UK Regenerative Medicine Platform

Annual Report 2018

BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

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Contents

1. Introduction

Dr Rob Buckle: Chief Science Officer MRC

The UK Regenerative Medicine Platform (UKRMP) was established in 2013 to address the translational challenges set out in the Strategy for UK Regenerative Medicine[1], published in 2012. The key objective has been to ensure that regenerative medicine research – which seeks to repair and/or replace and regenerated damaged cells tissues and organs – connects seamlessly from discovery science through to clinical and commercial application in order to help realise the great promise of revolutionising healthcare across a wide range of chronic diseases and illnesses.

Run as a single joint programme supported by the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council (MRC), the initial £25M tranche of funding has drawn together the major players in UK regenerative medicine, encompassing experts spanning 20 universities from across the fields of developmental and stem cell biology, tissue engineering, gene therapy, cellular therapeutics, biomaterials (scaffolds and matrices), nanoscience, bioengineering, and chemical biology. This expertise has been organised into five interdisciplinary and complementary research themed Hubs, supported by five disease specific projects, which collectively have provided an integrated programme with the goal of providing new knowledge, insights, tools and technical solutions for the wider benefit of the field.

During the course of funding the Platform has honed in on a number of exemplar clinical areas, bringing together the critical mass of expertise to make substantial preclinical progress in the areas of neural regeneration in Parkinson's Disease, regeneration to address liver disease, the repair of retinal degeneration in the eye and bone and joint repair. The Platform has also generated novel research tools and materials such as characterised cell lines, cell scaffolds and reagents for cell targeting and tracking, to establish an 'open science' resource as well as providing training and support for a wide range of imaging modalities and manufacturing processes needed for therapeutic development across the wider regenerative medicine community.

The Platform has grown since its inception to see engagement with over 25 companies including close alignment with the Cell and Gene Therapy Catapult. Moreover, the Platform has also provided a focus for international connectivity, with collaborative research projects now established with groups in France, Germany, Sweden, Netherlands and the USA, all of which aim to address the knowledge-gaps in the translation of stem cell and regenerative biology towards application.

Overall the Platform has created a globally recognised and fully connected national programme that is meeting its objective of pulling through excellent discovery science in a format attractive to the commercial development required for the clinical delivery of regenerative medicine products.

In the following pages, this fourth annual report of the UKRMP provides further detail of the activities and progress across the five Hubs and disease-focused projects over their final year of funding. It also highlights the value of the integrated initiative in the development of a new generation of regenerative medicine researchers and presents the outputs from the Hub teams that should be of value to the wider community.

Looking forward

Since the inception of the UKRMP programme in 2013 the field has matured considerably, with recent clinical successes with advanced therapies stimulating renewed pharma interest with a surge in deals with SMEs and universities to incorporate cell & gene therapies into their pipelines. The cell and gene therapy market is estimated to grow to $21bn/year worldwide by 2025[2].

Nevertheless, despite the success achieved thus far, there remain a number of knowledge gaps and scientific challenges to overcome including how we best target therapies to ensure efficacy and safety, how we overcome adverse immune responses, and how we provide economically sustainable and reproducible manufacturing and scale up.

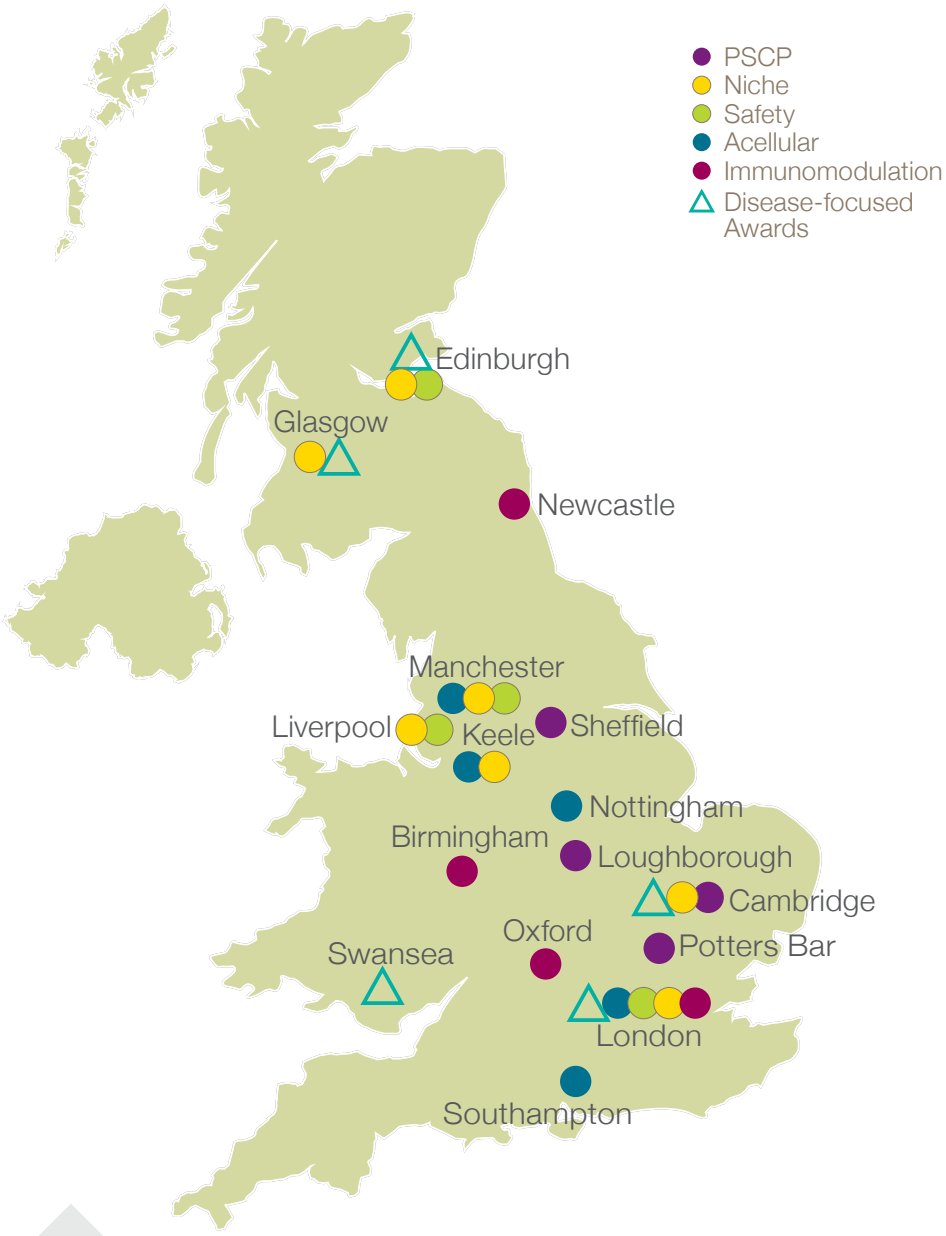
1 www.ukrmp.org.uk/wp-content/uploads/2014/06/A-Strategy-for-UK-Regenerative-Medicine.pdf
2 Advanced Therapies Manufacturing Taskforce Report 2016

With the stage 1 activities and funding for the five Hubs and disease projects now complete, second stage funding has been provided to the Platform through an evolved structure that builds on the strengths of the initial investments while providing renewed focus on driving those projects with established proof of concept towards clinical application. £17M funding has been provided under UKRMP2 to support three new Hubs from 2018-2023, addressing the themes:

- Pluripotent stem cells and engineered cells
- Engineered cell environment
- Acellular/smart materials

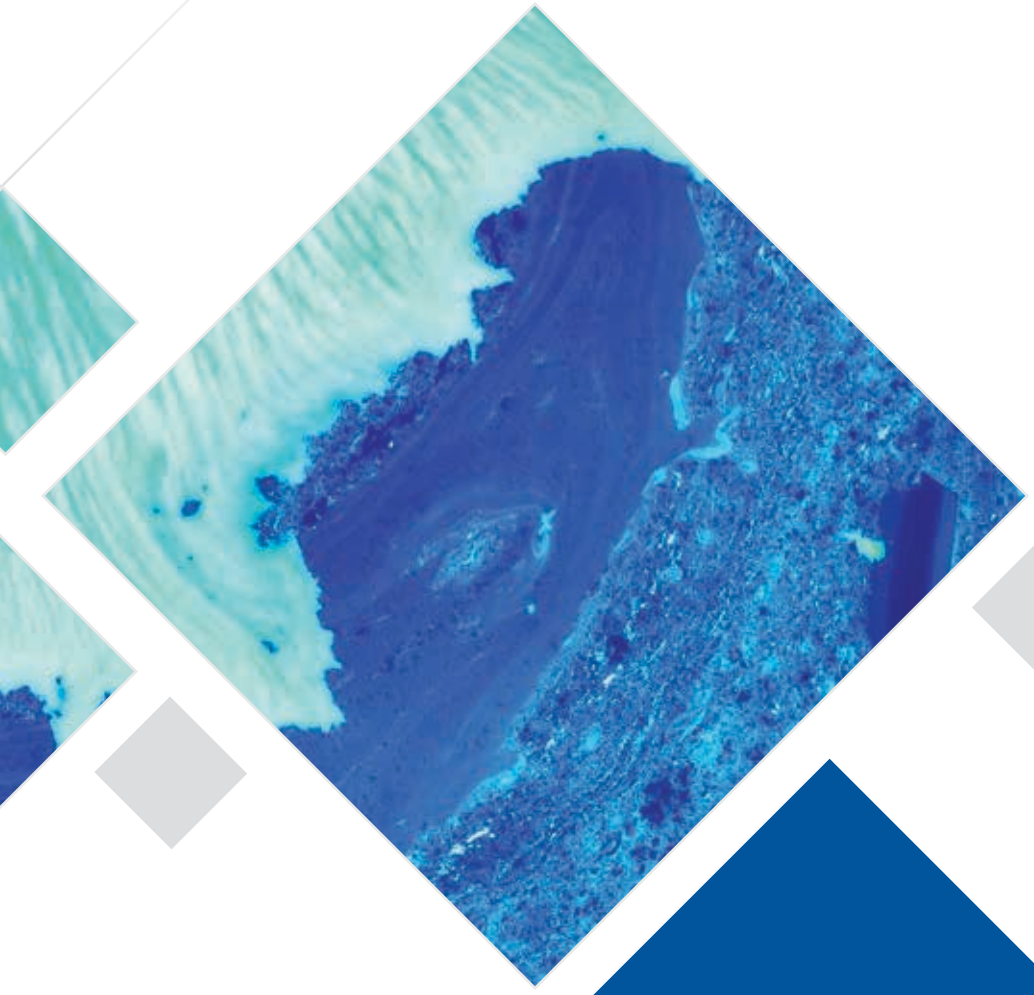
The new hubs will continue to provide a critical mass of expertise and a national resource that can be utilised by other UK research groups in both academia and industry, with the expectation that progress over the next few years will provide a route map for the development and testing of regenerative medicine products to help underpin a burgeoning sector in the UK life science industry.

UKRMP Hubs And Awards



2. Hubs

2.1 Cell behaviour, differentiation and manufacturing Hub
2.2 Engineering and exploiting the stem cell niche Hub
2.3 Safety and efficacy, focussing on imaging technologies Hub
2.4 Acellular approaches for therapeutic delivery Hub
2.5 Immunomodulation Hub



2. 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, Marcelo Rivolta and Ivana Barbaric, (Zoe Hewitt – Project Manager)
- **Wellcome Trust/ MRC Stem Cell Institute, University of Cambridge**, Austin Smith, Roger Barker, Ludovic Vallier, Robin Franklin and Cedric Ghevaert
- **Centre for Biological Engineering, Loughborough University**, David Williams, Rob Thomas and Mark McCall
- **UK Stem Cell Bank, NIBSC-MHRA**, Glyn Stacey and Jack Price
- **Wellcome Trust Sanger Institute, Cambridge**, Mike Stratton and Kosuke Yusa
- **Babraham Institute, Cambridge**, Wolf Reik
- **University of Lund**, Malin Parmar
- **University College London**, Pete Coffey and Amit Nathwani
- **University of Liverpool**, Chris Goldring and Patricia Murray

Industrial Partners

- Lise Morizur (iSTEM, Évry, France)
- Heiko Zimmerman (IBMT, Fraunhofer, St Ingbert, Germany)
- Roger Burgin (Sartorius)
- Paul De Sousa (Roslin Cells)
- Andreas Bosio (Miltenyi Biotec)
- Jonathan Thon (Platelet Biogenesis)

What

The Pluripotent Stem Cell (PSC) Platform combined experts in PSC biology, genetic analysis and clinical delivery with leaders in cell manufacturing, safety and regulatory science. We have been addressing critical translational bottlenecks by focusing on four key objectives:

- To establish protocols for reproducible production, expansion, quality and safety qualification of PSCs.
- To develop methods to detect and minimise the occurrence of functionally significant genetic or epigenetic variants during PSC manufacturing.
- To standardise PSC differentiation protocols for deriving, manufacturing and banking therapeutically relevant lineage-specific intermediate stem or progenitor cells.
- To provide qualified processes for manufacturing regulatory and clinically compliant PSC products.

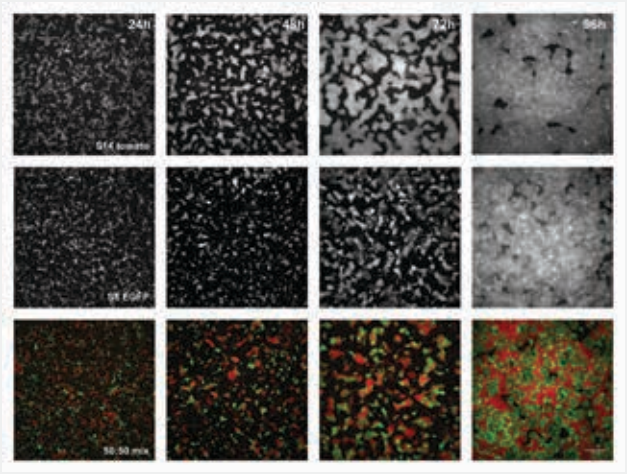
Scientific Achievements

PCSP has accelerated the work around the translation of a dopaminergic cell based therapy from hPSC (Barker group). This has led, in collaboration with colleagues at the University of Lund, to the development of a GMP protocol for the manufacture and cryopreservation of these cells for trialling in patients with Parkinson's disease, a condition that affects over 130,000 people in the UK. Working with the regulatory authorities (MHRA one stop-shop), the CGT Catapult, Roslin Cells and Miltenyi Biotec, the necessary processes and assays for clinical translation have been developed. The groups involved are now on the verge of taking an RC17 human ES cell-derived product through the final preclinical stages of manufacturing and testing to a clinical trial using externally obtained funding. Planning is underway for the necessary testing of the final GMP product that will be made at the Royal Free Hospital GMP facility in London and Barker is seeking further funding from the EU, Horizon 2020, to support the first clinical trials of these cells. Similarly, PSCP has also contributed to translating an R&D-based protocol for the production of megakaryocytes (MK) and platelets from hPSC (Ghevaert group) into a GMP-ready protocol. As a result, this project is also now closer to starting human trials in an area of great clinical need.

In collaboration with Platelet Biogenesis, applications have been made to Innovate UK. Notably, the application of in vitro derived platelets has great potential, with reach beyond disease application and including post-trauma treatment in many areas, such as of explosive devices and terrorist attacks, in both civilian and military circles.

Our work in the manufacturing space, has focused on automation, (in collaboration with TAP, Sartorius and Miltenyi Biotech) and particularly around process transfer and improvement from upstream settings (both in scientific and technology development) to a manufacturing setting. Comparability and dealing with the consequences of process change during the product development process is a very challenging area for the industry and PSCP experience has highlighted the significance of error handling and software for comparability. The learning from this has directly fed into the work of the start-up company, Advanced Bioprocess Services, and consequently to developers. It has also led to a significant interface with regulators (particularly the MHRA) and standards organisations (including NIST and NIBSC), for example at a PSCP workshop held at Trinity Hall Cambridge (Williams, et al., 2016) on the issue of comparability and its reporting, and hence making a contribution towards the development of regenerative medicine policy.

A significant focus of the Hubs activities over the final stages of the grant has been on assessing the genetic and epigenetic variation of human PSCs and its impact on regenerative medicine. We have concentrated on two key aspects; safety concerns and the issues associated with the impact of genetic variants on robust manufacture of cellular products. Human PSC cultures exist as mixed populations, comprising subtle genetic and phenotypic compartments or sub-states. These populations are subject to mutations and these appear in a non-random manner, suggesting that these changes provide a selective advantage to cells that possess them. It is not clear how these mutations may influence the efficacy and safety of hPSCs in a clinical context, not only in the manufacturing of differentiated derivatives, but also in the potential for neoplasia following transplantation. The teams of Rob Thomas (Loughborough) and Ivana Barbaric (Sheffield) have explored and evaluated approaches to modelling the growth behaviour of genetic variant and normal hPSCs. The objective was to develop models that can predict the relative performance of normal and variant cells under different operational conditions, and thereby define the effect of different manufacturing strategies on the rate of emergence of genetic variant populations. Data generated by Dr Oliver Thompson at the University of Sheffield mixing a genetically variant version of H7 (H7S6) and its wild type counterpart (H7S14) has been successfully integrated into such a statistical model.

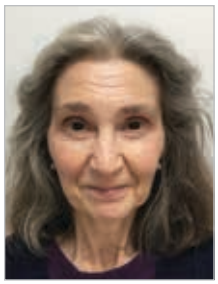


A four-day time course showing cell growth of H7(S14) wild type (tomato) and H7(S6) variant (EGFP) and a 50:50 mixed population. Image capture on the Nixon Biostation CT provided data input for statistical modelling.

This model will now be further developed within UKRMP2 (Pluripotent Stem Cell and Engineered Cell (PSEC) Hub) into a hypothesis based mechanistic dynamic model to provide us with a basis for better manufacture process design.

The promise and potential of hPSCs in the fields of regenerative medicine and personalised therapeutics is enormous, but not all hPSCs are created equal. The propensity for different hPSC lines to generate specific cell types is highly variable. It has been shown that the epigenetic variation between hPSCs lines can lead to differential differentiation capacity (Butcher et al., 2016; Nishizawa et al., 2016). As a result, the burden, both in terms of time and cost, of assessing many different hPSC lines is currently hampering the progress of regenerative medicine. Within PSCP we have begun to address this issue in two ways.

Firstly, in a project between the labs of Reik, Andrews, Barker and Ghevaert, **Dr Melanie Eckersley-Maslin** (pictured) has been investigating how differential DNA methylation may contribute to the differences between hPSC lines. In this study, we identified three clinical grade hESCs (MasterShef lines) with restrictions in differentiation capacity. Several samples, of all three lines growing in different labs, have been generated and have now been Whole Genome Bisulphite Sequenced. Within PSEC this data will be analysed to determine if establishment of methylome variation can then reveal a relationship between the propensity to differentiate towards a certain lineage and the particular signature seen. This signature may then inform product developers which hPSC lines are best capable of differentiating into their desired lineage and by so doing act as a QC assay.



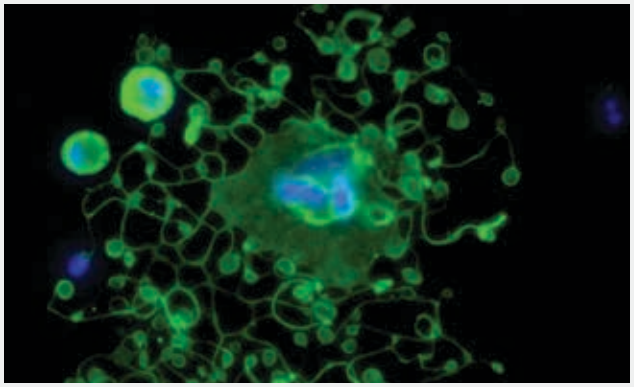
A second project brings together the Smith, Reik, Barker and Ghevaert labs to explore how acquired epigenetic alterations in hPSC cultures can be abrogated by 'resetting' hPSCs to an earlier developmental or naïve state. This has been shown (Takashima et al., 2014; Theunissen et al., 2014) to reverse acquired epigenetic alterations in hPSCs cultures. **Dr Amanda Evans** from the Ghevaert group has assessed 18 clinically available hPSC lines and has shown that one third of them showed robust, reproducible production of megakaryocytes (MKs), the precursors of blood platelets, in the forward programming system developed in the Ghevaert lab (Moreau et all 2016). Historically, forward programming employs the concurrent exogenous expression of three transcription factors: GATA1, FLI1 and TAL1 using lentiviruses and naïve resetting has been successful in this context. Using a recently developed polycistronic targeting vector (Bertero 2016), several lines, with different propensities to become MKs, have been engineered for inducible forward programming to reduce experimental variation. The groups have sought to establish whether such differentiation biases can be erased by resetting cells to a naïve state using the chemical resetting techniques developed by the Smith group (Guo, et al., 2017). Analysis of these data and validation of this approach will be completed through an ongoing collaboration with an RCUK Innovation/ Rutherford Fund Fellow and be exploited to optimise selection of hPSC lines for therapeutic purposes.

Hub Growth

As the project draws to end, PSCP is committed to achieving its objectives and delivering its goals and this has meant bringing in Cedric Ghevaert at the University of Cambridge. His work focuses on the production of MKs, the cells that release blood platelets, using forward reprogramming and genome editing. This has allowed the PSCP to investigate further the issues of genetic variation in another well-developed pre-clinical application, while also further developing another potential therapeutic hPSC derived product for clinical use.

Industrial collaborations

PSCP partners at Loughborough University, Prof Rob Thomas and Dr Mark McCall, have set up two start-up companies: Advanced Bioprocess Services (June 2016) and Advanced Bioprocess Design (Software component) (May 2016). These vehicles partner with Loughborough University to provide process development and design services to the Regenerative Medicine industry based on specialised tools developed through UKRMP and parallel Research Council funded programs. An increasing portfolio of clients including UK leaders such as ReNeuron, CGTC and Asympote as well as several US partners demonstrates the value of the developed approaches. The company-funded activities currently support two full time members of staff and anchor key development expertise in the UK.



A proplatelet forming Megakaryocyte stained with alpha tubulin (green) and Dapi (blue).

Executive Committee member, Prof Glyn Stacey, has also gone on to start-up two new UK registered independent consultancy companies. SSCBio Ltd provides strategic direction, advice and education in the life sciences and has worldwide activity with clients in the USA, Japan and Europe. The second, the International Stem Cell Banking Initiative Ltd, has been established on a not-for-profit basis and benefits from, and engages with UKRMP and ISCI partners in its international meetings. These included a 2-day workshop held June 2018 at the University of Melbourne and a symposium at the Korean Society for Stem Cell Research in Seoul, in September 2019.

PSCP partners have had several commercial interactions through the course of the programme. Through the hESC-derived dopaminergic-cell based therapy programme we have worked closely with Miltenyi Biotec, particularly around reagents to do with the development of the ES dopamine cell protocol and QC assays, as well as the potential for using their closed production system (Prodigy machine). As a result of this interaction, one of these machines is now at Loughborough University where it is being explored for making midbrain dopamine cells for clinical use in Parkinson's disease, in addition to generating generic learnings related to semi-automated production systems that are likely to be of interest to the wider regenerative medicine field.

In addition, we have worked with Biolamina in relation to undifferentiated hPSC expansion and its transfer to automation. They have also been involved in developing the differentiation protocol for hESC-derived dopamine cells. The team led by Roger Barker working on hPSC-derived dopamine cells are now advising several companies around this therapy and have worked with LCT Therapeutics in New Zealand over a different cell based approach for Parkinson's disease.

Furthermore, PSCP researchers are working with an American based company, Platelet Biogenesis, relating to the use of the forward programming technology used for hPSC-derived megakaryocytes. The PSCP involvement in this project has allowed the group to formalise this relationship and to negotiate a Sponsored Research Agreement with the company, which has led to two joint applications for external funding. Clinical trials are now being planned on both sides of the Atlantic (in AML patients in the US and healthy volunteers in the UK).

Several other commercial interactions undertaken by PSCP partners have been through consultancy and provision of advice, notably via Loughborough University Enterprises Ltd (LUEL). For example, while he was a PSCP Research Associate, Amit Chandra delivered consultancy to Yposkei on the design and equipping of its facility before he joined them in January 2017. Further, Professor David Williams advises A*Star, Singapore, on its strategy for regenerative medicine manufacturing and the SIMTech, the Singapore Institute of Manufacturing Technology on biomanufacturing. He also continues to collaborate with BioMan at MIT to influence the growth of manufacturing technology capability in Massachusetts, and is now on the Scientific Advisory Boards of two growing start-ups; Flodesign Sonics in Wilbraham Massachusetts and the Electro-Spinning Company on the RAL campus in Harwell, Oxfordshire.

Networking Activities

PSCP has engaged with a broad range of academic scientists and relevant stakeholders from industry including product manufacturers and developers, clinical users and regulators in a series of workshops. With the International Stem Cell Initiative (ISCI), we have jointly organised two meetings on genetic variation. The first was a knowledge-gathering workshop consisting of mainly international academics, to determine the current state of this field. The outcome of this meeting, held at the Jackson's Laboratory in Bar Harbor, Maine USA in Oct 2016, was published in Stem Cell Reports (Andrews et al 2017). As a follow up, a second workshop to discuss the "Significance of Genetic Variants for the use of Pluripotent Stem Cells in Regenerative Medicine" was held in Sheffield UK in October 2017. This meeting established the need and feasibility for setting up an 'International Expert Group' to collate and monitor the genetic and epigenetic variants that arise during hPSC culture and to provide a framework to facilitate risk assessment for clinical applications of hPSC derivatives. Participation was again international and included several public funding agencies, e.g. MRC (UK), NIH (USA), AMED (Japan) and CIRM (California), regulators from the FDA and MHRA, academic experts and product developers (both academic and industrial). There was general agreement that there is a need for an International Expert Group of the type proposed, but there were varying views on its remit and scope. A preliminary steering group has been formed to further develop this group including members of PSCP and the concept was presented at the 4th International Alliance for Biological Standardisation conference on Cell Therapy Manufacturing in Los Angeles, June 2018.

In addition, in an aim to promote the research of the wider UKRMP network, we organised a cross UKRMP hub meeting in conjunction with the British Society for Cell and Gene Therapy and the British Heart Foundation Centres, in Cardiff (19th-21st April 2017). The UKRMP session programme highlighted talented UKRMP researchers from across all five hubs, and several of the PSCP team were included on the BSGCT main meeting programme (Barbaric, Ghevaert, Thomas and Rivolta). In February 2018, in conjunction with the Francis Crick Institute in London, we organised an open international scientific meeting to disseminate the major outputs of the PSCP to an international delegation of interested parties. Almost 200 people attended this meeting with representation from international academics, industry, publishing organisations, regulators and other government agencies from across the world. Our speakers included; Prof Kevin Eggan (Harvard University), Prof Christine Mummery (Leiden University) Prof Oliver Brüstle (University of Bonn) and Lt. Col. Graham Lawton (MoD) amongst others. The event was widely praised by the attendees as an excellent event.

Conclusions/ Future Directions and Recommendations

PSCP has had far-reaching impacts on the development of hPSCs for applications in human healthcare. Our primary beneficiaries have been basic and translational academic scientists, engineers and disease specific clinicians. This partnership has led to a broader understanding of the challenges faced in regenerative medicine and has produced researchers with increased skill sets to start to overcome those challenges earlier in the lifespan of a product's development. PSCP have laid the groundwork for the development of safe and effective applications of PSC-derived therapies, it is now the turn of the teams involved in PSEC to deliver innovative approaches to the rate-limiting steps of hPSC-based cell replacement therapies to enable their clinical delivery and commercial development within the UK.

Outputs

- Resources available to the community, see Section 4.
- Publications as a direct result of Hub activities, see Annex 4.

2.2 Engineering and exploiting the stem cell niche Hub

Director: Professor Stuart Forbes, University of Edinburgh

Who

- **University of Edinburgh**, Stuart J Forbes, Charles ffrench-Constant, David Hay, Bruno Peault, Anna Williams, Mark Bradley, Pierre Bagnaninchi, James Dear, Jenny Cusiter (Project Manager), Julie Wallace (Administrator)
- **University of Liverpool**, Anthony Hollander
- **University of Cambridge**, Robin Franklin, Ludovic Vallier
- **Imperial College London**, Molly Stevens
- **Keele University**, Alicia El Haj, Ying Yang
- **King's College London**, Anil Dhawan, Shukry Habib, Tamir Rashid, Fiona Watt
- **University of Manchester**, Sue Kimber
- **University of Strathclyde**, Nick Tomkinson

What

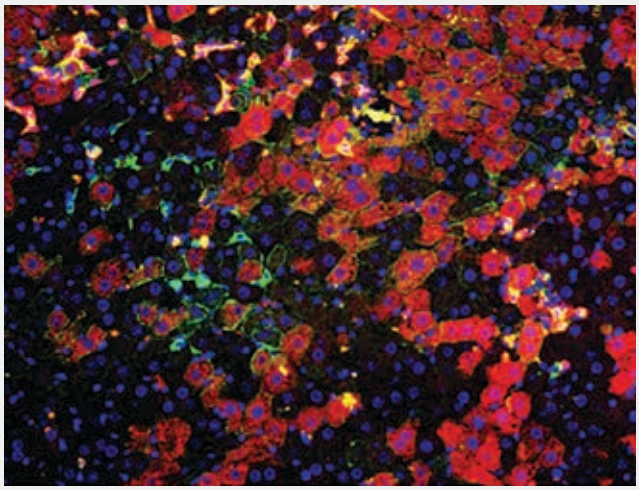
The UKRMP Niche Hub focuses on understanding and exploiting the signals that stimulate cartilage, liver and neural tissue repair in order to develop tools and technologies for regenerating tissue. We aim to advance the knowledge we accrue from in vitro and in vivo model systems into translational outcomes by taking information from those model systems and applying them to human tissues.

Scientific Achievements

Highlights of achievements across the Niche Hub for each of our main objectives include:

Development of better cells for transplantation and screening purposes

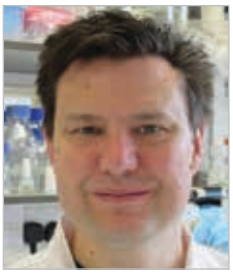
Liver disease comprises a significant and increasing clinical burden resulting in over 10,000 deaths per year in the UK alone. Organ transplantation, whilst effective is limited by availability of donor organs, surgical risk and requirement for life long immunosuppression. Seeking alternative therapeutic strategies has therefore become an increasingly urgent priority for our field. UKRMP Niche Hub researchers have shown that cholangiocytes (cells normally found in the bile duct) can function as liver stem cells during impaired hepatocyte regeneration; Wei Yu Lu, a post-doctoral research fellow from the Forbes group, has developed a model of combined liver injury and inhibition of hepatocyte proliferation that causes physiologically significant levels of regeneration of functional hepatocytes from biliary cells. Defining this regenerative pathway may allow researchers to enhance this pathway for therapeutic benefit and potentially provide a new source of cells for cell therapy.



Lineage tracing of ductular derived hepatocytes (red) derived from labelled biliary cells (yellow) when hepatocyte proliferation is inhibited.

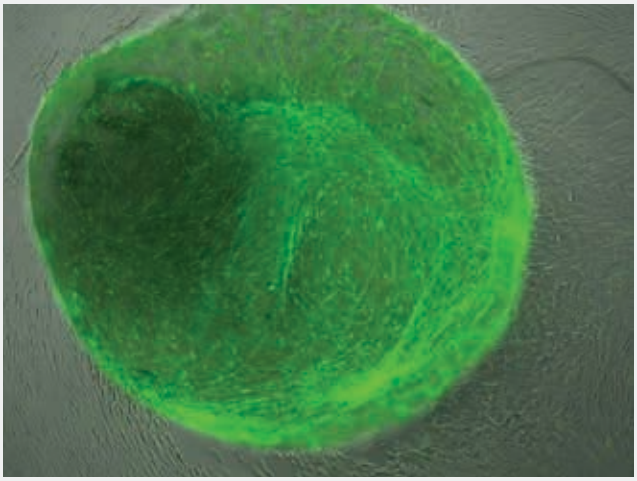
The UKRMP Niche Hub previously developed robust and scalable hepatocyte differentiation protocols that can be successfully applied to clinical grade cell lines. Niche Hub researchers have now developed a high throughput semi-automated stem cell derived hepatocyte differentiation protocol. Using the UKRMP Chemistry and Computational Biology of the Niche (CCBN) research facility, Kate Cameron, a post-doctoral research fellow from the Hay group, has developed a workflow for miniaturisation and multiplexing of the hepatocyte cell culture which when linked to a cell painting method allows for the identification of cellular components using fluorescently tagged probes. This has the potential to be used during the drug development process for toxicology screening.

The cartilage work programme has investigated embryonic derived chondrocytes as a potential allogenic cell therapy with reduced immuno response side effects. A large animal study investigating appropriate scaffolds/constructs is underway. The serum-free chondrocyte differentiation protocol developed by Aixin Cheng, a post-doctoral research fellow from the Kimber group, has also been successfully translated into the laboratories at Keele University by Nicky Foster and Matt Shepherd, a PhD student and post-doctoral research fellow from the El Haj group, to establish an ES 3D chondrogenic platform. This protocol has been reproducibly defined allowing the team to look at the response of 3D organoids to mechanical stimulation in culture.



Stuart Cain, a post-doctoral research fellow from the Kimber group, has developed a robust protocol for differentiation of induced pluripotent stem cells into endothelial cells and smooth muscle cells. UKRMP researchers are now using these protocols to produce vascularised bone to demonstrate translation. Several tools and technologies have been developed during this work package including a selection of high quality extracellular matrix (ECM) recombinant proteins and a lentiviral expression system.

Sebastiaan Zijl, a researcher from the Watt group, has completed an initial Topochip screen (survey of topographies that promote keratinocyte differentiation) in collaboration with Materiomics who are based in Maastricht, identifying features for a mechanistic screen. An algorithm has been developed to predict features that promote differentiation of cells with rounded or spread morphologies. Optimal surfaces have been fabricated in collaboration with Kelvin Nanotech for further mechanistic experiments to support keratinocyte differentiation at sufficient scale. In pilot experiments, it has been confirmed that the optimised surfaces promote differentiation of spread keratinocytes, providing a platform to explore the signalling pathways involved. This is of practical importance for future clinical applications of human iPSC.

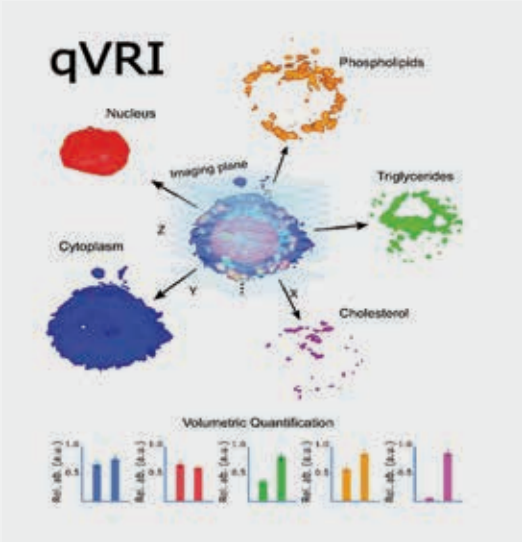


Live image of iPSC derived endothelial cells expressing green fluorescent protein, embedded in a hydrogel plug. A complex network was formed after 2 weeks of growth.

Identification of molecular targets for drug-based regenerative medicine

Niche Hub researchers have developed an assay for chondrogenesis which is the process required for cartilage regeneration; Chao Li, a post-doctoral research fellow from the Hollander group established cell culture and assay protocols enabling high throughput screening for chondrogenesis. This platform has the potential to screen large compound libraries looking for small molecules and biological agents that promote repair and regeneration of cartilage.

"Tools and technologies have been developed that will benefit the sector; significant advances have been made in developing protocols and platforms that will drive translation of regenerative biology towards the development of new treatments for patients. Importantly, the UKRMP experience is helping to develop and mentor the regenerative medicine community of the future."
– Stuart Forbes



Quantitative Volumetric Raman Imaging: simultaneous imaging of multiple biomolecules in biologically relevant 3D cell culture environments

Development of ways to measure tissue regeneration

Mads Bergholt, Jean-Phillipe St-Pierre and **Andrea Serio** (pictured) from the Stevens group at Imperial College, London, have developed a number of tools and technologies that can be used for label-free, non-invasive and non-destructive characterisation of cells and tissues. The UKRMP research team have shown that Raman spectroscopy can provide novel insights into the zonal organisation of native and tissue-engineered articular cartilage permitting comparison of real cartilage tissue to engineered tissue. The Stevens group have also developed online quantitative monitoring of live cell engineered cartilage growth using diffuse fibre-optic Raman spectroscopy which offers the ability to non-destructively monitor construct growth online and can be adapted to a broad range of tissue engineering applications in regenerative medicine towards controlled clinical translation. A computational framework for label-free quantitative volumetric Raman imaging (qVRI) has also been developed allowing researchers to simultaneously image multiple biomolecules in biologically relevant three-dimensional (3D) cell culture environments can contribute greatly to the understanding of complex cellular mechanisms and cell-material interactions.

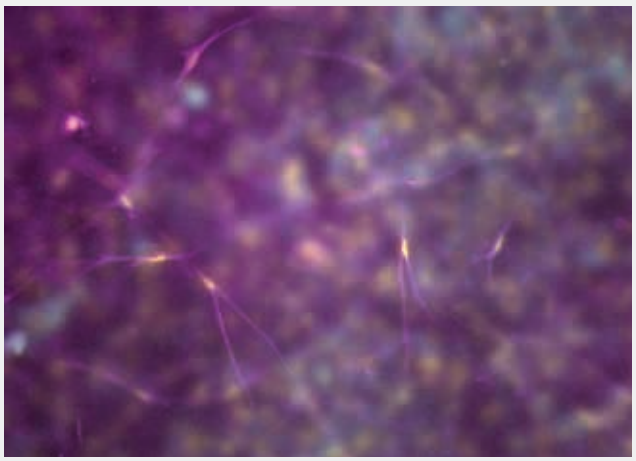
A novel optical instrumentation, MechAScan, has been developed from a collaboration between the Bagnaninchi group in Edinburgh and Yvonne Reinwald, a postdoctoral fellow from the El Haj group in Keele. This proof of concept device uses a combination of hydrostatic forces and elastography to provide a tool for mechanical characterisation of tissue engineered constructs online in a bioreactor. Follow on funding from the EPSRC has been awarded to develop this technology through to commercial applications (see below).

Hub Growth

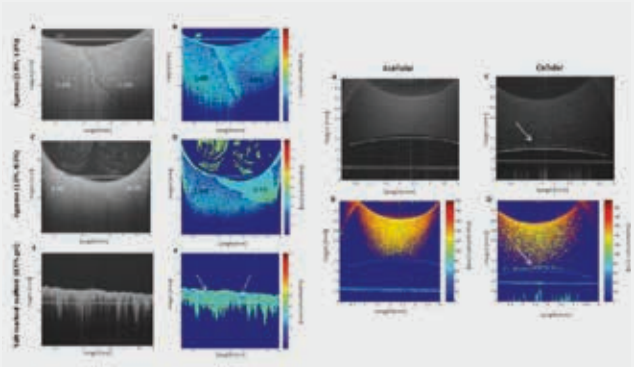
The El Haj and Habib groups have collaboratively developed a stable Wnt platform that is able to maintain adult and embryonic stem cell populations; this work was carried out by Molly Lowndes, a post-doctoral research fellow from the Habib group and Mike Rotherham, a postdoctoral fellow from the El Haj group. The simple chemistry used for Wnt immobilisation allows for adaptation to new materials and other developmental signals and this method can also be incorporated into tissue engineering platforms in which depletion of the stem cell pool restricts the complexity and maturity of the tissue developed.

James Dear has been announced as a joint winner of the 2017 Rosetrees Trust Interdisciplinary prize; the main aim of the prize is to promote collaborative research between medicine and engineering and will allow the development of a prototype device to rapidly diagnose drug-induced liver damage based on the results from the UKRMP funded partnership project.

The Rashid group have also developed a high throughput, high content imaging platform to empirically quantitate 'hepatocyteness' against a validated benchmark (freshly isolated primary adult hepatocytes). Using the new tool, ECM proteins capable of driving iPS hepatocytes closer to primary cells have been screened before validating both their physiological relevance and importance for drug screening



Wnt platform maintains a mesenchymal stem cell population and induces migration and osteogenic differentiation in 3D culture within one week. (Yellow: Dapi, Magenta: osteogenic marker Osteocalcin). This image is an extended focus of 100 um.



MechAScan – an on-line tool for characterisation of elastic modulus in engineered tissue constructs in a bioreactor

Networking Activities

An Industry Engagement event was held in collaboration with the MRC CRM in Edinburgh in May 2017 titled "Regeneration Innovation". The main aim of the event was to strengthen links with industry. There were multiple presentations from UKRMP Niche Hub researchers and as a result there are ongoing discussions with multiple industry partners concerning future research collaborations and commercialisation of research.

The Niche Hub held a Dragon's Den Commercialisation Workshop in collaboration with the UKRMP Immunomodulation Hub in February 2017 using the successful format previously deployed by the UKRMP Acellular Hub. UKRMP researchers pitched to a panel of Industry Dragons who supplied feedback and advice for translating and commercialising research outputs. Kate Cameron (Hay group) was the unanimous winner of the Workshop on the day and was selected for her pitch "Cytochroma" a high content toxicity screening platform based on outputs from UKRMP funded research.

The Niche Hub also held a High Content Imaging Event in March 2018 in collaboration with the Society for Biomolecular Imaging and Informatics. A world leading line up of speakers from academia and industry presented their research with a focus on their technological capabilities and the recent advancements in regenerative medicine due to imaging and informatics. UKRMP research outputs were presented during a flash talk session. The event was finished with networking and laser show entertainment. The following day, an interactive training and development workshop was held with a focus on the use of three different software packages for analysing imaging data: CellProfiler (Broad Institute), HCS StratomineR (Core Life Analytics) and Spotfire HCP (Perkin Elmer).

"Working in this multi-disciplinary network has helped to foster long term collaborations that have leveraged follow on funding to ensure that projects continue to be translated towards the clinic. Interdisciplinary interactions have added value to project outputs and researchers have focused on developing relevant and useful outputs." – Alicia El Haj

Future Directions

The Niche Hub aims to drive research outputs towards clinical therapies by developing cell therapies as well as improving "endogenous" tissues repair. We have successfully leveraged follow on funding including £2M (MRC DPFS) to determine whether human HPCs/ductular cells isolated from non-transplantable human liver have potential as a future clinical cell therapy for liver disease. £1M has been awarded (EPSRC) to further develop the "MechaScan" technology; a high through put imaging modality to characterise the identity of cells and type of cell division. The Raman spectroscopy work packages have led to the testing of Raman as a non-invasive imaging modality to determine the usability of a liver for transplant purposes (MRC Confidence in Concept).

We are continuously looking for commercial partners in order to engage with industry and are keen to discuss ideas and projects that will accelerate the progress of regenerative medicine from the laboratory to the clinic.

Outputs

- Resources available to the community, see Section 4.
- Publications as a direct result of Hub activities, see Annex 4.

2.3 Safety and efficacy, focussing on imaging technologies Hub

Director: Professor Kevin Park, University of Liverpool

Who

- **University of Liverpool**, Kevin Park (Director), Chris Goldring, Dean Naisbitt, Mathias Brust, Marta Garcia-Finana, Raphael Levy, Patricia Murray, Antonius Plagge, Harish Poptani, Lorenzo Ressel, Matt Rosseinsky (Deputy Director) and Bettina Wilm (Claire Hutchinson – Project Manager)
- **University of Manchester**, Stephen Williams, Nick Ashton, Marie-Claude Asselin, Sue Kimber, Kostas Kostarelos, Rachel Lennon and Adrian Woolf.
- **University College London**, Mark Lythgoe, Paul Beard, Tammy Kalber, Quentin Pankhurst and Martin Pule
- **University of Edinburgh**, Stuart Forbes, David Hay and Dan Antoine
- **University of Glasgow**, Dave Adams, Marc Clancy, Patrick Mark, and Rhian Touyz
- **University of Illinois, Chicago**, USA, Natalia Nieto
- **University of Sheffield**, Peter Andrews (PSCP Hub)
- **University of Cambridge**, Roger Barker (PSCP Hub)

What

Our focus was to provide a clearer understanding of the potential hazards (and associated risks) of Regenerative Medicine Therapies (RMTs) so that these new medicines can be accelerated into the clinic with full confidence.

The key areas for the Hub in the final phase were studies using our multimodal imaging approaches for both stem cells and immune cells (in the same animal) to investigate phenotypic changes following cell administration and establishing the effect of regenerative medicine therapies (RMTs) on multi-organ function in acute injury.

Safety and efficacy questions addressed within the Safety Hub generate knowledge to bridge RMT biology from cognate preclinical models to safe introduction into man; the technologies platform developed within the Hub can have a major impact on the translation of RMTs into the clinic.

Scientific achievements

During the final 12 months of the Safety Hub programme, we advanced our triangulation approach of imaging technologies alongside mechanistic biomarkers and traditional histopathological validation for functional assessment following both acute and chronic injury.

The Hub identified novel clinically translatable magnetic resonance imaging (MRI) biomarker protocols for both liver and kidney disease. We assessed three organ parameters in one animal in the same session through development of quantitative non-invasive imaging to establish effect of injury on function.

Our chemists continue to be engaged in the development of new particles and are synthesising conjugates for long-term evaluation using two imaging modalities, allowing both whole body and target organ imaging, specifically for cells that alter their phenotype rapidly in culture.

Application of a bimodal imaging strategy to monitor the safety of a human ESC-based therapy for Parkinson's disease

Working with Professor Roger Barker and Pam Tyers, Cambridge, we applied a bimodal imaging strategy based on bioluminescence and magnetic resonance imaging (MRI) to monitor the safety of a human ESC-based therapy in an immunocompromised rat strain. This partnership addressed the need to acquire in vivo imaging data to facilitate the translation of an ESC-based regenerative medicine therapy for Parkinson's

disease to the clinic. The project is thus highly relevant to the aims of the future UKRMP2 programme: i.e. development of ESC and iPSC-based regenerative medicine therapies for various human diseases, such as Parkinson's disease, and the development and application of appropriate imaging strategies for monitoring the safety and efficacy of RMTs in vivo.

Dr Arthur Taylor has used imaging to; (i) track the viability and integration of ESC-derived dopaminergic precursors using bioluminescence; (ii) assess the tumourigenicity risk of undifferentiated ESCs vs ESC-derived dopaminergic precursors using bioluminescence; and (iii) observe the intracranial distribution of the cells using MRI; and at the end-point, assess the ability of the cells to integrate with the host's brain tissue using transmission electron microscopy and confocal microscopy of tissue sections.

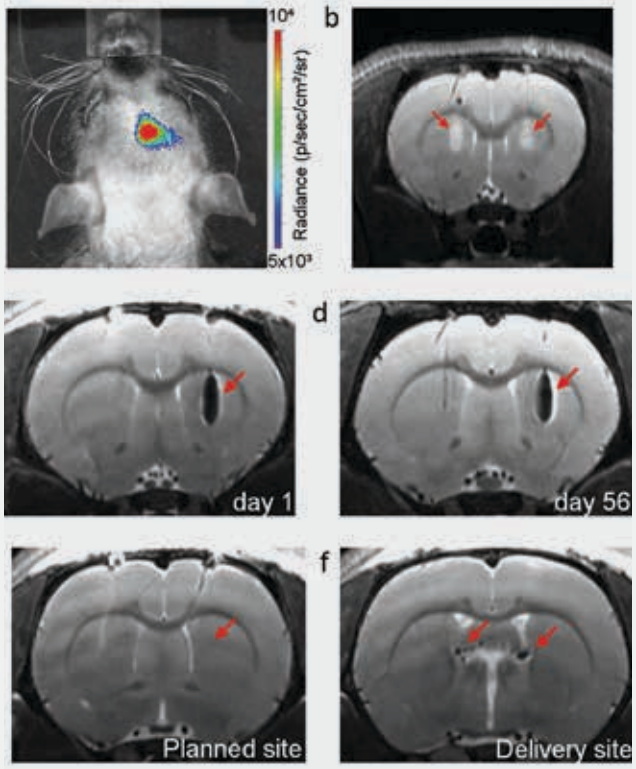


Image 1a and b. Assessment of ESC tumorigenicity. One of the possible risks of using ESC-based therapies is the formation of tumours (teratomas). Here, we used BLI and MRI to monitor the tumour formation potential of undifferentiated ESCs (positive control) that were injected into the left and right hemisphere of rat brains. Imaging of a rat head, 27 days post cell administration showed strong bioluminescence signal (a) indicating cell proliferation. MRI at the same time point (b) showed tumour formation seen in the form of abnormal hyperintense (bright) contrast (red arrows). Image 1c and d. Using MRI to monitor the intracranial distribution of cells. Dopaminergic progenitors derived from ESCs were injected into both hemispheres of a rat brain. The cells in the left hemisphere were additionally labelled with SPIONs enabling us to track their intracranial distribution. Imaging on days 1 (c) and 56 (d) post administration reveals minimal migration from the site of injection (red arrow), where the cell deposits are seen as hypointense (dark) contrast. In contrast to (b), no abnormal contrast is seen on the left hemisphere, confirming that differentiated cells do not form tumours. Image 1e and f. Using MRI to monitor the safe delivery of cells. Here, cells were labelled and injected as described above; however, no hypointense contrast was seen on the site of injection (e). A detailed analysis of the brain via MRI revealed that cells were administered to the wrong site, and injected into the ventricles of the brain. This resulted in the cells migrating to unexpected regions (f).

Imaging two cell types at the same time in the same animal

As an addition to the Hub's toolkit for cell tracking, in order to look at two cell types in the same animal using whole body imaging, Dr Toni Plagge and Dr Arthur Taylor developed a dual luciferase imaging strategy, which enables different cell types to be distinguished at the same time with bioluminescence. Within the Centre for Preclinical Imaging (CPI) University of Liverpool, Arthur labelled macrophages and mesenchymal stromal cells (MSCs) with the two different luciferase reporters. The cells were administered to a healthy mouse and imaged 24 hours later. It is possible to see MSCs (green) and macrophages (red) trapped in the lungs with a proportion of macrophages in the liver (image 1). This approach can be used to assess not only the initial biodistribution of both cell types but also the change in biodistribution over time in injured animals to help address the function of macrophages following stem cell administration.

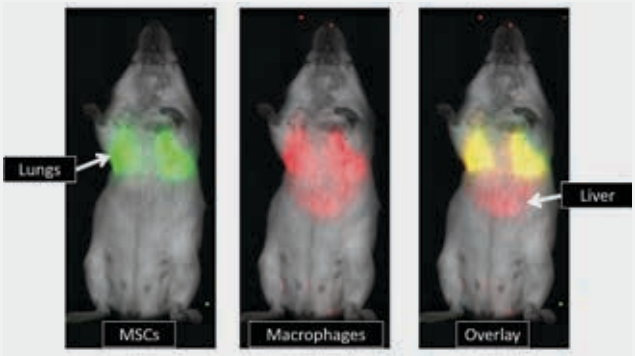


Image 2. Using a newly developed dual luciferase imaging strategy we are able to label and image two different cell populations in one imaging session.

"To evaluate safety and efficacy we have developed a multi-modal imaging technology platform and utilised mechanistic biomarkers that enable evaluation and characterisation to assess the effects of administered cells on host tissues. By understanding homing, fate and mechanism of action, it will be possible to refine cell-based therapies to make them safer and more efficacious."
Kevin Park

Novel imaging biomarkers for liver fibrosis using non-invasive MRI

John Connell, working at the Centre for Advanced Biomedical Imaging at UCL, has developed a novel imaging biomarkers for liver fibrosis using non-invasive MRI. This disease is characterised by extensive deposition of tough collagen throughout the liver as a consequence of the chronic wound healing response after liver injury. As new cell based regenerative medicines are being developed to treat liver fibrosis, new ways of staging the disease without resorting to invasive biopsy are urgently needed. MRI can give images of the body with high resolution, and indicate the location and extent of disease. The amount of blood that perfuses into the liver can be quantified by MRI, and measuring this both before and during a carbon dioxide (CO2) gas challenge allows us to see how easily blood vessels can dilate. The collagen and activated hepatic stellate cells that we see in liver fibrosis prevent the vessels from dilating as they should. This method developed in mice is now being tested in the clinic on volunteers in the hope of future use in liver fibrosis patients receiving cell therapy.

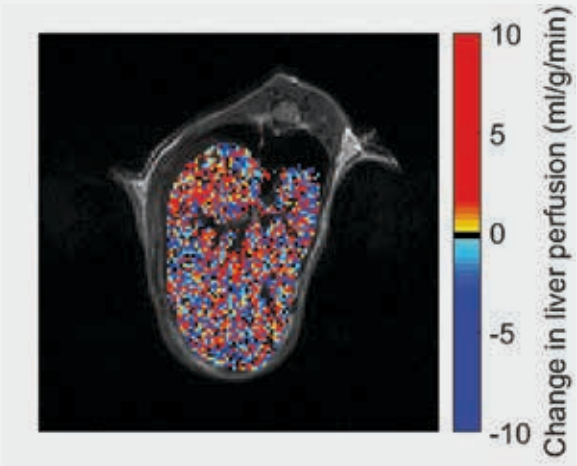


Image 3. MRI of mouse with early stage liver fibrosis. Perfusion was measured before and during a CO2 gas challenge to probe vasoreactivity. Mice with early stage fibrosis display a significant reduction in perfusion across the liver compared to controls.

he engineered nanoscaled iron oxide nanoparticles that efficiently label stem cells, enabling them to generate better contrast when imaged using magnetic resonance imaging. He applied this technique to establish how stem cells distribute within the major organs under different routes of administration. With colleagues that implemented an arterial route of stem cell administration, he obtained a detailed view of their localisation in the kidneys, where it was found that cells accumulate preferentially in the blood capillaries of the glomerulus, an essential part of the kidney's filtration unit. Kinetic imaging allowed a spatio-temporal overview of their delivery and subsequent clearance from the kidneys, which, when combined with data obtained via optical imaging, revealed their short persistence and poor survival in this organ.

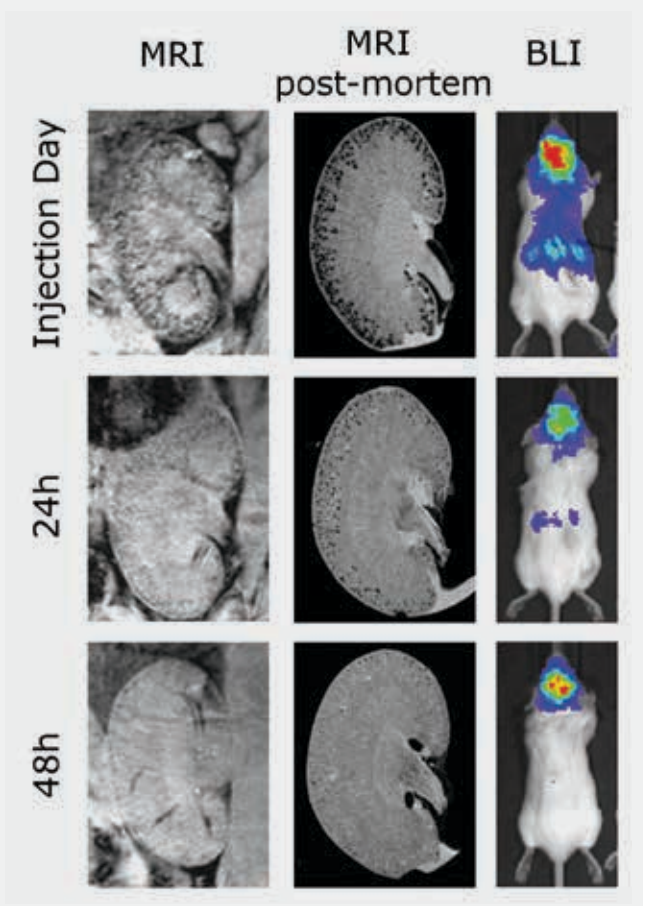


Image 4. Short-term fate of mouse Mesenchymal Stromal Cells (mMSCs) imaged in vivo and post-mortem. MRI (in vivo, post-mortem), and Bioluminescence (BLI) images of the kidneys immediately, 24h or 48h after IC administration of SPION-labelled mMSCs.

Dynamic Imaging of Cell Fate

Arthur Taylor, working at the University of Liverpool, is integrating data from a range of imaging modalities to obtain a comprehensive view of the trafficking and fate of stem cells post administration in rodent models of kidney disease. In a fruitful collaboration with chemists, Interestingly, even when cells die they can exert a positive outcome in a range of diseases and we are currently investigating these effects. For that purpose, Arthur developed a novel combination of optical reporter genes to allow us to track the fate and biodistribution of both mesenchymal stromal cells and immune-relevant cells concomitantly (Image 2). This enables the identification of critical milestones in the interplay between exogenously administered cells and the immune system.

Emphasis on functional MRI imaging linked to conventional biomarkers as a tool for future therapeutics

Abigail Chahil, a PhD student from Liverpool who worked with Professors Kevin Park and Harish Poptani validated a quantitative, non-invasive MRI protocol to characterise changes in liver physiology that surpasses the need for liver biopsies in assessing the severity of injury. By correlating clinical biomarkers of liver injury alongside histological evaluation and MRI derived biomarkers, it was possible to assess the damage and the pathophysiology of the liver during the event of acute liver injury. This provides information on diffusion of water molecules in the liver suggesting micro-necrosis, liver fat/water ratios indicating fat content, and the possibility of a potential MR-imaging marker T2 relaxation time, for acute liver injury.

Abby observed a consistent trend in both quantitative MR markers and serum biomarker results. Having successfully identified the changes within the MRI parameters in a paracetamol-induced toxicity model, liver injury can be further analysed using these imaging methods to provide information into the mechanistic insight of future therapeutics.

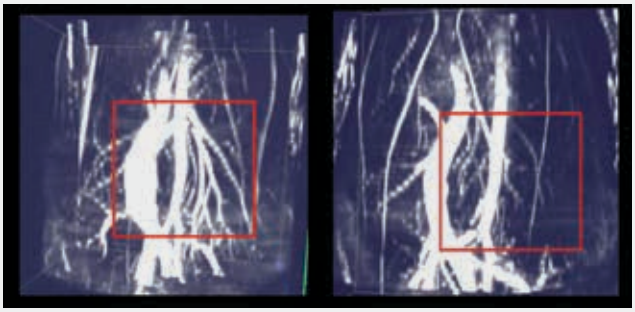


Image 5. MRI maximum intensity projection angiography data of murine blood vessels before and 24h after paracetamol treatment. Vessel occlusion is observed around the region of the right hepatic vein (red box) in the liver 24 hour after paracetamol overdose treatment.

Networking activities

The Safety Hub was involved with two workshops during the final 12 months of the award. In November 2016 we collaborated with the UKRMP Immunomodulation Hub to bring stakeholders together to discuss MSCs and the Roadmap to clinical translation. The workshop covered MSC activity in the UK for both clinical and scientific applications. Discussion included understanding the mechanisms of cell therapies and moving from bedside to bench and back again; how a unifying approach to manufacturing therapies should be adopted with manufacturing strategies in place from the outset; and availability of funding streams for basic regenerative medicine science. From a clinical perspective, the increasing costs of trials is considered a particular challenge, and attendees concluded there is a need for a national registry to capture trial data to feed back to researchers. A commentary from the meeting has been published in Future Medicine's Regenerative Medicine.

In March 2017, the Safety Hub hosted the workshop "Imaging for biodistribution, function and safety assessments of the liver" to address the issue of how imaging can provide better understanding and prediction of drug-induced liver injury. In conjunction with the MRC Centre for Drug Safety Science the workshop was attended by representatives from pharmaceutical and biotechnology companies, contract research organizations, regulatory agencies and academia. Several case studies were presented which focused on how different imaging modalities can be used and when they may be implemented in the evaluation of drug-induced liver injury in the preclinical setting, and on the challenges of using imaging modalities.

Conclusions, future directions and recommendations

During the Safety Hub programme, we developed a preclinical toolbox for any organ or application by using cell tracking in conjunction with functional and anatomical imaging for physiological, pharmacological, and toxicological safety assessments. Imaging strategies give insight into efficacy and safety of therapeutic agents, and can remove the disconnect between disposition of cells and the understanding of mechanisms. Tumourgenicity remains a major concern for the field of regenerative medicine, with the location of cells and potential for malignant transformation remaining a key issue. These unknowns need to be further addressed with mechanism-based work, and the Safety Hub has developed the tools to tackle this.

As in all novel therapies, clinical pull-through is vital. By addressing clinically relevant problems using cognate animal models, researchers in UKRMP2 can link into the expertise of the Safety Hub to address safety issues in man that will have an impact on the field.

Outputs

- Resources available to the community, see Section 4.
- Publications as a direct result of Hub activities, see Annex 4.

2.4 Acellular approaches for therapeutic delivery Hub

Director: Professor Kevin Shakesheff (pictured), University of Nottingham
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
- **University of Southampton**, Richard Oreffo
- **Keele University**, Alicia El Haj
- **University of Manchester**, Julie Gough, Sue Kimber (Niche Hub), Ailine Miller and Stephen Richardson
- **Cardiff University**, Alastair Sloan
- **University of Birmingham**, Liam Grover
- **MRC Centre for Regenerative Medicine, University of Edinburgh**, Stuart Forbes (Niche Hub)
- **University College London**, Robin Ali, Richard Day
- **University of Cambridge**, Stephano Pluchino
- **University of Liverpool**, Rachel Williams
- **University of Paris Descartes**, Philippe Menasché
- **King's college London**, Fiona Watt (Immunomodulation Hub)

- **Clinical Spokes** include James Fawcett/Roger Barker (Cambridge), Philip Newsome (Birmingham), Sheila MacNeil, (Sheffield), Ilyas Khan (Swansea), and Krish Raganuth (Nottingham), Rachel Oldershaw (Liverpool)
- **Other collaborators** – Steve Badylak (Pittsburgh), Rob Quirk (Locate Therapeutics), Fergal O'Brien (RSCI Dublin), Cell and Gene Therapy Catapult, BioPoly Inc.

What

This Hub was formed in 2013 with the aim of creating new advanced materials and technologies that can promote cell survival and function at the intended site of regeneration, facilitate localisation of drugs to augment tissue regeneration and guide tissue self-assembly in 3D architectures.

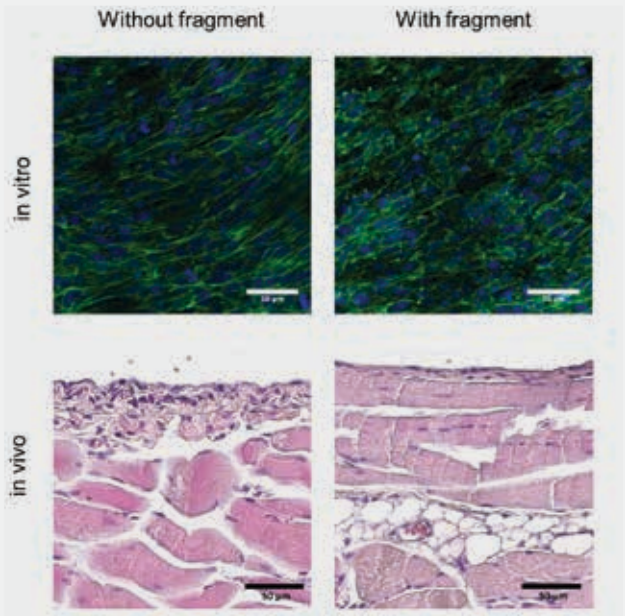
At the Hub's core are five materials and tissue engineering groups, who together with a network of clinical spokes and new partnerships have created several platform technologies for cell injection, intracellular delivery of molecules, magnetic mechano-activation and polymer-peptide hybrid scaffolds. These advances have been successfully implemented by the Clinical Spokes to improve tissue regeneration in a number of tissue types, disease areas and pre-clinical models.

As we moved into our final year there was a marked increase in international collaborative activity across Europe and the US, plus expansion of our industrial links. With a number of patent filings across the Hub, the intellectual property position was strengthened leading to a number of licensing deals and opportunities. One key objective was to see these transformative advances translated into clinical use.

Scientific Achievements

Targeting epithelial-to-mesenchymal transition (EMT) as a strategy to prevent fibrosis

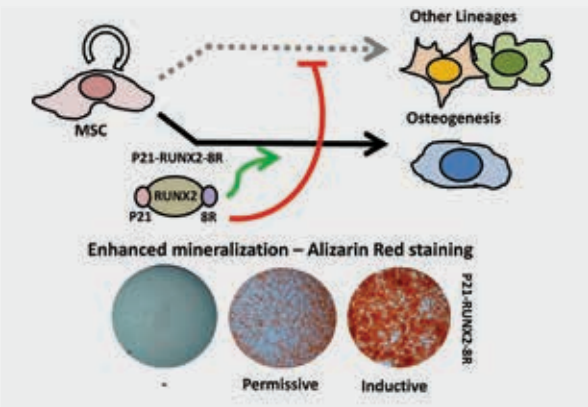
In their landmark publication in 2017 (C. Horejs, J.-P. St-Pierre, J.R.M. Ojala, et al Nature Communications. 2017. 8: 15509), the Stevens Group has shown the promising potential of biomaterials functionalized with active fragments based on cryptic sites within proteins. The epithelial-to-mesenchymal transition (EMT) causes epithelial cells to transdifferentiate into myofibroblasts, playing a major role in fibrogenesis, or the formation of scar tissue. Drugs that target the mitigation of EMT have shown promise but clinical trials have highlighted their drawbacks in inducing secondary and off-target effects. We have recently reported a new strategy addressing a new approach to prevent EMT in a localised manner. We functionalised a biomaterial with the fragment and demonstrating the suppression of EMT under inflammatory conditions in vivo.



Biomaterials functionalised with an active cryptic fragment of laminin-111. The functionalised biomaterial was interfaced with tissues in vivo, resulting in peritoneal tissues exhibiting features similar to healthy tissue.

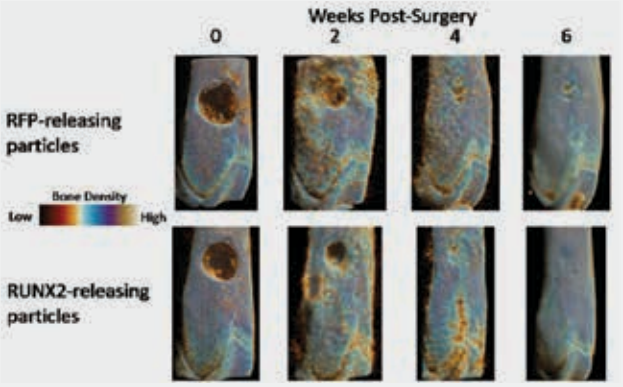
Protein Fusion Technology

Following on the patented works of Dr James Dixon on the efficient intracellular delivery system, GET system, **Dr Lalitha Thiagarajan** has demonstrated optimised-delivery of transcription factor, RUNX2 to induce osteogenesis in hMSC. At the University of Nottingham, they have successfully optimised the use of GET system in mRNA delivery which offers a very efficient reprogramming strategy for clinical application without genomic integration and provides a predictable protein expression pattern. Lalitha and colleagues have optimised protocols for mRNA delivery in clinically relevant cell types (hMSCs) and hard-to-transfect, non-proliferative cell types (cardiomyocytes).



Schematic diagram of GET-RUNX2 delivery optimization to achieve efficient osteogenesis induction and enhanced mineralization in human Mesenchymal Stem Cells.

Collaborating with the group of Prof. Fergal O'Brien (RSCI, Dublin, Ireland) the GET system has been successfully used to deliver the expression of bone morphogenetic protein 2 (BMP2) and vascular endothelial growth factor (VEGF) plasmids to enhance bone repair in animal models in conjunction with collagen-based scaffold and mesenchymal stem cells. They could achieve full bridging of a critical size bone defect in rats, with a high level of bone regeneration within the defect. This is now to be applied for cartilage based regenerative strategies and will be employed to large animal models for several orthopaedic applications.



GET CT scans showing bone formation at drill defect site: representative images are shown of the drill defect site over a 6 week time period in a mouse implanted with HBMSCs on a scaffold containing either RFP-GET-releasing particles or RUNX2-GET-releasing particles.

Nottingham, working with one of the core hub laboratories in Southampton has further exemplified the GET system as a platform technology. Dr Stuart Latham, in Professor Richard Oreffo's lab, has progressed in vitro findings into a pre-clinical animal model and has shown successful delivery of red fluorescent protein (RFP) via the P21 and 8R GET peptides system to murine calvariae in vivo as shown by detection of fluorescence in isolated calvariae 24 hours after injection. Current studies have extended these observations and confirmed RFP expression in cultured osteoblasts isolated from the injected calvaria 5 days after injection, as well as detection of RFP expression in the calvaria two weeks following injection. These results indicate protein delivery using GET provides long-term protein expression not observed by RNA delivery using the same system.

Cell-derived delivery system

As part of a partnership project, **Ms Camille Marijon** has performed exciting work with Prof Molly Stevens' group at Imperial College London (ICL) and Prof Philippe Menasché's group at the University of Paris. Camille has developed rat models of myocardial ischemia/reperfusion and permanent myocardial infarction, which have already proven useful for testing different therapies developed by the

group, including nanoneedles for epicardial reprogramming, an auxetic conductive patch for heart repair and an innovative anti-fibrotic biomaterial. Marijon also developed close collaborations with Daniel Stuckey's team at University College London that has extensive expertise in cardiology and biomedical imaging to support her work with state-of-the-art techniques and knowledge.

This partnership project has delivered extracellular vesicles (EVs) for applications in cardio-repair. The Stevens Group has high quality protocols for isolating, purifying and characterizing EVs to treat myocardial infarct. EVs are part of the cellular secretome and their constituents, such as exosomes, can contain powerful cargo that control paracrine signaling (ACS Nano 2017). They are building upon expertise gained since the beginning of this Partnership Project to deliver engineered EVs to injured sites. This platform technology has enormous potential, real clinical relevance, and we will validate the capabilities of this approach to stimulate and direct tissue repair within small and larger animal models in collaborations. Applications are potentially relevant across tissue types and multiple disease areas (e.g. cardiac delivery and osteochondral repair).

Novel peptide gels for human corneal endothelial cell transplantation

In Prof Rachel Williams lab at the University of Liverpool they have successfully developed an ex vivo model of the cornea which we can use to determine the optimal method to attach their novel peptide hydrogels to the posterior surface of the cornea. They have demonstrated that primary endothelial cells adhere to the gel and are maintained in culture for at least 7 days. 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. The main aim of this project was to develop cultured synthetic corneal endothelial grafts composed of a single-layered human corneal endothelium on our novel peptide gel. This will enable the production of many endothelial grafts from one human donor cornea. This technology will be further developed as part of the new UKRMP2 funded Smart Materials Hub being led by Professor Molly Stevens (Imperial College).

Hub Growth

The collaboration between Dr Rachel Oldershaw (University of Liverpool and Prof Mike McNicholas (University Hospital Aintree) received partnership funding to develop a medical device to support the delivery of stem cells to aid in the repair of anterior cruciate ligament injuries. Working with US Company, BioPoly Inc. they have established efficacy in a rabbit model and are progressing towards human clinical trials. Another partnership project led by Dr Richard Day (UCL) involved collaboration with regulatory experts at the Cell and Gene Therapy Catapult to gain a clear understanding of the regulatory landscape in order to achieve compliance with EU GMP manufacture and to generate an investigational medicinal product dossier (IMPD).

UKRMP funding has allowed for demonstration of clinical utility with several materials and technologies leading to further downstream development since Acellular Hub activities concluded. The GET- delivery system has been licensed to Locate Therapeutics Ltd, who have been successful in gaining Innovate UK Biomedical Catalyst Funding to develop a new surgical product that will cure diabetic patients of a specific type of severe back pain. This will utilise GET and will aim to deliver and prime stem cells for more effective bone formation (see Future Directions below).

Networking

The last twelve months have proved to be a busy time for Hub investigators with numerous presentations and invitations to speak at international events. For example, presentations have taken place in the US (Stevens), Australia (Stevens), China (Oreffo), Denmark (Oreffo) Austria (Oreffo) and Spain (Levis).

The UKRMP Symposium "Advanced material for cell and biologics delivery", was held as part of TERMIS-EU in Davos, and provided an opportunity to exchange ideas with leaders in the field.

"The Hub has provided a springboard for many early career researchers who have progressed to independent careers across the world. The collaborative spirit of UKRMP and the focus on transition should give them a foundation for successful careers in regenerative medicine." – Kevin Shakesheff

Conclusions/Future directions/ Recommendations

The last two years have seen a shift from in vitro development and validation of smart materials, through ex vivo and in vivo testing in pre-clinical models. With this shift along the translational pathway has come increased input from regulatory and industry experts to ensure that each technology platform will meet the stringent requirements for use in the clinical setting. Commercialisation and the net value of the projects have also been evaluated through the support of SAB members, commercialisation workshops and site visits. Several successful Hub projects have secured follow on funding to further develop and translate technologies to the clinic. More than £2m has been awarded as a result of the cohesive research activities both within the Hub and in collaboration with other UKRMP Hubs, for example the ARUK award where magnetic nanoparticle (MNP) and MRI (magnetic resonance imaging) technologies are being used to track MNP-labelled cells in a large animal model. This project was carried out in collaboration with Prof Alicia el Haj's group at Keele and Dr Michael Burrows from the University of Liverpool (UKRMP Safety Hub), Dr Frances Henson of Cambridge University and Dr James Dixon from the University of Nottingham.

The Hub has proved to be an outstanding platform for the post-doctoral researchers involved, not only has it facilitated the opportunity for brokering international collaborations and improvement of skills through time spent in other laboratories, but it has acted as a career stepping stone. Two former post-doctoral researchers have moved to faculty positions, Dr Jenny Puetzer is now Assistant Professor in the Department of Biomedical Engineering, with an affiliate appointment in the Department of Orthopaedic Surgery, at Virginia Commonwealth University and Dr Jean-Philippe St-Pierre is Assistant Professor in the Department of Chemical and Biological Engineering at the University of Ottowa.

Dr Lisa White used the UKRMP post as a springboard for an Anne McLaren Fellowship at the University of Nottingham. Her role in the UKRMP Acellular Hub was to develop polymeric microparticles for controlled release of GDF6. Her independent fellowship leads to a permanent assistant professorship at Nottingham.

Dr Deepak Kumar has moved from Manchester to the University of Oxford where he has joined the Molecular Neurodegeneration Research Group as Stem Cell Facility Research Manager. While Dr Christine Horejs joined the Nature Reviews Materials team as an Associate Editor in September 2017.

Company formation and growth is an important aspect of biomaterials and acellular technologies translation. Typically, large pharmaceutical and healthcare companies have the global sales presence to support the distribution and marketing of biomaterials products but will not take the risk of investing in product development. This creates a need to incubate technologies through early regulatory stages within SMEs. The UKRMP Hub has been very active in this area. Renovos Biologics Limited has been set up during UKRMP 1 to commercialise work from Richard Oreffo's lab in Southampton with co-founder Dr Jon Dawson. The company offers a portfolio of products to meet the needs of the orthopaedic regenerative medicine industry, by supporting researchers with novel solutions, and by addressing the unmet clinical needs within the orthopaedic space. http://renovos.co.uk/.

Technology development funded by UKRMP through the Acellular Hub has also facilitated collaborative research with industry partners, levered additional funding and resulted in licensing opportunities. Locate Therapeutics Ltd is a Nottingham based regenerative medicine product development company and interaction with UKRMP was helpful in securing investment of £2 million to take an acellular technology and a cell therapy to investigational new drug status (IND) in the US in 2020. The company has licensed 2 technologies from the UKRMP programme and provides support for University of Nottingham research programmes.

Additionally, the thermoresponsive materials developed in the Shakesheff lab in Nottingham have progressed through ISO-10993 testing to licensing by Hereaus Medical with intended commercial launch within 2 years.

One of the key objectives of the Acellular Hub was to progress technologies towards the clinic, the demonstration of proof of concept and clinical efficacy for several clinical exemplars has allowed for downstream development to progress. Moving forward, smart biomaterials have demonstrated significant potential in the treatment of a range of conditions affecting the eye, musculoskeletal system and liver.

Outputs

- Resources available to the community, see Section 4.
- Publications as a direct result of Hub activities, see Annex 4.

2.5 Immunomodulation Hub

Director: Professor Fiona Watt, King's College London

Who

- **King's College London**, Fiona Watt, Francesco Dazzi; and from the MRC Centre for Transplantation, Giovanna Lombardi and Steven Sacks
- **University College London**, Robin Ali
- **The Francis Crick 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

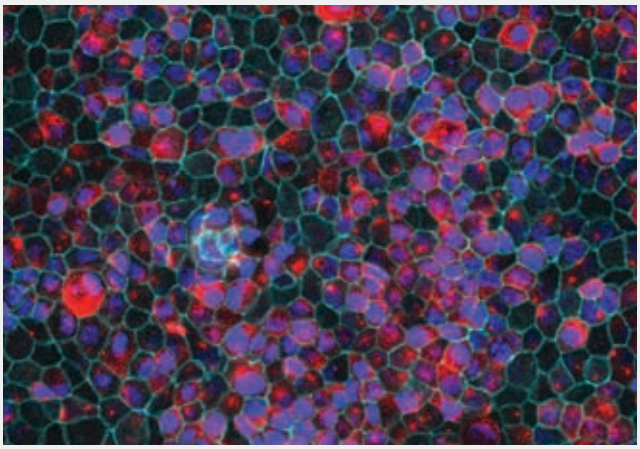
We have pooled our collective knowledge and sharing experimental tools to answer three questions:

1. How do iPSC-derived cells signal to the host innate and adaptive immune system?
2. When transplanted, how do these cells provoke adaptive immune responses?
3. How does the process of inflammation contribute to tissue repair and influence the fate of transplanted cells?

Scientific Developments

How do iPSC-derived cells signal to the host innate and adaptive immune system?

Induced pluripotent stem cells (iPSCs) are cells that have been reprogrammed from a mature adult state to a less mature embryonic-like stem cell. IPSCs are pluripotent, meaning they have the potential to become many different cell types found in the body and research has developed such that exposing iPSC's to specific molecular signals can stimulate them to become a specific cell type. Since they can become multiple cell types, iPSC's have substantial therapeutic potential. From a therapeutic perspective, one of the major advantages that iPSC-derived cells have over stem cells from other sources (for example those harvested directly from adult or neonatal tissues) is that iPSCs can be generated from the host's own cells, which in theory should circumvent the host's immune response that occurs after transplantation of foreign cells. However, the immunogenicity of iPSCs is still not fully understood hence we have focussed on two iPSC-derived cell types to investigate this mechanism – differentiated liver cells known as hepatocytes (iPSC-derived hepatocytes) and differentiated eye cells known as retinal pigment epithelium (iPSC-derived RPE).

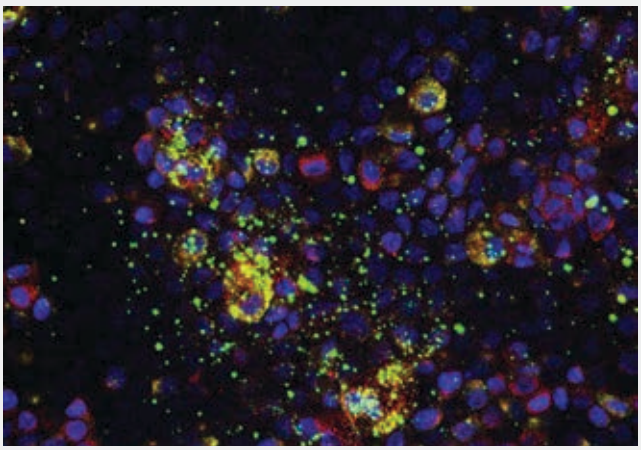


Monolayer of human iPSC-derived retinal pigmented epithelium (RPE) expressing Collectin-11 (red) under hypoxic conditions.

At King's College London, Professor Giovanna Lombardi and her research associate Dr Raul Elgueta investigated the immunological characteristics of iPSC-derived hepatocytes – including those from Dr Tamir Rashid's laboratory (Stem Cell Niche Hub) – as a potential strategy to use in transplantation. To determine whether the iPSC-derived hepatocytes are indeed like normal adult hepatocytes in the liver, Giovanna and Raul conducted an in-depth comparison of the levels of HNFalpha and SERPINA proteins commonly found in adult hepatocytes. The results indicated that there were similar levels of these proteins in each cell type. To further investigate

how the iPSC-derived cells react to an immune response, they exposed them to the inflammatory cytokine IFN-gamma. IFN-gamma had no effect on the appearance or morphology of the cells and there were no changes in the levels of HNFalpha and SERPINA. To assess the potential that these cells have of modulating an immune response, iPSC-derived hepatocytes were screened for the expression of certain cell-surface molecules involved in such processes (HLA class I, II, CD80, CD86, CD40 and PD-L1). These studies indicated that the iPSC-derived hepatocytes were similar to normal adult hepatocytes (specifically they showed constitutive expression of HLA class I (A, B, C), but not class II (DR, DP, DQ) or co-stimulatory molecules). Furthermore, treatment with inflammatory IFN-gamma upregulated the expression of certain cell-surface molecules (specifically CD40, PD-L1 and HLA class I), some of which can be immuno-suppressive. Together, these results are a promising indicator for the potential use of iPSC-derived hepatocytes for transplantation. Giovanna and Raul also examined the effects of iPSC-derived hepatocytes on T cell activity, another key indicator of the capacity of these cells to induce an immune response. They achieved this by growing the iPSC-derived hepatocytes alongside healthy human T cells (CD8+ or CD4+) obtained from peripheral blood mononuclear cells (PBMCs) and measuring T cell proliferation as an indicator of T cell activation. The iPSC-derived hepatocytes did not induce T cell proliferation but appeared to suppress it when simulated by adding anti-CD3/CD28 beads to the T-cells. Interestingly, they also found that levels of IL-10, which suppresses the immune system expression, is increased whereas expression of inflammatory IFN-gamma is decreased in T-cells grown alongside the iPSC-derived hepatocytes. They determined that cell-to-cell contact between the iPSC-derived hepatocytes and T cells is necessary for this immunosuppressive effect and that the process involves the release of a soluble factor from iPSC-derived hepatocytes, which downregulates the T cell receptor signalling cascades responsible for T cell proliferation. This mechanism, which is key to how iPSC-derived hepatocytes prevent T cell activity that is required for an immune response, is clearly advantageous if iPSC-derived cells are to be transplanted into patients.

Professor Steven Sacks and his research associate Giorgia Fanelli at King's and Professor Robin Ali and his research associate **Anai Gonzales-Cordero** at UCL investigated the immunological characteristics of iPSC-derived RPEs. They focused on collectin-11 (CL-11), a pattern recognition molecule, which in recognition of a foreign antigen can trigger the complement pathway immune response. In the eye, it is hoped that a more detailed knowledge of the relationship between CL-11 and

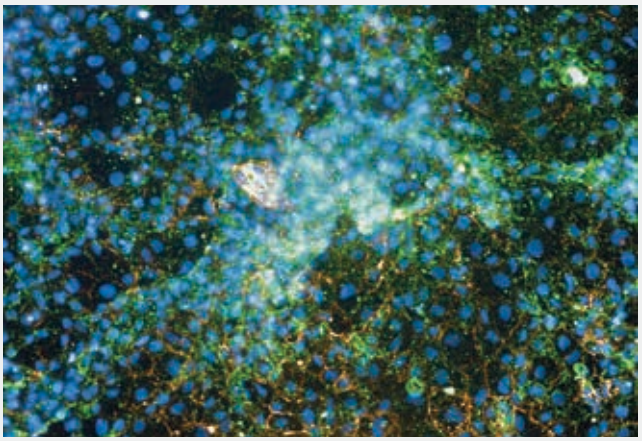


Representative immunofluorescence image showing co-expression of CL-11 and MAC (Yellow) on the surface of hypoxic-stressed iPSC-derived RPE cells. MAC (red), CL-11 (green) nuclei (blue) are also shown.

complement activation may provide insights for understanding the potential inflammatory and immune responses of the host environment to iPSC-derived RPE cells following transplantation. The team determined that CL-11 is expressed in the human eye with similar levels found in iPSC-derived RPE cells compared to adult RPE. To evaluate whether the stresses that can affect cells during transplantation would alter the levels of CL-11 they subjected the cells to low oxygen levels (hypoxia) and found that CL-11 levels increased. Additionally, CL-11 can facilitate cell death in RPE-derived iPSCs by triggering the complement signalling cascade, activation of which results in the co-ordination of effector proteins (such as the membrane attack complex or MAC) that form a pore in the cell membrane which irreparably damages it. For this complement signalling cascade to be engaged, specific receptors on the surface of the cell and another known as MASP-2, which mediates tissue injury, must respectively bind to and interact with CL-11. Together, the results from these studies shed some light on the relationship between CL-11 and the complement pathway in RPE-derived iPSCs.

When transplanted, how do these cells provoke adaptive immune responses?

At the Centre for Stem Cells & Regenerative Medicine at King's College London Professor Fiona Watt, Professor Francesco Dazzi and research assistant **Iacopo Bicci** produced iPSC-derived hepatocytes utilising the method created by Professor David Hay (Stem Cell Niche Hub). In collaboration with Dr Celine Filipi from Professor Anil Dhawan's laboratory (KCL, Denmark Hill) Iacopo evaluated his IPSC-derived hepatocytes against mature adult human liver cells and found encouraging similarities in the biomarker expression between the two. This showed that iPSC-derived hepatocytes used within the Hub are very similar to hepatocytes found in a normal human liver and hence are a useful model.



Differentiated iPSC-derived hepatocytes showing albumin expression. Blue is DAPI (nuclei), green is Albumin and red is E-cadherin, all human.

To investigate how these iPSC-derived hepatocytes provoke an adaptive immune response they used "humanised mice" which is an animal model system that use genetically modified mice to mimic normal and diseased liver conditions found in humans. To replicate the "normal" human liver environment Giovanna and research assistant Daniel Mc Cluskey used a genetically modified immune-deficient mouse (specifically NOD/SCIDgc-/-) in which the immune cells in the mouse's blood have been replaced with immune cells from human blood (either human peripheral blood mononuclear cells (PBMCs) or human CD34+ cells). To model a diseased liver Dr Marcus Dorner (Imperial College London) has used immunodeficient FNRG mice (specifically fah-/- NOD rag1-/- IL2rγnull) in which the liver has been repopulated with human cells lacking the enzyme fumaryl acetoacetate hydrolase (FAH), which is required for proper liver cell functioning. To evaluate whether transplanted cells provoke an adaptive immune response the team have transplanted human iPSC-derived hepatocytes to the liver in these humanised mice. To date, the hepatocytes have been shown to engraft in the FNRG mice and the presence of Albumin (produced by the iPS-derived hepatocytes) has been detected in the sera of these mice for up to 20 days, indicating that the transplanted cells have survived and are functional. Once these results have been further validated, the animals will be reconstituted with CD34+ human cells and the immune responses to iPS-derived hepatocytes will be evaluated.

Dr Giorgia Fanelli (PDRA in Steven Sacks' group), in collaboration with Moorfields Eye Hospital, is also using a humanized mouse model to address the safety and the feasibility of transplanting donor (allogeneic) iPS-RPE cells to the eye. This model was developed in Giovanna Lombardi's lab and "humanises" NOD scid gamma mice (NSG) by engrafting them with human peripheral blood mononuclear cells (PBMCs) which replaces the mouse's immune cells with human ones. Giorgia injected human iPS-RPE cells into the sub-retinal space of these mice and allowed them to remain there for 14 days. She subsequently analysed the immunogenicity of the cells by measuring the levels of human and mouse T Cells (CD4 and CD45 and mouse CD45) in the RPE/choroid suspension. The data from these preliminary experiments indicted that there was some infiltration of T cells suggesting that, although the eye is an immune privilege site, the transplantation of allogeneic human iPS-RPE cells can evoke an immune response.

Hub members have also been utilising immune-deficient mice to make progress on CL-11 in RPE transplant studies. The work showed that the transplanted cells survived and established after transplantation. Experiments to determine how CL-11 regulates transplantation in humanised mouse models are ongoing and preliminary results suggest that the transcription factor HIF-1a and an enzyme fucosyltransferase-1 (FUT1) play a role in this. Full elucidation of this mechanism may lead to new transplantation strategies specifically designed to limit the risk of rejection and improve the rate and effectiveness of engraftment.

How does the process of inflammation contribute to tissue repair and influence the fate of transplanted cells?

To study how damaged tissue within the body can be repaired, Professor Sian Harding and Dr Susanne Sattler (Imperial College London) used a genetically–modified mouse line kindly provided by Prof Caetano Reis e Sousa in which a subpopulation of immune cells (CLEC9A dendritic cells) are labelled and can be easily tracked. Susanne's studies in these mice suggested that CLEC9A has a role in maintaining healthy heart tissue, possibly by ensuring that the immune system will not attack the heart. Susanne also induced myocardial damage in these animals to understand the role of these cells during injury and disease and discovered that lack of CLEC9A protects from immune-mediated damage to the heart. This may be due to changes in infiltration of immune cells, a process that occurs after a heart attack and leads to tissue damage.

As an alternative to surgical MI-induction, Sian and her team have also developed a model of a one-off injection of isoproterenol. These mice can then be used to assess chronic immunological responses post-MI and their effect on heart regeneration in mice. Preliminary data showed that this form of inducing heart damage was comparable to surgical methods for the analysis of longterm immune responses. The data from these experiments have since been used for a follow up grant application to the NC3R to further characterise and optimise as well as widely disseminate the model, which would have significant impact in reducing the number of mice needed for experiments such as this in the future.

Using mice from Fiona Watt, research associate Dr Matthias Friedrich from Professor Fiona Powrie's laboratory (University of Oxford) studied the role of subpopulations of lineage-traced fibroblasts in colitis, an inflammatory disease of the intestine. This follows on from earlier work from Fiona Watt's laboratory showing that different fibroblast lineages have different contributions to skin wound healing. Based on this work, the Powrie lab found Pdgfra-expressing fibroblasts as a major gut-resident population, with high capability to produce inflammatory mediators (cytokines) and tissue repair components (growth factors and extracellular matrix). These properties identify Pdgfra+ fibroblasts as an appealing target for further investigations in wound healing and inflammation.is hoped that these studies will lead to new therapies that involve the delivery of specific fibroblast lineages that are beneficial in resolving the inflamed intestinal tissue found in conditions like colitis.

Networking Activities

The UKRMP Niche Hub and Immunomodulation Hub held a Dragons Den Commercialisation Workshop on Thursday 23rd February 2017 at the Centre for Stem Cells and Regenerative Medicine at KCL, London. A panel of industry experts presented topics focussed on translation of research and then judged pitches from UKRMP researchers. The winner of the workshop was Kate Cameron (Hay Group, CRM, Edinburgh) who presented "Cytochroma: Stem cell derived liver cells in a screening platform to identify toxic compounds". The runner up was Yvonne Reinwald (El Haj Group, Keele) who presented "MechaScan: linking bioreactor technology with Optical Coherence Elastography". Both pitches were submitted to the TERMIS Business Plan Competition in Davos, Switzerland. Kate was awarded second prize and now aims to develop Cytochroma as a business proposition.

In May 2017, the Hub and NHSBT held a workshop focussing on clinical research with islets for the treatment of diabetes. Devised by James Shaw and held at the Institute of Transplantation, Newcastle University, approximately 50 delegates attended, including international experts with first-hand experience in translating islet regenerative medicine approaches into the clinic. The workshop covered topics including; microtissue transplantation for pancreatic beta-cell failure, clinical tissue replacement therapy, cellular immunotherapy, a case study by ViaCyte in Canada – the first stem cell-derived islet replacement therapy for the treatment of diabetes in clinical trials, a roundtable discussion on scaling up microtissue transplantation for the clinic, investment by funders, implementation of advanced therapy medicinal products (ATMPs) and new approaches, resources and stakeholders. Based on the discussions at the workshop, a White Paper will be produced on how to transform current treatment for diabetes to beta cell replacement and full insulin independence.

In June 2017, Fiona Watt hosted a meeting to bring together liver specialists from KCL and Edinburgh to discuss using NIHR BRC funds to facilitate transplantation of hepatocytes derived from pluripotent stem cells within the next 5 years. The meeting was attended by academics from King's College London including Davide Danovi, Dusko Illic, Roger Williams (Foundation for Liver Research), Anil Dhawan, Tamir Rashid, Celine Filippi, Iacopo Bicci, Curtis Asante, Steve Sacks, Mark Peakman and Maria Serra. Also present were Jack Price (NIBSC), Luca Urbani and Shilpa Chokshi from the Foundation for Liver Research, and Mike Lyne, Chris Fisher, Drew Hope, Natasha Ajraam and Patrick Ginty from the BRC. Different approaches to cell therapies in liver disease were discussed including encapsulation of adult hepatocytes in alginate capsules, differentiation of iPSCs into hepatocytes and the pros and cons of using iPSCs or hECSs.

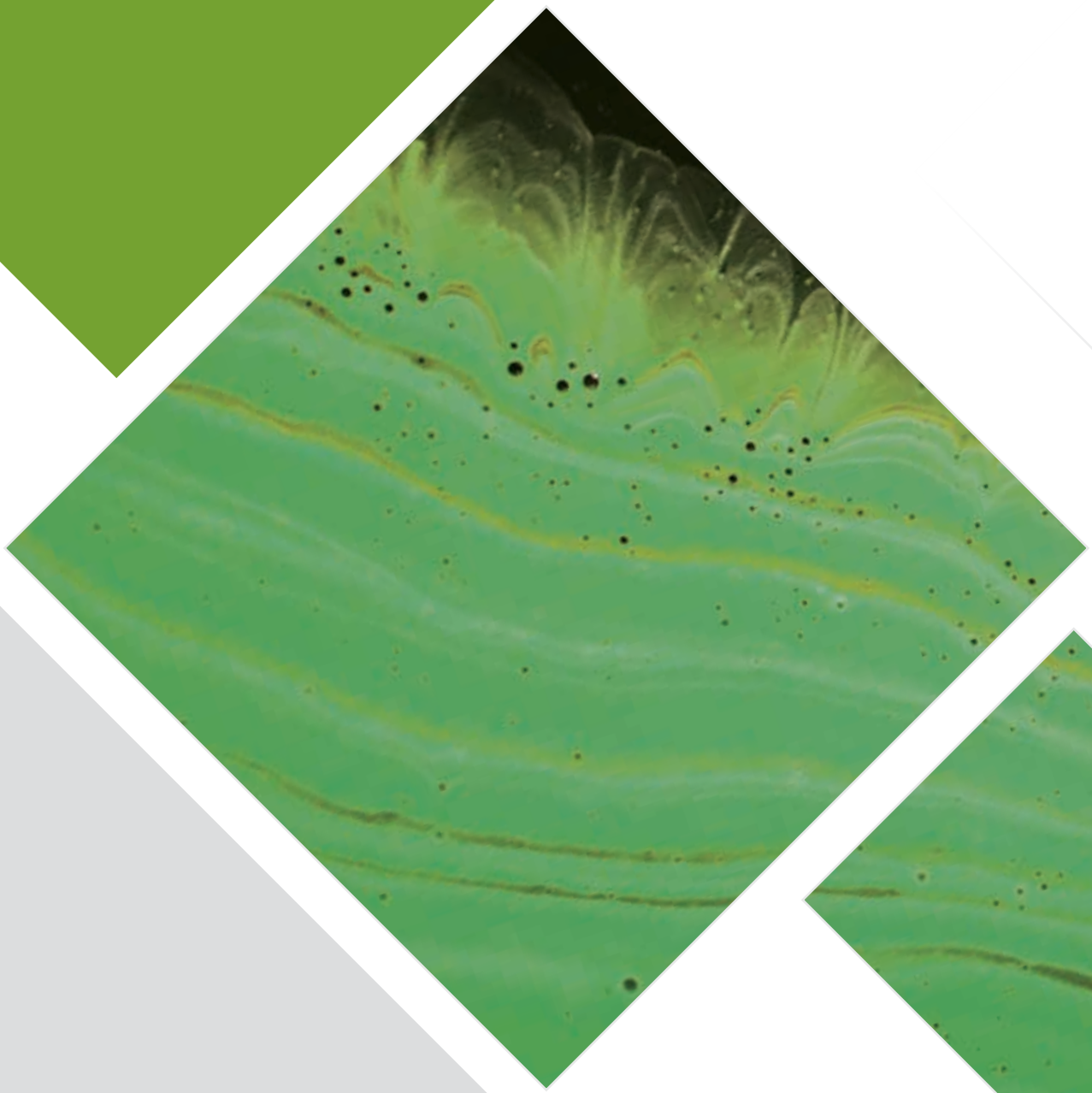
A follow up meeting was held in May at the Centre for Stem Cells & Regenerative Medicine in February 2018. Clinician scientists Roger Williams, Anil Dhawan and Tamir Rashid attended the meeting along with researchers Celine Filippe, Steven Sacks, Mark Peakman, Luca Urbani, Ragai Mitry and representatives from the Cell and Gene Therapy Catapult. It was agreed by the attendees that encapsulated hepatocytes derived from pluripotent stem cells (i-Heps) are worth pursuing as a bridge treatment for ACF. The KCH alginate encapsulation method was favoured as it has MHRA approval for an adult hepatocyte/MSC trial. The input of members of the Cell and Gene Therapy Catapult in matters such as standardisation, safety, efficacy and international academic/commercial competition was very beneficial. Since the meeting, research assistants in Fiona Watt's and Giovanna Lombardi's lab have made good progress in testing i-HEPs for their in vivo functionality and defining the standards for measuring i-Heps against adult hepatocytes.

Conclusions

In summary, the Hub has contributed a comprehensive understanding of how the immune system can be modulated to enhance cell therapies involving both cell transplantation in the retina and the liver and endogenous tissue repair in the heart and intestine.

Outputs

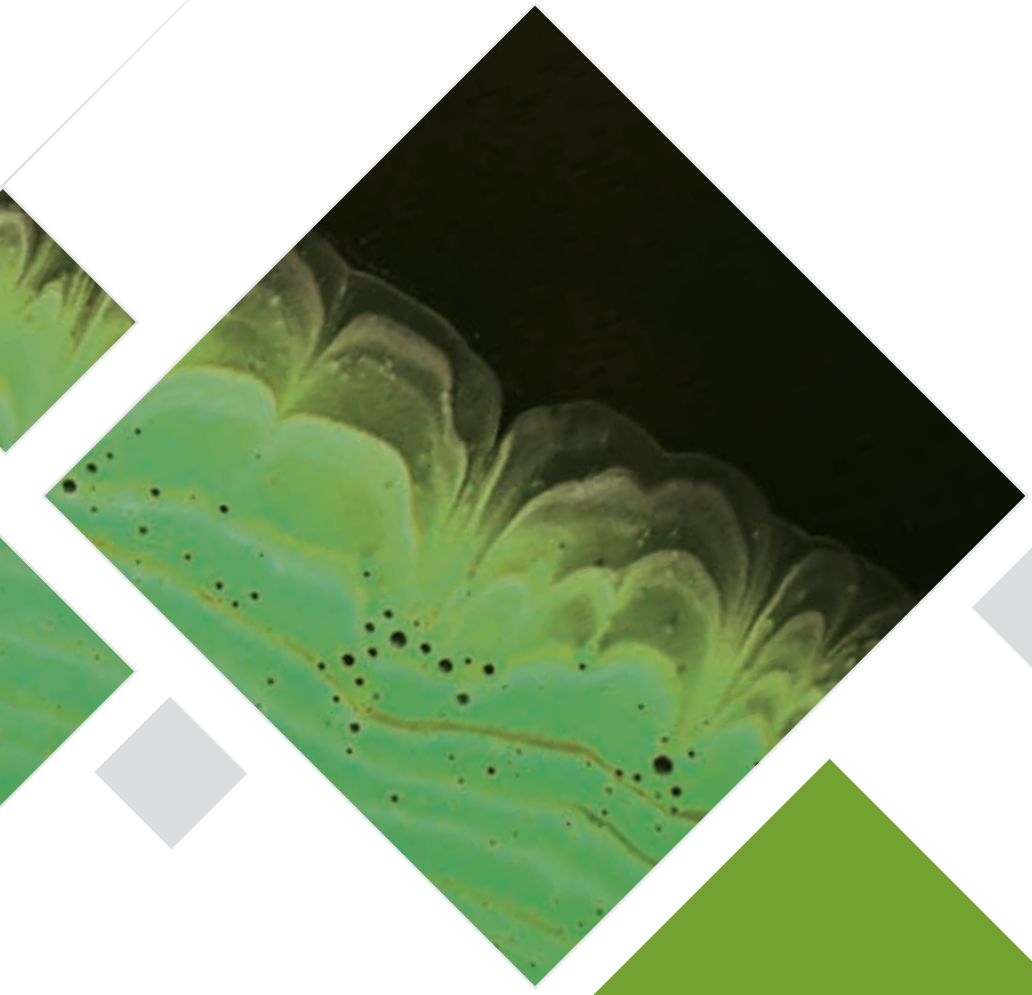
- Resources available to the community, see Section 4.
- Publications as a direct result of Hub activities, see Annex 4.



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)
3.2 Professor David Hay (University of Edinburgh)
3.3 Dr Ilyas Khan (Swansea University)
3.4 Professor Andrew McCaskie (University of Cambridge)
3.5 Professor Manuel Salmeron-Sanchez (University of Glasgow)



3. Disease Focused Projects

3.1 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 AMD.

Age-related macular degeneration (AMD) is now the commonest cause of vision loss in the developed world. The commonest sub-type of the condition is the dry form, caused by the loss of Retinal Pigment Epithelial (RPE) cells, a layer of the retina critically supporting the function and survival of the light capturing photoreceptors essential for sight.

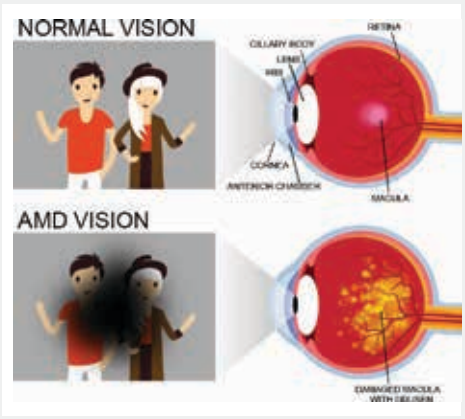
Recently it has become possible to derive fully differentiated RPE cells from stem cells created from adult tissue such as skin. We are proposing to create RPE cells from the skin of patients with AMD. This will allow us to consider autologous transplantation for those patients.

We have a bank of patient skin cells which have been reprogrammed into pluripotent stem cells. In the final year of the project, we have taken one of the patient lines and produced a bank of differentiated RPE employing our previous clinically approved (MHRA) manufacturing protocol. The RPE were then tested for contaminating proliferating cells and presence of oncogenic mutations. This has led to a number of both in-vitro and in-vivo tests to examine the risk of teratoma and tumour formation.

As such, a pathway to clinic for the use of induced pluripotent stem cell therapies will be developed in the UK with regulatory approval.

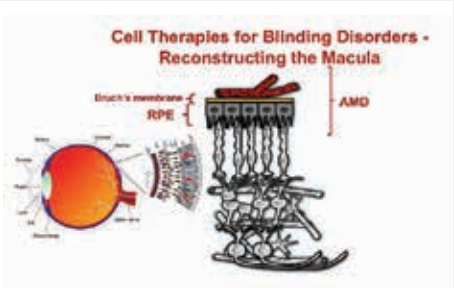
Outputs

Publications as a direct result of project activities, see Annex 4.



Schematic presentation of the visual field through a healthy eye, and the eye of an age related macular degeneration (AMD) patient.

The portraits of two patients with AMD as they see themselves.



Schematic of the eye and layers of the retina effected in AMD.

"To produce a therapeutic source of cells from the patient themselves, thus eliminating the need for immunosuppression, is of immense value."

3.2 Professor David Hay (University of Edinburgh)

The development of 3-dimensional implantable liver organoids

Liver disease is the 5th most common cause of death in the UK and kills more people than diabetes and road deaths combined. The only curative option for end-stage cirrhosis, and acute liver failure is liver transplantation. However, organ availability cannot meet demand and many patients die on the waiting list. Those who undergo transplantation require lifelong treatment with increased risks of infection, cancer, kidney and heart disease. Thus, there is a clear need to identify alternatives to liver transplantation.

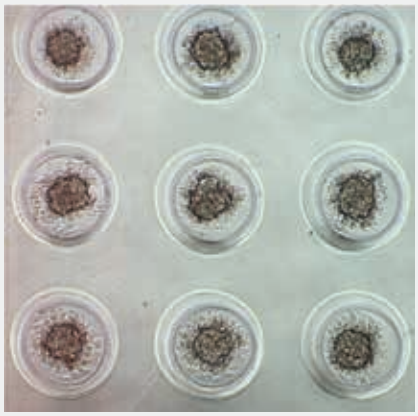
Recent studies have shown that human cells can form small fragments of liver like tissue. While providing proof of concept, the tissue is very small and lacks sufficient liver function. To address this, we have assembled a team with complementary expertise to reliably produce human liver tissue with clinically relevant function.

We have developed scalable methodology to produce human stem cell derived liver tissue at scale with stable and long-term function (>250 days), representing a valuable technology for academic and industrial scientists. Stem cell derived hepatospheres have also been produced from research and GMP grade pluripotent stem cell lines and implanted in vivo into two clinically relevant models of compromised liver function. Notably, hepatospheres provided critical liver support, leading to a reduction in disease markers and a stable increase in body weight in recipients, but not controls. We believe that the project output so far provides significant progress in the quest to deliver renewable human liver tissue for human biomedical application.

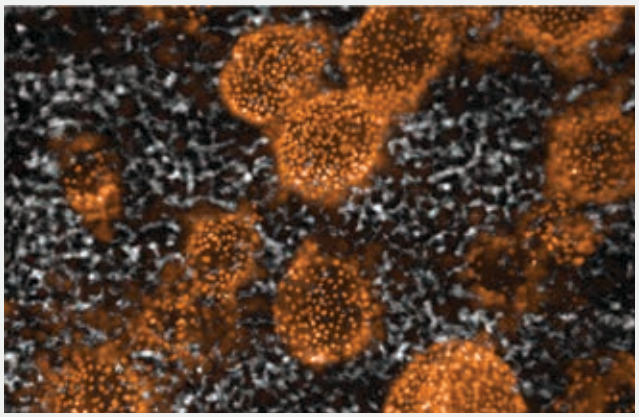
"It is now possible to produce large numbers of human liver spheres from stem cells at an acceptable cost. Most notably, the cells remain stable, active and viable for over 250 days in culture."

Outputs

Publications as a direct result of project activities, see Annex 4.



Stem cell derived hepatospheres are made at defined size in microwell 'factories'



Stem cell derived hepatospheres (Orange – HNF4 alpha staining) living on implantable fabrics

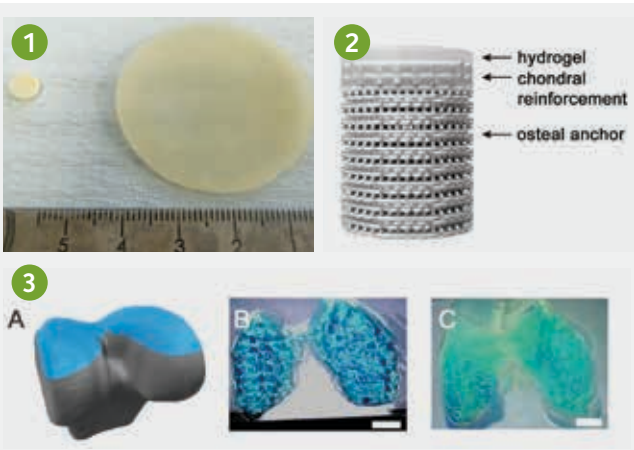
3.3 Dr Ilyas Khan (Swansea University)

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

Focal joint defects in articular cartilage, if untreated, progressively degenerate causing chronically painful osteoarthritis. To forestall this eventuality, we are using scalable technologies to design osteochondral implants able to withstand the intense biomechanical environment in the knee.

Articular cartilage-derived progenitors grown on porous microcarriers are being used as a cell source to tissue engineer new replacement cartilage. Cell-laden microcarriers can act as scaffold units that when aggregated produce larger structures. To date, we have grown cartilage discs of up to four centimeters in diameter, enough to cover a whole joint. Anchoring cartilage to the joint is critical for successful implantation, but pilot studies have shown the standard methods of fixation are unreliable. We undertook pilot preclinical studies to evaluate novel osteal anchors, where we showed that bioprinted polycaprolactone anchors remain fixed in place and integrate with existing bone (Mancini et al). Results of the latter study will reduce the number animals required for preclinical trials.

Our work in understanding the process of maturation has led us to discover the critical role that lysyl oxidases (LOX), in particular LOXL1, play in producing stiffer cartilage (Zhang et al). Furthermore we have uncovered the role of bone morphogenetic protein-9 in not only potently stimulating cartilage production but surprisingly in also directing tissue maturation. Ultimately we will combine the various elements to produce an integrated implant for preclinical testing, using this data to move along the translation pipeline and contributing to new and existing strategies (Levato et al).



1. Cartilage discs 6mm and 400mm in diameter biofabricated using chondroprogenitor-laden microspheres that have undergone chondrogenic differentiation for 28 days. 2. Bioprinted osteal anchor. The anchor is made from polycaprolactone with six zones that gradually increase in porosity with depth. The uppermost layer houses a hydrogel/microcarrier implant behind a fibre-reinforced sheath. 3. Bioprinting anatomical structures. CAD model of femoral condyle (A) with articular cartilage highlighted in blue. Bioprinted gelatin-methycrylate (GelMa) bio-ink with sacrificial hydrogel (B). GelMa bioprinted directly on top of a femoral condyle (C) and removal of supporting hydrogel. Scale bar 5mm.

"Long-term analysis of cartilage integrity during osteoarthritic degradation implies repair of remaining tissues is a viable strategy of slowing the progressive loss of function. The molecules we have discovered during this study will allow us to target biological pathways to enable this form of therapeutic intervention."

Outputs

Publications as a direct result of project activities, see Annex 4.

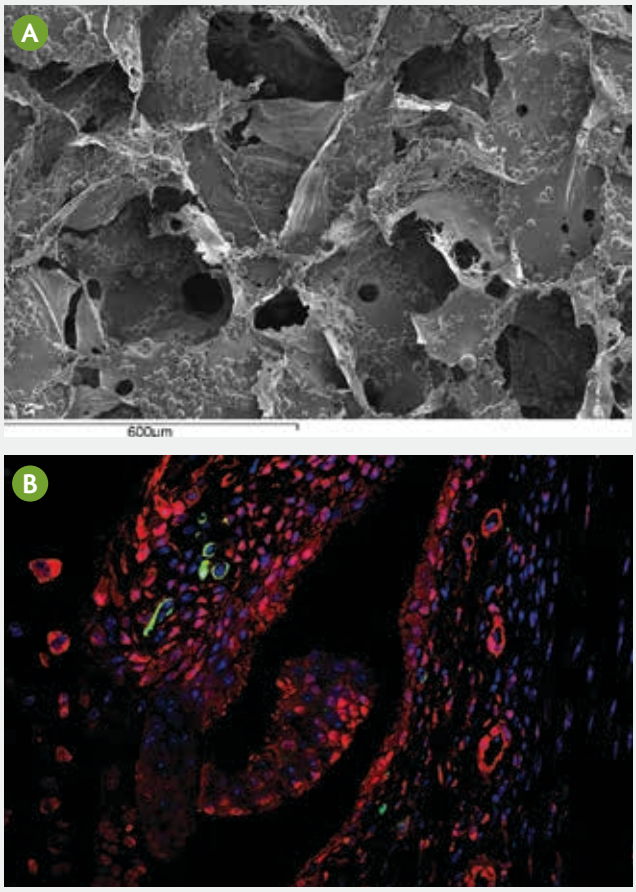
3.4 Professor Andrew McCaskie (University of Cambridge)

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

The SMARTSTEP programme addresses osteoarthritis (OA), 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. We have established a translational pathway focused on the repair and regeneration of cartilage (the articular surface of a joint) at an early stage, to reduce the progression of joint damage and 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 (MSC). Our approach targets these cells 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 cell behaviour by modulating recruitment, proliferation and chondrogenic differentiation of endogenous MSC – the key steps that might help repair cartilage.

We have now completed our initial work to design and manufacture scaffold material based on collagen in different specifications using ice templated manufacturing to vary both pore size and crosslinking, including some formulations with added microparticles. We have completed biological assessments, including cartilage forming ability (chondrogenesis) of MSC populations when cultured with the scaffold designs, and have selected the optimum specification for ongoing development for the clinic. In terms of the molecules, we have generated, selected and validated a single cell-derived clone of Agrin expressing cells for consistent and optimal production. The use of Agrin has been successful in vitro and we now have demonstrated encouraging results, in terms of cartilage repair, with in vivo models of joint injury. We have recently taken our selected molecule and material combinations through to the final pre-clinical development. We hope this will ultimately lead to the clinical goal of providing affordable, easy to apply treatments, deliverable as a day case.



A.Poly(lactic-co-glycolic acid) (PLGA) microparticles incorporated in a 3D ice templated collagen scaffold. B.Microscopy showing fluorescently tagged (red and green) cells repairing the injured cartilage after treatment with agrin.

3.5 Professor Manuel Salmeron-Sanchez (University of Glasgow)

Synergistic microenvironments for non-union bone defects.

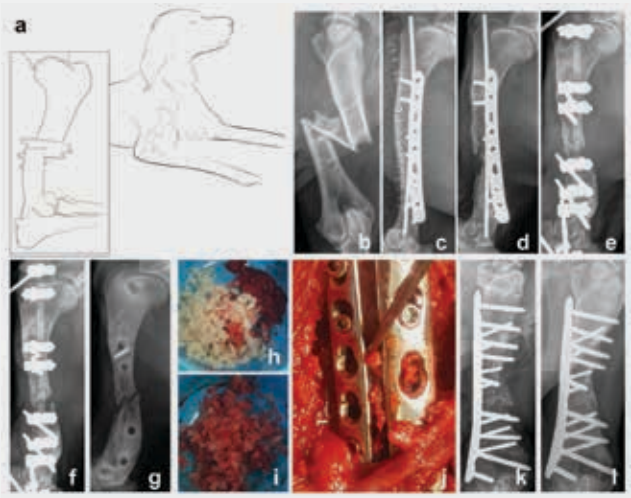
Translation of regenerative medicine research to the clinic is usually slow and often not viable. We have developed a simple and robust therapeutic solution for non-union bone defects up to pre-clinical stages. We use a functional material polymerised on the surface of implants and grafts to present human growth factors (BMP-2 in particular) in a safer and effective manner.

During the third and final year of the project we have focused on demonstrating and understanding the in vivo behaviour of our functional plasma polymerised poly(ethyl acrylate) (pPEA) coatings.

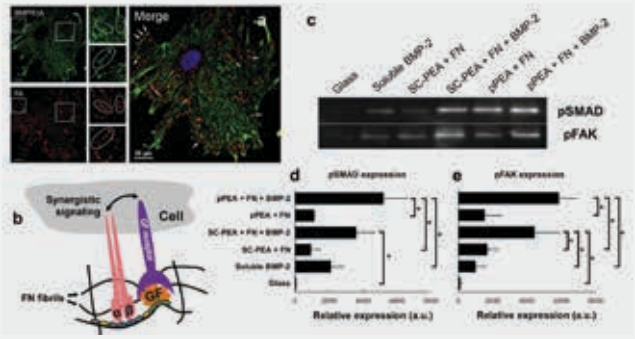
- We have further characterised coating parameters on 3D structures, the bioactivity of BMP-2 on these surfaces, and have optimised in vivo use conditions.
- We have finalised analysing results from a murine non-healing radial bone defect model performed last year, which has shown enhanced bone formation.
- We have successfully performed a critical size defect in a sheep model. Results are currently being analysed in Nottingham.
- We have performed a veterinary case study, successfully healing a non-union humeral fracture in a dog. A two-year-old Münsterländer dog had a non-union fracture with poor prognosis after two surgeries, with limb amputation being considered. The fracture fixation was revised using allograft bone chips coated with pPEA on which FN and BMP-2 were adsorbed (BMP-2 concentration was 50 µg/mL). This concentration is 30-fold lower than that used in human clinical standards. Radiographs seven weeks after surgery showed fracture union and by five months the dog had resumed normal exercise.

Outputs

Publications as a direct result of project activities, see Annex 4.

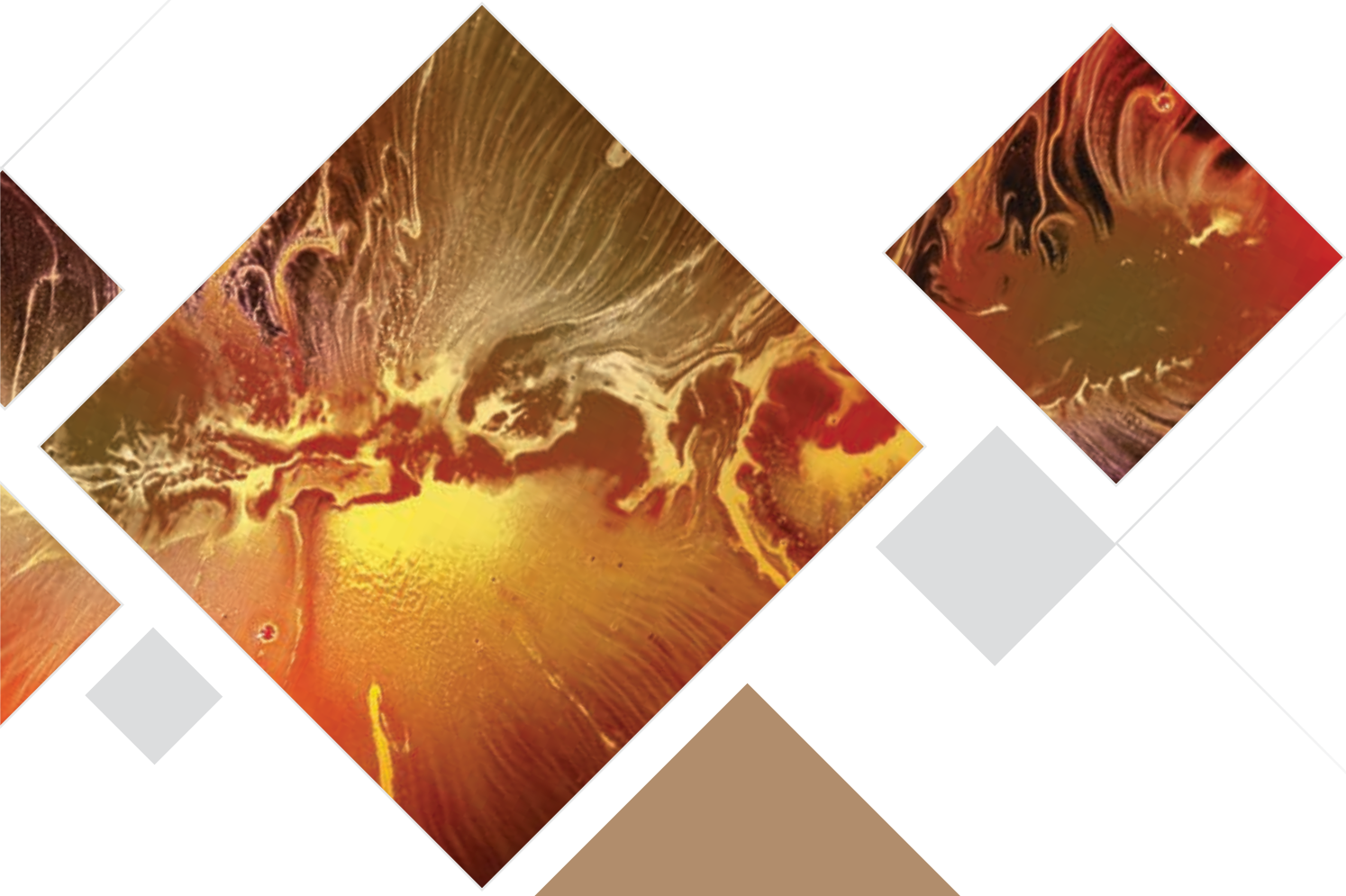


Humeral fracture healing in a dog treated with coated bone chips. (A to G) schematic and radiographs of fracture and two surgeries that led to a no-union. (H) to (J) Preparation of bone chips coated with plasma polymerized PEA, adsorbed fibronectin and BMP-2. Mixing with bone marrow. Chips used to fill fracture gap. (K) Post-operative radiograph and (L) evidence of fracture union seven weeks after surgery.



In vitro characterization of hMSC behavior on various surfaces. (a, b) Synergistic signaling. Co-localization assay of BMP receptor 1A (green) and focal adhesions (red). (c to e Western blotting, relative expression of pSMAD and pFAK, expressed by hMSCs after 1 h in culture.

4. Hub Resources Available to the Community



4. Hub Resources Available to the Community

One of the aims of the UKRMP in overcoming the barriers to regenerative medicine being used in mainstream therapies is the development of new tools, reagents and protocols which can be utilised by the wider research community. By making such resources accessible to groups in both academic and industrial domains, it is anticipated that progress may be accelerated. A number of such outputs are available through the Hubs. These include the following:

Resource	Description	Hub	Contact	Further information
Tools and Reagents	Stem Cell Lines			
	MasterShef clinical grade human embryonic stem (hESC) lines	PSCP	via the UK Stem Cell Bank (UKSCB) enquiries@ukstemcellbank.org.uk	MasterShef (MShef) 01-09 hESC lines derived on Human Feeders in KOSR media. MShef 10 & 12 derived on Human Feeders in Nutristem, MShef11, 13 and 14 derived feeder-free in Nutristem media. Both clinical (EU-CTD compliant) and research grade versions are available – cell banks for the latter could also be made available through the UKSCB. http://www.nibsc.org/ukstemcellbank
	Matched pairs of wild type and genetic variant clonal hPSC cell lines.	PSCP	Peter Andrews p.w.andrews@sheffield.ac.uk	Fully characterised cell lines carrying a known genetic variant and a normal wild type version of the same cell line.
	Mouse Lines			
	AhCreMdm2 flox, inducible mouse model for liver injury	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Lu et al. Nature Cell Biology 2015; 18 (8): 971. doi:10.1038/nbt.3275
	Pdgfr-fibroblast-labelled mice	Immuno	Fiona Watt fiona.watt@kcl.ac.uk	Driskell RR et al. 2013. Nature, 504(7479):277-81
	Pu.1 macrophage-labelled mouse line	Immuno	Fiona Watt fiona.watt@kcl.ac.uk	Weber C et al. 2016. Cancer Res., 76(4):805-17.
	Clec9A+ dendritic cell-labelled mouse line	Immuno	Caetano Reis e Sousa Caetano@crick.ac.uk	Schrami B et al. 2013. Cell, 154(4):843-58.
	NOD/SCIDγc-/- humanised mouse line	Immuno	Giovanna Lombardi giovanna.lombardi@kcl.ac.uk	Xiao F et al. 2016. Br J Pharmacol., 173(3):575-87
	Humanised Fah-/- mouse line	Immuno	Marcus Dorner m.dorner@imperial.ac.uk	Billerbeck E et al. 2016. J Hepatol. 65(2):334-43.

Resource	Description	Hub	Contact	Further information
Tools and Reagents	Disease Models			
	Ovine medial femoral condyle defect model for bone repair	Acellular	Jane McLaren Jane.mclaren@nottingham.ac.uk	McLaren et al. Eur Cell Mater. 2014 Jun 8;27:332-49
	Murine and ovine models for bone formation	Acellular	Janos Kanczler J.Kamczler@soton.ac.uk	Tayton E et al. J Biomed Mater Res A. 2015 Apr;103(4):1346-56. doi: 10.1002/jbm.a.35279. Epub 2014 Jul 23.
	Ex vivo bone formation and angiogenic models in chick	Acellular	Janos Kanczler J.Kamczler@soton.ac.uk or Robin Rumney R.M.Rumney@soton.ac.uk	Smith EL et al. Eur Cell Mater. 2013 Sep 11;26:91-106; discussion 106. Review
	Optimised Isoperotonol and resiquimod mouse models of cardiac inflammation	Immuno	Susanne Sattler s.sattler@imperial.ac.uk	Information available upon request
	Cell labelling, delivery reagents and other tools/reagents			
	Validated extracellular matrix (ECM) arrays • Fibronectin full • FnIII 7-14 • N-terminal 29-kDa fragment of fibronectin (Fn29K) • Fibrillin-1 PF8 • Fibrillin-1 PF9 • Fibrillin-1 PF17.1 • Fibrillin-2 PF17.2 • Laminin5 LG4-LG5 • Laminin5 LG1-LG3 • BMP-2 containing fraction • Fibulin-5	Niche	Stuart Cain stuart.a.cain@manchester.ac.uk	Information available upon request
	Xeno-free cell culture media	Niche	Dave Hay davehay@talktalk.net	Information available upon request
	R-Spondin tethered beads	Niche	Tamir Rashid tamir.rashid@kcl.ac.uk	Information available upon request
	Large scale production of Wnt protein	Niche	Shukry Habib shukry.habib@kcl.ac.uk	Information available upon request
	Lentiviral reporter vectors • pCHD-TCF-LEF-nLUC-P2A-tagRFP-EF1a-copGFP • pCHD-4COL2E-nLUC-P2A-tagRFP-EF1a-copGFP • pCHD-BRE-nLUC-P2A-tagRFP-EF1a-copGFP	Niche	Stuart Cain stuart.a.cain@manchester.ac.uk	• Lentiviral wnt reporter with nanoLUC and tagRFP reporters and copGFP selection • Collagen 2 reporter with SOX9 reporter element. Nanoluc and tagRFP repoters and copGFP selection • BMP Reporter with nanoluc and RFP reporter and GFP selection

Resource	Description	Hub	Contact	Further information
	Cell labelling, delivery reagents and other tools/reagents			
	Inducible lentiviral vectors • pCHD-TRES3G-MCS-EF1a-tagBFP-T2A-TetOn3G • pCHD-TRE3GS-MSC-EF1a-iRFP720V2-T2A-TetOn3G	Niche	Stuart Cain stuart.a.cain@manchester.ac.uk	• 3rd Generation tet inducible vector with EF1a promoter and tagBFP reporter. • 3rd Generation tet inducible vector with EF1a promoter and iRFP720 reporter
	Super Paramagnetic Iron Oxide Nanoparticles (SPIONS) for labelling and tracking macrophages and stem cells	Safety	Matt Rosseinsky m.j.rosseinsky@liverpool.ac.uk	Barrow et al. Contrast Media Mol Imaging. 2016 Jun 30. doi: 10.1002/cmmi.1700
	Silica coated Gold Nanorods (GNRs) for labelling and tracking macrophages and stem cells	Safety	Raphael Levy rapha@liverpool.ac.uk	Comenge J et al. ACS Nano. 2016 Jun 20. doi: 10.1021/acsna no.6b03246
	MBP-iRFP720-E2A-Luciferase vector	Safety	Toni Plagge plagge@liverpool.ac.uk	Vector has the Myelin-basic-protein promoter instead of the generally active EF1a promoter. This promoter drives expression of the reporter genes in oligodendrocytes (cells that express the myelin basic protein).
	Lentivirus plasmids • 2nd generation lentivirus vector pHIV-iRFP720-E2A-luciferase. • pHIV-Tyrosinase-eGFP (as a fusion protein) • pHIV-Tyrosinase-eGFP-IRES-Luciferase • pHIV-Tyrosinase-IRES-Luciferase • pHIV-LSSO-NLuc lentivirus vector	Safety	Toni Plagge plagge@liverpool.ac.uk	Comenge et al. Accepted eLife Jun 2018. doi. org/10.1101/199836 For bicistronic expression of iRFP720 fluorescent protein and firefly luciferase via an E2A element from the EF1alpha promoter (also available with an IRES element replacing E2A) Functionally tested in HEK293 cells Functionally tested in HEK293 cells Functionally tested in HEK293 cells Lentivirus vector expressing LSSmOrange-NanoLuc fusion protein from the general EF1α promoter for bioluminescence resonance energy transfer (BRET) imaging (emission 572 nm). Tested in vitro and in vivo; substrate furimazine. Gives superior bioluminescence signal compared to firefly luciferase.

Resource	Description	Hub	Contact	Further information
Tools and Reagents	Liposome-based formulation of indo-cyanine green (ICG-Lipo), for labelling and tracking macrophages and various other cells including stem cells	Safety	Kostas Kostarelos kostas.kostarelos@manchester.ac.uk Dhifaf Jasim dhifaf.jasim@manchester.ac.uk	Mazza M. et. al. Advanced Healthcare materials, 2017. DOI: 10.1002/adhm.201700374
	Biofunctionalised cryptic extracellular matrix to target epithelial to mesenchymal transition	Acellular	Benjamin Pierce b.pierce@imperial.ac.uk	Horejs c et al. Proc Natl Acad Sci U S A. 2014 Apr 22;111(16):5908-13. doi: 10.1073/ pnas. 1403139111. Epub 2014 Apr 3.
	Porous collagen scaffolds and modifiable hydrogels for articular cartilage repair.	Acellular	Benjamin Pierce b.pierce@imperial.ac.uk	Parmar PA et al. Biomaterials. 2015 Jun;54:213-25. doi: 10.1016/j.biomaterials.2015.02.079. Epub 2015 Apr 11. Parmar PA et al. Adv Healthc Mater. 2016 Jul;5(13):1656-66. doi: 10.1002/adhm.201600136. Epub 2016 May 24. Parmar PA et al. Biomaterials. 2016 Aug;99:56-71. doi: 10.1016/j.biomaterials.2016.05.011. Epub 2016 May 10.
	Porous PLGA microspheres for use as injectable cell carriers	Acellular	Omar Qutachi omar.qutachi@nottingham.ac.uk	Qutachi et al. Acta Biomater. 2014 Dec;10(12):5090-8. doi: 10.1016/j.actbio.2014.08.015. Epub 2014 Aug 23
Protocols	Cost effective protocols for growing hepatocyte-like cells from human pluripotent stem cells suitable for mass production of clinical grade cells	Niche	Dave Hay dave.hay@talktalk.net	Stem Cell Reports. 2015; 5 (5): 1250-1262. doi: 10.1016/j.stemcr.2015.10.016. PMID: 26626180
	High throughput semi-automated stem cell derived hepatocyte differentiation protocol	Niche	Dave Hay davehay@talktalk.net	Information available upon request
	Techniques for measurement of lead microRNAs in patients with acute liver injury	Niche	James Dear james.dear@ed.ac.uk	Nature Scientific Reports 5, Article number: 15501 (2015) doi:10.1038/srep15501
	Protocol for differentiation of ECs from iPSCs	Niche	Stuart Cain stuart.a.cain@manchester.ac.uk	Information available upon request
	Protocol for enhanced human liver stem cell growth (proliferative and stability)	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Information available upon request
	Protocol for isolation of viable human HPCs from transplant rejected liver	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Information available upon request

Resource	Description	Hub	Contact	Further information
Protocols	Protocol for expansion of stable human HPCs	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Information available upon request
	Protocol for cryopreservation of HPCs	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Information available upon request
	Protocol for serum-free chondrocyte differentiation from hESCs	Niche	Sue Kimber sue.kimber@manchester.ac.uk	Information available upon request
	Raman spectroscopy protocol for integration and analysis of multiple analytical datasets	Niche	Ben Pierce b.pierce@imperial.co.uk	J. Biophotonics 2016; 9 (5), 542–550 doi 10.1002/ jbio.201500238
	Protocol to measure Raman images of tissue-engineered cartilage	Niche	Ben Pierce b.pierce@imperial.ac.uk	Information available upon request; manuscript submitted for consideration
Technologies	Acellular			
	Fabrication and subsequent culture of tubular tissues	Acellular	James Dixon james.dixon@nottingham.ac.uk	Othman et al. Biofabrication. 2015 Apr 14;7(2):025003. doi: 10.1088/1758-5090/7/2/025003
	3D printed scaffolds and 3D bioprinting of constructs for bone repair	Acellular	Jing Yang jing.yang@nottingham.ac.uk Felicity Rose Felicity.rose@nottingham.ac.uk	Ruiz-Cantu L et al. Biofabrication. 2016 Mar 1;8(1):015016. doi: 10.1088/1758-5090/8/1/015016. Sawkins MJ et al. Biofabrication. 2015 Jul 2;7(3):035004. doi: 10.1088/1758-5090/7/3/035004.
	Safety			
	Methods for detecting common genetic changes in PSC Cultures	PSCP	Ivana Barbaric i.barbaric@sheffield.ac.uk	Human pluripotent stem cells (hPSCs) can adapt to in vitro conditions by acquiring non-random genetic changes that render them more robust and easier to culture (eg trisomies of chromosomes 1, 12, 17 and 20). hPSCs should therefore be regularly screened for such aberrations but this necessitates a good understanding of the sensitivities of different methods used. An assessment has been made to understand the limits of mosaicism detection by commonly employed methods such as chromosome banding, quantitative PCR, fluorescent in situ hybridization and digital droplet PCR. Baker D et al. Stem Cell Reports (submitted 29th March 2016 - under consideration).

Resource	Description	Hub	Contact	Further information
Technologies	Safety			
	Random sequence control material for detection of viral contamination via Next Generation Sequencing (NGS).	PSCP	Glyn Stacey Glyn.Stacey@nibsc.org	An evaluated set of potential control materials and procedures for use in optimisation and control of NGS detection of adventitious agents.
	Screening			
	Tools for drug toxicity screening based on stem cell derived hepatocytes	Niche	Dave Hay dave.hay@talktalk.net	Stem cell derived liver tissue for transplant and human safety screening Cameron et al. Stem Cell Reports. 2015 Dec 8;5(6):1250-62. doi: 10.1016/j.stemcr.2015
	Screening strategies for remyelination	Niche	Anna Williams anna.williams@ed.ac.uk	Exp Neurol. 2011 Jul;230(1):138-48. doi:10.1016/j.expneurol.2011.04.009. PMID:21515259
	ES chondrogenic Platform	Niche	Alicia El Haj a.j.el.haj@keele.ac.uk	Information available upon request
	Screening strategies for endogenous liver regeneration	Niche	Stuart Forbes stuart.forbes@ed.ac.uk	Raven et al. Nature 207 July 12; 547: 350. doi:10.1038/nature23015
	Screening strategies for chondrogenesis	Niche	Anthony Hollander a.hollander@liverpool.ac.uk	Information available upon request
	Raman spectroscopy platform for analysis of zonal organisation of cartilage	Niche	Ben Pierce b.pierce@imperial.ac.uk	Bergholt et al. ACS Cent. Sci. 2016 Nov 16; 2(12): 885. doi:10.1021/acscentsci.6b00222 Protocol and data set available at: https://zenodo.org/record/163327#.We72zFtSyUl
	Online quantitative monitoring of live cell engineered cartilage growth using diffuse fibre-optic Raman spectroscopy	Niche	Ben Pierce b.pierce@imperial.ac.uk	Bergholt et al. Biomaterials. 2017 Jun 14; 140: 128. Doi:10.1016/j.biomaterials.2017.06.015 Protocol and data set available at: https://zenodo.org/record/321251#.We72TFtSyUl
	Hetero spectral lipidiomics workflow for biomolecular profiling of remyelination in multiple sclerosis	Niche	Ben Pierce b.pierce@imperial.ac.uk	Information available upon request
	High throughput, high content imaging platform to evaluate "hepatocyteness" of cells	Niche	Tamir Rashid tamir.rashid@kcl.ac.uk	Protocol and software available

Resource	Description	Hub	Contact	Further information
Data sets	Whole Genome Sequencing, RNASeq and Bisulphate Sequencing of 2 hESC lines; and sub-clonal hESC derivative lines	PSCP	Peter Andrews p.w.a@sheffield.ac.uk	A total of 80 sub-clonal lines from single clones of both MShef4 and MSheff11 hESC lines have been sequenced (Whole Genome, Bisulphate and RNAseq) to assess mutation rates. These clones and their sequence are available to qualified investigators for further study.
	Immunoprofiles of: • iPSC-derived hepatocytes • retinal pigment epithelial (RPE) cells • cardiomyocytes	Immuno	Giovanna Lombardi (hepatocytes) giovanna.lombardi@kcl.ac.uk Giorgia Fanelli (RPE) giorgia.fanelli@kcl.ac.uk Fang Xiao (cardiomyocytes) fang.xiao@kcl.ac.uk	Information available upon request
Equipment	Microscopy			
	Microscope Slide Scanner Media Cybernetics	Niche/ CCBN*	Alex Raven s1351928@sms.ed.ac.uk	http://www.crm.ed.ac.uk/equipment/microscope-slide-scanner
	Raman Microscope Renishaw InVia	Niche	Ben Pierce b.pierce@imperial.co.uk	http://www.imperial.ac.uk/vibrational-spectroscopy-and-chemical-imaging/facilities/raman-spectrometers/
	Raman Microscope Renishaw InVia	Niche/ CCBN	Colin Campbell colin.campbell@ed.ac.uk	http://www.crm.ed.ac.uk/equipment/renishaw-invia-raman-microscope
	Photothermal microscope, and cell tracking velocimeter Fluorescent lightsheet microscope.	Safety	Raphael Levy rapha@liverpool.ac.uk	https://www.liverpool.ac.uk/integrative-biology/facilities-and-services/centre-for-cell-imaging/
	Imaging			
	Operetta High content imaging	Niche/ CCBN	Eoghan O'Duibhir eoghan.oduibhir@ed.ac.uk	http://www.crm.ed.ac.uk/equipment/operetta-high-content-microscope
	Non-destructive cell imaging platform applicable in bone and cartilage regeneration research	Niche	Pierre Bagnaninchi Pierre.Bagnaninchi@ed.ac.uk	
	Quantitative volumetric Raman imaging of 3D cell culture	Niche	Ben Pierce b.pierce@imperial.ac.uk	Kallepitis et al. Nature Communications. 2017 Mar 22; 8:14843. doi:10.1038/ncomms14843
	9.4T MRI, benchtop 1T MRI, SPECT/CT, PET/CT, photoacoustic, ultrasound, bioluminescence, X-ray CT	Safety	Tammy Kalber t.kalber@ucl.ac.uk	http://www.ucl.ac.uk/cabi

* The Computational and Chemical Biology of the Stem Cell Niche

Resource	Description	Hub	Contact	Further information
Technologies	Imaging			
	9.4T MRI scanner, MSOT photoacoustic, IVIS bioluminescence, ultrasound	Safety	Harish Poptani harishp@liverpool.ac.uk	https://www.liverpool.ac.uk/translational-medicine/research/centre-for-preclinical-imaging/
	SQUID magnetometer	Safety	Matt Rosseinsky m.j.rosseinsky@liverpool.ac.uk	Barrow et al. Biomater. Sci., 2015,3, 608-616 doi:10.1039/C5BM00011D
	7T MRI, 3T benchtop MRI, bioluminescence, PET	Safety	Steve Williams steve.williams@manchester.ac.uk	http://research.bmh.manchester.ac.uk/imaging
	Phase imaging microCT, serial block face SEM imaging and light sheet microscopy	Acellular	Richard Oreffo Richard.oreffo@soton.ac.uk Anton Page A.Page@soton.ac.uk	Southampton Imaging http://www.southampton.ac.uk/microscopy/index.page Xradia XRM-410 Phase enhanced high resolution µCT Gatan 3-view microscope and LaVision Ultramicroscope light sheet microscope.
	Manufacture			
	DB FACS Aria III Fusion, High speed cell sorter	Niche	Fiona Rossi fiona.rossi@ed.ac.uk	http://www.crm.ed.ac.uk/equipment/bd-facs-aria-iii-fusion
	Electrospinner IME Technologies	Niche/ CCBN	Siobhán Dunphy s.dunphy@ed.ac.uk	http://www.crm.ed.ac.uk/equipment/ime-electrospinning-device
	Femtosecond Laser 3D structure fabrication	Niche/ CCBN	Robert Thomson r.r.thomson@hw.ac.uk	http://www.crm.ed.ac.uk/equipment/femtosecond-laser
Workshop Reports/ Papers	2016 Assessing the Safety of Human Pluripotent Stem Cells and Their Derivatives for Clinical Applications.	PSCP	Peter Andrews p.w.andrews@sheffield.ac.uk	Andrews PW, et al. Assessing the Safety of Human Pluripotent Stem Cells and Their Derivatives for Clinical Applications. Stem Cell Reports 2017, doi: http://dx.doi.org/10.1016/j.stemcr.2017.05.029
	2015 Assessment of Source Materials for Cell Based Medicines Workshop Report	PSCP/ Safety	Glyn Stacey Glyn.Stacey@nibsc.org	Stacey G, et al, Science-based assessment of source materials for cell-based medicines: report of a stakeholders workshop. Regen Med. 2018 Vol13 (8) https://doi.org/10.2217/rme-2018-0120
	2015 Comparability Workshop Report	PSCP	David Williams D.J.Williams2@lboro.ac.uk	Regen Med. 2016 Jul;11(5):483-92. doi: 10.2217/rme-2016-0053. Epub 2016 Jul 12
	2015 Nanoparticles Workshop Report	Safety	Raphael Levy rapha@liverpool.ac.uk	In preparation

Resource	Description	Hub	Contact	Further information
Workshop Reports/ Papers	Preclinical imaging methods for assessing the safety and efficacy of regenerative medicine therapies	Safety	Chris Goldring c.e.p.goldring@liverpool.ac.uk	npj Regenerative Medicinevolume 2, Article number: 28 (2017) https://doi.org/10.1038/s41536-017-0029-9
	2017 MSCs: Roadmap to clinical Translation	Immuno/ Safety	Francesco Dazzi francesco.dazzi@kcl.ac.uk	Regen Med 2017 Vol. 12, No. 8 doi.org/10.2217/rme-2017-0097
Services	Stem cell cytogenetics – diagnostics and characterisation	PSCP	Duncan Baker duncan.baker@sch.nhs.uk	https://www.sheffieldchildrens.nhs.uk/our-services/sheffield-diagnostic-genetics-service/laboratory-services.htm#cytogenetic

5. Building the Next Generation and Supporting Career Development in Regenerative Medicine

5. Building the Next Generation and Supporting Career Development in Regenerative Medicine

An objective of UKRMP has been to develop a new generation of Regenerative Medicine researchers. In so doing, the UKRMP researcher alumni have been able to progress their careers in many different directions. As a result of the researchers' exposure to sophisticated laboratory techniques, manufacturing paradigms, regulatory requirements, commercialisation, UKRMP Alumni have dispersed down several different paths from international faculty positions, management roles and positions in industry. The section below provides case studies from each of the individual Hubs.

Pluripotent Stem Cell Platform Hub

Research Assistant **Andrew Wood**, at the University of Sheffield was involved in developing the quality management systems and quality control procedures needed to generate clinical grade PSCs. He was instrumental in developing protocols for process transfer from developer to non-specialist manufacturing sites to enable comparability measurements across sites. In 2016, Andy obtained a role as a Quality Officer within Sheffield Children's NHS foundation Trust, to develop their quality practises to meet regulatory and accreditation requirements.

"The training I received whilst working with researchers in the PSCP was invaluable and inspired me to pursue my career in a Quality setting." Andy Wood

Dr Loriana Vitillo, formerly Post-Doctoral Research Associate (PDRA) at the University of Cambridge, developed translatable standard operating procedures to differentiate PSCs into neural precursors for clinical applications. Additionally, Loriana produced the short science film "Dish Life" – what scientists really feel about the stem cells they look after. The film won several Science Film Festival awards and whilst being shown at the Imagine Science Film Festival in October 2017 made the New York Times "10 things to do in NY". Loriana went on to take up a position at Havas, a global company specialising in many areas including healthcare communication but has returned to regenerative medicine research working with the Pete Coffey team at UCL.

"Being a PDRA within PSCP was a fast track route for professional development. Working with top leaders in the regenerative medicine/cell therapy field provided an ideal framework to gather crucial skills in the translation of stem cell research." Loriana Vitillo

Dr Amit Chandra a former PDRA at Loughborough University, became an Innovation Officer at Yposkesi; a contract development manufacturing company for gene and cell therapies established in November 2016 in Ile-de-France. Amit's work for PSCP focused on developing tools to measure comparability or manufacturing protocols using automated platforms and involved collaboration with clinicians and PSC specialist biologists. Amit is working to set up the Yposkesi cell-therapy production facility, which is due to start production on clinical batches in 2021.

"These projects have developed my skills in the area of regulated manufacturing of regenerative medicine products." Amit Chandra

Engineering and exploiting the stem cell niche Hub

Dr Wei-Yu Lu, a former PDRA at the University of Edinburgh is now a Group Leader at the University of Birmingham. Wei's UKRMP research outputs include tools and technologies such as an immunodeficient mouse model with genetically induced hepatocyte ablation to facilitate functional in vivo repopulation studies with stem cell derived hepatocytes. He developed protocols for enhanced human liver stem cell growth (proliferative and stability); isolation of viable human HPCs from transplant rejected liver; expansion of stable human HPCs; and cryopreservation of HPCs.

"Being part of the Niche hub allowed me to have a broader perspective due to interdisciplinary collaboration and helped me to "think bigger" about my research questions." Wei-Yu Lu

Dr Kate Cameron, a former PDRA within the Hay group at the University of Edinburgh developed a stem cell derived hepatocyte differentiation protocol; this process has been patented and licensed to a biotechnology company, Biolamina based in Sweden. Using the differentiation protocol, Kate developed a high throughput semi-automated screening platform that can be used for drug toxicity testing and is being validated in collaboration with AstraZeneca. Kate was also the runner up at the TERMIS 2017 Business Plan Competition pitching 'Cytochroma', an automated high throughput drug toxicity screening platform, which she is developing into a commercial proposition.

"The UKRMP workshops, conferences and annual meetings built up my confidence in discussing my scientific work and generated many new collaborations. The UKRMP also introduced me to strong female role models who have been inspiring, encouraging and incredibly supportive to many young female researchers." *Kate Cameron*

Dr Yvonne Reinwald, a former UKRMP Niche Hub PDRA within the El Haj group at Keele University is now a Lecturer in Biomedical Engineering at Nottingham Trent University focusing on the evaluation of the performance of bioreactors for tissue engineering and clinical application. Her UKRMP Niche Hub outputs included the development of a non-destructive cell imaging platform based on biomechanics, with direct applications in bone and cartilage regeneration research. She was awarded the Robert Brown Early Stage Investigator Award of the Tissue and Cell Engineering Society in 2016.

"The UKRMP has enabled me to collaborate with academics and researchers across the UK on a variety of projects, and to network and widen my understanding of research commercialisation." *Yvonne Reinwald*

Safety and efficacy, focussing on imaging technologies Hub

Dr Philip Starkey-Lewis has continued at the University of Edinburgh with Professor Stuart Forbes to further explore the efficacy and safety of macrophage therapy for acute liver injury. He is liaising with the Scottish National Blood Transfusion Service to build on UKRMP findings and assess whether human macrophages recapitulate the findings observed with mouse macrophages. Philip also collaborates with Novartis to characterise the humanised colony stimulating factor 1 (CSF1) protein, using injury models employed during UKRMP, as a therapy for liver disease.

"The learning and understanding of macrophage biology obtained during UKRMP provides a platform to better understand and test immunomodulatory medicines, like CSF1 in the setting of liver disease." *Philip Starkey-Lewis*

Dr Lauren Scarfe – undertook her PhD at the University of Liverpool from 2013-2017, with a thesis, entitled 'Investigating the safety and efficacy of regenerative medicine therapies in mouse models of kidney disease'. In October 2017, Lauren moved to Nashville as a PDRA in Mark deCaestecker's lab, within the Division of Nephrology at Vanderbilt. While primarily involved in a project investigating the role of macrophages in acute kidney injury and the effects for therapeutic purposes, she also oversees a project testing a pre-clinical lead drug in various complex models of acute kidney injury in mice with co-morbidities, such as diabetes and older age.

"During my PhD, I attended a workshop in the USA teaching techniques in experimental mouse kidney injury. Networking at this event enabled me to make contacts which led to a position at Vanderbilt University Medical Center in Nashville, USA." *Lauren Scarfe*

Dr Mike Barrow – is a sales engineer for rheology and particle characterisation at Anton Paar Ltd. Rheology is the flow of matter, with rheometers used to understand a liquid or solid's mechanical properties. Particle characterisation instruments can be used to measure particle size, zeta potential, and refractive index. Within the Safety Hub Mike 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).

"Working on the UKRMP multi-disciplinary project I gained direct experience in both rheology and particle characterisation but also valuable insight into new techniques, making the transition into sales possible." *Mike Barrow*

Acellular approaches for therapeutic delivery Hub

Dr Jenny Puetzer – started as Assistant Professor within the Department of Biomedical Engineering at the Virginia Commonwealth University in January 2018. Her lab develops tissue engineered orthopaedic replacements. Within the Hub she led work on designing specialized materials that drive stem cells to repair and replace damaged cartilage, bone, and ocular tissue. She co-authored several seminal publications and was also awarded the UKRMP Special Merit Prize.

"The Acellular Hub gave me the opportunity to develop novel materials specifically primed for easy translation to the clinic and was an invaluable opportunity to meet and collaborate with researchers across the UK." Jenny Puetzer

Dr Derfogail Delcassian – Derfogail's Hub research focused on designing acellular biomaterials that can control immune cell function. Derfogail is currently based jointly between MIT, Harvard Medical School and the University of Nottingham, collaborating closely with UKRMP members and leading a research team within the Anderson and Langer labs at MIT, focused on accelerating organoid transplant therapies for Diabetes-1 towards the clinic. Following completion of this secondment, Derfogail intends to establish her independent research group focused on immunoengineering strategies for TERM therapies.

"Being part of the UKRMP Network has helped to support my research in immunoengineering and has facilitated my collaborations with world class researchers around the globe." Derfogail Delcassian

Dr Deepak Kumar – is now the Stem Cell Facility Research Manager within the Molecular Neurodegeneration Research Group at the University of Oxford. Deepak attributes his successful move to Oxford as a result of working in the high calibre environment of the Hub. As a PDRA at the University of Manchester, Deepak was responsible for developing an endoscopically injectable hydrogel for the treatment of Barrett's oesophagus as a postoperative treatment for stricture management after surgical removal of cancerous tissue.

"Working for the UKRMP has provided me with a world of knowledge and experience, to be a thorough and accurate scientist, and the opportunity to collaborate with experts across our field nationwide." Deepak Kumar

Immunomodulation Hub

Dr Helen Marshall, former Hub PDRA at Newcastle University is now the Technical Project Lead at FUJIFILM Diosynth Biotechnologies. As a PDRA Helen was instrumental in establishing and optimising assays to assess the effects of biochemical stress on iPSC-derived hepatocytes and contributed to valuable dataset resources that are publicly available on the UKRMP website.

"The UKRMP hub provided ample opportunities for research project management, networking, post-doctoral development and working with industry. These skills were essential in my successful transition from academia to industry." Helen Marshall

Dr Jasmine Penny, former Hub PDRA at University of Birmingham is now the European and International Funding Officer at University of Birmingham. Jasmine established a technique for successfully isolating human hepatocytes from adult livers and provided these hepatocytes to investigators at King's College London (KCL) who carried out immunoprofile assays. The hepatocyte isolation and immunoprofile protocols are publicly available on the UKRMP website.

"The UKRMP project helped develop my strategic thinking and networking with collaborators. The skills gained and developed have proved very valuable when assisting academics with high profile grant applications." Jasmine Penny

Dr Raul Elgueta, former Hub PDRA and Operational Lead at KCL is now Lead Immunologist at Centauri Therapeutics. Raul was instrumental in maintaining operational links and quality control within the Hub and was commonly a point of contact for many of the PDRAs and RAs. Raul contributed to online resources comprising various immunoprofile assays and cell purification protocols. Raul also assisted the project manager in establishing collaborative efforts between different Hubs.

"UKRMP gave me the tools necessary to acquire the knowledge and the expertise in translational medicine. The opportunity to be the Operational Leader of the Immunomodulation Hub improved my leadership skills." Raul Elgueta

6. UKRMP Special Merit Prize

6. UKRMP Special Merit Prize

This past, year two UKRMP special merit prizes have been awarded to acknowledge and reward Hub researchers who have demonstrated outstanding activity in providing connectivity across the Hubs and Platform to deliver its mission.

The prizes were awarded to:

- Dr Zoe Hewitt, University of Sheffield (Project Manager PSCP Hub)
- Dr Jenny Puetzer, Imperial College London (Acellular Hub)

Dr Jenny Puetzer and Dr Zoe Hewitt

Zoe and Jenny received the awards for promoting interdisciplinary team science across the regenerative medicine community, key to the ethos of the UKRMP. The awards recognise their proactive and creative research leadership, making the most of developing and implementing new methods and opportunities. In short, they went beyond 'business as usual' and embraced the collaborative Hub and Platform ethos to help address the translational barriers of regenerative medicine.

Zoe of the University of Sheffield is the Project Manager at the Pluripotent Stem Cell Platform Hub and her activities included leading joint working with other Hubs to ensure that stem cell research informs safety decisions of advanced therapies for patients. She also organised international collaboration activities and a joint conference with the British Society for Gene and Cell Therapy.

Jenny, a post-doc at Imperial College London and a member of the Acellular Technologies Hub, led the design and promotion of innovative new materials for future use in the clinic. These include specialized materials designed to drive stem cells to repair and replace cartilage, bone and tissue damaged in eye injuries. The materials have been adopted by Hub users across the Platform thanks to her guidance

Nominations for this annual competition, were made by the Hub Directors.

Annexes

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UKRMP Hub research teams

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Hub Publications since previous report

Annex 1

UKRMP Governance

Executive Group

- **Dr Rob Buckle,** Chief Science Officer, MRC
- **Professor Ian Greer**, President and Vice Chancellor, Queen's University Belfast, UK; Chair UKRMP Programme Board
- **Dr Philippa Hemmings**, Head of Healthcare Technologies, EPSRC
- **Dr David Pan**, Programme Manager UKRMP
- **Professor Melanie Welham**, Chief Executive, BBSRC

Programme Board

- **Professor Ian Greer (Chair),** Queen's University Belfast, UK
- **Professor Frances Balkwill**, Queen Mary University of London, UK
- **Professor Nissim Benvenisty**, The Hebrew University of Jerusalem, Israel
- **Professor Kenneth Boheler**, Johns Hopkins University, USA
- **Dr Gillian Burgess**, Vertex Pharmaceuticals Inc, UK
- **Dr Nigel Burns**, Cell Medica, UK
- **Professor Jöns Hilborn**, Uppsala University, Sweden
- **Dr Bo Kara**, GlaxoSmithKline plc (GSK), UK
- **Dr Andrew Lynn**, University of Cambridge, UK
- **Professor Marc Peschanski**, I-STEM Paris, France
- **Professor Dr Petra Reinke**, Berlin-Brandenburg Centre for Regenerative Therapies, Germany
- **Professor Anne Rosser**, Cardiff University, UK
- **Associate Professor Louise van der Weerd**, Leiden University Medical Center, The Netherlands
- **Professor Paul Whiting**, Alzheimer's Disease Research UK UCL Drug Discovery Institute, UK
- **Dr Jonathan Appleby (Observer)**, Cell Therapy Catapult, UK

Annex 2

UKRMP – 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 first in human clinical trial in Parkinson's Disease*
  - *Comparability of automated expansion of PSC at three international sites*
  - *The consequences of cryptic genetic variants in cultures of human Pluripotent Stem Cells for safety and efficacy of applications for regenerative medicine – PSCP/Safety Hubs and Stage II Coffey Project*

- 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*
  - *Assessment of the tumorigenic potential of a frequent ES cell genetic variant, 20q.11.21 amplicon, in a liver engraftment model; Safety/PSCP/and Niche Hubs*
  - *Evaluating the biodistribution and toxicity of a pluripotent stem cell-based therapy for Parkinson's disease – Safety/PSCP Hubs*

- 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*
  - *Development of a medical device to support the delivery of cell therapies in surgery*

- 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*
  - *Dissecting the molecular function of stem cell-derived extracellular vesicles (EVs) in educating the host inflammatory niche – Immunomodulation/Acellular Hubs*

UKRMP – Disease focused awards

- 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 Pete Coffey, University College London
  Scalable production of RPE cells from induced pluripotent stem cell under GMP conditions for cellular replacement therapy of the dry form of Age-related macular degeneration (AMD). £1.6M
- Dr David Hay, MRC Centre for Regenerative Medicine, University of Edinburgh
  The development of 3 dimensional implantable liver organoids. £1.6M
- Professor Andrew McCaskie, University of Cambridge
  (SMART STEP) Stepwise Translational Pathway for Smart Material Cell Therapy. £1,6M * (£0.64M RC, £0.53M ARUK, Reumafonds £0.43M)
- Professor Manuel Salmeron-Sanchez, University of Glasgow
  Synergistic microenvironments for non-union bone defects. £1,005k # (£0.54M RC, £0.46M ARUK)

* *partnered with Arthritis Research UK and Reumafonds*

\# *partnered with Arthritis Research UK*

MRC regenerative medicine capital awards

UKRMP-linked

- Professor Peter Andrews, University of Sheffield. Pluripotent Stem Cell Platform – Capital Investment, £3.1M
- Professor Cay Kielty, University of Manchester. Regenerative medicine: instrumentation for flow cytometry and cell printing. £0.7M
- Professor Stuart Forbes, University of Edinburgh. The Computational and Chemical Biology of the Stem Cell Niche, £5.0M
- Professor Sheila MacNeil, University of Sheffield. Open-access biomaterials microfabrication and non-invasive imaging facilities for Regenerative Medicine, £0.7M
- Professor Richard Oreffo, University of Southampton. Southampton Imaging: 3D imaging at millimetre to nanometre scales for regenerative medicine using multiple complimentary modalities, £1.2M
- Professor Brian Park, University of Liverpool. In vivo imaging technologies to assess the efficacy and safety of regenerative medicine therapies, £3.3M
- Professor Molly Stevens, Imperial College London. State of the Art Biomaterials Development and Characterization of the Cell-Biomaterial Interface, £1.2M

Capital awards out with 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

UKRMP 2 – Hub awards (2018-2023)

- **Professor Roger Barker, University of Cambridge**
  The Pluripotent Stem Cells and Engineered Cell (PSEC) Hub (£4.1M)
- **Professor Stuart Forbes, MRC Centre for Regenerative Medicine, University of Edinburgh**
  The Engineered Cell Environment Hub (£4.1M)
- **Professor Molly Stevens, Imperial College London**
  Acellular / Smart Materials – 3D Architecture Hub (£4.1M)

Annex 3

UKRMP Hub research teams

PSCP Hub

- **Dr Elsa Abranches**, National Institute for Biological Standards and Controls
- **Dr John Alexander**, University of Sheffield
- **Mr Duncan Baker**, University of Sheffield
- **Dr Nick Blair**, University of Cambridge
- **Dr Charlotte Chapman**, National Institute for Biological Standards and Controls
- **Mr James Clarke**, University of Cambridge
- **Dr James Crutchley**, Loughborough University
- **Ms Mercy Danga**, University of Cambridge
- **Dr Melanie Eckersley-Maslin**, The Babraham Institute, Cambridge
- **Dr Amanda Evans**, University of Cambridge
- **Dr Ross Hawkins**, National Institute for Biological Standards and Controls
- **Mr Jason Halliwell**, University of Sheffield
- **Ms Xiaoling He**, University of Cambridge
- **Dr Pretti Holland**, Loughborough University
- **Dr Tuzer Kalkan**, University of Cambridge
- **Mr Owen Laing**, University of Sheffield
- **Dr Moyra Lawrence**, University of Cambridge
- **Mr Thomas Mattimoe**, University of Sheffield
- **Dr Marta Milo**, University of Sheffield
- **Dr Serena Nik-Zainal**, The Wellcome Trust Sanger Institute, Cambridge
- **Dr Orla O'Shea**, National Institute for Biological Standards and Controls
- **Dr Venkat Pisupati**, University of Cambridge
- **Mr Allan Shaw**, University of Sheffield
- **Miss Emma Shaw**, University of Sheffield
- **Dr Sujith Sebastian**, Loughborough University
- **Dr Maryam Shariatzadeh**, Loughborough University
- **Dr Oliver Thompson**, University of Sheffield
- **Dr Ferdinand von Meyenn**, The Babraham Institute, Cambridge

Niche Hub

- **Dr Kate Cameron**, University of Edinburgh
- **Dr Wei Yu Lu**, University of Edinburgh
- **Dr Chao Li**, University of Liverpool
- **Dr Mads Bergholt**, Imperial College London
- **Dr Jean-Phillipe St-Pierre**, Imperial College London
- **Dr Andrea Serio**, Imperial College London
- **Dr Mike Rotherham**, Keele University
- **Dr Matt Shephard**, Keele University
- **Nicola Foster**, Keele University
- **Dr Yvonne Reinwald**, Keele University
- **Dr Molly Lowndes**, King's College London
- **Sebastiaan Zijl**, King's College London
- **Dr Stuart Cain**, University of Manchester
- **Dr Aixin Cheng**, University of Manchester
- **Dr Pinyuan Tian**, University of Manchester

Safety Hub

- **Dr John Connell**, University College London
- **Dr Stephen Patrick**, University College London
- **Dr Jack Sharkey**, University of Liverpool
- **Dr Arthur Taylor**, University of Liverpool
- **Dr Shiva Seyed Forootan**, University of Liverpool
- **Dr Dhifaf Jasim**, University of Manchester
- **Dr Rashida Lathan**, University of Glasgow
- **Abigail Chahil**, PhD Student, University of Liverpool

Acellular Hub

- **Ms Mahetab Amer**, University of Nottingham
- **Dr Derfogail Delcassian**, University of Nottingham
- **Dr Omar Qutachi**, University of Nottingham
- **Dr Jane McLaren**, University of Nottingham
- **Dr Lalitha Thiagarajan**, University of Nottingham
- **Dr Deepak Kumar**, University of Manchester
- **Dr Hareklea Markides**, Keele University
- **Dr Ben Pierce**, Imperial College (Research Co-Ordinator)
- **Dr Jenny Puetzer**, Imperial College
- **Ms Camille Marijon**, Imperial College
- **Dr Jean-Philippe St-Pierre**, Imperial College
- **Dr Hannah Levis**, University of Liverpool
- **Mr Tristan Dell**, Imperial College
- **Ms Katya Pchelintseva**, Imperial College
- **Dr Amy Gelmi**, Imperial College
- **Dr Carolyn Ibsen**, Imperial College
- **Dr Akemi Nogiwa-Valdez**, Imperial College (Data Manager)
- **Dr Miina Ojansivu**, Imperial College

Immunomodulation Hub

- **Dr Marcus Dorner**, Imperial College London
- **Dr Raul Elgueta**, King's College London
- **Dr Giorgia Fanelli**, King's College London
- **Dr Matthias Friedrich**, University of Oxford
- **Dr Anai Gonzales-Cordero**, University College London
- **Dr Ana Ortega-Prieto**, Imperial College London
- **Dr Susanne Sattler**, Imperial College London
- **Mr Matteo Battilocchi**, King's College London
- **Mr Iacopo Bicci**, King's College London
- **Mr Daniel McCluskey**, King's College London

Annex 4

Hub Publications since previous report

PSCP Hub

2018

- *Scanning the horizon for high value-add manufacturing science: accelerating readiness for the next generation of disruptive, high-value curative cell therapeutics*. Hourd P and Williams DJ. Cytotherapy 2018 Vol 20: 5 pg 759-767. doi: 10.1016/j.jcyt.2018.01.007
- *The Challenges of First-in-Human Stem Cell Clinical Trials: What Does This Mean for Ethics and Institutional Review Boards?* Barker RA, Carpenter MK, Forbes S, Goldman SA, Jamieson C, Murry CE, Takahashi J, Weir G. Stem Cell Reports. 2018 May 8;10(5):1429-1431. DOI: 10.1016/j.stemcr.2018.04.010
- *Assessment of established techniques to determine developmental and malignant potential of human pluripotent stem cells.* The International Stem Cell Initiative (Corresponding Author, P.W.Andrews), Allison TF, Andrews PW, Avior Y, Barbaric I, Benvenisty N, Bock C, Brehm J, Brüstle O, Damjanov I, Elefanty A, Felkner D, Gokhale PJ, Halbritter F, Healy LE, Hu TX, Knowles BB, Loring JF, Ludwig T, Mayberry R, Micallef S, Mohamed JS, Muller FJ, Mummery CL, Nakatsuji N, Ng ES, Oh SKW, O'Shea O, Pera MF, Reubinoff B, Robson P, Rossant J, Schuldt BM, Solter D, Sourris K, Stacey GN, Stanley EG, Suemori H, Takahashi K, Yamanaka S. Nature Communications 2018, doi. 10.1038/s41467-018-04011-3
- *New approaches for brain repair—from rescue to reprogramming*. Barker RA, Gotz M & Parmar M. Nature volume 557, pages329–334 (2018). doi:10.1038/s41586-018-0087-1.
- *Identification and single cell functional characterisation of a novel endodermally biased pluripotent sub-state in human embryonic stem cells*. Allison TF, Smith A JH, Anastassiasdis K, Sloane-Stanley J, Biga V, Jones M, Barbaric I, Gokhale PJ, Andrews PW. Stem Cell Reports, 2018, doi: https://doi.org/10.1016/j.stemcr.2018.04.015

2017

- *Neural grafting for Parkinson's disease: challenges and prospects*. Stoker TB, Blair NF, Barker RA. Neural Regen Res 2017;12:389-92 DOI: 10.4103/1673-5374.202935
- *Assessing the Safety of Human Pluripotent Stem Cells and Their Derivatives for Clinical Applications*. Andrews PW, Ben-David U., Benvenisty N., Coffey P., Eggan K., Knowles BB., Nagy A., Pera M., Reubinoff B., Rugg-Gunn PJ & Stacey GN. Stem Cell Reports 2017, doi: http://dx.doi.org/10.1016/j.stemcr.2017.05.029
- *Epigenetic resetting of human pluripotency*. Guo G, von Meyenn F, Rostovskaya M, Clarke J, Dietmann S, Baker D, Sahakyan A, Myers S, Bertone P, Reik W, Plath K, Smith A (2017) Development 144: 2748-2763, doi: 10.1242/dev.146811.
- *(2017) Regenerative Medicine: Advances from Developmental to Degenerative Diseases*. Blair NF, Frith TJR & Barbaric I. Advances in Experimental Medicine and Biology Book Series (AEMB, volume 1007): Personalised Medicine Chapter 12 pp 225-239, doi: 10.1007/978-3-319-60733-7_12
- *Preclinical imaging methods for assessing the safety and efficacy of regenerative medicine therapies*. Scarfe L, Brillant N, Kumar JD, Ali N, Alrumayh A, Amali M, Barbellion S, Jones V, Niemeijer M, Potdevin S, Roussignol G, Vaganov A, Barbaric I, Barrow M, Burton NC, Connell J, Dazzi F, Edsbagge J, French NS, Holder J, Hutchinson C, Jones DR, Kalber T, Lovatt C, Lythgoe MF, Patel S, Patrick PS, Piner J, Reinhardt J, Ricci E, Sidaway J, Stacey GN, Starkey Lewis PJ, Sullivan G, Taylor A, Wilm B, Poptani H, Murray P, Goldring CEP, Park BK. NPJ Regen Med. 2017 Oct 19;2:28. doi: 10.1038/s41536-017-0029-9. eCollection 2017.
- *Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era*. Barker RA, Parmar M, Studer L, Takahashi J. Cell Stem Cell. 2017 Nov 2;21(5):569-573. doi: 10.1016/j.stem.2017.09.014.

2016

- *Detecting genetic mosaicism in cultures of human pluripotent stem cells*. Baker D., Hirst AJ., Gokhale PJ, Juarez M., Williams S, Wheeler M., Bean K., Allison TF., Moore HD, Andrews PW., Barbaric I. Stem Cell Reports, 2016. DOI: http://dx.doi.org/10.1016/j.stemcr.2016.10.003.
- *Chapter 7 – Strategies for bringing stem cell-derived dopamine neurons to the clinic: A European approach (STEM-PD)*. Kirkeby A., Parmar, M., & Barker, RA. (2017) Progress in Brain Research, Volume 230, Pages 165-190. https://doi.org/10.1016/bs.pbr.2016.11.011

2018

- *Extracellular Matrix Molecule-Based Capture of Mesenchymal Stromal Cells Under Flow*. Massam-Wu T, Cain SA, Kielty CM. Methods Mol Biol. 2018; 1722: 249-560. doi:10.1007/978-1-4939-7553-2_16.
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- *Real-time and non-invasive measurements of cell mechanical behaviour with optical coherence phase microscopy*. Gillies D, Gamal W, Downes A, Reinwald Y, Yang Y et al. Methods. 2018 Mar 1;136:126-133. doi:10.1016/j.ymeth.2017.10.010. Epub 2017 Oct 31.
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2017

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- *Hydrostatic pressure in combination with topographical cues affects the fate of bone marrow-derived human mesenchymal stem cells for bone tissue regeneration*. Reinwald Y, El Haj AJ. J Biomed Mater Res A. 2017 Oct 6. doi: 10.1002/jbm.a.36267.
- *Promoting in vivo remyelination with small molecules: a neuroreparative pharmacological treatment for Multiple Sclerosis*. Medina-Rodríguez EM, Bribian A, Boyd A, Palemo V, Pastor J et al. Sci Rep. 2017 Mar 3;7:43545. doi: 10.1038/srep43545.
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- *Immobilized WNT Proteins Act as a Stem Cell Niche for Tissue Engineering*. Lowndes M, Rotherham M, Price JC, El Haj AJ, Habib SJ. Stem Cell Reports 2016; 7(1): 126-137. doi:10.1016/j.stemcr.2016.06.004. Epub 2016 July 12.

Safety Hub

2018

- *Multimodal cell tracking from systemic administration to tumour growth by combining gold nanorods and reporter genes*. Comenge J, Sharkey J, Fragueiro O, Wilm B, Mathias Brust M, Murray P, Levy R, Plagge A. eLife 2018;7:e33140 DOI: 10.7554/eLife.33140
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2017

- *Roadmap to clinical translation: insights from a UK regenerative medicine platform workshop on mesenchymal stromal cells*. Asante CO, Dazzi F. Regen Med. 2017 Dec 15. doi: 10.2217/rme-2017-0097.
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