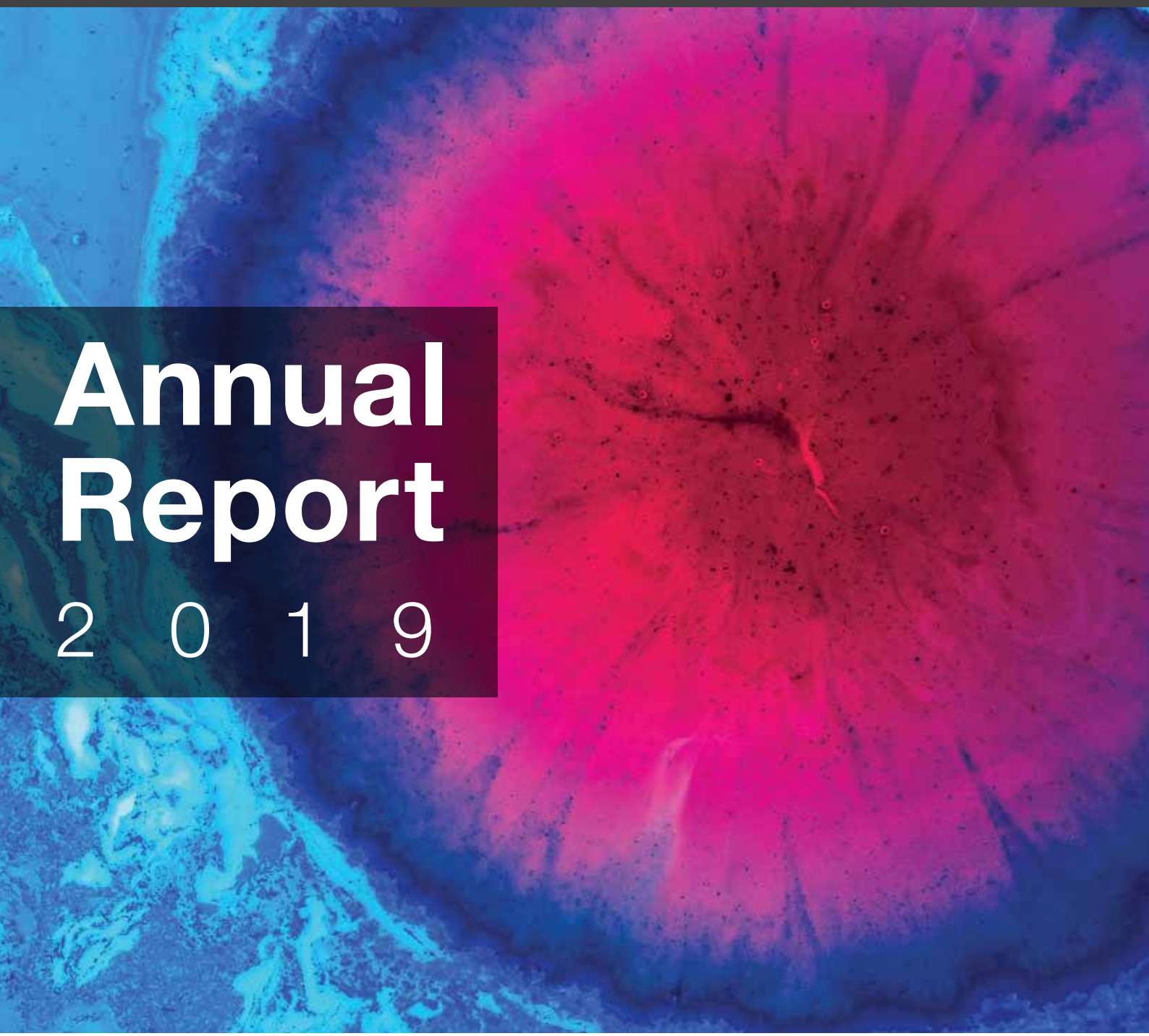
UK Regenerative Medicine Platform

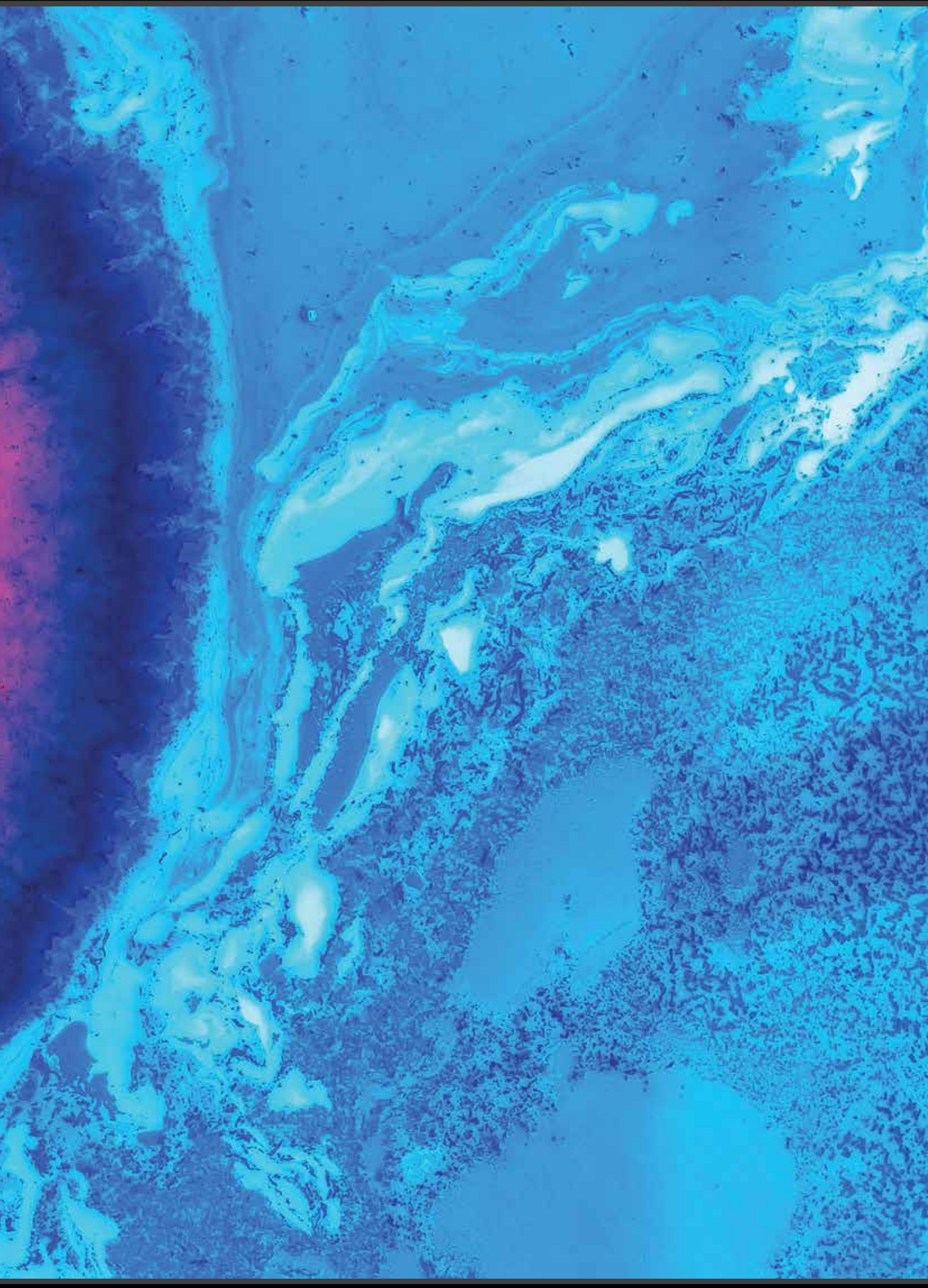


Annual Report 2019

Biotechnology and Biological Sciences Research Council

Engineering and Physical Sciences Research Council

Medical Research Council



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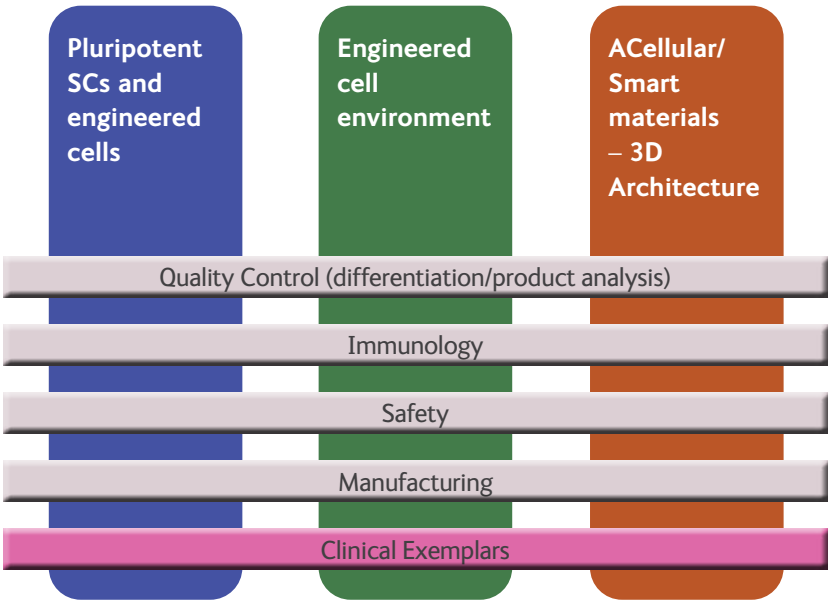
1. Introduction

Dr Rob Buckle: Chief Science Officer MRC

The UK Regenerative Medicine Platform (UKRMP) is a £42m national initiative addressing the key translational challenges in regenerative medicine. Established in 2013 by the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council (MRC), the UKRMP is a unique programme that brings together the leading players in regenerative medicine across 16 different universities. This coalescence of expertise, innovation and technological capability, connected to commercial and clinical end-users, provides the critical mass that is essential for the development of novel advanced therapies seeking to repair or replace damaged or diseased human cells or tissues to restore normal function.

The second phase of UKRMP began in 2018, and the Platform has evolved and consolidated to now comprise of three strong interdisciplinary and complementary research Hubs that collectively provide a national resource through the generation of new tools, protocols and resources that can be utilised by other UK research groups in both academia and industry. As evidenced in the following pages, the new Hubs are building on past relationships to maximise collaborations and tackle major challenges, from assessing the effect of chromosomal abnormalities on the growth of human pluripotent stem cells, through to developing microparticles to induce cell engraftment and mitigate immunological rejection during cell therapies. Together, the Hubs' mission is to advance regenerative medicine by overcoming outstanding hurdles to the translation of innovative concepts to clinical testing, for example by developing streamlined approaches for the manufacture of human Pluripotent stem cells, understanding how the host tissue environment (its niche) influences stem cell engraftment and behaviour, and generating scaffolds and matrices to support cell therapies in vivo.

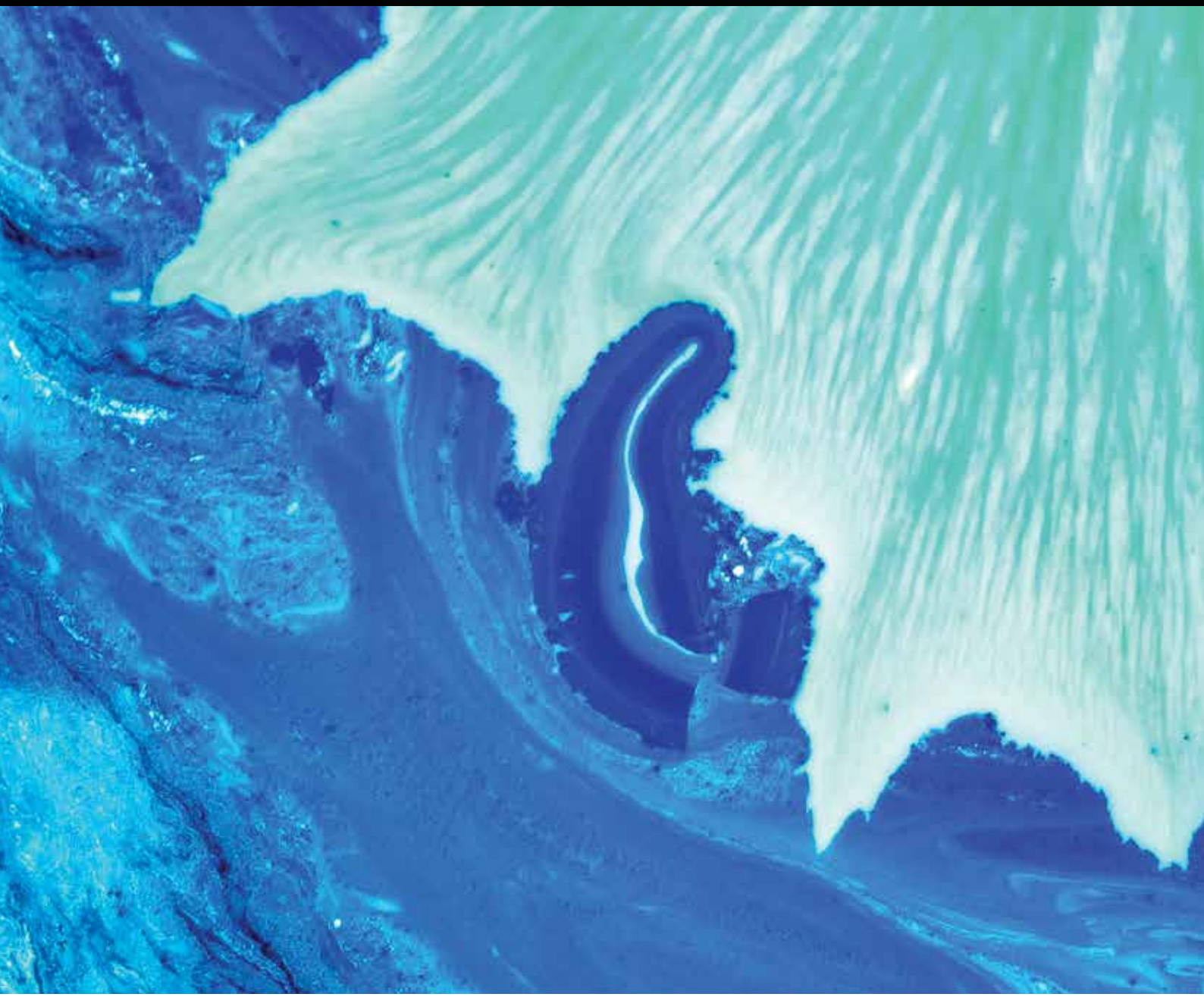
In addition to the Hubs, cross-cutting programmes are being developed which link to or expand upon aspects of the science being progressed through the Hubs. These include safety, immunology and manufacturing – themes with broad relevance and potential for impact across the Platform, and for the national and international research community.



The three Hubs have built on the successful programmes from the first tranche of funding, establishing their refreshed identity on the back of phase 1 momentum. This past year has also seen the UKRMP's programmes attract new UKRI fellowships and expand to address the immunological issues faced by developments in regenerative medicine, with the commencement of three new projects that collectively link across all three UKRMP Hubs. These are seeking to understand the signalling pathways of circulating immune cells during injury and develop approaches to remove HLA molecules to reduce immune responses to transplanted cell therapies. This strategic enhancement of the current Platform base should also help progress the translational activities of the research groups. On this front, the Hubs continue to work towards self-sufficiency, developing commercial activity, working closely with the Cell and Gene Therapy Catapult and engaging with the MHRA as well as pharmaceutical companies.

The Platform will continue to see further growth with, for example, recent additional strategic awards bringing in new clinical exemplars including multiple sclerosis and diabetes as well as developing key tools such as mathematical modelling and organ-on-a-chip designs.

This 5th annual UKRMP report provides further detail of the activities across the second phase of the Platform, describing the progress of the three Hubs and the direction of the new cross-linking strategic investments. It also highlights the emerging outputs from the Hub teams which should be of value to the wider research community. The described work lays the foundations for exciting translational research outputs in the coming years.

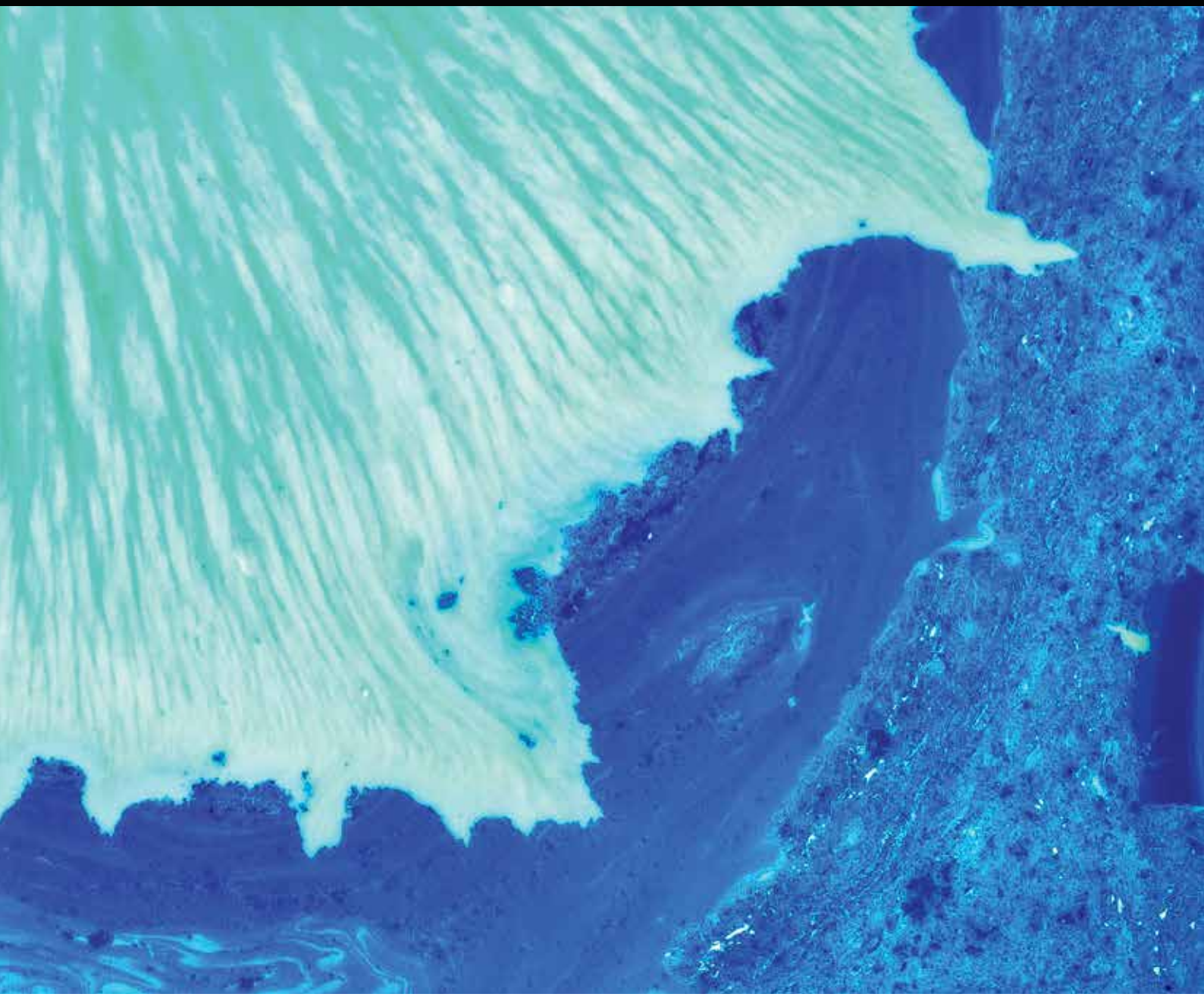


2. Hubs

2.1 Pluripotent Stem Cells and Engineered Cells Hub

2.2 Engineered Cell Environment Hub

2.3 Smart Materials Hub



2.1 Pluripotent Stem Cells and Engineered Cells Hub

Director: Professor Roger Barker, University of Cambridge
Co-Director: Dr Cedric Ghevaert, University of Cambridge

Who

- **University of Cambridge**, Roger Barker, Cedric Ghevaert, Florian Merkle and Serena Nik-Zainal
- **University of Sheffield**, Ivana Barbaric, Marta Milo and Zoe Hewitt (Project Manager)
- **Loughborough University**, Robert Thomas
- **Babraham Institute, Cambridge**, Wolf Reik

What

The Pluripotent Stem Cell and Engineered Cell (PSEC) Hub aims to advance regenerative medicine by overcoming the key outstanding hurdles in moving human Pluripotent Stem Cell (hPSC) based cellular therapies from the lab to the clinic for the standard treatment of patients. Our research builds on that which was undertaken by the Pluripotent Stem Cell Platform (PSCP) in the first iteration of UKRMP.

Our programme of work aims to:

1) Define and understand the biological significance of commonly acquired (epi)genetic changes in hPSCs as a result of growing them in the laboratory and/or manipulation and elucidate the implications of recurrent (epi)genetic changes for the ultimate therapeutic use of such hPSC-derived products.

2) Develop predictive models for hPSC (and genetically modified hPSC) -based therapeutic process design and control to better define the risks that may arise when manufacturing such products, including a pathway for regulatory integration, to facilitate clinical application.

3) Develop a translational pipeline, including quality control criteria, for the process of gene editing of hPSCs considering efficiency and consistency, off-target effects and emergence/ selection for genetic abnormalities to improve hPSC differentiation whilst reducing their immunogenicity. This is critical given that any hPSC-derived product is likely to induce a host immune response that would require the use of immunosuppressive drugs, which can have major side effects. Thus, making the cells less immunogenic through gene editing could offer obvious advantages therapeutically.

Scientific Developments

Human PSCs have the ability to produce any specialised cell type and hence, represent a powerful source of specialised cells for use in regenerative medicine therapies. In order to be therapeutically useful, hPSCs should be devoid of any errors in their genetic material (i.e. genetic changes) that could compromise their safety upon transplantation into patients, such as genetic changes linked to tumour development. Previous work in the field has established that by growing the cells in the laboratory for extended periods, hPSCs tend to acquire certain genetic changes, including gains of additional chromosomes. Of all the abnormalities that have been reported in hPSC cultures to date, the most frequently observed are gains of chromosomes 1, 12, 17 and 20. The commonality of such aberrations across different hPSC lines and across different laboratories growing hPSCs worldwide, led to the notion that a gain of one of these chromosomes confers an advantage to the cells, allowing them to have enhanced survival or proliferation in culture. Such behaviour of hPSCs is potentially concerning as it could lead to uncontrolled proliferation or aberrant behaviour of hPSC-derived specialised cells when transplanted into patients.

Safety of hPSC derivatives for use in cellular therapies

Within Theme 1 of PSEC, one of the challenges we are addressing is this question of the safety of hPSC derivatives for use in cellular therapies. One aspect of our work entails assessing the effect of commonly gained chromosomal abnormalities on hPSC growth and their ability to produce specialized cell types. In addition, we are also looking at the functional properties of specialized cells derived from genetically aberrant hPSCs to ascertain whether common chromosomal abnormalities make any difference to the behavior of cells we need to make and use in the clinic. As an essential pre-requisite for carrying out such studies, **Dr Christopher Price** (Barbaric Lab, Sheffield) has developed hPSC lines with and without the common genetic changes we have found (gains of chromosomes 1, 12, 17 or 20 as a sole abnormality, and hPSC lines with complex aberrations, such as a gain of several additional chromosomes within the same cell). Such a panel of lines represents an excellent toolbox for in-depth studies of the effects of common genetic changes on different aspects of hPSC behavior, including the functionality and safety of the specialized cells derived from hPSCs. The outcome of this work will help us reveal why commonly seen chromosome changes occur in hPSCs, how the recurrent changes impact on the properties of the final cellular product and how hPSCs could be grown in a way that suppresses these genetic changes in hPSC cultures.

Manufacture of cellular products

Another important challenge in the production of medical products from living cells is the ability to manufacture a consistent product and at a scale which will ensure that we can make enough for all patients that need such a treatment. Within PSEC, Theme 2 seeks to investigate this issue. In particular, **Dr Preeti Holland** (Thomas lab, Loughborough and in collaboration with the Barker team, Cambridge) is addressing this issue for the production of dopaminergic nerve cells for the treatment of Parkinson's disease. One critical question that we are addressing is how sensitive the manufactured cell product is to the manufacturing process, in other words if we slightly change one part of the manufacturing process does this dramatically change what we make in terms of the type and functionality of the dopamine nerve cells. Currently, there are no systematic methodologies to satisfactorily address this question due to the complexity of the manufacturing process and the complex specification of our final product. Preeti is taking a dual approach to address this problem. She is exploring methods to mathematically predict the outcome of the manufacturing process (different types of models from simple straight-line predictions to significantly more complex ones) combined with multiple different ways of defining the final cell product (using a method called statistical cluster analysis that automatically groups similar cells together). Both of these aspects of the manufacturing process need to be considered simultaneously, as ultimately, we need to know how predictable and stable such a process has become and what we are finally making in terms of the types of nerve cells so generated. The work so far has shown that the differentiation process (i.e. the making of specific dopamine cells from non-specific hPSC) is acutely sensitive to certain specific inputs very early on in manufacturing process. We are now defining how we can better model and control all this as well as considering how this variation evolves over a full process, and therefore provide a rationale for the level of control required to guarantee a consistently safe and effective clinical product.

The ability to change a cell's DNA through gene editing has opened a lot of possibilities in our quest to derive new therapies from hPSCs. In particular, this would allow us to make a cell therapy compatible with all patients without having to worry about the patient's immune system rejecting the cells. In addition, stem cells could also be modified in order to better generate the type of cells we intend to use to treat specific diseases. Modifying the DNA of a cell is however a procedure that needs to be both efficient and accurate. Within Theme 3, we have developed a methodology to enable us to test various ways of editing the DNA of hPSCs to find the one that does both of these things. This has included testing various reagents that are suitable for clinical use in order to inform future procedures to make banks of hPSCs from which therapies for human use can be derived.

In addition to establishing a robust internal network of collaborative work, one of the goals from our first year was to establish a dynamic collaborative network more widely across the whole RMP. Together with the other two UKRMP Hubs, we have organised two cross-platform workshops bringing together people working in Regenerative Medicine but with different complementary expertise. The first was a two-day interdisciplinary workshop entitled "**Regenerative Medicine meets Mathematical Modelling: Discovering Symbiotic Relationships**" at St Anne's College Oxford. The meeting was attended by more than 70 delegates from 25 different institutions and interfaced wet lab based scientists, with experts in mathematics, modelling, computer sciences and computational biology. Over the two days, groups of delegates formed and worked intensely to devise suitable projects to apply for the pump priming funding that the hubs had made available for such work. Twelve high quality applications were received and we were able to award pump priming funding to the top five rated projects (four funded from UKRMP and one from matched University of Oxford/ Industry funding). One of these projects was awarded to a

PSEC Postdoctoral Researcher **Dr Venkat Pisupati** and his collaborator Dr Joanne Jones (University of Cambridge) in an interdisciplinary project involving Dr James Philips and Dr Rebecca Shipley (UCL), who both have expertise in using engineered biomaterials with cells and mathematical modelling.

Clinical trials using hPSC-derived dopaminergic neurons are already being planned for the treatment of Parkinson's disease, which is caused by the degeneration of dopaminergic nerve cells in part of the brain called the substantia nigra and affects both motor and non-motor functions in patients. However, successful transplantation of hPSC-derived dopaminergic nerve cells depends on their survival and the effectiveness of the therapeutic cells following grafting. Optimising parameters such as cell seeding density and spatial distribution can require extensive experimentation which hampers progress in this area. This pump priming project aims to use a multidisciplinary approach to determine the optimal seeding density and distribution of therapeutic cells in a candidate biomaterial in order to promote transplanted cell survival. A mathematical model of the competing factors, validated against experimental data, will provide a rational and widely-applicable strategy for the possible use of biomaterials to further improve on cell transplantation not just for Parkinson's disease.

Within PSEC, the behaviour of PSC-derived dopaminergic nerve cells in a range of microenvironments will be quantified, which will be used to parameterise a computer model of cellular behaviour at UCL. This model will be tested experimentally. The data obtained will be fed back into the computer model for several cycles to optimise the design for in vivo testing. The methodology proposed here aims to become a standard in the field of tissue engineering by approaching the design of cellular biomaterials by leveraging and integrating methods from mathematical modelling, cell biology, biomaterials science and bioengineering. The framework developed within this project is flexible and can be easily employed as future material and cell technology options evolve for any type of clinical application.

"I find it extraordinary that even after just 12 months the interactions between the partners of the hub as well as outside collaborators has already led to the generation of key data that will support funding application for a future first-in-human study with an exemplar tissue. It demonstrates the power of the multidisciplinary platform approach to cellular therapies." – Cedric Ghevaert, Deputy Director

The second workshop was another two-day event organised in conjunction with the British Pharmacological Society (BPS). Entitled "**Safety for Stem Cell-Derived Therapies: Exploring Trends and Future Technologies**", this meeting highlighted to industrial and academic delegates where progress to the clinic has been made but where also there are still significant gaps in how safe the stem cell-derived therapies really are. This includes questions relating to how such cells behave when combined with smart materials. Over 100 delegates from more than 40 institutions/ businesses from 5 different countries were represented, including delegates from both the US and UK regulatory authorities.

Hub Growth

In addition to our co-PIs and research teams, the PSEC Hub also has two independent research fellows (UKRI/Rutherford Fund Fellows) who are affiliated with our hub and our research activities. **Dr William Kuan**, from the University of Cambridge began his fellowship in May 2018. The primary objective of his fellowship is to develop a clinically more relevant animal model of Parkinson's disease, which can then be used to validate novel therapies including hPSC-derived dopamine transplants. One of the main hurdles of therapeutic development in Parkinson's disease is the lack of good experimental models, which need to recapitulate the progressive nature of disease pathology, as well as affecting only certain populations of nerve cells in different areas of the brain- as is seen in patients dying with Parkinson's disease. By delivering a pathological species of a protein implicated in Parkinson's disease through the circulation (alpha synuclein), he has demonstrated that behavioural and pathological features of Parkinson's disease, similar to those observed in the early stage patients, can now be reproduced in rodents. Furthermore, by carefully tracking the progressive decline of behavioural function in these lesioned animals, he has defined the relevant outcome measures, as well as the optimal time-point for therapeutic intervention. Through this affiliation, the PSEC team now have a more robust model through in which their hPSC-derived dopaminergic nerve cells can be effectively tested.

In July 2019, **Dr Stefan Schoenfelder**, from the Babraham Institute was awarded a two year UKRI/Rutherford Fund fellowship. His fellowship focuses on a subset of hPSC, induced pluripotent stem cells (iPSCs) and the molecular mechanisms underlying why they turn into the cells they

"Over this first year it has been amazing to see the way in which the work has come together and grown, both within our hub and across the whole UKRMP network, as we strive to make hPSC therapies a reality for patients."
– Roger Barker, Director

do when grown in culture under different differentiation conditions. This is important because although hundreds of iPSC lines have been derived and stored in biobanks, these cells lines display very different properties when they are differentiated into bespoke cell types. Some can be grown effectively into, for example, brain cells but not into liver cells, whereas for other cell lines it is the opposite- even though the starting cells superficially look the same. Stefan's research aims to understand the molecular basis of this phenomenon. In particular, he focuses on specific regions in the genome called enhancers, which function as 'molecular switches' to turn on sets of genes and is testing the hypothesis that genetic differences in these switches confer individual iPSC lines with different properties, including their differentiation potential – namely their ability to give rise to specific cell types for applications in biomedicine. This will enable screening iPSC lines to improve our protocols and procedures for regenerative and personalised medicine.

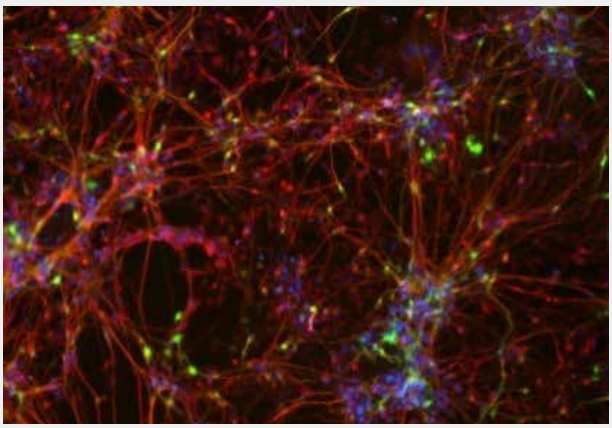


Figure 1: Immunostaining of TH (green) and β-tubulin III (red) in differentiated neurons at day 30 derived from the MasterShef7 embryonic stem cell lines.

Industrial collaborations

In our drive to become self-sufficient, the PSEC team are actively engaging with Industry. We are currently working towards setting up collaborations with AstraZeneca and Elpis BioMed. In addition, members of our Executive Team sit on Scientific Advisory Boards of a number of small to medium size businesses including MacoPharma, Elpis, Platelets Biogenesis and Rockend as well as advise larger companies such as Novo Nordisk and Bayer.

Future Directions

PSEC has so far managed to develop new platforms to facilitate the translation of hPSC-derived products to the clinic at the genetic, gene editing and manufacturing levels. This will lay the foundation for our future work that seeks to streamline the development of these new therapies for human use, working with industry and academia as we seek to change the face of clinical practice for many diseases that could be amenable to such treatments in the UK.

Outputs

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

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

2.2 Engineered Cell Environment Hub

Director: Professor Stuart Forbes, University of Edinburgh
Co-Director: Professor Alicia El Haj, University of Birmingham

Who

- **University of Edinburgh,** Neil Carragher, Jenny Cusiter (Project Manager), Elaine Emmerson, Stuart J Forbes (Director), David Hay, Julie Wallace (Administrator)
- **University of Cambridge**, Mark Birch, Kevin Chalut, Robin Franklin, Andrew McCaskie
- **University of Birmingham**, Alicia El Haj (Deputy Director)
- **King's College London**, Shukry Habib, Fiona Watt
- **University College London**, Rob Hynds, Sam Janes, Marko Nikolic

What

The UKRMP Engineered Cell Environment (ECE) Hub will consider two translational strategies for damaged organs.

(1) Developing cell therapies for damaged organs: successful cell therapies require a better understanding of how cells behave in the environment they engraft. Our approaches span clinical applications, aiming to improve transplanted cell performance.

(2) Promoting endogenous repair of damaged organs: using human stem cells, we will create automated assays to study the behaviour of stem cells and identify signals that optimise repair. We will use drug and small molecule libraries approved for clinical use to identify potential compounds that can promote stem cell expansion and differentiation.

Three clinical exemplars (liver, joint and lung repair) have been selected with potential for tangible clinical gains and are well positioned to provide the "pull through" from basic stem cell science and regenerative biology. Stem cell scientists and tissue engineers are partnered with clinician scientists familiar with leading clinical trials and the pathways to translation.

We have 3 overarching goals:

- Understanding and improving the physical properties of aged and injured tissue niches;
- Developing artificial niches to act as regenerative signals for tissue formation and repair;
- The discovery and development of novel targets to promote endogenous tissue repair.

Scientific Developments

Liver Work Package: Liver transplantation remains the only definitive treatment of patients with end stage liver disease. Demand for livers far outweighs available donor organs; only a minority of patients receive an organ transplant. Cell therapies are a potential alternative treatment: the use of hepatocytes (functional liver cells) for the treatment of metabolic liver disease has been demonstrated in a clinical setting. However there are a number of barriers that prevent wide-spread application including cryopreservation (freezing and thawing of cells), limited cell engraftment, immune rejection and poor long term function. The UKRMP ECE Hub is looking to address some of these barriers. The Forbes group have shown that adult hepatic progenitors (adult liver stem cells) can produce functioning hepatocytes (Nature 2017); these cells can be isolated and expanded

in the laboratory (Nat Cell Biol 2015). An alternative cell type developed by the Hay group includes stem cell derived hepatocytes (Stem Cell Reports, 2015); these cells potentially provide an unlimited and off-the-shelf supply, as well as opportunities for patient specific cell therapies.

The Carragher/Hay groups are looking at using small molecules to encourage cell growth, maturity and function. Clinically approved compound libraries are being screened to identify additives which optimally maintain hepatoblast (liver cell precursor) or adult hepatic progenitor cell identity and enhance differentiation (for maturity and function). The production of stem cell-derived hepatoblasts has now been up-scaled to a 96-well format. Any results will be validated using preclinical disease models to assess improvements in engraftment efficiency and long-term performance of these cells.

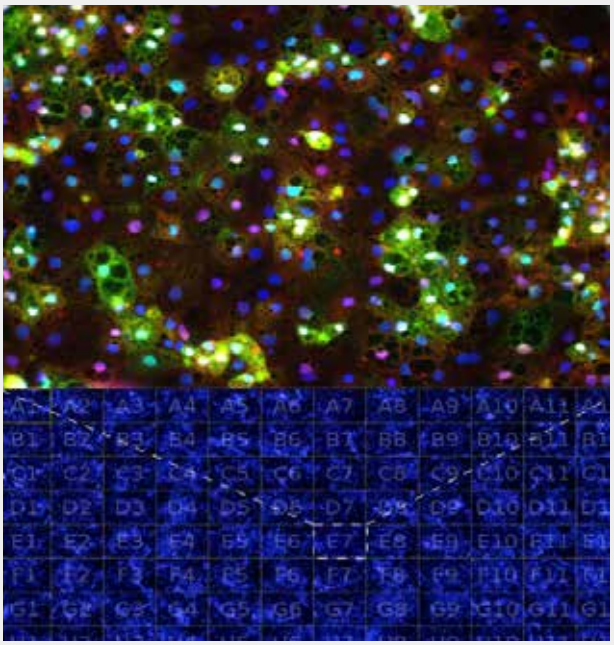


Figure 1: Stem cell-derived human hepatocyte-like cells grown on a 96-well plate.

The Forbes group has developed a disease model of liver senescence which will be used by **Dr Victoria Gadd**, UKRMP post-doctoral research fellow, to define the repopulation capacity of stem cell derived hepatocytes and adult hepatic liver progenitors. Short-term safety studies of adult hepatic progenitor cells and mature hepatocyte-like-cells have been tested in this model and long-term studies are currently underway.

The Franklin/Chalut groups are exploring the influence of tissue mechanics on the regenerative process of the liver. The liver fails to regenerate properly after chronic injury usually leading to the development of scar tissue known as fibrosis. The main feature of fibrosis is the stiffening of the liver tissue. However, it is unknown how the mechanics of the environment surrounding liver cells affects their ability to regenerate. Understanding the influence of tissue mechanics on liver regeneration is a clear imperative to identify new therapeutic solutions for liver disease. **Dr Nejma Belaadi**, UKRMP post-doctoral research assistant, is characterising the physical properties of aged and diseased liver tissue using atomic force microscopy and is also changing the mechanical environment of the liver cells using hydrogels with tunable stiffness. It is expected that this will lead to a better understanding of the underlying molecular mechanisms affecting the ability of liver cells to regenerate.

Joint Work Package: Osteoarthritis (OA) is a major worldwide healthcare burden that can severely impact on patients making it difficult for them to walk, sleep and work. OA causes progressive breakdown of articular cartilage and bone, often leading to severe joint pain and poor function. Traditional treatments include joint replacement in the most severe cases or "key-hole" surgeries for those that are less advanced. These less invasive procedures aim to either clean the site or to encourage a natural inflammatory response, whereby the patient's own cells are recruited to help repair the damaged tissue. Injectable therapies, containing cells which have been pre-optimised outside of the body, can be administered at the same time.

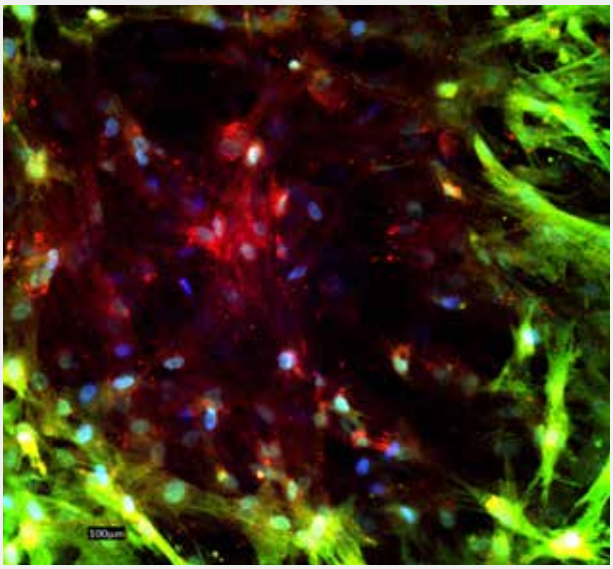


Figure 2: Human bone marrow-derived stem cells cultured in collagen hydrogels for 14 days, under chondrogenic conditions, express cartilage markers (green) in the outer regions, but not in the middle (red). Cell nuclei are blue.

UKRMP ECE Hub research aims to understand how the cells that are already within these tissues can be activated to help contribute to the repair of bone and cartilage. The McCaskie/Birch groups are interested in immature cells that

Figure 3: A therapeutic protein (Wnt) immobilised onto micro-beads regulate stem cell splitting to generate one stem cell and another mature cell generating tissue structures in 3D.

have the potential to become bone and cartilage forming cells and how their maturation to directly lay down new tissue is balanced by their potential to play a role signalling to other cell types, including immune cells that contribute to the process of tissue repair and regeneration. **Dr Francesca Beat**on, UKRMP post-doctoral research assistant will perform studies using a preclinical model of microfracture (an orthopaedic procedure where a hole is created from the articular joint surface through cartilage and bone into the bone marrow cavity releasing cells to stimulate repair) and will investigate the potential for the protein signalling factor attached to the surface of a biomaterial to facilitate the restoration of osteochondral structure.

"The UKRMP ECE Hub has constructed a multidisciplinary team with stem cell and regenerative biologists partnering clinician scientists across three important disease themes. We hope these teams will be well placed to drive discovery science outputs towards the clinic." – Stuart Forbes

The El Haj group has developed a fluid gel, containing cells and chemical cues to enhance their performance, which can potentially be delivered via injection to joint sites. **Dr Nicola Foster**, UKRMP post-doctoral research fellow, will test the efficacy of these fluid gels by using them as a vehicle to turn stem cells into cartilage-producing cells. Another option for cartilage repair is to engineer constructs which can replace damaged tissue. In order to do this, suitable cells and materials in which to grow them need to be identified. Over time, these biomaterials should degrade and be replaced by substances produced by the cells. The El Haj group are working to develop new materials which can be modified with chemical cues from the body in order to encourage stem cells to grow and to differentiate into cartilage-producing cells.

The Habib group has pioneered the technology of immobilising Wnt proteins to synthetic surfaces (Science 2013) showing that Wnt is essential to maintain a variety of stem cell types and control asymmetric cell division. The Habib group is currently studying the mechanisms that stem cells use to identify localised Wnt, the mechanisms of breaking cellular symmetry and the bioenergetics required for this process. In future, the group aim to develop new bioengineering strategies to deliver Wnt proteins to different tissues in vivo to access their effect on regeneration.

Lung Work Package: Airways connect the lung to the outside environment by transporting air to the alveoli (small air sacs) where gas exchange occurs. Therefore, the epithelial cells that line the airway are vulnerable to numerous environmental insults throughout a person's lifetime. Maintaining the integrity of this lining is essential for protecting the lungs. The airway epithelium undergoes slow but constant renewal, but in response to pollutants, viral and bacterial infections there is a rapid process of repair and regeneration that restores the injured epithelium. However, abnormal repair processes can lead to irregular organisation and integrity resulting in the pathogenesis of many respiratory diseases. Defining novel factors that control airway regeneration is critical to be able to influence stem cell activation and differentiation. Respiratory diseases affect one in five people in the UK and related hospital admissions have risen at three times the rate of all other admissions. The goal is to identify components that promote regeneration and repair of the lung in the hope of restoring normal epithelial function and protection against further damage.

The Janes/Watt groups are exploring strategies for promoting epithelial stem cell maintenance and regeneration in order to gain an understanding of the environment in which the cells reside. The Janes group routinely isolate adult airway epithelial cells from bronchoscopy biopsies, and subsequently expand these cells in vitro ("in a dish"). These cell cultures can be maintained in the lab indefinitely, providing models for airway diseases like cystic fibrosis, asthma and infections. The Janes/Watt groups have also grown airway epithelial cells as three-dimensional (3D) structures that are embedded in a matrix, allowing self-organisation into tissue-like structures with relevant cell types. **Dr Kyren Lazarus**, UKRMP post-doctoral research fellow, will utilise these culture systems to identify compounds that drive airway stem cell activation and differentiation using high throughput, high content screening (in collaboration with the Carragher group). The Watt group have identified a potential conserved mechanism that prevents uncontrolled stem cell growth.

Hub Growth

Partnership Funding

The Hub established five new partnership projects at the end of 2014 which expanded the Hub and its breadth of expertise considerably. All of these projects are progressing well and are delivering tangible outputs. Work on defining a **translational niche for tissue engineered products** has led to the development of a non-destructive cell imaging platform based on biomechanics, with direct applications in bone and cartilage regeneration research. Research on niche **fabrication for chondrocyte differentiation** has resulted in the generation of graphene oxide-based substrates capable of supporting hESCs differentiation of mesodermal to chondrogenic progenitors. Work with the **Acellular Hub** has shown that BMP-2 particles are able to support chondrogenesis to the same extent as soluble BMP-2 and allowed testing of a variety of hydrogels for 3D chondrogenesis. The project aimed at enhancing tissue growth in a dynamic environment shows promising leads for improving bone repair based on findings that implantation of collagen/MSC beads ex vivo in chick femurs leads to enhanced bone regeneration. The role of **tethered Wnt** has been established in the creation of a platform for directed 3D cues to mesenchymal stem cells in a 3D model using PLGA/collagen. Partnership research to identify **new liver toxicity markers** has generated a point of care platform for measurement of lead microRNAs in patients with acute liver injury, work which has led to pharma collaboration and a patent.

"A key objective of UKRMP is training the next generation of regenerative medicine researchers. To develop new treatments for patients requires the skills and expertise of a collaborative interdisciplinary team; skills that we hope to foster. The UKRMP ECE Hub team embodies this ethos and provides a range of career development opportunities." – Alicia El Haj

Future Directions

UKRMP ECE Hub research programs are established and producing results; we are looking to develop collaborations with translational and commercial partners. We are especially 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.

For further information or access to the tools and resources, contact the ECE Hub project manager Jenny Cusiter: jennifer.cusiter@ed.ac.uk

2.3 Smart Materials Hub

Director: Professor Molly Stevens, Imperial College London
Co-Director: Professor Richard Oreffo, University of Southampton

Who

- **Imperial College London**, Molly Stevens, Jonathan Jeffers
- **University of Nottingham**, Kevin Shakesheff, Felicity Rose, Lisa White, Ricky Wildman
- **University of Edinburgh**, Stuart Forbes, Mark Bradley
- **University of Glasgow**, Manuel Salmeron-Sanchez
- **University of Manchester**, Alberto Saiani
- **Queen Mary University of London**, Alvaro Mata
- **University College London**, Robin Ali
- **University of Liverpool**, Rachel Williams
- **University of Oxford**, Andrew Carr
- **University of Southampton**, Richard Oreffo, Nicholas Evans, Jon Dawson

What

The UKRMP smart materials hub's core goals are: 1) to develop new types of biomaterials and fully evaluate their safety and efficacy, 2) to demonstrate clinical translatability and pull through of our smart material technologies and move towards real-world applications in the eye, liver, and musculoskeletal system, 3) to actively harness partnerships with manufacturing, commercial, and regulatory bodies to ensure that our translational process is effective, and 4) to develop the hub itself into an effective body for translational research that can guide the next generation of regenerative medicine scientists.

In our initial year, we have focused on the development and initial evaluation of several new classes of biomaterial. We have made strong progress and have already fulfilled a number of our milestones. Methods of synthesis to achieve materials with the initially specified properties have been identified and optimised in a number of cases, and extensive characterisation undertaken. We are in a strong position to continue to move into the next phase of development, in which we will test the efficacy of our materials in models of disease in the eye, liver and musculoskeletal system.

Scientific Developments

Scientific Achievements

New materials for the musculoskeletal system

The hub is developing a wide range of potential materials for use throughout the musculoskeletal system; specifically, within bone, tendons, and cartilage. Bone scaffolds based on a novel octetruss architecture (Reznikov et al, 2017) are being fabricated from titanium, a non-degradable polymer (Nylon) and a degradable polymer (poly-ε-caprolactone-triacrylate). Following synthesis, these scaffolds are being functionalised with secondary coatings to either support biomineralization or sequester growth factors to aid bone repair (Figure 1). The titanium and nylon scaffolds have been fabricated by selective laser sintering (SLS) and coated with; i) poly(ethylacrylate) (PEA), polydopamine to sequester and release cell-supporting growth factors, ii) mineralising peptides to support mineralisation, and iii) elastin-like recombinamers. Exciting developments are underway within the tendon biomaterial program. Electrospun fibre material candidates have been synthesised (Figure 2), their mechanical properties evaluated, and the fibres are now being produced under GMP and ISO 13485 guidelines. Following a meeting with the MHRA to discuss the requirements for progression to human trials, further data

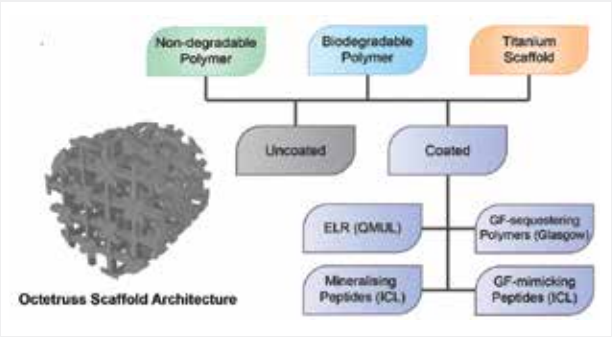


Figure 1: Work plan for development of bone scaffolds. Titanium and the non-degradable polymer are undergoing coating testing, and the degradable polymer is still being developed. Inset shows octetruss scaffold architecture (Reznikov et al, 2017).

is being acquired including a full chemical compositional analysis and an additional *in vivo* study in rabbits. By working closely with regulatory authorities at an early stage, the translation potential and timeframe to patient benefit of this work has been maximised.

Figure 2: Materials in development for tendon repair.

Cartilage tissue is multizonal, and a particular challenge for developing appropriate cartilage replacement scaffolds is the fabrication of scaffolds with a similar complex architecture. At Imperial College, zonally microstructured scaffolds mimicking cartilage tissue have been fabricated using a combination of techniques including electrospinning, porogen leaching and directional freezing. The mechanical properties of these scaffolds are being characterised and optimised, and the development of biofunctionalization strategies is ongoing.

A collaboration between the Centre for Additive Manufacturing (Prof Ricky Wildman) and Regenerative Medicine and Cellular Therapies (Prof Felicity Rose) at the University of Nottingham has provided a new opportunity for **Dr Robert Owen** to explore the application of additive manufacturing to create geometrically defined structures for application in bone repair. Dr Owen's work has focussed on the identification of candidate materials for the fabrication of porous microparticles by two-photon polymerisation (2PP), and, critically, Robert has successfully produced a number of microparticles of varying defined geometries and porosities. These structures have now been printed in an array format to allow rapid screening of the influence of geometry on mammalian cell behaviour. The assessment of human mesenchymal stem cell interaction with these microparticles will start soon to identify geometries that support cell ingrowth and cell differentiation to bone.

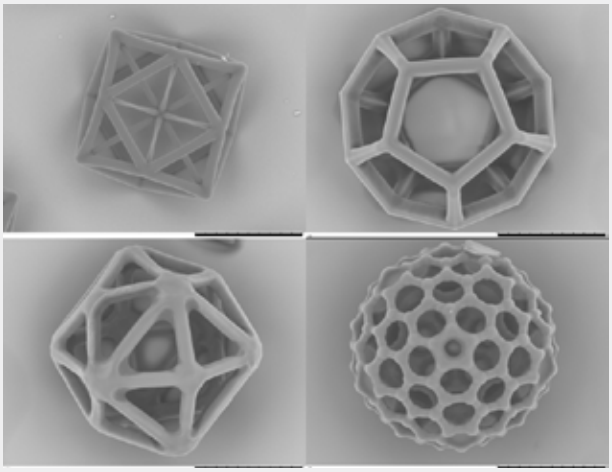


Figure 3: An example defined geometry microparticle designs fabricated by 2PP. (Scale bar: 50 μm.)

New materials for the eye

Following on from successful work in the first UKRMP hub, materials are being developed to mimic the corneal stroma. This would allow the production of several grafts from a single donor cornea. This work is being led by researchers in Prof. Rachel William's lab at the University of Liverpool and researchers in Prof. Molly Stevens' lab at Imperial College London (ICL). At ICL, **Dr. Jonathan Wojciechowski** is developing these gels from GelMA. These gels have to satisfy challenging strength and transparency requirements, so that they do not break during or after implantation or, importantly, obstruct vision. Gels with excellent transparency (>95%) and compressive stiffness have now been achieved. In order to maximise tensile strength and encourage cell infiltration into the scaffold, Dr Wojciechowski and colleagues are investigating 3D printing techniques to achieve gels with microstructural and nanostructural organisation. A microscale mesh-like architecture would allow deep cell infiltration and nutrient transport. A recently-developed technique that exploits shear forces at the 3D printing nozzle could allow deposition of aligned GelMA fibres, mimicking the aligned collagen fibres that allow the natural stroma to achieve strength and transparency. Materials to support repair of the retina are also being developed. Photoreceptor cells can be cultured in vitro and transplanted into damaged retinal tissue but tend to lose their polarity and therefore fail to integrate properly. At ICL microstructured sheets with predefined containers for photoreceptors are being developed, intended to allow the cells to be grown and

"'I am pleased with the progress of the development of candidate materials to aid repair within the musculoskeletal system. Our interactions with regulators, advisory panel members and our approach to enhanced biocompatibility testing will aid our development process and facilitate translation in the future – a key goal of this UKRMP programme." – *Prof Richard Oreffo*

transplanted as an aligned sheet. Transplantation of fragile tissue sheets into the eye is challenging, and so an injector has been designed to deliver the sheet down the barrel of a needle. This work has been supported by a new exciting and emerging collaboration with the ICL Aeronautics department, using fluid dynamics modelling to aid design of a structure that minimised shear stress on the injected sheet.

Liver

Work on materials for liver regeneration has begun. At Nottingham, **Dr Derfogail Delcassian** (Nottingham /MIT) has developed PLGA microparticles that carry IL-10 and IL-33 – these are intended to induce cell engraftment and mitigate rejection during cell therapies to replace damaged liver tissue. These microparticles have been tested in *in vitro* and *in vivo* models and are continuing to be developed. In parallel, **Dr I-Ning Lee** (Nottingham) has also developed PLGA microparticles for the release of VEGF and KGF. In this case, the PLGA microparticles were galactosylated via a new synthetic route. These microparticles have tuneable size and surface properties and will also be investigated for applications in the liver.

Hub Growth

Progress within the smart materials hub is excellent. We have, to date, successfully completed 8 milestones and 2 deliverables. The hub continues to develop in line with its long-term goals to maximise research translatability. Discussion with the MHRA at an early stage of research was illuminating and allowed us to direct our work on materials for tendon repair appropriately for later translation, following GMP and ISO standards for synthesis and carrying out suitable testing. Following this, we will work to bring appropriate early-stage discussions with regulatory authorities into our other work packages. Our Safety and immunology and our Manufacturing, Commercial and Regulatory Panels have provided significant input to the research programmes.

We have also pursued greater integration of mathematics and machine learning into our research. This has already resulted in a CDT-funded PhD student on fluid dynamics relating to the function of our cartilage replacement materials. A networking event took place in January 2019 in Oxford on Mathematical Modelling and Regenerative Medicine and resulted in pump-prime funding for three projects associated with the hub, with a second event scheduled for Q4 2019 to inform on experimental design within the hub.

Future directions

We are delighted with the progress in our first year, which has resulted in the development and initial evaluation of several new classes of biomaterial. We are excited to move into the next phase of development, in which we will test the efficacy of our materials in models of disease in the eye, liver and musculoskeletal system.

In-line with the long-term goals of the Hub, we will maximise research translatability. Following our discussions with the MHRA for our tendon repair work, we will continue to bring appropriate early-stage discussions with regulatory authorities into all work packages. .

We will continue to integrate mathematics and machine leaning in to the Hub through future collaborations.

Outputs

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

For further information or access to the tools and resources, contact the Smart Materials Hub project manager Chloe Stockford: chloe.stockford@imperial.ac.uk

"'I am excited by the progress made by the smart materials hub in our first year. We have built a fantastic team and are well on track to producing innovative new materials with real translational potential for clinical applications." – *Prof Molly Stevens*

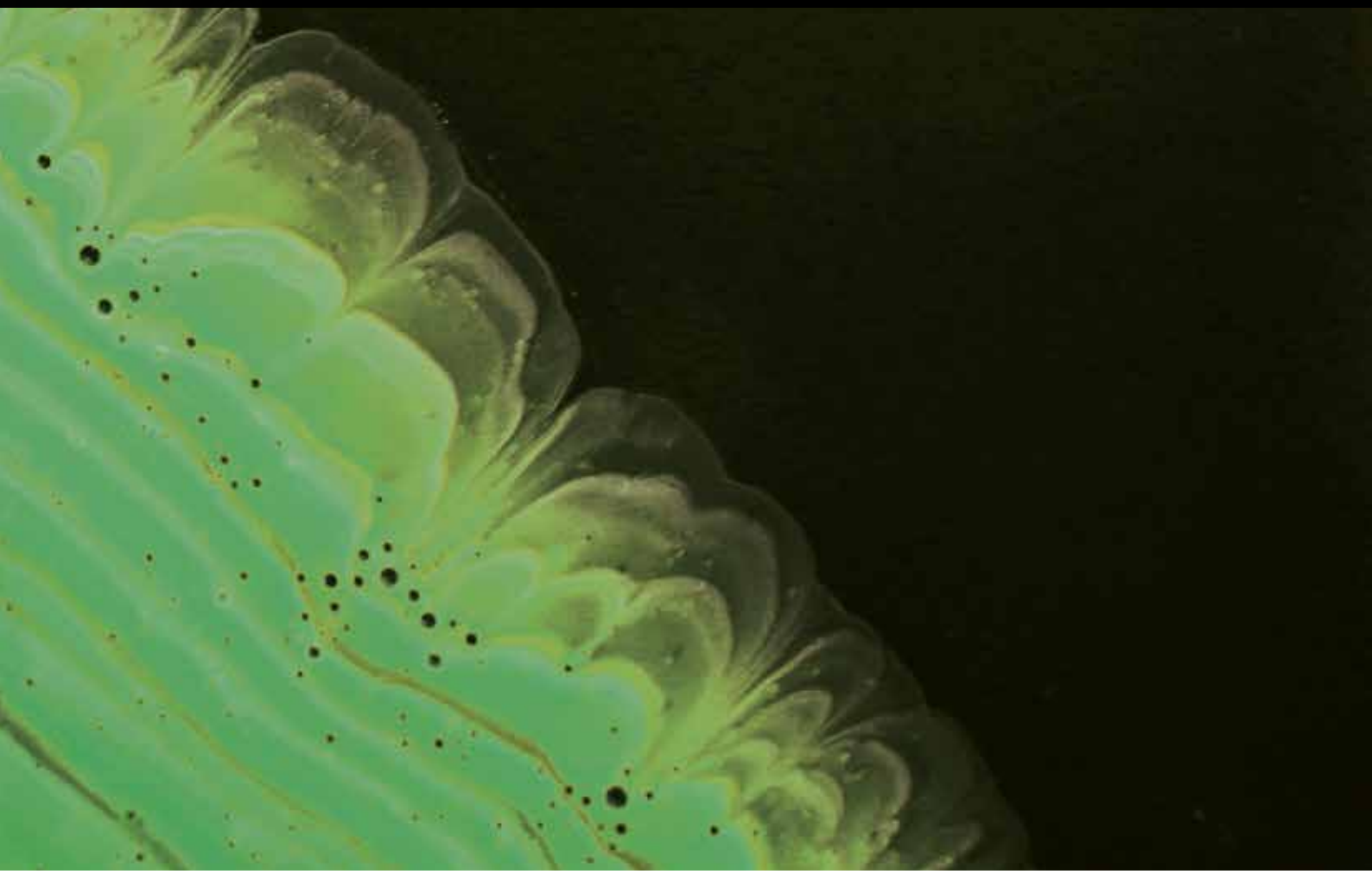
3. Immunology Projects

This strategic funding for the Platform is supporting three immunology-focused projects which collectively are addressing the immunological issues faced by developments in regenerative medicines as defined by the three UKRMP2 Hub themes.

3.1 Professor Ling-Pei Ho (University of Oxford)

3.2 Professor Giovanna Lombardi (King's College London)

3.3 Professor Waseem Qasim (University College London)



3.1 Professor Ling-Pei Ho (University of Oxford)

Alveolar regeneration and tissue resident immune cells

Our programme of studies investigates the contribution of tissue resident immune cells to lung regeneration in chronic disease, focusing on alveolar regeneration in idiopathic pulmonary fibrosis (IPF) (Fig A). IPF is a severe, progressive fibrosing lung disease with limited treatment. Lung transplant affords the only chance of survival beyond 5 years in aggressive or advanced disease. However, scarcity of organs and surgical risks restrict this approach, and increasing efforts are being made in regenerative medicine approaches like endogenous alveolar regeneration. There is evidence that the pathogenesis of IPF is driven by alveolar epithelial cell dysfunction, followed by aberrant regeneration of epithelium. In more advanced disease, a large number of immune cells, not usually found in normal lungs (Fig. B), are found in the interstitium and likely to impact on regeneration. However, it is unclear how they do this. In this programme, we will examine the composition of lung resident immune cells in chronic fibrosis (IPF), determine which lung tissue-resident immune cell(s) (TRICs) influence alveolar epithelial regeneration after injury and define how they exert their effect(s).

Our three Work Packages across Oxford, Newcastle and King's College London will adopt a multi-faceted but cohesive approach to explore our objectives. Across the three centres, we will

(i) map the resident tissue immune cells to regenerating alveolar epithelium in human IPF lung samples to determine the types of TRICs that co-localise to normal and aberrant alveolar regeneration in human lungs (Newcastle-Oxford collaboration. Work Package 1)

(ii) determine the types, frequency, function and signaling pathways of circulating immune cells and TRICs during injury and normal or aberrant (fibrosis) regeneration time points in bleomycin murine model of injury, regeneration and fibrosis (intra-tracheal bleomycin model) (Oxford. Work Package 2)

(iii) test the hypothesis that a subset of regulatory T cells (Jag1+ Tregs) interact with CD103+ dendritic cells via Jag-Notch signalling to enable regeneration of type II alveolar epithelial cells after injury (KCL. Work Package 3).

These studies will complement each other and provide a detailed examination of the immune cell network in the regenerating alveolar niche in human lungs, ex vivo lung models (3D alveolar organoids) and murine models. We will utilize advanced technology including tissue and cell CYTOF, multi-colour high resolution immune-profiling, single-cell RNA sequencing, crispr-Cas9 gene-editing and judicious use of genetically engineered murine models including the high definition confetti-reporter technology for lineage tracking.

"Our programme of studies brings together investigators from Oxford, KCL and Newcastle to focus on the role of immune cells in lung regeneration in chronic disease. There is limited treatment for progressive fibrosing lung disease and regenerative medicine offers a potential new avenue. We are excited to be part of the Hub and look forward to contributing to, and benefiting from, the collaborative network" – Ling-Pei Ho

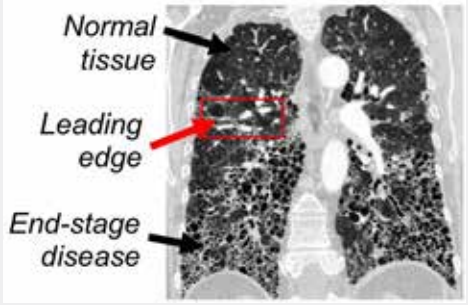


Figure 1: Computerized tomographic image of an IPF lungs showing normal and end stage disease (the latter marked by fibrosis and aberrant regeneration)

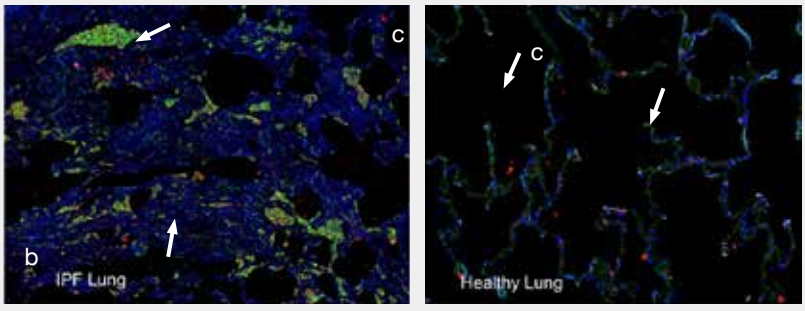


Figure 2: Immunostaining of IPF lungs clusters of CD206+ (green) alveolar macrophages (a), lining metaplastic alveolar epithelium, compared to normal lung. The interstitium is also grossly expanded (b)compared to healthy lungs and contain large numbers of cells (blue DAPI staining). C= normal alveolar space lined by unicell-layered AEC (LPH, Oxford).

3.2 Professor Giovanna Lombardi (King's College London)

The development of 3-dimensional implantable liver organoids

Human embryonic stem cells (hES) and human induced pluripotent stem cells (iPSCs) are cells that have been reprogrammed, by specific molecular signals, to become many different cell types and for this reason they can be used as unlimited renewable source for cell therapy targeted to treat several diseases. Once transplanted in patients, the main challenge is represented by the immune rejection, namely the activation of the innate and adaptive immunity leading to cell loss. To date, the immunogenicity of these products is still not fully understood hence we have focussed on hES-derived dopaminergic cells, hES- and iPSC-derived hepatocytes to develop an immunological platform useful for testing the immunogenicity of different hES and iPSCs products available for cell therapy. Giovanna Lombardi from King's College London and Kourosh Saeb-Parsy from Cambridge University are investigating both in vitro and in vivo immunogenicity of the hES- and iPSC-derived hepatocytes, while Joanne Jones from Cambridge University is studying the hES-Derived dopaminergic cells. We have already developed a common strategy for the in vitro evaluation of the cell products creating a common platform where the standardized protocols and their SOP are shared and available for testing different cell preparation. This includes the evaluation, by flow cytometer, of the main molecules involved in the activation of the adaptive immunity. This panel has been tested with hES-derived hepatocytes and dopaminergic cells. A protocol for testing in vitro the Immunogenicity and the immunoregulatory function of our cells has been developed. This includes co-culture of cell products with allogeneic peripheral blood mononuclear cells (PBMCs).

1) Application of the standardized flow cytometer

We have focussed on the main molecules involved in the activation/inhibition of both CD4+ and CD8+ lymphocytes: HLA-ABC (MHC-I), HLA-G (MHC-I), HLA-DR (MHC-II) and co-stimulatory/co-inhibitory receptors such as CD86, CD80, CD40 and PDL-1. The results obtained (Figure 1) clearly indicate that hES-derived hepatocytes express HLA-ABC while CD86, CD80, CD40, HLA-G, HLA-DR and FAS-L are absent (similar results were obtained with iPS-derived hepatocytes).

2) Immunogenicity and the immunoregulatory function of our cells

hES-derived hepatocytes do not induce cell proliferation and reduce the percentages of TNF-α producing lymphocytes (Figure 2). The percentage of IFN- γ producing T lymphocytes were also reduced while no differences were found in IL17 and IL10 producing cells. When PBMC were induced to proliferate, the presence of hES-derived hepatocytes reduced CD4 and CD8 proliferation and their capacity to produce pro-inflammatory cytokines. The results suggest an immunoregulatory function of the hES-hepatocytes.

"Allogeneic stem cells could provide an 'off the shelf' product for regenerative medicine, however are likely to elicit an immunological response. Advances that we have made in promoting transplantation tolerance may be helpful in overcoming this obstacle and enhancing their clinical utility" – Giovanna Lombardi

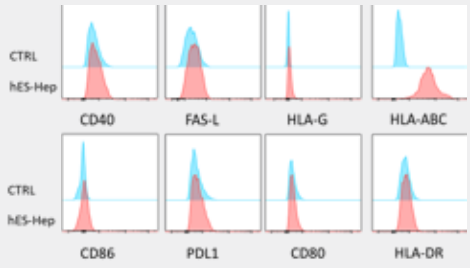


Figure 1: Representative histograms derived from one hES-derived hepatocytes cell line. Cells have been detached and stained using our antibody panel. Analysis has been executed after cell-death exclusion

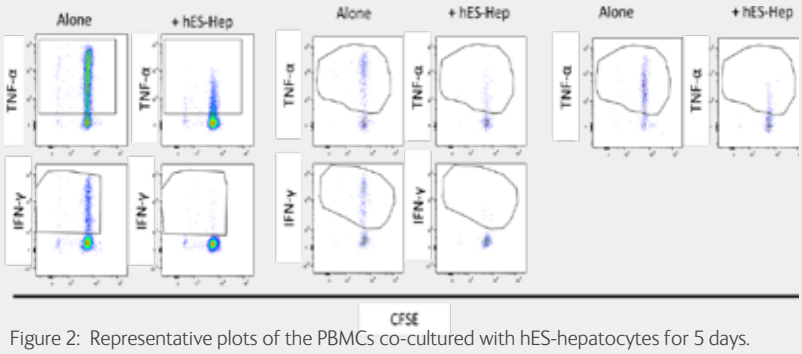


Figure 2: Representative plots of the PBMCs co-cultured with hES-hepatocytes for 5 days. Cytokine producing cells evaluation was executed after stimulation with PMA/Ionomycin for 4hrs.

3.3 Professor Waseem Qasim (University College London)

Universal cells to overcome immunological barriers in regenerative medicine

Universal' human pluripotent stem cell (uHPSC), engineered to avoid HLA mediated recognition and rejection, could open the door to 'off-the-shelf' regenerative therapies. Technologies to precisely target HLA genes are evoloving rapidly, and include CRISPR/Cas9 and base-editors, which are being deployed alongside lentiviral vectors to modify HPSC.

Disruption of HLA class 1 has been achieved at high efficiency by targeting the common β2 microglobulin aspect, but in some downstream applications the protein may be required for effective cell function, and so additional strategies to target specific alpha chain loci are also being tested. Disruption of HLA class II expression has been achieved by disruption of a common transcription factor CIITA. To address the possibility of 'missing-self' immune responses, vectors have been synthesized expressing non-polymorphic HLA class I variants, HLA-G or HLA-E.

Collaborative investigations are underway to develop downstream protocols to differentriate HPSC to macrophage or hepatocyte lineages, and once optimised, suitable parent lines will be subjected to HLA editing procedures and characterised in detail.

"Lessons learnt from using CRISPR/Cas9 to generate universal T cells are now being applied to HPSC. We can remove HLA molecules, the flags that would otherwise trigger immune responses, at high efficiency. The technology is evolving rapidly & new base-conversion genome-editors are already being enlisted, and this should help improve safety and quality" – Waseem Qasim

4. Hub Resources Available to the Community

Building on from UKRMP1, a key aim of UKRMP2 is the development of new tools, reagents and protocols which can be utilised by the wider research community, using shared learning to accelerate progress in the regenerative medicine field. Hub outputs are continually evolving and in addition to the significant number of resources produced through the first phase of the platform, the following are also accessible to external research groups:

4 Hub resources available to the community

Resource	Description	Hub	Contact	Further information
Cell lines	Matched pairs of wild type and genetic variant clonal hPSC cell lines.	PSEC	Ivana Barbaric i.barbaric@sheffield.ac.uk	Cell lines carrying a known genetic variant (or combination of variants) and a normal wild type on the same genetic background.
Tools and Reagents	Human bone marrow stromal cells (HBMSCs) – Skeletal Stem and progenitor cells from OA and OP patients for research	Smart Materials	Prof Richard Oreffo	Disease specific and normal HBMSCs
Tools and Reagents Technology	Synthesis of peptide-modified multi-arm poly-ε-caprolactone.	Smart Materials	Prof Molly Stevens	Custom peptide synthesis and synthesis of peptide-polymer conjugates.
	Mineralising Materials	Smart Materials	Prof Alvaro Mata	Elsharkawy et al, Nature Communications 2018, 9(2145).
	Self-assembling hydrogels	Smart Materials	Prof Alvaro Mata	Redondo-Gomez et al, Biomacromolecules 2019, 20(6), 2276-2285
	Multi-zonal scaffold production	Smart Materials	Prof Molly Stevens	Electrospinning, porogen leaching, and directional freezing.
	Targeted delivery and controlled release microparticles	Smart Materials	Dr Lisa White	Galactosylated polymers, triblock co-polymers and microparticle fabrication
Technology	Quantification and analysis of protein secondary structure	Smart Materials	Prof Alvaro Mata	Elsharkawy et al, Nature Communications 2018, 9(2145).
	Molecular patterning inside hydrogels	Smart Materials	Prof Alvaro Mata	Aguilar et al, Advanced Functional Materials 2018, 28(15).
	3D printing with self-assembling bioinks	Smart Materials	Prof Alvaro Mata	Hedegaard et al, Advanced Functional Materials 2018, 28(16).
Equipment	Custom Formlabs Form 2 SLA Printer	Smart Materials	Prof Molly Stevens	Formlabs Form 2 printer has been modified to print custom resins. https://formlabs.com/3d-printers/form-2/
	Centre for Additive Manufacturing	Smart Materials	Prof Ricky Wildman	This has been tailored for MSK work untaken in the Hub. https://www.nottingham.ac.uk/

5. Annexes

Annex 1

Annex 2

Annex 3

Annex 4

Annex 1

UKRMP Governance

- Dr Rob Buckle - Chief Science Officer, MRC
- Professor Paul Moss - Chair UKRMP Programme Board
- Dr Philippa Hemmings - Head of Healthcare Technologies, EPSRC
- Professor Melanie Welham - Chief Executive, BBSRC

Programme Board

- Professor Paul Moss (Chair) - University of Birmingham, 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 – previously director of Cell Medica
- Professor Jöns Hilborn - Uppsala University, Sweden
- Dr Bo Kara - Evox Therapeutics
- Professor Dr Petra Reinke - Berlin-Brandenburg Centre for Regenerative Therapies, Germany
- Professor Anne Rosser - Cardiff University, UK
- Assoc Professor Louise van der Weerd - Leiden University, The Netherlands
- Professor Christine Mummery – Leiden University, The Netherlands
- Professor Gerry Graham – University of Glasgow, UK

Annex 2

UKRMP – Hub awards

- Professor Roger Barker, University of Cambridge
  The Pluripotent Stem Cells and Engineered Cell (PSEC) Hub - £4.1M

- Professor Stuart Forbes, University of Edinburgh
  The Engineered Cell Environment Hub - £4.1M

- Professor Molly Stevens, Imperial College London
  Acellular / Smart Materials – 3D Architecture Hub - £4.1M

UKRMP – Immunology awards

- lProfessor Ling-Pei Ho, University of Oxford
  Defining the role of tissue-resident immune cells in alveolar epithelial cell regeneration - £887k

- Professor Giovanna Lombardi, Kings College London
  Immunogenicity test platform - in vitro and in vivo - £926k

- Professor Waseem Qasim, University College London
  Universal cells to overcome HLA barriers in regenerative medicine - £836k

UKRMP – Strategic awards

- Dr Rocio Sancho, Kings College London
  PEG-based hydrogels for iPSCs-derived regenerative therapies for diabetes - £414k (co-funded with JDRF)

- Professor Hazel Screen, Queen Mary University of London
  MICA: Organ-on-a-chip models for safety testing of regenerative medicine products - £505k

- Professor Anna Williams, University of Edinburgh
  Do adult human oligodendrocytes remyelinate poorly and can we change this to better treat progressive multiple sclerosis? - £519k (co-funded with MS Society)

- Professor Sarah Waters, University of Oxford
  MICA: Exploiting in silico modelling to address the translational bottleneck in regenerative medicine safety - £609k

Annex 3

UKRMP Hub research teams

PSEC Hub

- Professor Roger Barker, University of Cambridge
- Dr Cedric Ghevaert, University of Cambridge
- Dr Florian Merkle, University of Cambridge
- Dr Serena Nik-Zainal, University of Cambridge
- Dr Ivana Barbaric, University of Sheffield
- Dr Marta Milo, University of Sheffield
- Professor Robert Thomas, Loughborough University
- Professor Wolf Reik, Babraham Institute, Cambridge
- Dr Maria Rostovskaya, Babraham Institute
- Dr Hanif Ghanbar, Loughborough University
- Dr Preeti Holland, Loughborough University
- Dr Moyra Lawrence, University of Cambridge
- Dr Venkat Pisupati, University of Cambridge
- Dr Christopher Price, University of Sheffield
- Dr Dylan Stavish, University of Sheffield
- Mr Duncan Baker, University of Sheffield/ Sheffield Children's NHS Foundation Trust

ECE Hub

- Professor Neil Carragher, University of Edinburgh
- Dr Elaine Emmerson, University of Edinburgh
- Professor Stuart J Forbes, University of Edinburgh
- Professor David Hay University of Edinburgh
- Dr Mark Birch, University of Cambridge
- Dr Kevin Chalut, University of Cambridge
- Professor Robin Franklin, University of Cambridge
- Professor Andrew McCaskie, University of Cambridge
- Professor Alicia El Haj, University of Birmingham
- Dr Shukry Habib, King's College London
- Professor Fiona Watt, King's College London
- Dr Rob Hynds, University College London
- Professor Sam Janes, University College London
- Dr Marko Nikolic University College London
- Dr Josephine Barnes, University College London,
- Dr Francesca Beaton, University of Cambridge
- Dr Nejma Belaadi, University of Cambridge
- Ms Tjasa Bensa, King's College London
- Dr Nicola Foster, University of Birmingham
- Dr Victoria Gadd, University of Edinburgh
- Dr Kyren Lazarus, University College London
- Mr Ian Smith, University of Edinburgh
- Mr Joshua Reeves, King's College London

Smart Materials Hub

- Imperial College London, Molly Stevens, Jonathan Jeffers
- University of Nottingham, Kevin Shakesheff, Felicity Rose, Lisa White, Ricky Wildman
- University of Edinburgh, Stuart Forbes, Mark Bradley
- University of Glasgow, Manuel Salmeron-Sanchez
- University of Manchester, Alberto Saiani
- Queen Mary University of London, Alvaro Mata
- University College London, Robin Ali
- University of Liverpool, Rachel Williams
- University of Oxford, Andrew Carr
- University of Southampton, Richard Oreffo, Nicholas Evans, Jon Dawson
- Dr. Liang He, University of Liverpool
- Dr. Jonathan Wojciechowski, Imperial College London
- Dr. Axel Moore, Imperial College London
- Dr. James Armstrong, Imperial College London
- Dr. Marco Cantini, University of Glasgow
- Dr. Peter Childs, University of Glasgow
- Dr. Robert Owen, University of Nottingham
- Dr. I-Ning Lee, University of Nottingham
- Dr. Karen Marshall, University of Southampton
- Dr. Pierre-Alexis Mouthuy, University of Oxford
- Dr. Sarah Snelling, University of Oxford
- Dr. Emma West, University College London
- Dr Abshar Hasan, QMUL
- Eliana Lingard, University of Manchester
- Nischal Rai, University of Manchester
- Raya El Laham, Imperial College London
- Julia Wells, University of Southampton

Annex 4

Hub Publications since previous report

2019

- *Rapid PCR Assay for Detecting Common Genetic Variants Arising in Human Pluripotent Stem Cell Cultures*. Laing O, Halliwell J, Barbaric I. 2019 Current Protocols Stem Cell Biology. 49(1):e83. doi: 10.1002/cpsc.83

- *The cell in the ink: Improving biofabrication by printing stem cells for skeletal regenerative medicine*. Cidonio G, Glinka M, Dawson JI, Oreffo ROC. Biomaterials, 2019. doi.org/10.1016/j.biomaterials.2019.04.009

- *Immunogold FIB SEM: Combining Volumetric Ultrastructure Visualization with 3D Biomolecular Analysis to Dissect Cell–Environment Interactions*. Gopal S, Chiappini C, Armstrong JPK, Chen Q, Serio A, Hsu C-C, Meinert C, Klein TJ, Hutmacher D, Rothery S, Stevens MM. Advanced Materials, 2019. doi.org/10.1002/adma.201900488

- *Osteogenic and angiogenic tissue formation in high fidelity nanocomposite Laponite-gelatin bioinks*. Cidonio G, Alcala-Orozco CR, Lim KS, Glinka M, Mutreja I, Kim YH, Dawson JI, Woodfield TBF, Oreffo ROC. Biofabrication, 2019. doi. org/10.1088/1758-5090/ab19fd

- *Printing bone in a gel: using nanocomposite bioink to print functionalised bone scaffolds* G. Cidonio, M. Cooke, M. Glinka, J.I. Dawson, L. Grover, R.O.C. Oreffo.. Materials Today Bio. doi: 10.1016/j.mtbio.2019.100028

- *The design and in vivo testing of a locally stiffness-matched porous scaffold*. Ghouse S, Reznikov N, Boughton OR, Babu S, Ng KCG, Blunn G, Cobb JP, Stevens MM, Jeffers JRT, Applied Materials Today, 2019. doi: 10.1016/j.apmt.2019.02.017

- *3D gelatin-chitosan hybrid hydrogels combined with human platelet lysate highly support human mesenchymal stem cell proliferation and osteogenic differentiation*. Re F, Sartore L, Moulisova V, Cantini M, Almici C, Bianchetti A, Russo D. Journal of Tissue Engineering, 2019. doi: 10.1177/2041731419845852

- *Individual response variations in scaffold-guided bone regeneration are determined by independent strain- and injury-induced mechanisms*. Reznikov N, Boughton O, Shaaz Ghouse AE, Weston, Collinson L, Blunn G W, Jeffers JRT, Cobb J, Stevens MM. Biomaterials, 2019. doi. 10.1016/j.biomaterials.2018.11.026

- *Residue-Specific Solvation-Directed Thermodynamic and Kinetic Control over Peptide Self- Assembly with 1D/2D Structure Selection*. Lin Y, Penna M, Thomas MR, Wojciechowski JP, Leonardo V, Wang Y, Pashuck ET, Yarovsky I, Stevens MM. ACS NANO, 2019. doi. 10.1021/acsnano.8b08117

- *Spatiotemporal quantification of acoustic cell patterning using Voronoi tessellation*. Armstrong JPK, Maynard SA, Pence IJ, Franklin AC, Drinkwater BW, Stevens MM. Lab on a Chip, 2019. doi.10.1039/C8LC01108G

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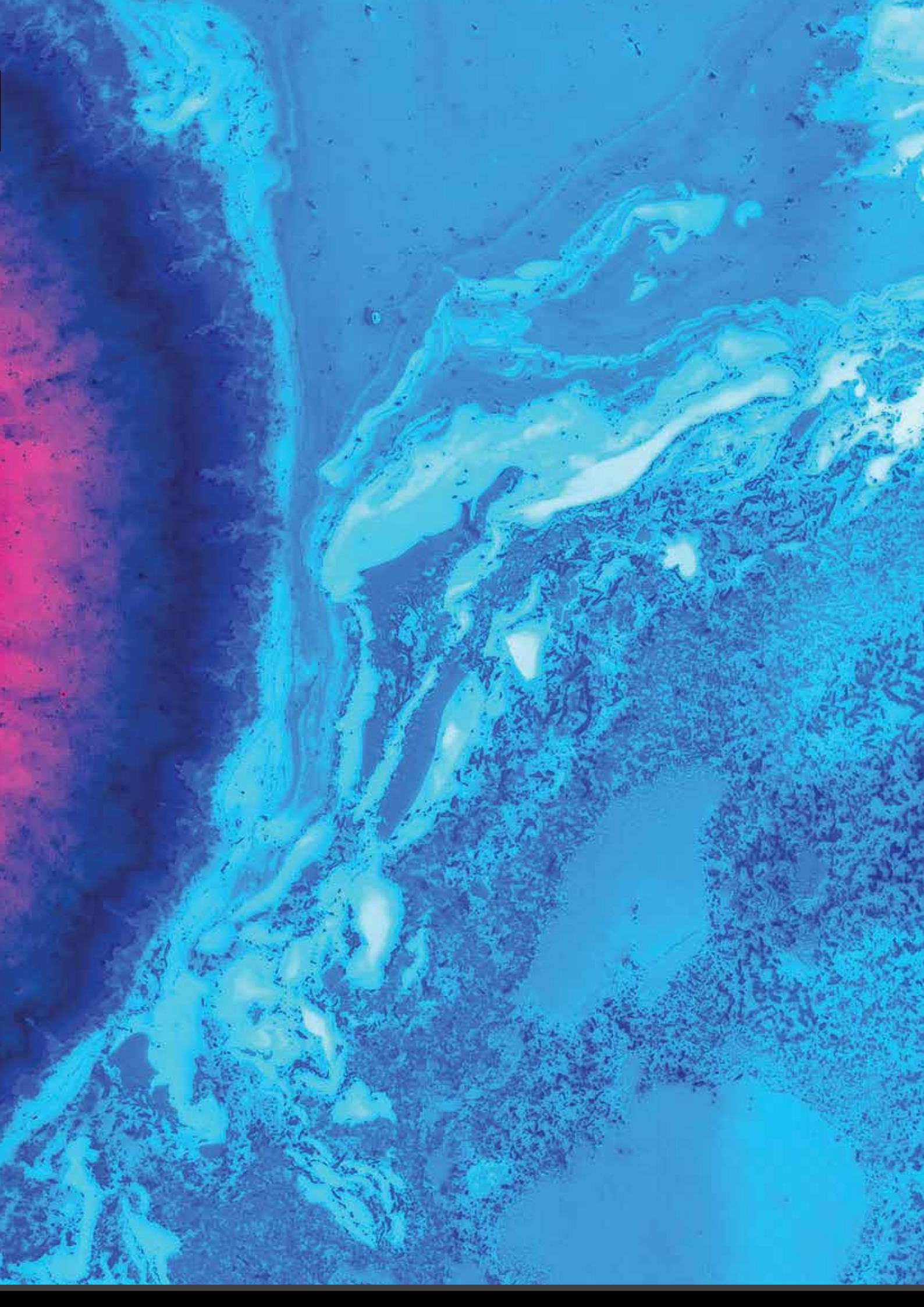

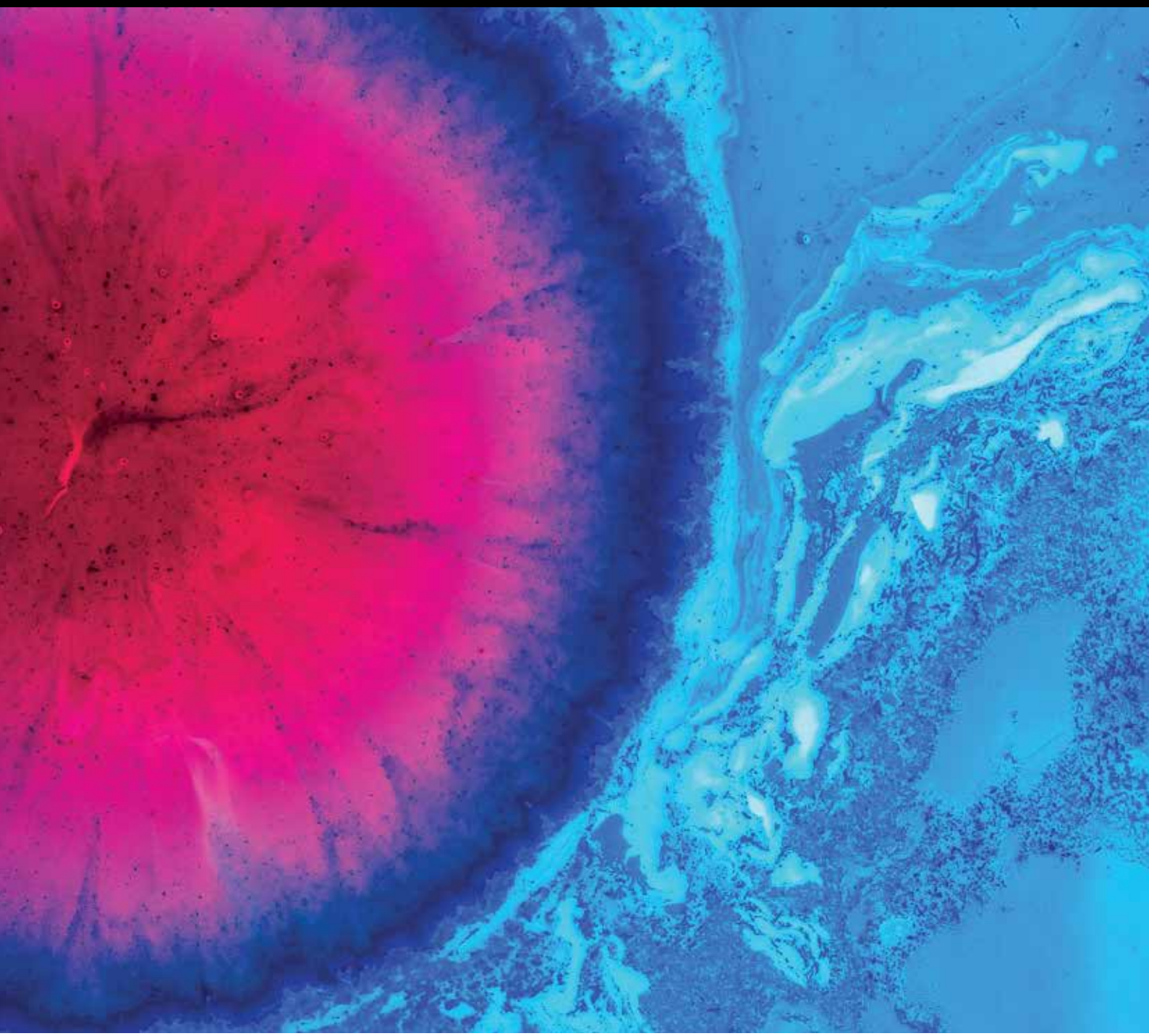

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