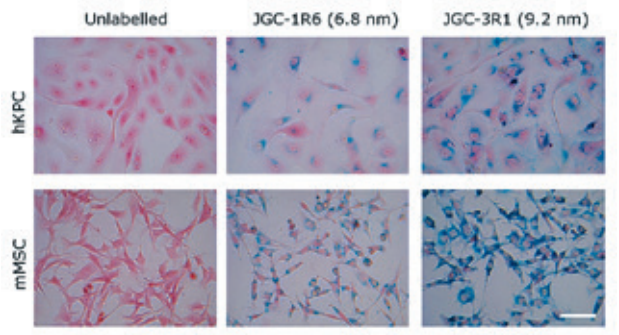
We are now in a position to address fundamental scientific issues in regenerative medicine in a comprehensive fashion.

Scientific Developments

Over the past 12 months, the Hub has established a toolkit of novel nanoprobes and reporters for cell tracking, complemented with state-of-the-art multimodal imaging. In tandem with the Hub's interdisciplinary expertise, we are employing these resources to work towards our objectives of evaluating safety and efficacy of transplanted cells in relevant pre-clinical models. Of particular note are the following:

Superparamagnetic iron oxide nanoparticles (SPIONs)

Mike Barrow, working under the supervision of Dave Adams and Matt Rosseinsky, has developed a library of dextran coated SPIONs with varying surface charge and iron oxide core size, possessing the ability to be directly internalised by cells for organ-focussed tracking using Magnetic Resonance Imaging (MRI). Increasing surface charge has led to six-fold increase in uptake of particles into a murine mesenchymal stem/stromal cell (MSC) line and higher MRI contrast, with negligible change in cell viability. The trend of increased uptake and viability with SPIONs of larger core size has also been observed with mouse bone marrow-derived macrophages (BMDMs).



Increased SPION core size improves cell uptake. Human kidney cells and mouse MSC labelled at 50 µg [Fe]/ml for 24 hrs. (Scale bar = 25µm.)

Informed by continuous feedback from cell biology a greater understanding of how various SPIONs interact with cell types is now known, allowing Mike to develop new nanoparticles with optimised uptake, retention, and causing minimum interference with cell function. This information is providing the basis for a quantitative dataset for the effective use of SPIONs to use across the Hub and UKRMP as a whole.

Gold nanorods (GNRs)

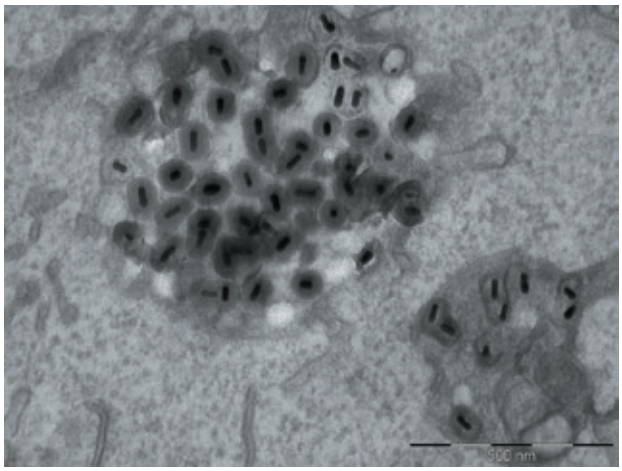
GNRs, which unlike SPIONs cannot be degraded by cells, have been synthesised with different ligands and coatings. GNRs serve as contrast agents in photoacoustic imaging (PAI), an emerging non-invasive imaging technology which allows whole body distribution to be observed.

Murine MSCs have been successfully labelled with both PEG-GNRs and silica-coated GNRs and monitored in vivo using PAI. Working with these two types of GNRs ensures versatility and sensitivity; PEG-GNRs can be further functionalised linking with peptides, proteins, etc., and silica-coated GNRs with different shell thicknesses have been generated. It is important for GNR cores to be separated by at least 50nm to minimise plasmon coupling inside cells which ensures preservation of the optical signature and, therefore, give much greater sensitivity than uncoated GNRs.

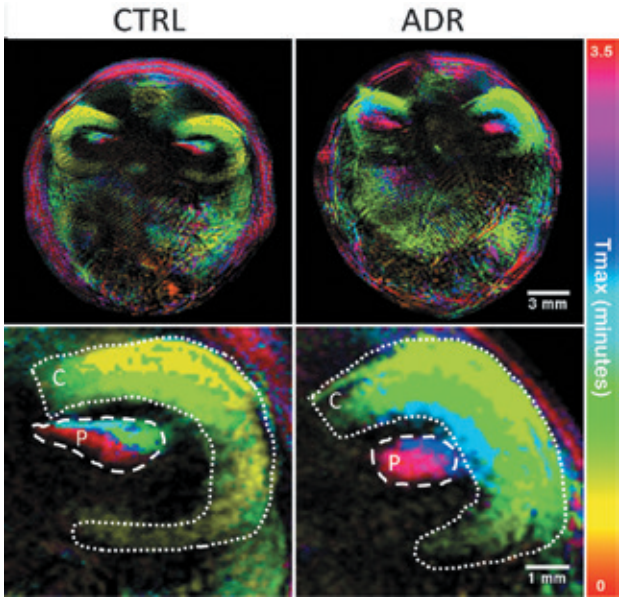
After confirming GNRs are not toxic and are colloidally stable in vitro, therapeutic cells are labelled with GNRs for tracking in pre-clinical injury models using PAI. Currently we are labelling luciferase+ MSCs with GNRs and are able to track the biodistribution and proliferation of these cells in the same animal over time, using PAI and Bioluminescence imaging.

Monitoring efficacy of regenerative medicine therapies in individual animals over time

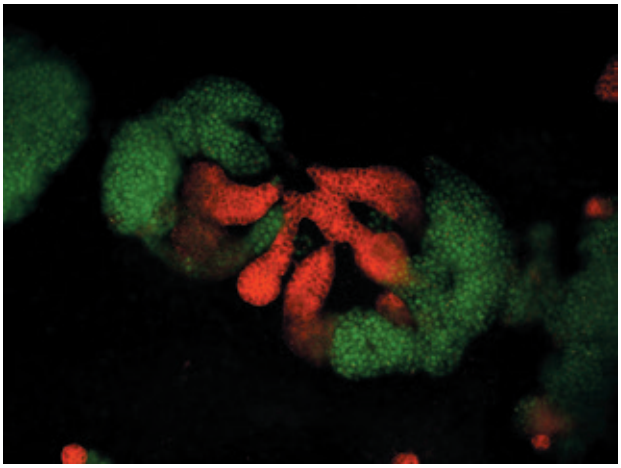
Using novel technologies to measure kidney function non-invasively in the adriamycin (ADR) mouse renal injury model (which mimics the human disease of focal segmental glomerulosclerosis), we can predict the onset and extent of glomerulosclerosis; this has not previously been possible in small rodents. The combination of a transcutaneous device, that can assess glomerular filtration rate in conscious mice, and Multispectral Optoacoustic Tomography (MSOT), that can directly visualise mouse kidneys and monitor function, gives a significant advantage because until now, no other biomarker has been able to predict structural damage in the kidney.



Labelling of mouse MSCs in vitro with Silica Coated GNRs



MSOT temporal colour maps showing the clearance of IRDye in ADR-administered mice (C=cortex, P=pelvis). Images generated in collaboration with iThera Medical.



Formation of 3D organelle-like structure between ECAD+ Epithelial cells (red) and WT1+ nephron progenitors (green) differentiated from hES cells

"The Hub has made significant progress developing novel tools for cell tracking. By utilising these agents with cutting-edge imaging technologies, in combination with functional and translational mechanistic biomarkers we are gaining new insight into the mechanisms whereby administered cells are ameliorating injury." – *Kevin Park*

Lentiviral vectors for cell tracking

Post-doctoral fellow **Ioannis Bantounas** has developed lentiviral vectors for tracking cells using bioluminescence and fluorescent imaging and these are now being used in vivo in hESC-derived cells. Using robust assays for testing cell proliferation, survival and cytotoxicity in hESCs and their derivatives, Ioannis is assessing stem cell viability and phenotype following incorporation of these reporter systems. He is also using CRISPR/Cas9 technology to insert reporter genes under the control of endogenous, lineage-specific promoters in hESCs, in order to trace their differentiation in real time in preclinical models.

In addition to this work, using efficient recently-published protocols, Ioannis is also differentiating hESCs to nephron progenitors, the safety and efficacy of which will be tested in the Hub kidney disease models.

Hub Growth

Partnership funding

The Hub's capabilities have been expanded through its partnership funding by implementing step changes from the original programme of work based on our two main areas of interest, liver and kidney.

The new avenues of research include investigating adipose-derived regenerative cells to improve the health of donor kidneys, led by clinician Marc Clancy; novel imaging probes for cell tracking developed by Kostas Kostarelos; magnetic targeting of therapeutic cells, Quentin Pankhurst; and extending our links with the Niche Hub with a focus on novel mechanistic biomarkers for macrophage-based therapeutics incorporating international expertise from Natalia Nieto, expert in mechanisms and animal models of liver fibrosis, giving both Hubs direct benefit.

Other

The Hub received a substantial capital award from MRC to develop a Centre for Pre-Clinical Imaging at the University of Liverpool. Along with established technologies at UCL and University of Manchester, this has significantly enhanced our in vivo imaging capabilities. Professor Harish Poptani, a new Hub collaborator based at Liverpool, is working alongside imaging colleagues at Manchester and UCL. Harish, appointed in 2014 from University of Pennsylvania, has expertise in small animal imaging, with particular expertise in magnetic resonance imaging (MRI) in both the pre-clinical and clinical setting.

Industrial collaborations

The Safety Hub is working with GE Healthcare on a short-term project to investigate the suitability of one of its products as a cell tracking agent, which may lead to further collaborations with Safety Hub partners. New Hub partner, Marc Clancy in collaboration with SME Cytori, is isolating adipose derived regenerative cells from body wall fat of rats.

Networking Activities

A key step before new medicinal products can be routinely applied is defining essential safety assessment criteria in the manufacturing process to enable reliable rapid translation of treatments with potential. This is particularly so for cell-based regenerative medicinal therapies. Consequently the PSCP Hub and the Safety and Efficacy Hub held a

"A key focus going forward will be to expand our multimodal imaging strategies so that we can determine the safety profile for administered stem/progenitor cells, for example to assess whether they differentiate appropriately, maintain their phenotype, and/or present any risk of becoming tumourigenic in the longer term." – *Kevin Park*

workshop in January 2015, bringing together scientists, regulators, industry and other stakeholders, to develop a clearer understanding of the potential hazards to inform the UKRMP programme on the new methodologies needed to assess and control these risks. A review from this meeting will be published later this year.

A workshop on 'Nanoparticles for Cell Tracking' was held in Liverpool in September 2015, with the aim of assessing developments in the field and identifying short- and long-term strategies for stem cell tracking.

Future directions

Directing the differentiation of human pluripotent stem cells to nephron progenitors. Given Adrian Woolf's extensive knowledge of kidney development, combined with Sue Kimber's experience of directing human pluripotent cells to the mesodermal lineage (the lineage from which nephron progenitors are derived), we have included testing the efficacy and safety of hESC-derived nephron progenitors in the Hub kidney disease models; the inclusion of these cells adds significant value to our Hub programme. The abilities of such differentiating human kidney cells to engraft into native kidneys and ameliorate chronic kidney disease will be assessed within the Hub.

Outputs

- Publications as a direct result of Hub activity (see Annex 4)
- Tools and resources
    - Gold Nanorods - Silica coated GNRs, and PEG-capped GNRs which offer the possibility to link other molecules of interest (this option on a case by case basis).
    - 2nd generation Lentivirus vector pHIV-iRFP720-E2A-Luciferase for bicistronic expression of iRFP720 fluorescent protein and firefly luciferase via an E2A element from the EF1alpha promoter (also available with an IRES element instead of E2A).
    - Lentivirus plasmids (functionally tested in HEK293 cells):
        - pHIV-Tyrosinase-eGFP (as a fusion protein)
        - pHIV-Tyrosinase-eGFP-IRES-Luciferase
        - pHIV-Tyrosinase-IRES-LuciferaseResources
    - In vivo imaging facilities at Liverpool, Manchester and CABI, UCL, including 3T, 7T and 9.4T MRI scanners, Photoacoustic, bioluminescence, fluorescence, PET-CT, SPECT-CT, and ultrasound imaging technologies for evaluating safety and efficacy of RMTs in animal models. Photothermal microscope, and cell tracking velocimeter for nanoparticle characterisation. Fluorescent lightsheet microscope.

For further information or access to the tools and resources, contact the Safety Hub project manager Claire Hutchinson:
Claire.Hutchinson@liverpool.ac.uk

2.4 Acellular approaches for therapeutic delivery Hub

Director: Professor Kevin Shakesheff, University of Nottingham (pictured). Co-Director: Professor Molly Stevens, Imperial College London

Who

- **University of Nottingham**
  Kevin Shakesheff, Felicity Rose and James Dixon (Sharon Crouch – Project Manager)
- **Imperial College London**
  Molly Stevens
- **Southampton University**
  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)

New Partners over the past 12 months

- **Cardiff University**
  Alastair Sloan
- **MRC Centre for Regenerative Medicine, University of Edinburgh**
  Stuart Forbes (Niche Hub)
- **University College London**
  Robin Ali, Richard Day
- **University of Birmingham**
  Liam Grover
- **University of Cambridge**
  Stefano Pluchino
- **University of Liverpool**
  Sajjad Ahmad, Rachel Williams
- **University of Manchester**
  Sue Kimber (Niche Hub), Ailine Miller, Stephen Richardson

What

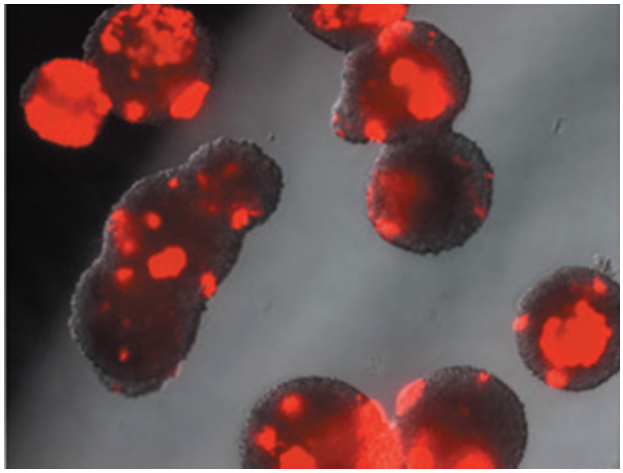
We aim to create new advanced materials and technologies that protect and nurture cells from the final steps of manufacturing through to tissue formation within the patient. Materials can redefine the local environment of cells post-administration and can protect cells from damaging conditions throughout the product life cycle. Therapeutic delivery systems build on principles of biomaterials design and drug delivery to create final products in which the efficacy of cell therapies or the mobilisation of the patient's own stem cells are maximised.

The second year of operation has seen excellent progress in all our projects with publications, patents and presentations on new materials, nanotechnologies and tissue engineering. Especially pleasing has been the career development opportunities for staff at the early stages of their research endeavours. We have seen a number of new groups join the Hub to focus on pre-clinical translation in a wide range of tissue types. These Clinical Spokes and Partnership Projects have brought a clinical and commercial focus to our science and we report on some of the early successes below.

Scientific Developments

Protein fusion technology

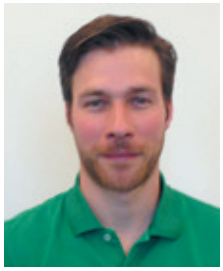
Protein transduction domains (PTDs) are powerful non-genetic tools that allow intracellular delivery of molecules to modify cell behaviour. **James Dixon** (University of Nottingham) has developed a novel fusion protein technology that enables efficiencies of up to two-orders of magnitude higher than previously reported in cell types considered hard to transduce. We are using this technology to program human mesenchymal stem cells into bone and cartilage for orthopaedic regenerative medicine. We have filed four patents resulting from this work and have exploited the Hub network/format to adapt our technology to benefit those working in other UKRMP Hubs.



Cell-type specific transduction of monomeric red fluorescent protein in differentiating embryoid bodies (mouse embryonic stem cells)

Biomaterials to prevent fibrosis

Fibrosis is a result of excess of extracellular matrix accumulated within a tissue in reaction to inflammation. Attempts at developing therapeutic interventions to mitigate epithelial-to-mesenchymal transition (EMT) and prevent fibrosis have been plagued by off-target secondary effects. The goal of the research project of post-doctoral fellows **Jenny Puetzer** and **Jean-Philippe St-Pierre** (Imperial College London) is to develop a functionalised biomaterial that can be interfaced with an epithelial layer to specifically inhibit EMT locally via integrin interactions and thus reduce the fibrotic response.



The Stevens Group has developed an electrospun PCL membrane functionalised with the fragment via a polydopamine coating and demonstrated that it could inhibit the phenotypic transition of epithelial cells in response to inflammation, whilst their release of degradation enzymes is also suppressed.

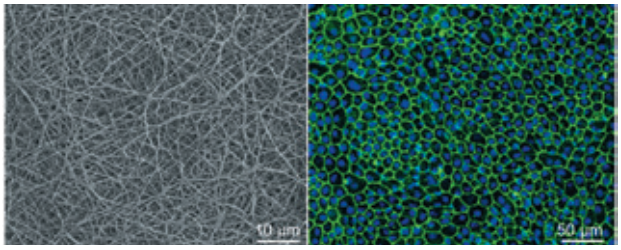
Clinical spokes

It is early days for the 8 Clinical Spokes but these teams have some promising early results and work from Sheffield and Liverpool Universities is highlighted here.

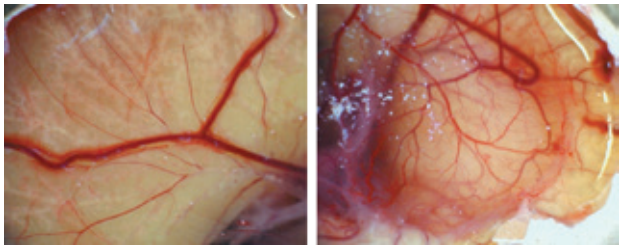
Skin Repair: Non-healing wounds are a silent but costly epidemic for health care systems worldwide. While tissue engineered skin can be produced for patients with extensive skin or chronic wounds it will fail to survive in the absence of blood vessels connecting the tissue with the body's vasculature.

The technology being developed is the use of small injectable biodegradable microspheres to deliver VEGF (vascular endothelial growth factor) which instructs the endothelial cells lining nearby vessels to sprout and grow towards the hypoxic tissue. Sheila MacNeil and Anthony Bullock at Sheffield have shown these microspheres promote growth and migration of endothelial cells, thus taking a significant step forward to effective skin repair for currently non-healing wounds.

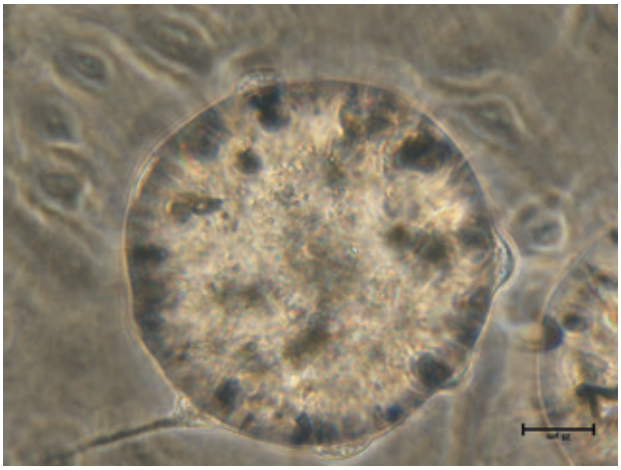
Anterior Cruciate Ligament (ACL): Traumatic rupture of the ACL is a frequent occurrence in young, highly active individuals and requires surgical reconstruction with a soft tissue graft to restore joint stability and function. Healing of the graft at the site of bone attachment is slow, impeding return to recreational and occupational activity and also increasing the risk of developing early onset degenerative diseases such as osteoarthritis. To address this significant clinical need Rachel Oldershaw and team at Liverpool are using the patient's own stem cells, combined with degradable polymer scaffolds that facilitate their surgical transplantation and retention at the site of surgery as well as promoting effective formation of new tissue.



Nanofibrous PCL scaffold (136 ± 5.39 nm fibre diameter) and mESC-derived RPE cells immunostained for tight junction proteins.



Increased vasculature growth promoted by VEGF loaded microspheres. Fertilised chicken egg chorioallantoic membranes, control left, VEGF treated right.



Brightfield image of human mesenchymal stem cells attached to the surface of PLGA microparticles

Hub Growth

Partnership funding

The addition of new partnership projects has expanded the capabilities and expertise within the Acellular Hub.

Projects include that of Richard Day's group at UCL who has developed an innovative therapeutic system involving attachment and growth of muscle cells on degradable cell microcarriers composed of TIPS microparticles. To facilitate delivery of muscle cells, particularly into sub-optimal inflamed tissue environments that exist following trauma or injury, they are investigating the co-delivery of a drug from the microcarriers that will increase the likelihood of muscle cell survival.

SEM micrograph of PLGA microspheres

Rachel Williams and Sajjad Ahmad (University of Liverpool) have developed cultured synthetic corneal endothelial grafts composed of a single-layered human corneal endothelium on their novel peptide gel. Diseases of the corneal endothelium (such as Fuchs endothelial dystrophy) result in significant loss of vision and are one of the commonest reasons for corneal transplantation. Optimisation of the properties of the gel, the surface modification to promote the growth of a stable endothelium and the surgical implantation procedure could lead to improved treatment options to overcome these blinding conditions.

Additionally, through the partnership funds we have been able to extend and complement on-going work and carry out a valuable proof of concept study trial in sheep to monitor and control stem cell behaviour using magnetic nanoparticles.

Industry collaborations

We continue to develop relationships with our industry partners; this year PLGA microparticles were supplied to Neotherix for testing in their systems. The results are very positive and we look forward to expanding the collaborative research programme in the coming 12 months.

Networking Activities

A joint meeting with the National Centre for Replacement, Refinement and Reduction was held in April 2015 at the Stevenage Bioscience Catalyst. The meeting brought together industrial teams using in vivo tests for efficacy and safety testing, UKRMP Hub representatives and many other

"In the first 2 years of the Hub we have patented and exemplified new classes of materials and molecular technologies that hold great promise in controlling stem cell differentiation. Through our partnership awards and pre-clinical spokes our collaborative teams are using these technologies to develop therapies able to regenerate and repair musculoskeletal tissues, cornea, retina, nerve cells within the brain, skin, liver and teeth". – Kevin Shakesheff

"The next and equally exciting phase of the Hub's maturation is to exemplify the clinical potential of new delivery technologies and materials. We have a number of breakthrough technologies that should be the foundation for commercial and clinical successes for the UK" – *Molly Stevens*

academics to explore whether regenerative medicine, organ- and cell-based technologies offer significant potential for predicting drug product failure prior to clinical (human) or preclinical (animal) trials. A meeting report will be published in late Autumn 2015 with five recommendations for future structures and activities that can capitalise on the UKs strengths in drug discovery, stem cell science and non-animal technologies.

We were delighted that Hareklea Markides, a Hub postdoc in the El Haj group, won the award for best oral presentation at the 2015 Tissue and Cell Engineering Society Annual Meeting for her talk entitled "Remote cell activation for bone regeneration – a preclinical animal study".

Future Directions

The remaining 2 years of our Hub plan see a shift from establishing and developing core technologies to their application in pre-clinical demonstrators. This will be delivered through the clinical spokes and new partnerships, which are especially important in accelerating translation.

The Hub is keen to work with new groups who wish to improve cell and drug delivery and welcome external approaches by international groups and companies to engage in collaborative translational research.

Outputs

- Publications as a direct result of Hub activity (see Annex 4)
- Tools and resources
    - PLGA porous microspheres for use as injectable cell carriers;
    - Novel delivery protocols for proteins and modified RNAs (patent number WO2015092417);
    - Biofunctionalised cryptic extracellular matrix to target epithelial –to – mesenchymal transition;
    - Electrospun membranes;
    - Southampton Imaging is a portal to high end microscopy and imaging facilities within the University of Southampton; imaging modalities includes phase imaging microCT, serial block face SEM imaging and light sheet microscopy.

For further information or access to the tools and resources, contact the Acellular Hub project manager Sharon Crouch:
Sharon.Crouch@nottingham.ac.uk

2.5 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

What

We are pooling our collective knowledge and sharing experimental tools to answer three 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?

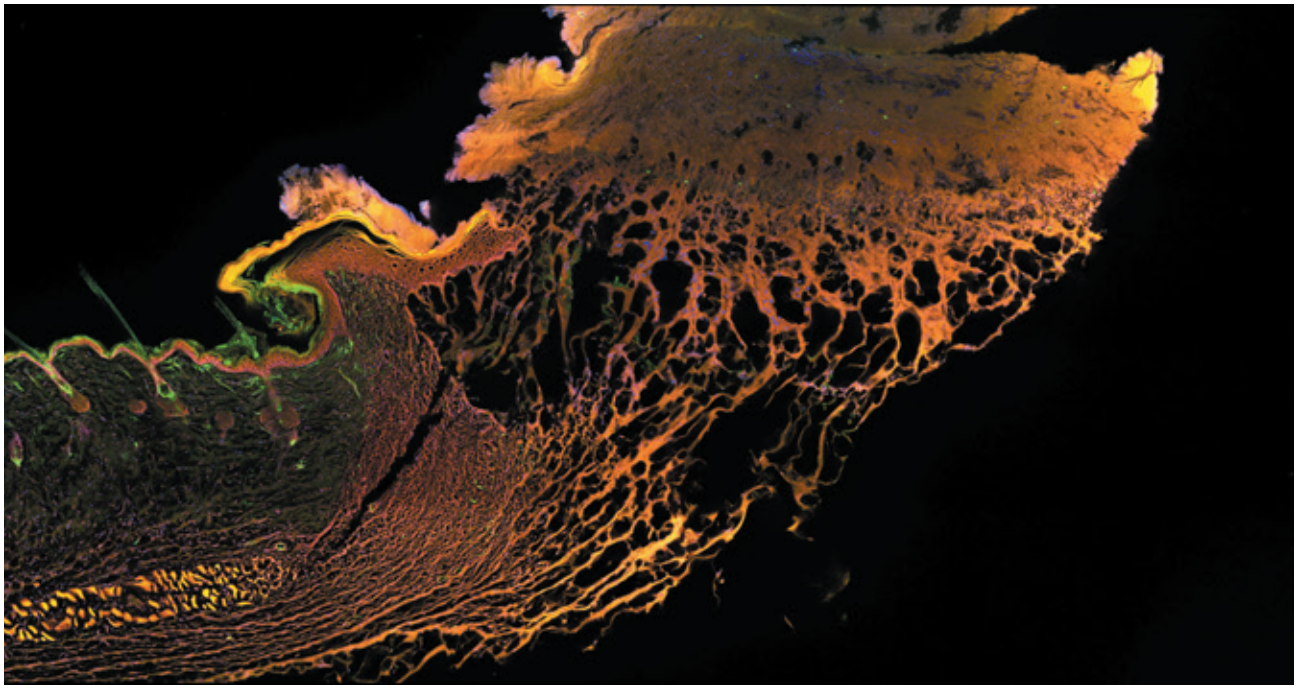
Scientific Developments

How do differentiated cells signal to the host innate and adaptive immune system?

There is particular interest in the therapeutic potential of cells that have been differentiated from pluripotent stem cells, but their immunogenicity is poorly understood. Our focus here is to carry out a systematic analysis of how differentiated cells signal to the immune system. We are achieving this by comparing cells differentiated from pluripotent stem cells with human cells isolated directly from the appropriate tissue. Our investigators at Birmingham University, Philip Newsome and his postdoctoral research assistant Jasmine Penny, have been optimising hepatocyte isolation from human liver and are currently sending human adult hepatocytes to Raul Elgueta at King's College London to begin immune phenotyping assays. Raul has also been characterising IPS-derived hepatocyes and is investigating whether these cells can induce the responses of allogeneic T cells.

A particular tissue of interest within the Hub is Retinal Pigment Epithelium (RPE) and RPE tissue production has now been established by **Peter Gardner**. Peter is a postdoctoral research assistant who studies immune regulation in the eye in the Robin Ali group at University College London. Although the eye is widely regarded as an immune privileged site, Robin had previously established that persistence of allografts is limited by immune responses. At present, Peter is investigating whether fibroblast lineages with different wound healing properties are also present in retinal tissue. Peter is also providing ES-derived RPE for immunoreactivity assays to other co-investigators, such as Giorgia Fanelli in the Sack's lab at the MRC/KCL Centre for Transplantation, in order to determine how these cells signal to the innate and adaptive immune system.

Giorgia is currently characterising the immune phenotype of RPE cells and is starting to characterise cellular responses to hypoxia, a process that underpins the activation of pro-inflammatory and fibrotic pathways in susceptible cells. Additionally, Giorgia and Sian Harding at Imperial College are in the process of setting up immunoreactivity assays in RPE and hepatocytes.

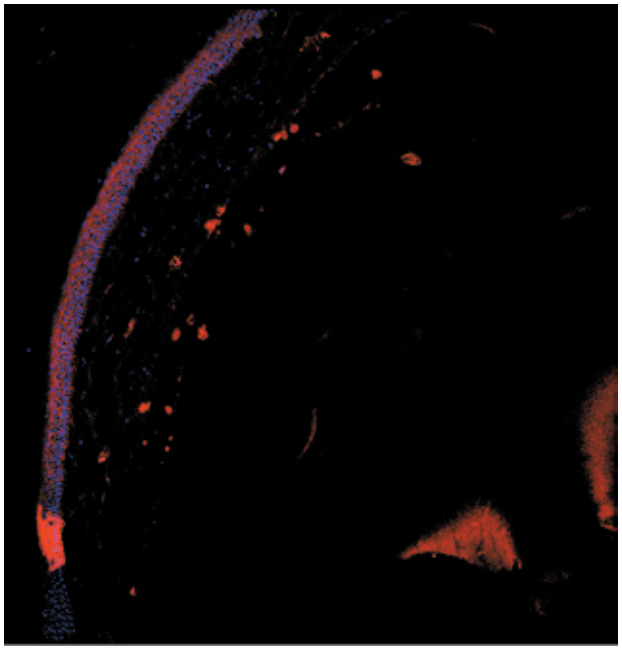


Immunostained mouse skin wound bed 7 days post-insult, lineage tracing cells (green) background (orange). The wound bed lacks hair follicles and is in the process of forming a scar.

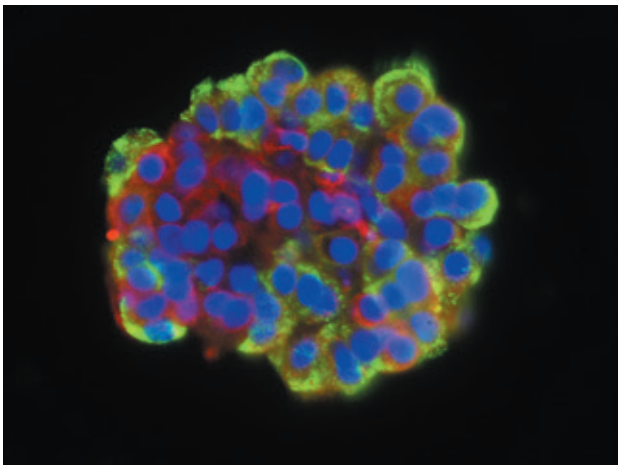
Helen Marshall is characterising appropriate markers (e.g. HLA-1 and 2) in islet populations in response to hypoxia. Specifically, she is investigating the hypoxic gene signature and the secretome in cultured human islets. Helen is part of the Diabetes Research Group at Newcastle University and is supervised by Professor James Shaw. She is interested in islet transplantation and the mechanisms behind graft failure. Recently published clinical data from the group has shown that development of donor specific antibodies within the first month post transplantation is a powerful predictor of rapid graft loss despite maintained immunosuppression. Helen is currently trying to model hypoxic and cytokine stress in isolated human islets to determine the impact on HLA Class I and II expression. This work will inform future studies by other co-investigators with both adult and stem cell differentiated cells from a range of tissues.

How do transplanted cells provoke adaptive immune responses?

Raul has also been able to utilise connectivity with the WT/MRC Human Induced Pluripotent Stem Cell Initiative (HipSci), a national iPS cell resource. HipSci's overall aim is to generate iPS cells from both healthy individuals and those with monogenic disease and to use these cells to discover how genomic variation impacts on cellular phenotype and to identify new disease mechanisms. Raul is working with cell lines from the HipSci programme and characterising these cells for their immunostimulatory capacity. In the long term, the hope is that we will be able to generate various differentiated cell types form the same, well characterised cell line that will be suitable for successful transplantation and sustained engraftment in preclinical models. In parallel, Raul is also currently establishing a liver injury model, which will be one of the models used in humanised mice



Fibroblast reporter (red) in a mouse cornea



Human islets stained for insulin (green) and HLA class I (red)

within the Hub for assessing the effectiveness of various immunoregulatory cell therapy approaches.

How does the inflammatory niche contribute to endogenous repair and influence the fate of transplanted cells?

Fiona Watt at King's and Caetano Reis e Sousa at the Francis Crick Institute have been providing transgenic mice to the other investigators for the study of lineage-traced fibroblasts, macrophages and dendritic cells in the retina, intestine, heart and skin. These immune responsive cells are heavily implicated in endogenous repair. Initial investigations are assessing fibroblast labelling in RPE and cardiac tissue. In addition, the Watt and Dazzi labs are analysing human skin fibroblast populations for their immunomodulatory properties

Networking Activities

We are currently in discussions about potential collaborative partnerships with companies focusing on high throughput cell phenotyping and skin fibroblasts. The Hub has also been able to leverage funding from the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London for pre-clinical research on human skin fibroblast subpopulations. More broadly, the Hub is seeking to establish collaborative projects with the PSCP, Safety, Acellular and Stem Cell Niche Hubs that will further expand both the capabilities and interconnectivity of all Hubs across the entire Platform.

The Immunomodulation Hub is holding a Workshop in December entitled "Immunomodulation of Stem Cells 2015" that will take stock of the current progress at the international level, involving delegates from academic and industrial stem cell and immunology communities.

Future Directions

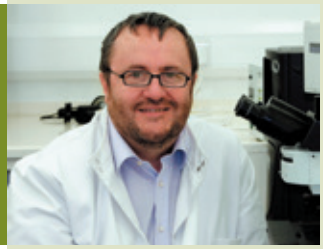
The uniqueness of this Hub is that we come from diverse clinical and non-clinical research backgrounds covering stem cell biology, innate and adaptive immunity, and whole organ transplantation. Now that we have a full team comprising co-investigators and postdoctoral research assistants, it is an exciting time as new synergies and collaborations begin to emerge within the Hub. From our work, we hope to develop a comprehensive understanding of immune system responses to allogeneic versus adult donor cells, as well as comparative profiles of donor cell therapies versus biological and materials. We expect these outputs to be hugely influential on future clinical trials in regenerative medicine

For further information contact the Immunomodulation Hub project manager Curtis Asante: curtis.asante@kcl.ac.uk.

"We have currently been investigating the role of different fibroblast subsets in tissue immunomodulation by comparing the gene expression profiles of fibroblasts of different origins. Our preliminary findings are exciting because they reveal unexpected differences in cytokine profiles, which we are currently investigating further. " – *Fiona Watt*

3. Disease Focused Projects

Second stage funding for the Platform is supporting five disease-focused projects undertaking translational programmes in areas ripe for clinical development.

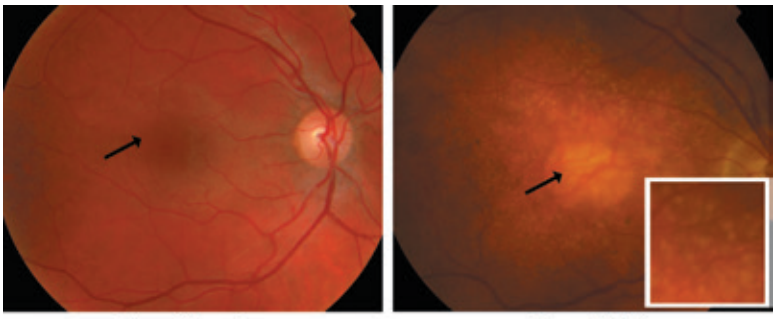


3.1 Professor Pete Coffey (University College London)

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 (AMD).

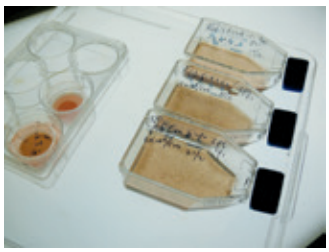
"Our major goal is to understand which cell source may determine the best outcome for cellular therapies."

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. Following on from this, to use the technology of induced pluripotent stem cells (iPSC) from cells derived from patients themselves, to produce a cell therapy which is effective in replacing those cells that deteriorate and die in AMD.



Macular region of a healthy patient and one with dry AMD, the drusen (small yellow deposits are magnified)

In November 2014, we met with the Medicines and Healthcare products Regulatory Agency (MHRA) to discuss our plans to treat AMD patients. The meeting was very informative centred on two issues: the manufacturing of iPSC's to clinical grade standard (cGMP) and the amount of pre-clinical safety testing that would be necessary for each individual patient cell line. The project from January 2015 has had two major goals: cGMP manufacturing of iPSC's and gaining ethical approval to take skin samples from individuals suffering from AMD. Prof Amit Nathwani and Dr Sajjida Jaffer have successfully transferred the production of clinical grade iPSC to the GMP facilities at the Royal Free Hospital with Dr Mark Lowdell. In September, the MHRA made a site visit to those facilities to finalise approval. Prof Lyndon da Cruz has received ethical approval for the collection of patient fibroblast, which will be used as the starting cell type for reprogramming into retinal pigment epithelial (RPE) cells. The ethical approval allows fibroblast collection and for those cells, after reprogramming and differentiation into RPE cells, to be transplanted back to the patient so that clinical trials can take place. Finally, we are working with the Cell behaviour, differentiation and manufacturing Hub to define novel cellular safety profiles such as high throughput fluidic whole genome and SNP analysis in iPSC manufacturing for cellular therapies.



Flasks of pigmented RPE cell monolayers differentiated from a patient's iPSC

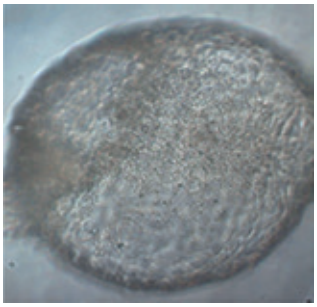
3.2 Dr David Hay (University of Edinburgh)

The development of 3-dimensional implantable liver organoids.

"We have delivered functional human liver tissue 'in a dish' which is stable in culture and amenable to large scale manufacture"

With liver disease being the fifth most common cause of death in the UK, and donor organ shortage a problem, there is a clear imperative to identify scalable alternatives to liver transplantation. We have embarked on an interdisciplinary programme of translational research which draws upon cell biology, chemistry, engineering and in vivo modelling.

The first year of the project focussed on delivering the correct software (in vitro engineered organoids) and hardware (prototype artificial liver device) to move toward preclinical testing. Standard operating procedures and cell banks have been established to deliver liver organoids. These structures display regular shape, and appropriate function over prolonged periods of time.

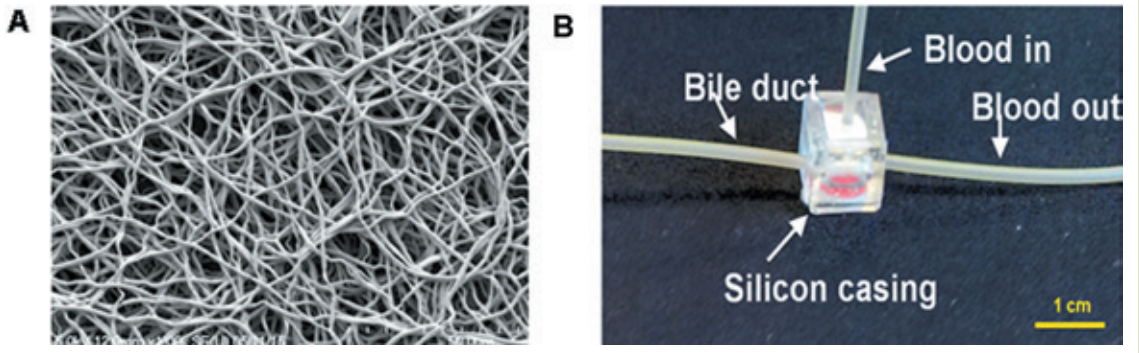


Human embryonic stem cell derived hepatocytes form organoid structures with endothelial and mesenchymal cells purified from adult liver.

To build the hardware, we have been working with chemists and engineers to identify GMP compatible materials and processes. These materials include electrospun synthetic polymers, to produce organoid interaction surfaces. The use of electrospinning, and other processes, has culminated in the formation of a compartmentalised prototype device which can be connected to host vasculature.

Organoid structures will be exposed to blood flow in the device. To model blood flow physiology and determine an optimal perfusion rate which does not lead to inflammatory mediators, we have embarked on collaboration with Kirkstall Limited using their Quasi-Vivo TM system.

To lock down the optimal process parameters for scalable manufacture and product development, we have developed new collaborations with Professor Marc Turner, (cell manufacture), Dr Will Shu (bioprinting) and Dr Michele Zagnoni (microfluidics). The next steps of the project are to test; our standard operating procedures with iPSC lines (Vallier lab, Cambridge) and; the capability of our in vitro derived organoids in relevant pre-clinical models of liver disease (Forbes lab, Edinburgh; Dhawan, lab London; and Newsome lab, Birmingham).

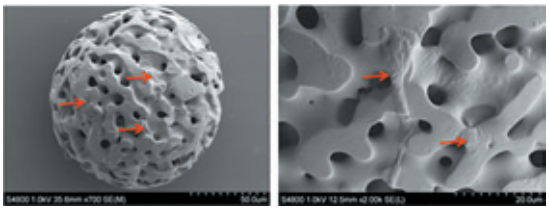


Electrospun polymers (A) used in a prototype 'mini liver' device (B) fabricated using GMP compliant materials and processes.

3.3 Dr Ilyas Khan / Professor Charlie Archer (Swansea University)

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

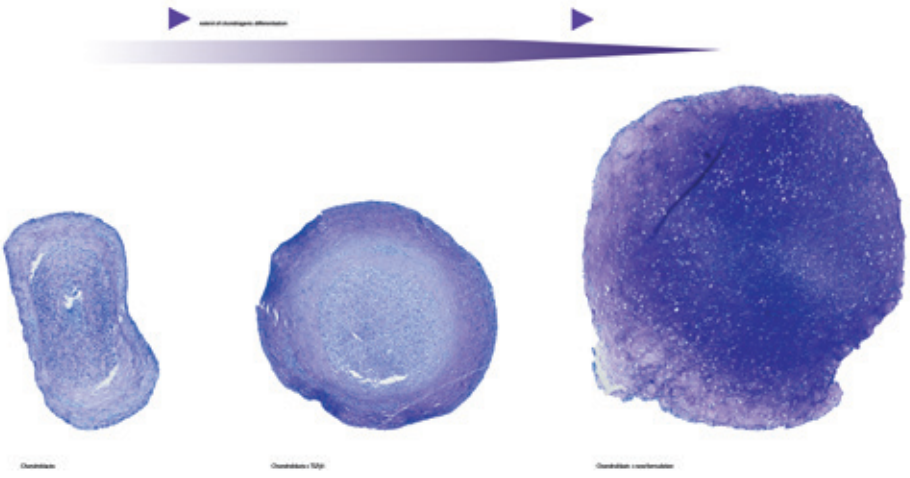
"Our goal is to produce cartilage implants that will promote pain free full joint movement."



Growth of articular chondroprogentiors (chondroblasts – red arrows) on porous gelatin microspheres.

The brief of this project is to produce an osteochondral graft that can be implanted into subjects allowing them to regain pain-free and full joint movement. The use of tissue-specific adult stem cells is central to our approach to repair damaged articular cartilage. The challenges we face are four-fold; can we grow enough stem cells to produce large quantities of tissue, will cells retain the ability to form cartilage, can we design suitable scaffolds that integrate the mineralized (bone) and non-mineralised (cartilage) components of the graft, and lastly, can we produce cartilage which is fully functional at the moment of implantation.

To solve the first challenge we have grown articular chondroprogenitors on porous gelatin microspheres using Wave™ technology. We have achieved excellent growth of cells but have faced new issues relating to premature differentiation of cells and problems associated with their removal from beads. We have generated two solutions to these problems, one of which is unique to cartilage cells and the other which may have general applicability to all users of Wave™ technology. Inducing stem cells to differentiate, on cue and as one, is critical to produce a useable mass of cartilage. Differentiation protocols for chondrocytes have not changed for decades and the prevailing thought is that using TGFß growth factors is sufficient. We have shown this assumption to be false, and that precocious and complete differentiation of chondroprogenitors is possible by other means. The work of the past year has provided a solid foundation on which we will attack the next two challenges, production of integrated and fully functional bioprinted osteochondral grafts, in collaboration with our partners based at the University Medical Centre, Utrecht.

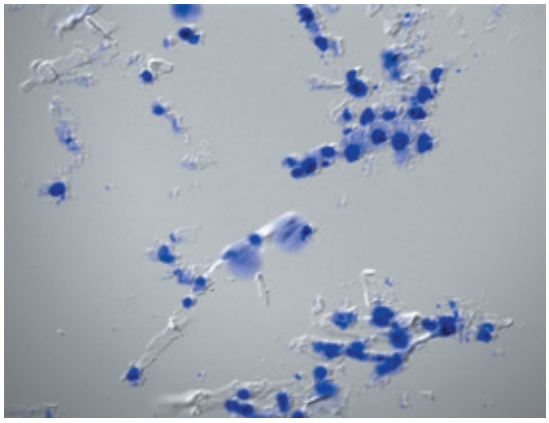


Chondroblast stained with toluidine blue to visualise differentiation through pellet culture.

3.4 Professor Andrew McCaskie (University of Cambridge)

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

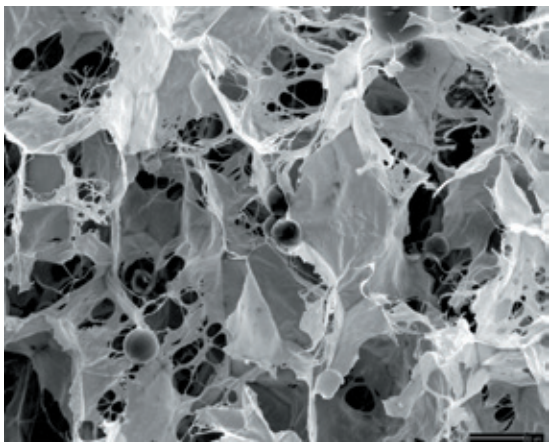
"We aim to repair cartilage by targeting the patient's own cells to bring about the repair, using a combination of materials and molecules in cell-free therapy."



Agrin expressing human cell line with collagen scaffold.

Osteoarthritis is a common 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, but surgical treatment options in earlier disease are limited. Our focus is on repair and regeneration of cartilage, which is the articular surface of a joint. The intervention would be at an early stage in order to reduce the progression of joint damage and hopefully delay the need for a joint replacement.

Within the adult human there are various cells that have the potential to bring about repair e.g. endogenous mesenchymal stem cells. Our approach is to target these cells and influence their behaviour using novel smart material technology together with the incorporation and controlled presentation of signalling molecules. Such a combination of a material and a molecule can change the behaviour of a cell by modulating signalling pathways to affect recruitment, proliferation and chondrogenic differentiation of endogenous mesenchymal stem cells – the key steps that might help repair cartilage. Our clinical goal is to make such treatments affordable, easy to apply and deliverable as a day case. The Smartstep Pipeline establishes a stepwise translational pathway from "bench to bedside" to facilitate core stakeholders and we hope to extend this beyond the consortium.



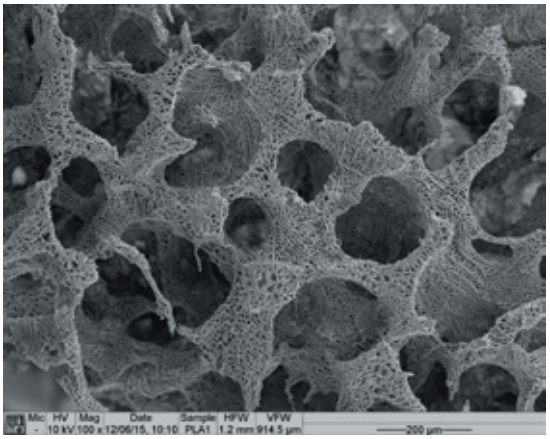
Porous collagen scaffold material

We started our work towards the end of 2014 and assembled the core research team. Our initial work packages have led to the design and manufacture of our first scaffold, which is based on collagen. In parallel, using a viral vector, a stable population of transduced cells has been produced which can be used as a vehicle to seed expressed agrin (one of our target molecules) into the scaffold. We have now optimised the seeding technology demonstrating that after 5 days the cells have fully populated the scaffolds with a homogeneous distribution. This approach, together with other scaffold and molecule combinations, will go forward to pre-clinical development in years 2 and 3.

3.5 Professor Manuel Salmeron-Sanchez (University of Glasgow)

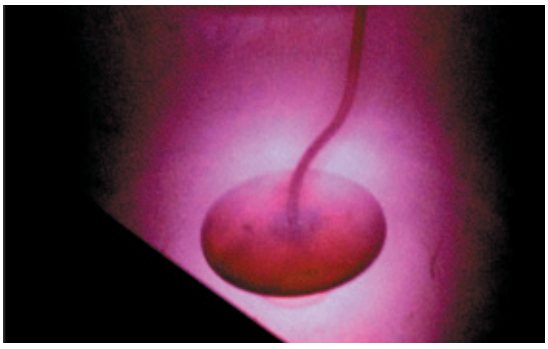
Synergistic microenvironments for non-union bone defects.

"We have engineered a combination of scaffolds with different architectures to present growth factors in a highly efficient way, to allow low dosage, increase safety and reduced costs."



Biodegradable scaffolds with large and small pores to promote cell differentiation and diffusion of nutrients.

This project presents 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 is being used for the safe and effective presentation of human growth factors to engineer synergistic microenvironments to enhance bone regeneration and vascularisation.



Plasma reactor to coat structural scaffolds with the functional material and promote growth factor binding.

The project has four well-defined and interconnected activities: i) synthesis of material systems - structural scaffolds and functional coatings, ii) engineering and characterisation of the interface - protein organisation on the material surfaces triggered by the functional material and growth factor binding, iii) Stem cell proliferation and differentiation within the engineered systems and iv) pre-clinical in vivo models.

During this first year we have been focused on putting together three different structural scaffolds and two coating technologies to achieve functional 3D constructs. Scaffolds differ in the architecture of the pores, we have selected 1) biodegradable construct that consists of spherical macropores (~250 μm) and micropores (~2 μm) using a freeze extraction and particulate leaching technology; 2) 3D printed fibres in a layer by layer cross deposition (pores ~500 μm) and 3) nanopatterned systems via our Swiss roll technology (this results in a construct that is similar to osteones in bones). In parallel, we have developed two technologies to coat these functional scaffolds. We have designed and built our own plasma polymerisation reactor that allows working with lower power to preserve the chemical integrity of the functional coating as well as physical technology based on a spray-drying system. We have characterised growth factor binding and we have tested the viability of the systems in vitro using stem cells.

4. The UKRMP Environment

4.1 Growth of the landscape

The establishment of the UKRMP and Cell Therapy Catapult, alongside other strategic investments that followed the publication of the Research Council/TSB (now Innovate UK) Strategy for UK Regenerative Medicine in 2012, has provided the infrastructure required to drive forward regenerative medicine from its discovery phase towards clinical impact. The growth of the Hubs over the past year, linking new partners across the UK and internationally, is providing a fully inter-connected network. Testaments to this are the new research programmes evolving out of the Hubs or with Hub linkage, which leverage expertise and resources and provide additional value. Moreover there is some evidence that this burgeoning landscape is beginning to deliver the goal of making the UK the preeminent place to work in the area, capable of attracting inward investment to the benefit of UK plc. Some highlights of this new activity are provided below:

1. MATCH study (MAcrophage Therapy for Liver Cirrhosis)

MRC / Innovate UK Biomedical Catlayst Award to Stuart Forbes, MRC Centre for Regenerative Medicine at the University of Edinburgh

A team led by Stuart Forbes, who form part of the Niche Hub, in collaboration with The Scottish National Blood Transfusion Service and the Cell Therapy Catapult, has been awarded £3M by MRC and Innovate UK to carry out the world's first clinical trial using monocyte-derived macrophages to treat liver cirrhosis (**MA**crophage **T**herapy for Liver **C**irr**h**osis or **MATCH**).

Accounting for around 4,000 UK deaths a year and huge costs for the NHS, liver cirrhosis is a common disease where scar tissue forms in the organ as a result of long-term damage. This damage can be inflicted by many causes including hepatitis, obesity, alcohol abuse and some genetic and immune conditions. The only successful treatment for the end-stage liver disease is an organ transplant, but this is severely limited by a lack of available donors and risks of rejection. Many people die each year waiting for an organ to become available. The team are hoping to reduce the need for transplantation by developing a new treatment for cirrhosis that exploits the liver's natural ability to regenerate itself.

Previous work from the group has provided proof of concept, where it was shown that macrophages help to reduce liver scar tissue and stimulate liver regeneration in mice[3]. The aim is to reproduce this in patients, and under the new study, the group will take blood cells called monocytes from patients with liver cirrhosis and turn them into macrophages in the lab, before re-injecting them into the patient as an autologous therapy. The study is composed of a phase I dose escalation study and phase II efficacy study of repeat macrophage infusions a month apart in participants with advanced liver disease, with 68-77 participants to be recruited and followed up for a period of 12 months.

"Liver cirrhosis is on the increase in the UK and is one of the top five killers. If successful, we hope that this approach could offer a new way to tackle the condition." - Stuart Forbes, of the MRC Centre for Regenerative Medicine at the University of Edinburgh

3. Proc Natl Acad Sci, 2013;110(16):6542-7, Nature Med 2012;18(4):572-9, Hepatology. 2011;53(6):2003-15

2. Development of Metrics and Quality Standards for Scale up of hPSCs

MRC Industry Collaboration Award to Professor Sue Kimber (University of Manchester) with Tokyo Electron Europe Ltd.

Expansion and banking of human pluripotent stem cells (hPSCs) and derived lineages poses a realistic option to support regenerative therapies for tissue repair, affordable to healthcare systems. However, there is currently a lack of affordable and scalable systems for the large-scale generation of hPSCs able to maintain defined quality metrics. The overarching goal of this project is the development and qualification of a novel system and open innovation platform for the automated scale up and monitoring of hPSCs, for subsequent differentiation into therapeutically valuable lineages.

This project is being delivered through a multicentre consortium, led by Sue Kimber who is also a member of the Niche Hub. It comprises the University of Manchester, University of Nottingham, UK Stem Cell Bank, Wellcome Sanger Institute and the European branch of the Japanese company Tokyo Electron Ltd (TEL). TEL has come to the UK to take advantage of its supportive regulatory environment and strong lead in standardisation and hPSC research. The partnership with TEL will combine deep hPSC analysis with state of the art bioinformatics and engineering approaches to develop and validate minimum sets of biomarkers that quantifiably define cell quality standards. It will also enable TEL to integrate other technologies to help further develop its fully enclosed Smart Cell System as a basis for scaling-up and banking quality controlled hPSCs, and potentially other cell types, for differentiation to therapeutically valuable lineages.

Links have already been established with the UKRMP Hubs, who along with the broader regenerative medicine community will benefit from open access to optimised protocols and datasets for culturing, monitoring and quantifying quality criteria of hPSCs. It is anticipated that novel resources and tools will be produced from the analysis of deep phenotyping data from a range of hPSC lines, of value to UK and international hPSC initiatives and ultimately many others using a range of cell sources.

3. Chemical and Computational Biology of the Niche Facility (CCBN)

www.crm.ed.ac.uk/facilities/ccbn

The CCBN is an interdisciplinary research facility funded by an MRC capital grant and the University of Edinburgh. It has been established to provide the space and resources for cutting-edge chemistry, bioengineering and computational biology to be carried out alongside stem cell biology and regenerative medicine research. This facility will be a national collaboration zone for the UK stem cell and regenerative medicine community, and is integrated with the UKRMP Niche Hub to accelerate the delivery of novel tools and technologies. Once fully operational, visiting researchers will be able to occupy dry-computational and/or wet laboratory space, with minimal barriers, to develop their particular research activity. The CCBN will be housed across two sites at the University of Edinburgh, contiguous with the MRC Centre for Regenerative Medicine (CRM) at the Little France campus and within the Institute for Genomics and Molecular Medicine (IGMM) at the Western General campus.

CCBN equipment includes:

- Biological/cell handling equipment (BD Fusion) and assessment equipment (Operetta and Columbus Imaging System, and a slide scanner) which are already fully commissioned and in operation within MRC-CRM, benefiting from existing biological/imaging expertise and technical support.
- Physical fabrication equipment including a nano-spinner (Prof Mark Bradley), a femtosecond laser inscription system (Dr Robert Thompson) and a Renishaw InVia Raman Microscope (Dr Colin Campbell), located within the Queen's Medical Research Institute at the Little France Campus to create an interface between stem cell biology and cutting edge synthetic materials and imaging science.

The equipment is already in regular collaborative use, bridging the biological and physical sciences. For further information and contacts for enquiries see www.crm.ed.ac.uk/facilities/ccbn.

4.2 Capacity building

Stem cell biology is now mainstream and popular amongst biomedical graduates, and the provision of PhD training in this area is highly competitive with other disciplines. This cadre is well supported through many UK higher education institutions and through MRC Institutes and Units, for example at the MRC Clinical Sciences Centre and Francis Crick Institutes in London, and the MRC Molecular Haematology Unit in Oxford. In recognition of the broad training needs for regenerative medicine, recent effort has been directed towards promoting interdisciplinary training. For example, both MRC and EPSRC Centre investments in the area provide strong postgraduate training programmes which link to clinical and physical science disciplines. These complement other targeted training programmes, such as the £11M investment in 2014 by EPSRC/MRC in three Regenerative Medicine Centres for Doctoral Training (in Leeds, Loughborough and Manchester). Details of these are provided below:

MRC Centre for Regenerative Medicine, Edinburgh

www.crm.ed.ac.uk

The MRC Centre for Regenerative Medicine (CRM) is a research institute based at the University of Edinburgh, established in 2008. It hosts 24 groups, bringing scientists and clinicians together in a multidisciplinary research environment dedicated to studying stem cells, disease and tissue repair to advance human health. A central feature of the CRM is its bespoke PhD programme in regenerative medicine, and in the past 8 years MRC Centre funding has supported 16 four-year PhD studentships. This specialised programme has also leveraged significant funding from additional sources, including University Scholarship schemes and UK charity training awards, increasing the intake to between 10 and 15 PhD students each year since 2008.

The format of the programme encompasses training in all aspects of regenerative medicine, including: two rotation projects within the CRM in the first 6 months of this 4-year programme; specialist taught components in key regenerative medicine-related technologies covering the basic use of techniques and equipment as well as more complex state-of-the-art applications; weekly discussion of key publications led by Principal Investigators; and training in public engagement and media engagement.

The WT/MRC Cambridge Stem Cell Institute

www.stemcells.cam.ac.uk/studentships/wtprogramme

The Wellcome Trust/MRC Cambridge Stem Cell Institute comprises the largest group of stem cell researchers in a single institution in Europe, spanning the full range of mammalian pluripotent and tissue stem cell research. This provides a broad basis for dedicated PhD training. The Wellcome Trust 4-Year PhD Programme in Stem Cell Biology and Medicine has been running since 2007 and was renewed in 2013. To date 30 students have been recruited to the Programme. Students may choose from 40 supervisors for their rotation projects and PhD laboratory, from basic science to clinical translation. Cross-disciplinary and collaborative projects are encouraged. Each year four places are funded by the WT Programme. In addition, the MRC fund one 4-Year 'Physical Biology' PhD student per year, targeted specifically to applicants with a physical, mathematical or computational sciences background. The University of Cambridge fund a further student place every second year.

In the first year students receive broad training in the conceptual foundations, experimental systems, practical techniques, and current state of knowledge in stem cell biology and medicine. This leads to an MRes degree, after which, students select their laboratory for their 3-year PhD research studies. During this time students organise a PhD seminar series for peer to peer presentations, participate in Institute seminar series, and are encouraged to present their work at conferences and contribute to public engagement.

EPSRC & MRC Centre for Doctoral Training in regenerative medicine, Manchester

www.regenmedcdt.manchester.ac.uk

The Manchester Centre for Doctoral Training (CDT) exploits the University's critical mass of non-clinical and clinical researchers in bioengineering, cell and tissue biology, clinical research and experimental medicine, all within a single-site biomedical campus.

The first cohort started in September 2014 and comprises 11 students (2 affiliated) of which 4 are industry-linked, whilst the second cohort of 11 students including 2 'medics' started in September 2015. Recognising that enrolled students have a variety of degree backgrounds, a bespoke training programme is run for the first six months which covers physical, chemical, biological and medical topics, and offers critical insights into how to translate biological discoveries both clinically and commercially. During their initial training, the students focus in towards their chosen research topic, and start their research project thereafter with interdisciplinary co-supervision. The PhD projects cover tissue regeneration, regulating inflammation, bioengineering and fabrication of biomaterials, in vivo imaging, and clinical and commercial translation. Throughout their training, students engage in numerous cohort and public engagement activities, have comprehensive instruction in a wide range of transferable skills, experience the clinical and commercial interfaces, and have opportunities to present data at national and international meetings and annual student-led conferences.

The Manchester CDT has a strongly outward-facing ethos, with many opportunities for interactions with other CDTs and UKRMP groups across the UK, with industry partners and internationally.

EPSRC & MRC Centre for Doctoral Training in regenerative medicine, Loughborough, Nottingham & Keele

www.dtcregen-med.com

The Centre for Doctoral Training (CDT) in Regenerative Medicine 4-year PhD programme is a partnership between Loughborough, Keele and Nottingham Universities. Since its original inception in 2008, it has taken in over 80 engineering, physical and biological science graduates with EPSRC, MRC, University and industrial funding.

Students start with a year-long training programme of taught and research-based modules designed to give them the core knowledge they will need as well as some practical skills prior to starting their PhD research. In addition, a business plan competition, industry visits, international secondments and clinical interface days help foster an appreciation of some of the global industrial, financial, and clinical challenges the field faces. As such, the graduates are equipped with the tools and skills needed to translate the potential of cell- or tissue-based therapies from bench to bedside and manufacture and delivery at scale.

A national young researchers' conference has been developed that is now run annually between this CDT and training programmes in regenerative medicine/tissue engineering based in Leeds, York, Sheffield and Manchester. In addition, the Future Investigators of Regenerative Medicine (FIRM: http://firmsymposium.com/) committee was also instigated by the CDT's students and has run two successful international symposia to date, attracting both international academic and industrial speakers as well as students and post-doctoral researchers.

EPSRC Centre for doctoral training in tissue engineering and regenerative medicine, Leeds

www.imbe.leeds.ac.uk/doctoral-training-regenerative-medicine

The EPSRC Centre for Doctoral Training in Tissue Engineering and Regenerative Medicine at Leeds will provide postgraduate research and training for 50 students, to research, develop and deliver regenerative therapies and devices, which can repair or replace diseased tissues and restore normal tissue function. A minimum of 10 places per year are available until 2018.

The programme includes an integrated MSc in Tissue Engineering and Regenerative Medicine which comprises compulsory and optional taught modules over the first two years with the majority studied in year 1, allowing a phased increase to full time research towards the end of year 2. Multidisciplinary research projects are available in a number of faculties and departments across the university including in the School of Mechanical Engineering, School of Biomedical Sciences, Medicine, Dentistry, Design and Chemistry.

Research projects already underway include creating biological scaffolds to repair tissues by regenerating a patient's own cells and developing practical stem cell-based therapies for musculoskeletal, cardiovascular and neural problems. These align with Leeds' expertise in musculoskeletal and cardiovascular systems, and the goal of promoting the development of effective acellular regenerative therapies for tissue repair at a lower cost, reduced time and reduced risk, compared to alternative and more complex cell therapy approaches.

4.3 Aligned investment in regenerative devices

The EPSRC Medical Technologies Innovation and Knowledge Centre (IKC) in Leeds

www.medical-technologies.co.uk

Established in 2009, the EPSRC Medical Technologies Innovation and Knowledge Centre (IKC) in Leeds has built a reputation for fostering close collaboration between industry and researchers and translating cutting-edge research into practical medical devices. The centre received £3M new funding from EPSRC in 2015, which will allow it to continue its work to 2020.

The IKC focuses on de-risking technologies to enable companies to engage more readily with potential commercial opportunities. Progressing technologies across the 'translation gap', where early stage research funding ends and the first private sector funding is secured, can present a significant barrier to progress. Over the past five years, the IKC has developed an approach to overcome this by developing an innovation platform which provides and embeds the expertise, skills, tools and processes to take regenerative devices from early stage research, through proof of concept, to the first commercial investment. As a result of this, the IKC has contributed to the development of 50 new products or services and helped to create, or support the growth of, five spin-out companies, leveraging an additional £20M private sector investment in industry each year to support new product developments.

Having now secured EPSRC funding for a further five years, the IKC is well-positioned to achieve its long term vision of creating a sustainable £1bn industry in regenerative devices. As a national centre, it will build partnerships with a UK-wide group of university and industry partners, leveraging additional innovation support from a range of sponsors. The tight focus on regenerative devices, which allows rapid and cost-effective translation, will continue, albeit addressing a wider range of clinical applications. The development of more industry-inspired projects will complement the IKC's academic-led research, drawing on the business insights that will help inform the strategy and goals. Capacity-building and skills development will underpin this longer term vision of a robust and sustainable UK regenerative devices sector.

Annex 1

UKRMP Governance

Executive Group

- **Dr Rob Buckle**, Director UKRMP, Director of Science Programmes, MRC
- **Professor Ian Greer**, Chair UKRMP Programme Board, Vice-President and Dean, Faculty of Medical and Human Sciences, The University of Manchester
- **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 Manchester, 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**, Alzheimer's Research UK/UCL Drug Discovery Institute, 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)
  Partnership programmes included within main award:
    - Development of GMP ES cell derived dopaminergic neurons in preparation for a clinical trial in Parkinson's Disease
    - Comparability of automated expansion of PSC at three international sites

- **Professor Stuart Forbes, MRC Centre for Regenerative Medicine, University of Edinburgh**
  Engineering and exploiting the stem cell niche Hub (£4.6M)
  Partnership programmes included within main award:
    - ECM matrix products for niche biomaterials and biology
    - New liver microRNA toxicity biomarkers – Niche/Safety Hubs
    - Delivering a niche for liver repair and chondrocyte differentiation – Niche/Acellular Hubs
    - ECM and Wnt interactions of human iPSC-derived hepatocytes
    - Defining a translational niche for tissue engineered products

- **Professor Kevin Park, MRC Centre for Drug Safety Science, University of Liverpool**
  Safety and efficacy, focussing on imaging technologies Hub (£4.6M)
  Partnership programmes included within main award:
    - Evaluation of the safety and efficacy in a novel preclinical therapy - regeneration of damaged renal tissue within donor kidneys
    - Development of novel cell tracking probes for nuclear and optical/photoacoustic imaging
    - Mechanistic biomarkers that guide the safe and effective utilisation of regenerative medicine therapeutics for liver fibrosis
    - Magnetic targeting of therapeutic cells for enhanced efficacy and safety of liver fibrosis treatment

- **Professor Kevin Shakesheff, University of Nottingham**
  Acellular approaches for therapeutic delivery Hub (£3.8M)
  Partnership programmes included within main award:
    - New materials:
        i. Extracellular vesicles (EV) that deliver mRNA
        ii. Self-assembling peptides that responsively change local elasticity
    - New materials for clinical applications:
        i. Microparticles for cell and drug delivery
        ii. Liposomal systems for dentine regeneration
        iii. A thin, rollable and transparent gel matrix for corneal endothelial cell transplantation
        iv. Development of fibrous material for cell delivery in the eye and tendon
    - Drug delivery systems to enhance engraftment of cells – Acellular/Niche Hubs
    - Biomaterial-based approaches to deliver extracellular vesicles for cardiac tissue repair

- **Professor Fiona Watt, King's College London**
  Immunomodulation Hub (£2.3M)
  Partnership programmes included within main award:
    - Micro-particles for the induction of immune modulation in the transplant niche – Immunomodulation/Acellular Hubs

UKRMP Stage II – Disease-focused awards

- 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

- Dr Ilyas Khan/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, Reumafonds £0.51M)*

- Professor Andrew McCaskie, University of Cambridge
  *(SMART STEP) Stepwise Translational Pathway for Smart Material Cell Therapy. £1.6M * (£0.64M RC, £0.53M ARUK, Reumafonds £0.43M)*

- 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, MRC Centre for Regenerative Medicine, 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 Kevin Park, MRC Centre for Drug Safety Science, 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 Raimondo Ascione, University of Bristol.
  Pre-clinical In-vivo Functional Imaging for Translational Regenerative Medicine, £2.8M

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

- 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

UKRMP Hub post-doctoral researchers

PSCP Hub

- Mr Duncan, Baker, University of Sheffield
- Dr Ivana Barbaric, University of Sheffield
- Dr Amit Chandra, Loughborough University
- Ms Catherine, Durance, University of Cambridge
- Dr Jason Halliwell, National Institute for Biological Standards and Controls
- Dr Ross Hawkins, National Institute for Biological Standards and Controls
- Dr Paul Hourd, Loughborough University
- Dr Marta Milo, University of Sheffield
- Dr Sujith Sebastian, Loughborough University
- Dr Julia Sung, National Institute for Biological Standards and Controls
- Ms Vasiliki, Symeonidou, University of Cambridge
- Dr Oliver Thompson, University of Sheffield
- Dr Loriana Vitillo, University of Cambridge
- Mr Andy Wood, University of Sheffield

Acellular Hub

- Ms Mahetab Amer, University of Nottingham
- Mr Abdulrahman Baki, University of Nottingham
- Dr Deepak Kumar, University of Manchester
- Dr Hareklea Markides, Keele University
- Dr Jane McLaren, University of Nottingham
- Dr Ben Pierce, Imperial College (Research Co-Ordinator)
- Dr Jenny Puetzer, Imperial College
- Dr Omar Qutachi, University of Nottingham
- Dr Robin Rumney, University of Southampton
- Dr Jean-Philippe St-Pierre, Imperial College
- Dr Lalitha Thiagarajan, University of Nottingham
- Dr Emma Wright, University of Nottingham
- Dr Scarlett Xue, University of Nottingham

Safety Hub

- Dr Ioannis Bantounas, University of Manchester
- Dr Mike Barrow, University of Liverpool
- Dr Joan Comenge, University of Liverpool
- Dr John Connell, University College London
- Dr Darsy Darssan, University of Liverpool
- Dr Marie Held, University of Liverpool
- Dr Inna Linnik, University of Manchester
- Dr Stephen Patrick, University College London
- Dr Parisa Ranjzad, University of Manchester
- Dr Jack Sharkey, University of Liverpool
- Dr Philip Starkey Lewis, University of Edinburgh
- Dr Arthur Taylor, University of Liverpool

Niche Hub

- Dr Mads Bergholt, Imperial College London
- Dr Eva Borger, University of Edinburgh
- Dr Stuart Cain, University of Manchester
- Dr Kate Cameron, University of Edinburgh
- Dr Aixin Cheng, University of Manchester
- Dr Huelyn Jones, Strathclyde University
- Dr Chao Li, University of Liverpool
- Dr Wei-Yu Lu, University of Edinburgh
- Dr Holger Schulze, University of Edinburgh

Immunomodulation Hub

- Dr Raul Elgueta, King's College London
- Dr Giorgia Fanelli, King's College London
- Dr Peter Gardner, University College London
- Dr Helen Marshall, Newcastle University
- Dr Jasmine Penny, University of Birmingham

Annex 4

UKRMP Hub publications

Niche Hub:

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Acellular Hub:

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UK Regenerative
Medicine Platform

Publication date: November 2015

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