Engineering and Physical Sciences Research Council

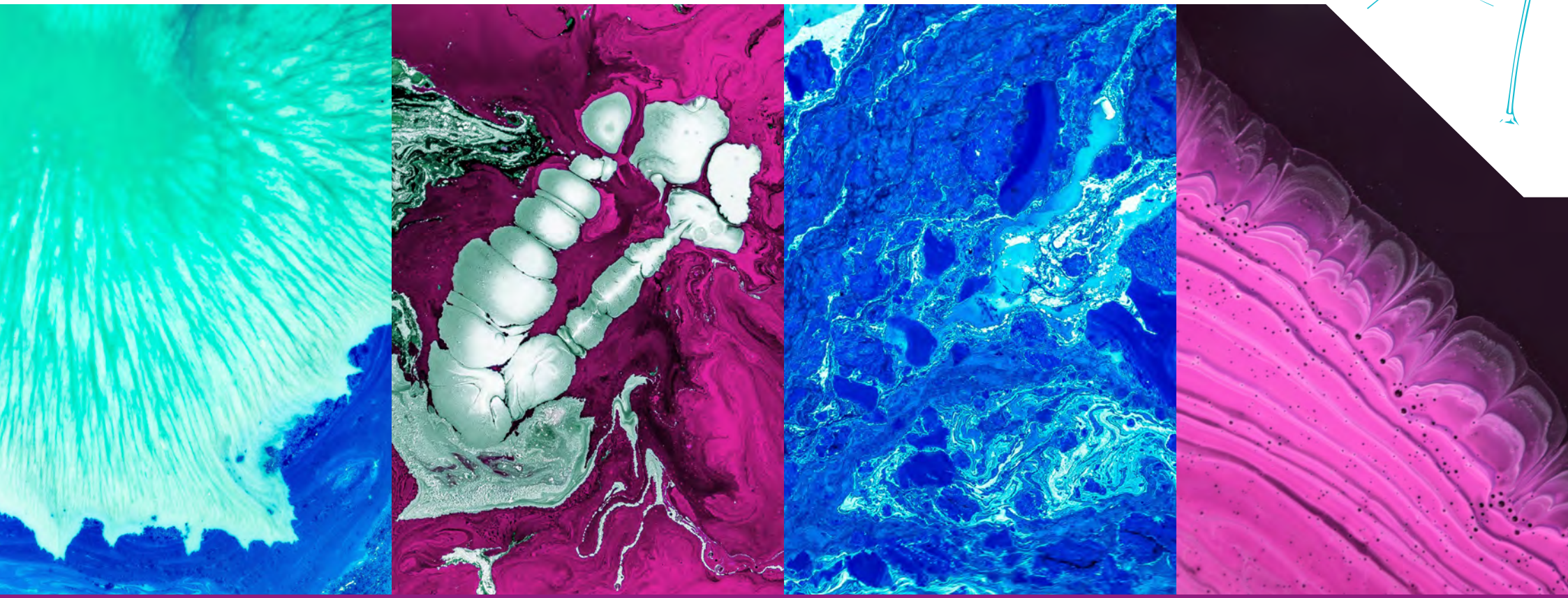
Biotechnology and Biological Sciences Research Council

Medical Research Council

UK Regenerative Medicine Platform

Annual Report

2021



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1. Introduction

Dr Rob Buckle,
Chief Science Officer,
Medical Research Council

The UK Regenerative Medicine Platform (UKRMP) is a £42m national initiative that brings together leading researchers from across 17 different universities to address the key translational challenges in regenerative medicine. Established in 2013 by the UK Research and Innovation's (UKRI) Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council (MRC), the UKRMP is now in its second phase, which began in in 2018.

The mission of the UKRMP is to overcome hurdles in bringing innovative regenerative medicine therapies to patients. This includes developing streamlined approaches for the manufacture of human pluripotent stem cells (hPSCs), 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*.

It has been two years since the previous report was published, and like the rest of the research community, the UKRMP has had to overcome major challenges posed by the coronavirus pandemic. Despite this, the Platform has continued to deliver exciting developments in the field of regenerative medicine and taken significant steps in progressing novel technologies towards the clinic. Now three years into Phase 2, this 2021 annual report showcases the scientific achievements of the Platform during this period.

Hub Highlights

Within the Pluripotent Stem Cells and Engineered Cells (PSEC) Hub, the Ghevaert group have been systematically optimising the process for genome editing of hPSCs which has led to collaborations with academics, industry and government organisations, including work on COVID19. The Barker group are developing a platform for testing the immunogenicity of human embryonic stem cell-derived dopaminergic neurons. This work feeds directly into a planned first-in-human clinical trial for the treatment of Parkinson's disease.

Researchers within the Engineered Cell Environment (ECE) Hub have shown that adult liver stem cells can produce functioning hepatocytes that can be expanded in the lab, as well as developing stem-cell derived hepatocytes that potentially provide an unlimited and off-the-shelf supply, innovations that may overcome the barriers that are currently preventing the use of cell therapies as an alternative to liver transplant. The Hub has also made advances in developing fluid gels containing stem cells and chemical cues to aid repair in cartilage disorders.

The Smart Materials Hub is developing a wide range of potential biomaterials for use throughout the musculoskeletal system. For example, Dr Jon Dawson is working on developing injectable nanoclay gels to activate stem cells for bone regeneration. Results from characterisation studies are being used to support a submission to regulatory agencies to trial this technology in patients, and the Oreffo Group are now working with researchers in Japan on a collaborative project to explore the early immune response to nanoclays as a springboard for bone repair processes.

Immunology and Strategic Projects

During the Platform's second phase, cross-cutting programmes have been introduced that expand upon key aspects of the science being progressed through the Hubs. These include safety, immunology and manufacturing – themes with broad relevance and potential for impact both across the Platform and the wider research community. Through these projects, UKRMP researchers are establishing 'universal' stem cells through gene editing and developing a test platform for examining the immunogenicity of hPSCs.

In 2019, a further call was launched by UKRI to bring new researchers into the platform, and to help address translational bottlenecks in regenerative medicine. Four research projects were supported, two of which were co-funded with the Juvenile Diabetes Research Foundation (JDRF) and the Multiple Sclerosis (MS) Society. Researchers working on these projects are developing hydrogels to deliver stem cells to diabetic patients, creating organ-on-a-chip models for pre-clinical safety testing of regenerative medicine technologies, investigating ways to improve the effect of drugs for multiple sclerosis, and developing mathematical models of stem cell therapies. The establishment of new projects like these continues to foster collaboration within and beyond UKRMP, focusing on translating regenerative medicine therapeutic approaches and technologies to the clinic.

Partnerships

The UKRMP aims to fully utilise the expertise within the Platform to tackle the key challenges facing the regenerative medicine field by developing networking activities and collaborations. The Platform continues to support and integrate with the wider regenerative medicine field by working with other key organisations including the Cell and Gene Therapy Catapult, Defence Science and Technology Laboratory, and regulators to ensure that we generate transformative and sustainable developments in regenerative medicine. In 2021, the Platform began fostering links with the Stem Cell Network in Canada and is developing an international seminar series and researcher exchange programme, to be launched in 2022.

2021 Regenerative Medicine Conference

Despite the move to working in a virtual environment, the Platform has continued to engage with the wider academic community to highlight advances in the regenerative medicine field. In September, the UKRMP hosted its second Regenerative Medicine Conference. The two-day virtual event centred around the themes of the UKRMP Hubs and hosted internationally-recognised keynote speakers, while early-career researchers from within the UKRMP delivered 'flash' presentations to showcase the breadth of the research undertaken across the Platform. Expert panels spanning industry and academia led open discussions on the emerging areas in regenerative medicine and the ingredients needed to successfully translate regenerative medicine technologies to the clinic while an adjoined Special Focus Day explored how the engineering and physical sciences can help to solve a wide variety of challenges in regenerative medicine[1].

Looking forward

Investment in the second phase of UKRMP will continue to support high-risk, innovative, and interdisciplinary programmes. Researchers continue to work with regulators at an early stage in therapy development to ensure that the translational potential of a technology is maximised, and the right data is collected to support translation towards the clinic. Investigators across the UKRMP are successfully obtaining further funding to translate research findings and continue the development of technologies initiated through the Platform. For example, researchers in the Smart Materials Hub have recently been awarded an MRC grant for preclinical testing of a novel material used to treat disease of the cornea.

The collaborations established through UKRMP2 have ensured real progress has been made against each Hub's aims while investment in cross-cutting projects has attracted new expertise into the Platform from academics, clinicians and industry. We look forward to seeing these collaborations underpin the much-anticipated transformative impact of regenerative medicine on human health in the future.

1 For more information go to https://www.ukrmp.org.uk/regenerative-medicine-and-advanced-therapeutics-virtual-conference/

"Promoting stem cell research and regenerative medicine is a priority for the MRC and has been ever since the field first emerged. The UKRMP supports high quality research that will generate scientific knowledge and help deliver the great promise of regenerative medicine to the benefit of patients."

Professor Fiona Watt, Former MRC Executive Chair

Remembering Professor Kevin Park 1951-2022

Professor Kevin Park was Director of the UKRMP1 Safety Hub at the University of Liverpool, where he was instrumental in bringing pharmacological approaches to regenerative medicine in the pursuit of safe and effective regenerative therapies. In doing so he was a model for the collaborative and interdisciplinary ethos that the UKRMP has been working to create. During his notable career which spanned nearly 50 years, Kevin worked across clinical and basic pharmacology and toxicology, and medicinal chemistry, and his contribution to improving drug safety both nationally and internationally benefitted individual patients, public health, Government policy and the pharmaceutical industry. Not only were his research contributions extensive, with over 700 publications in top journals and multiple prestigious prizes and awards, Kevin also supervised 135 PhD students over his career, many of whom now hold Professorial or senior industry positions themselves.

2. UKRMP2 Hub Updates

2.1 Pluripotent Stem Cell and Engineered Cell (PSEC) Hub

Director: Professor Roger Barker, *University of Cambridge*
Deputy Director: Professor Cedric Ghevaert, *University of Cambridge*
Partner Institutions: *The Babraham Institute, Loughborough University and the University of Sheffield*

The PSEC executive management team consists of its Director Professor Roger Barker (University of Cambridge) and its Project Manager Dr Zoe Hewitt (University of Sheffield) and includes representatives from each of the partnering institutions, who also lead the three research programme themes. Theme 1, our largest workstream, is led by Dr Ivana Barbaric (University of Sheffield) with Professor Wolf Reik (Babraham Institute) acting as deputy, Theme 2 is led by Professor Robert Thomas (Loughborough University) and Theme 3 by Professor Cedric Ghevaert (University of Cambridge), who is also the Deputy Director.

The overarching aim of the hub is to **facilitate and deliver a platform of technologies and expertise for translating any new human pluripotent stem cell (hPSC) based therapy to the clinic.**

To contextualise our research, we have used two clinical exemplars that sit at different stages along the therapeutic pipeline: hPSC-derived dopaminergic (DA) neurons for the treatment of Parkinson's disease and hPSC-derived megakaryocytes (MK) for the treatment of thrombocytopenia. We have recently expanded these exemplars to include hPSC-derived macrophages, enteric neurons and cardiomyocytes through linked projects and continue to seek out other opportunities to broaden these clinical exemplars further.

The three themes of our research programme each have specific aims which also crosslink to enhance our progress and impact for the field (Figure 1). These aims are:

(1) To define and understand the biological significance of commonly acquired (epi)genetic changes in hPSCs as a result of culturing and/or manipulation while also elucidating the implications of recurrent (epi)genetic changes for the therapeutic use of hPSC-derived products.

(2) To develop predictive models for hPSC (and genetically modified hPSC) -based therapeutic process design and control to enable optimal and defined risk manufacture, including a pathway for regulatory integration, to facilitate clinical application and first in human studies.

(3) To develop a translational pipeline, including quality control criteria, for the process of genome editing of hPSCs considering efficiency and consistency, off-target effects and emergence/ selection for genetic abnormalities as a means to improve hPSC differentiation and reduce their immunogenicity.

Key Scientific Contributions

Since PSEC began in June 2018, we have made a number of significant contributions to the Regenerative Medicine field:

- In order to understand which genetically variant cells pose a potential risk for cell therapy, the **Barbaric group** have first produced an updated catalogue of major genetic changes detected in hPSC cultures. Apart from confirming the previously reported recurrent nature of karyotypic abnormalities in hPSCs, this analysis revealed an emergence in prevalence of a couple of specific recurrent variants. This analysis provided an insight into aberrations that are most common in expanding hPSC cultures and allowed us to focus our research on designing improved strategies for their reliable detection and for minimising their occurrence. This work also produced a new partnership with WiCell.

Figure 1: PSEC infographic depicting the internal and wider UKRMP interactions

- To identify strategies for minimising the occurrence of common variants, the **Barbaric group** have analysed how the presence of recurrent genetic changes affects the behaviour of hPSCs under different culture conditions.
- Additionally, the **Barbaric group** have identified culture conditions that favour the emergence of particular variants, thus providing critical information for future cell expansion protocols. Importantly, their work has uncovered, for the first time, that the presence of variant cells has detrimental effects on neighbouring normal cells in culture (Figure 2). By identifying a molecular mechanism of such competitive interactions, they were able to devise new culture conditions to minimise the dominance of recurrent variants in expanding hPSC cultures.
- As an alternative approach to assessing critical genetic variants, the **Merkle group** have developed a method of using large mixed pools of tagged cell lines to look at competitive differences across many cell lines at the same time instead of screening individual cell lines.
- The **Reik group** has identified recurrent epi-mutations within hPSCs cultures and is now exploring how these may link with genetic variants and the selective advantages that we have identified.
- Within our manufacturing theme, the **Thomas group** have developed a statistical clustering analysis tool to identify data driven target populations, from within process data. This work allows for the identification of early predictors of manufacturing process control through correlations with critical quality attributes in end-product target profiles and has attracted significant interest from industry as it has the potential to greatly reduce the time needed to develop optimal culture conditions for any hPSC derived product.

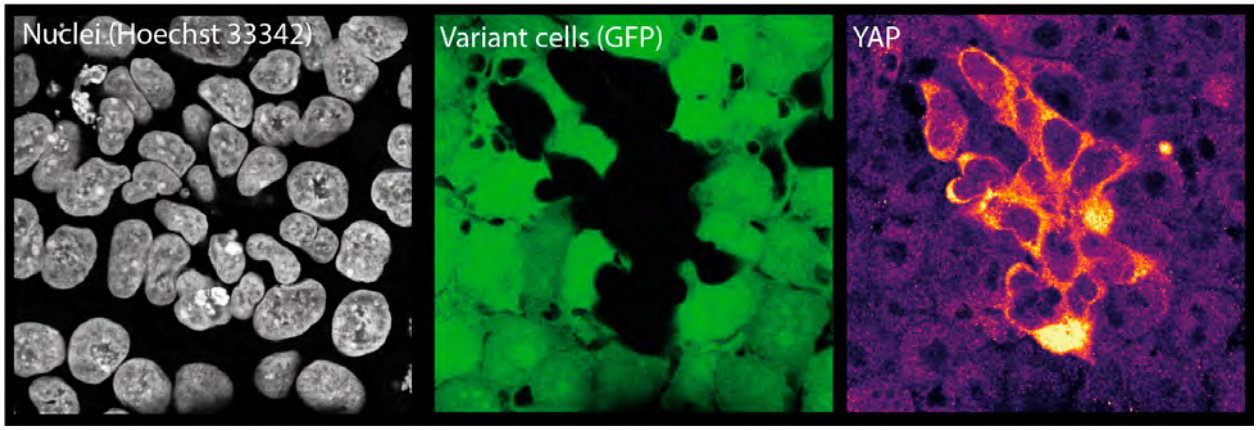


Figure 2: Wild-type human pluripotent stem cells are corralled by their genetically variant (green) counterparts into areas of high density. The corralling causes YAP (a protein involved in the regulation of proliferation and apoptosis) in wild-type cells to move from the nucleus to the cytoplasm (and subsequently lead to its loss through apoptosis), whereas the variant hPSCs are unaffected and maintain YAP in their nuclei (promoting proliferation).

"It is truly exciting to see how the work we do within the UKRMP PSEC Hub has now reached out to many other disciplines in a bid to answer some of the key questions that will need to be solved for hPSCs to be used routinely in the clinic. This includes engineers, mathematicians and computer scientists, and has shown just how powerful the approach can be if one looks to solve problems using a cross-disciplinary strategy."

Professor Roger Barker, Director of the Pluripotent Stem Cell and Engineered Cell Hub

- The **Ghevaert group** have been systematically optimising the process for genome editing of hPSCs (both knocking-in and knocking-out gene targets of interest) which has led to collaborations with academics, industry and government organisations, including work on COVID19.
- The **Barker group** have started to develop a platform for testing the immunogenicity of hESC-derived dopaminergic neurons, in conjunction with the 'humanised mouse' immunology project and have shown that such DA precursors behave similarly to their human foetal counterparts. This work feeds directly into a planned first in human clinical trial for the treatment of Parkinson's disease.

Networking Activities and Partner Projects

We have undertaken a number of activities to broaden our network and support the wider UK Regenerative Medicine field. This includes working with the British Pharmacological Society on the safety of stem cell-derived therapies and the Cell and Gene Therapy Catapult to address issues relating to IP and freedom to operate.

Working with facilitators from the Commercialisation and Impact Team at the University of Sheffield, we have explored the future directions and interactions for our hub with industry. This resulted in our participation in the Innovate UK Lean Launch Programme in May 2021, through which we have undertaken a market discovery journey for our services. Engaging, again collaboratively across the UKRMP network, with industrial partners and academic groups who are considering development of cell-based therapies. We have a number of ongoing dialogues, but are always keen to hold more.

The PSEC Hub has established several partnerships since 2018. Venkat Pisupati (PDRA, Barker lab) and University College London were awarded a pump-priming grant to use hPSC-derived neuronal progenitors with novel biomaterials to enable mathematical modelling of cell viability and oxidative stress. The Ghevaert lab has developed a partnership with the Ministry of Defence Science and Technology Laboratory, involving the Cell and Gene Therapy Catapult, and have a project to specifically translate the hPSC-derived MK protocol to clinic. The Ghevaert lab has also recently partnered with BHF Cambridge Cardiovascular Centre to secure funding to help with the COVID19 pandemic. Through this project, the optimised procedures developed in PSEC have been applied to a real-world situation. iPSCs were edited with specific knock-outs for candidate binding sites of SARS-CoV-2 found on the surface of platelets and megakaryocytes. The Ghevaert lab has also hosted an AstraZeneca visiting R&D scientist to work on developing HLA negative stem cells for wider clinical application.

The Thomas lab have partnered via Advanced Bioprocess Services with the Uniformed Services University and Geneva Foundation (USA) in a project looking at 'on-demand blood' which has supported a studentship looking at hPSC manufacturing modelling. The Barbaric Lab has established collaborative projects with WiCell, Broken String Biosciences, AstraZeneca, Albumedix, STEMCELL Technologies and Monash University to further establish and understand the mechanisms involved in genetic stability of hPSCs. The Barker lab is now working with Novo Nordisk on their planned hESC-derived dopamine cell trial in Parkinson's disease, due to start in 2022 in the UK.

Future Directions

As a network of academic experts from across the UK, spanning fundamental science through cell selection, manufacture and clinical trial design, with real-world experience of translating hPSC-derived cell therapies to the clinic, we believe that PSEC has a unique value proposition which will benefit the wider regenerative medicine community. With this in mind, we have recently taken part in the Innovate UK Lean Launch programme, and with the support of a Business Mentor, PSEC is gathering information from the market as to whether our skills can provide a valuable service to the community. Initial feedback indicates both a need and a desire for these services and therefore we are actively pursuing this moving forward.

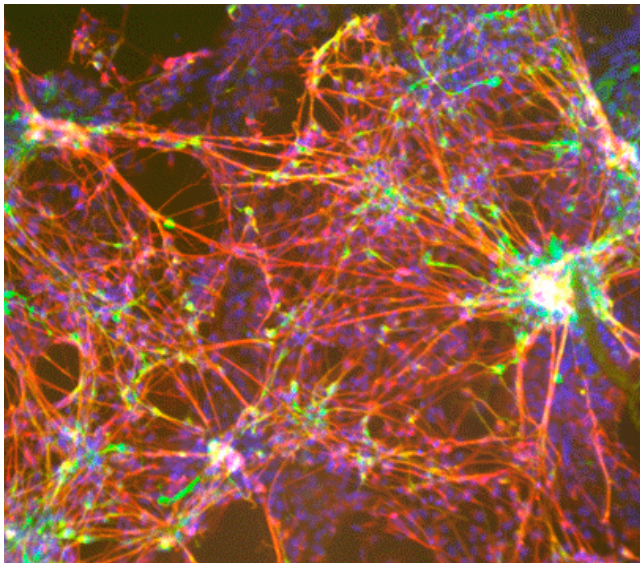
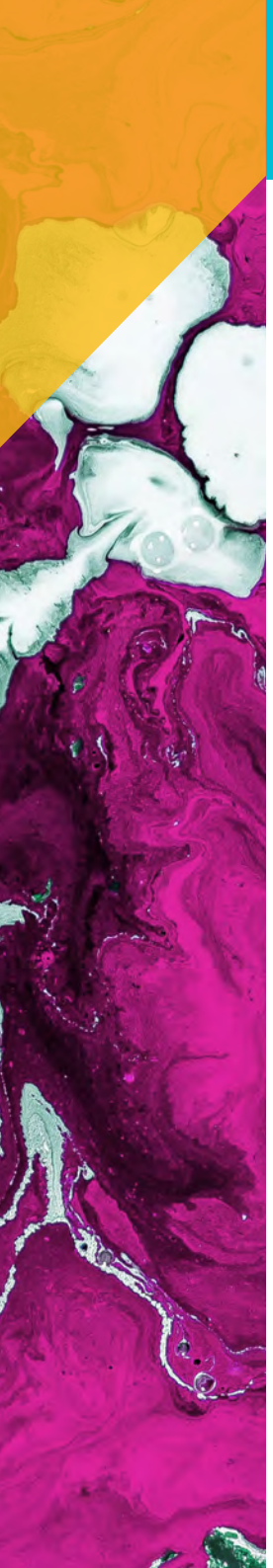


Figure 3: Human pluripotent stem cells (RC17) differentiated and matured to dopaminergic neurons, tyrosine hydroxylase (TH, green) β-tubulin (red), a pan-neuronal marker, DAPI staining nucleus (blue).



Pluripotent Stem Cell and Engineered Cell Hub case studies

Universal platelets for patients with rare blood groups

Patients with rare blood groups often struggle to find compatible platelets and other blood products when they need a transfusion. Universal platelets, which do not require being matched for blood type or Rhesus factor, could be a lifechanging solution to this problem.

Dr Cedric Ghevaert and Dr Moyra Lawrence at the University of Cambridge are working on reprogramming stem cells to generate universal platelets for use in transfusions. Platelets are responsible for clotting, and every year 280,000 platelet units are transfused in the UK into patients after trauma, surgery, cancer treatment or inherited bone marrow failure. Platelets are usually obtained from blood donations, so it can be tricky to find compatible matches for patients with rare blood groups. Platelets also have a short shelf-life, i.e. they can only be kept for 5-7 days at room temperature, so that at times of reduced donor availability, shortages can occur.

The team has already pioneered a system for generating a 'master cell' called a megakaryocyte from human induced pluripotent stem cells (iPSCs). Megakaryocytes are responsible for producing hundreds of millions of platelets every day, so this was the first step towards generating universal platelets in the lab. The team then used gene editing tools to develop a protocol to consistently make high-quality platelets from these megakaryocytes. Next, to convert this process from a laboratory experiment to a manufacturing process, the team transitioned from using lab-grade reagents to reagents compatible with large scale manufacturing, called GMP-compatible reagents. Good Manufacturing Process (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards.

This key step is crucial for accelerating progress into the clinic, so that universal platelets can be tested in clinical trials. These protocols and methods can also help other scientists working on making other products from stem cells. Being a part of the Pluripotent Stem Cell and Engineered Cell (PSEC) Hub of UKRMP allowed Dr Lawrence to work closely with a range of interdisciplinary experts, speeding up the dissemination of knowledge and best practice in the rapidly evolving field of regenerative medicine[1].

Reference: 1. Lawrence et al. (2021), npj Regen Med 6, 27.
https://doi.org/10.1038/s41536-021-00138-y

Survival of the fittest stem cells: new insights for stem cell culture

Studying how stem cell populations behave in prolonged culture conditions has led to new insights into a previously unexplained phenomenon. This advance in knowledge can help design strategies to minimize the negative effects of mutant stem cells and improve current protocols for expanding populations of stem cells for research and clinical applications.

Dr Ivana Barbaric and Dr Chris Price at the University of Sheffield are studying how populations of stem cells gain different mutations when grown in cell culture for prolonged periods of time. These mutations can eventually give some stem cells a fitness advantage so they can outcompete and kill the normal stem cells in the population. Understanding how this happens can help researchers develop strategies to minimize the damage, so that stem cells can be grown for clinical use in regenerative medicine.

The team has shown for the first time that mutant human pluripotent stem cells (hPSCs) become dominant in a stem cell culture population through competitive interactions that eventually eliminate the normal stem cells. This elimination happens when the mutant stem cells push and squeeze the normal stem cells, causing a redistribution of a key protein called YAP which then induces the normal stem cells to activate programmed cell death, or apoptosis. Manipulating the levels of YAP in cell culture can then shift the balance of power, removing the advantage from the mutant stem cells. Dr Price has used this insight to design cell culture conditions that reduce stem cell competition and provide a platform for optimizing ways to grow hPSCs safely for research and clinical applications[2].

Reference: 2. Price et al. (2021), Developmental Cell.
https://doi.org/10.1016/j.devcel.2021.07.019

2.2 Smart Materials Hub

Director: Professor Molly Stevens, *Imperial College London*
Deputy Director: Professor Felicity Rose, *University of Nottingham*
Partner Institutions: *University of Oxford, University of Southampton, University of Edinburgh, King's College London, University of Glasgow, University of Manchester and University of Liverpool*

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 move towards real-world applications in the musculoskeletal system, eye and liver, (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 and train the next generation of regenerative medicine scientists.

Over the past three years, the Hub has made significant progress with exciting early scientific success with inputs from all 9 institutions. Scientific outputs from the partner institutes include 124 peer-reviewed journal articles. We are in a strong position 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 Achievements

New materials for the musculoskeletal system

The Hub is currently investigating multiple potential materials for applications in the musculoskeletal system, specifically within bone, tendon and cartilage. Researchers at the University of Southampton, Imperial College London, the University of Nottingham and the University of Glasgow have been collaboratively investigating the development of innovative acellular materials based on 3D printed nylon, titanium and biodegradable polyester (polycaprolactone, PCL) scaffolds. These scaffolds are functionalised with biomimetic proteins, minerals and/or growth factors present in the bone microenvironment to augment bone formation by skeletal cell populations. Current focus has centred on PCL scaffold compositions as the biocompatible, biodegradable, acellular material for clinical translation. The chick egg vascular membrane was used to determine biocompatibility of the PCL material and growth factor-based coating as well as the ability of the coatings to support blood vessel formation in a dynamic biological environment prior to translation through larger preclinical animal models (Figure 1).

Concurrently, the University of Nottingham have been exploiting the geometrical freedoms of 3D printing to fabricate porous microparticle based biomaterials, amenable to injection-based orthopaedic surgical techniques, with different pore geometries. We have identified biomaterials that are amenable to 2-photon polymerisation and micro-stereolithography printing modalities and which support mesenchymal stem cell attachment; current work is now exploring the influence of pore geometry on MSC differentiation. Imperial College London have been working on the development of a microstructured implant for focal chondral and osteochondral lesions. The implant will provide the biomechanical and structural information to support physiological load bearing, lubrication, and integration with the surrounding cartilage and bone (Figure 2, page 12). Following successful biomechanical validation, Imperial College London have conducted viability testing using human stem cells.

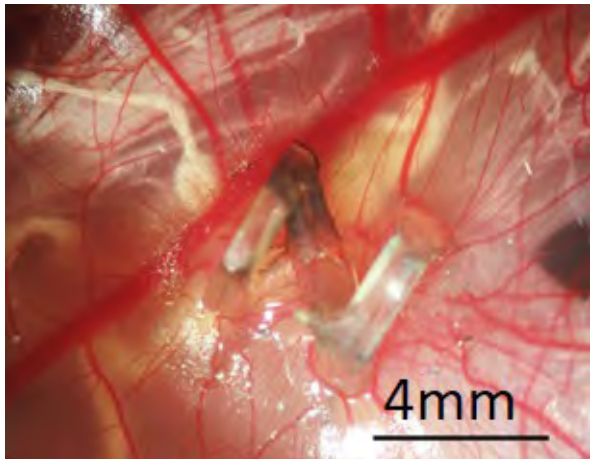


Figure 1: Growth factor coated PCL scaffold with surrounding thick, robust blood vessels.

These studies uncovered 2 key findings: First, one of the material phases was not stable at body temperature; thus, a post processing step will be introduced. Second, one of the processing solvents was forming an acidic salt in the structure. To resolve this, an alkaline salt is being introduced at the end of the fabrication procedure to neutralize the acid. Most recently, the team at Imperial College London are incorporating a subchondral bone mimic. The advantage of the osteochondral implant is that it requires no adhesives or sutures and uses bone ingrowth as a primary point of fixation.

Dr James Armstrong, an MRC/UKRI Innovation Rutherford Fund Fellow at Imperial College London, has been developing an innovative approach to grow complex tissues using sound waves (Figure 3, page 12). A small

portable device has been generated that produce ultrasound standing waves, which can facilitate and 'push' living cells into organized patterns, including clusters, lines, sheets, or columns. Cell patterns have been captured in hydrogels and used to grow aligned tissue structures, such as skeletal muscle, deep-zone cartilage, and cardiac tissue. These 'acoustically-patterned' tissues closer resemble the structure of their native counterparts and as such, offer new opportunities as clinical grafts or biological models.

New materials for the eye

Research has been progressing in the design and development of materials to treat conditions which lead to severe vision loss. Research is being performed by Professor Rachel Williams' team at the University of Liverpool and Professor Molly Stevens' team at Imperial College London to use bioengineered materials to replace components of the cornea. Collaborative research is also being performed by Professor Robin Ali's team at King's College London and Professor Molly Stevens' team creating novel approaches to regenerate retinal tissues using stem cells and innovative material strategies.

For corneal regeneration, the teams have built a family of peptide hydrogels based on poly-ε-lysine (pεK) and GelMA. The hydrogels can be synthesised with excellent transparency, high water content and appropriate mechanical properties for surgical handling able to support the attachment and growth of a monolayer of primary corneal endothelial cells and the ingrowth of corneal stromal cells. University of Liverpool and Imperial College London have collaborated to demonstrate that both the pεK and GelMA hydrogels can be printed producing structures that support both corneal epithelial and endothelial cells. The team have also developed site-specific chemistry to post-modify the 3D printed hydrogels with biomolecules such as peptides, proteins and antibody fragments to tailor the surface properties for optimal cell behaviour. For retinal regeneration, the teams of Professors Molly Stevens and Robin Ali are continuing to work at the interface of stem cell therapies and materials-based strategies with the aim of restoring vision lost due to degenerative retinal conditions.

New materials for liver regeneration

Research has been advancing in the design and development of materials to support cellular engraftment in the liver, as part of an overarching strategy to improve liver regeneration. Dr Lisa White's team at the University of Nottingham is collaborating with Professor Stuart Forbes' team at the University of Edinburgh to develop materials that release different cytokines to support cells transplanted into the liver.

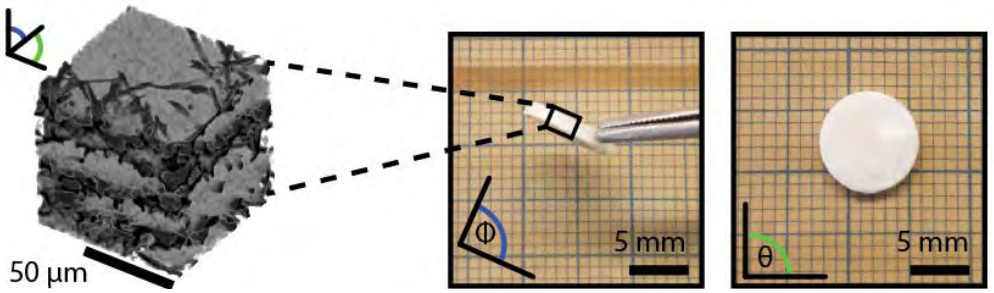


Figure 2: Nano computed tomography reconstruction (Left) of the cartilage implant (Right).

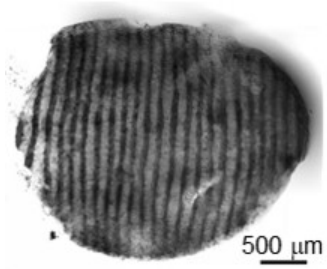


Figure 3: C2C12 in collagen Day 4, trapped cropped.

The Nottingham team led by Dr White have developed microparticle formulations using poly (lactic-co-glycolic acid) (PLGA) in combination with a galactose (Gal) moiety presented at the surface, that specifically binds to the asialoglycoprotein receptor (ASGPR) in hepatocytes. These microparticles are tuneable in size and surface properties and can include growth factors encapsulated within the microparticles and subsequently released at different rates. The team has demonstrated controlled *in vitro* release of vascular endothelial growth factor (VEGF) and is currently investigating release of clinically relevant immunomodulatory molecules from the Gal-PLGA formulations. The team is also developing microparticle fabrication methods to provide monodispersed particles for controlled drug release (Figure 4, page 14). In parallel, Professor Forbes' team at Edinburgh is conducting biodistribution studies Gal-PLGA formulations *in vivo* in mice.

Future Directions

The Hub continues to strengthen links across the UK and international research community together with Scientific Advisory Board (SAB) input and with regulatory authorities to deliver transformative and sustainable technologies in regenerative medicine industry. Working closely with the Safety and Immunology (SI) panel and the Manufacturing Commercial and Regulatory (MCR) panel, the Hub will continue to develop Target Product Profiles (TPPs) with high potential to maximise research translatability, addressing future clinical, industrial and regulatory needs. The translation project on new products for tendon repair continues apace at the University of Oxford, led by Professor Carr. The team has initiated requisite regulatory documentation work by implementing a basic quality management system (QMS) and generation of standard operating procedures (SOPs).

One of the key objectives of the Hub is to provide the UK regenerative medicine industry with researchers equipped with the necessary technical skills and competencies to take on leadership positions in this area. Current career development programmes in the Hub include a series of Early Career Researcher (ECR) workshops, mock interviews, podcasts, professional lab training and a Techcelerate programme (Imperial College London). The Hub will continue to help to bridge the gap between academia, medical practice, industry, and research funders by promoting interdisciplinary research excellence between these groups to meet our vision to produce the next generation of regenerative medicine scientists.

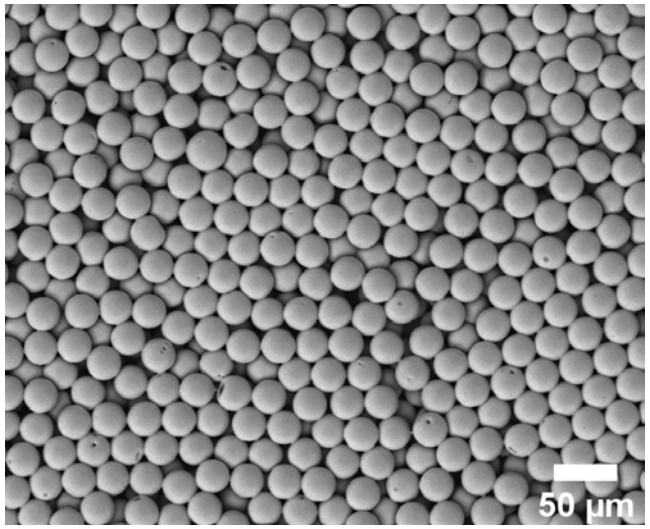
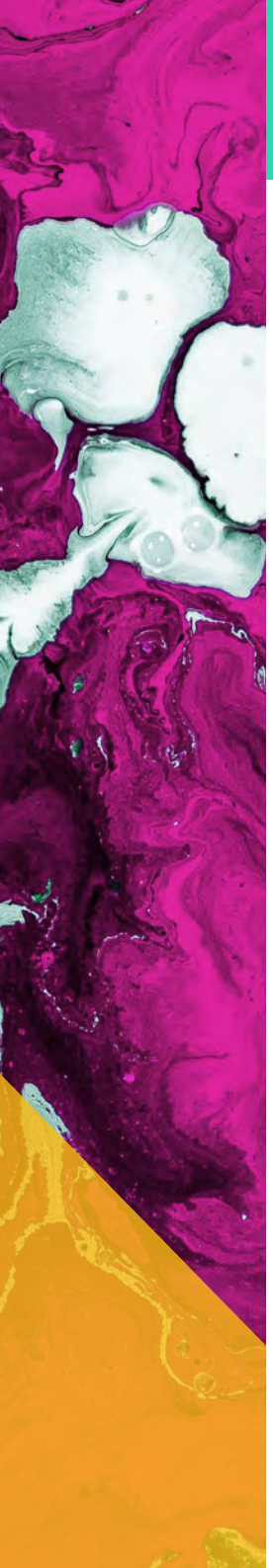


Figure 4: PLGA microparticles produced using microfluidics.

"I am excited by the progress made by the UKRMP Smart Materials Hub. This programme brings together 9 different universities across the UK, focusing on strategies for regenerating the eye, musculoskeletal system and the liver. To make real-life impact, we have set up key advisory groups to bring on-board manufacturing, safety, immunology and translational expertise. Some of the consortium's work is now progressing towards clinical trials, which is really exciting!"

Professor Molly Stevens, Director of the Smart Materials Hub



Smart Materials Hub case studies

BioYarn: stitches for tendons using regenerative medicine

Surgical interventions to repair torn tendons aren't always effective, and patients continue to experience significant pain and disability if the repair fails. Harnessing the power of regenerative medicine, using a novel synthetic material suture offers new hope to patients with this injury.

Tearing of the rotator cuff tendons affects around 25% of the population over the age of 60 and can result in significant pain and disability. Although management of these tears is often conservative, many patients undergo surgical interventions to attempt to generate a functional repair. Unfortunately, recent evidence has shown that 40% of repairs fail within 12 months irrespective of the surgical technique used, demonstrating the need for a new approach to tackle this problem.

Professor Andrew Carr and Professor Pierre-Alexis Mouthuy in Oxford are designing a synthetic material suture called BioYarn which mimics the natural environment required by cells to achieve a successful tendon repair. BioYarn utilises a technology called 'electrospinning' which uses electrical charges to create aligned microfibres out of a polymer solution. These biomimetic fibres can then be assembled into a multifilament suture using established textile technologies. In vivo, human cells respond to this biomimetic structure by migrating into the material and growing new tissue. Over time, the suture degrades to harmless by-products, leaving only natural repaired tissue in its place.

In order to transition from laboratory experiments to clinical use, the Oxford team has scaled up the manufacturing process to a manufacturing chain capable of significantly higher output. Additionally, the manufacturing environment has transitioned to an ISO 7 controlled cleanroom environment. These quality standards are crucial for accelerating therapies to clinical use. At the same time, the team have also progressed preclinical testing which follows guidance from the ISO standards surrounding medical device design and development. This work further helps to evidence the safety and efficacy of BioYarn, while complying with regulatory requirements established to allow a first in human clinical study to be performed using BioYarn.

Regenerating bone with nanoclay gels

Stem cell differentiation relies on key biochemical signals from the local environment surrounding them. This environment can be difficult to replicate when developing therapies using stem cells, as conventional biomaterials struggle to retain these biochemical signals. Nanoclays offer an exciting solution to this problem, as they can form gels that bind such biochemical signals to create environments favourable for stem cells to colonise.

Dr Jon Dawson at University of Southampton is working on developing injectable nanoclay gels to activate stem cells for bone regeneration. Stem cells can cure a variety of conditions by regenerating tissue. They are activated by powerful biochemical molecules from within their local microenvironment. Localising and retaining these bioactive molecules close to a healing site is key to the safety and efficacy of regenerative medicine applications. However, conventional biomaterials are often poor at retaining these molecules at the site of injury, and the molecules that stimulate the cells usually diffuse away.

The team have developed a nanoclay gel that can support stem cell growth and colonization. They have characterized the cellular response to nanoclay, including how it promotes the recruitment and entry of stem cells. The team also studied the potential effects of nanoclay degradation products on stem cell differentiation. They have shown that nanoclay gels can promote the entry of stem cells to a site of injury and promote remodelling, which is instrumental for bone regeneration. They also showed that the implanted nanoclay gels are degraded by cells and safely processed by the body. These results are now being used to support a submission to the FDA requesting a designated classification for this technology.

Intriguingly, the work has also opened new possibilities and collaborations for understanding the interactions of immune cells within the stem cell microenvironment. For example, the team showed that the early inflammatory response to the nanoclay actually promoted the subsequent regenerative action. The team in Southampton are now working with researchers in Japan on a new £600k three-year collaborative project to explore the early immune response to nanoclays as a springboard for bone repair processes.

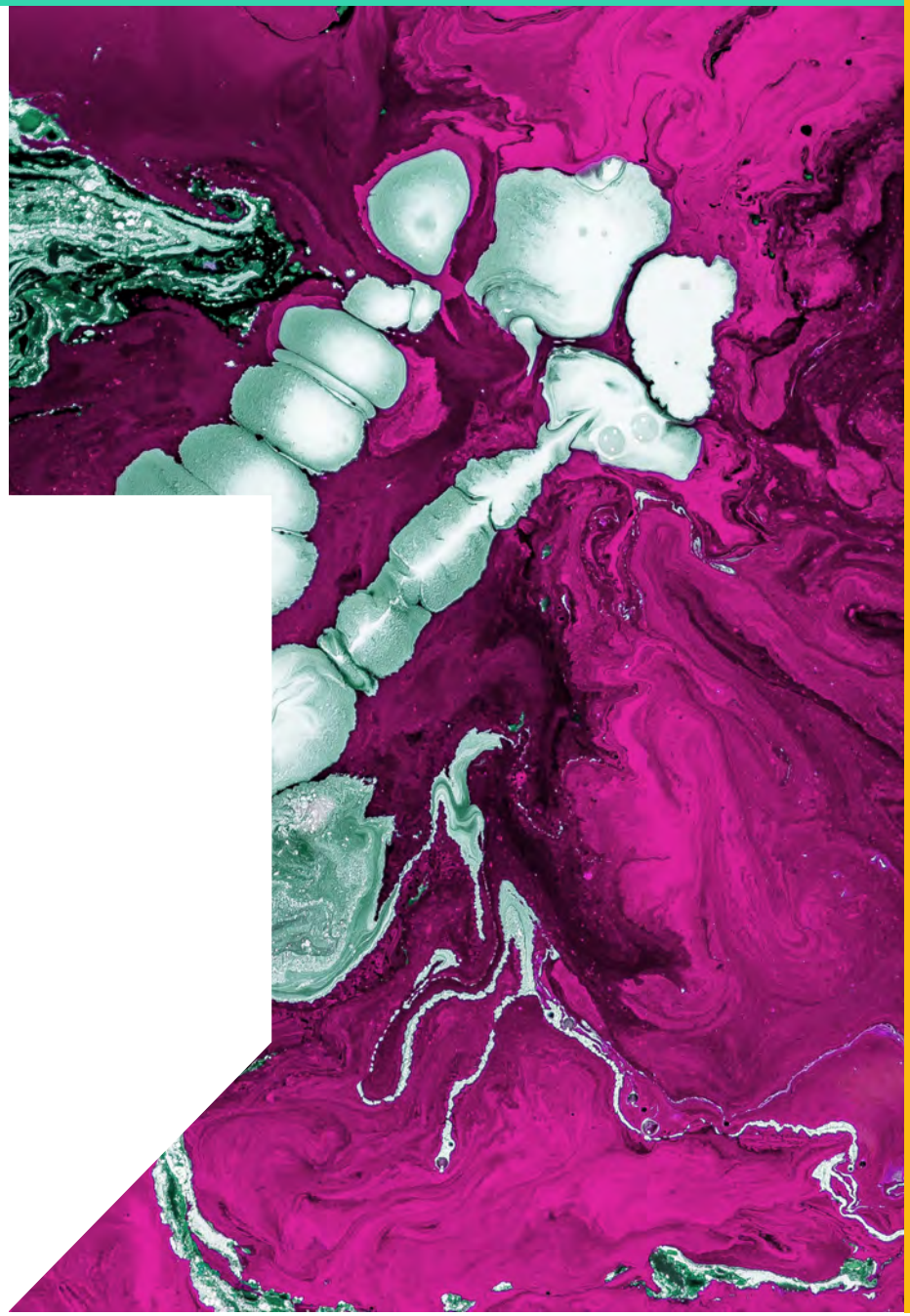
A little goes a long way: ultra-low dose growth factor treatments for bone repair

Sometimes broken bones do not heal even with the best surgical or nonsurgical treatments. These fractures can be treated successfully with growth factors, but it is expensive and comes with serious side effects because of the high doses of growth factors. New techniques to deliver growth factor treatments at ultra-low doses can help address this problem and help safely heal previously untreatable fractures.

Professor Manuel Salmeron-Sanchez at the University of Glasgow has developed a type of polymer coating called PEA (poly ethyl acrylate) that spontaneously organises key proteins in the extracellular matrix of bone tissue into a network that stimulates signalling of the key growth factor, BMP-2. This in turn allows the researchers to use ultra-low doses of BMP-2, which avoid the serious side effects such as ectopic bone formation and high risk of cancer that are sometimes seen with BMP-2 treatment.

The team used ceramic granules coated with PEA to successfully treat several bone defects in pre-clinical models. The team also first demonstrated efficacy in a small animal model where they demonstrated bone regeneration using 100 times less BMP-2 compared to levels typically used in this model. In parallel, researchers had the opportunity to treat a veterinary patient, Eva, a 2 years-old dog who was run over by a car which shattered the bones in her leg. Though her fractured humerus was fixed with conventional plates, a subsequent infection of the fracture led to a defect where the broken bones did not heal correctly. They successfully treated Eva's fracture with their PEA-coated granules.

Since then, the team have successfully treated another twelve veterinary cases (dogs and cats) with different challenging fractures. The researchers are currently testing a large animal model with the technology in collaboration with researchers at the University of Nottingham, with promising early results. The team is currently working in partnership with a company in Spain (Histocell) to move the manufacturing of the polymer coating to standardised quality conditions to facilitate the regulatory approvals needed for progressing this exciting research into clinical trials.



2.3 Engineered Cell Environment (ECE) Hub

Director: Professor Stuart Forbes, *University of Edinburgh*
Deputy Director: Professor Alicia El Haj, *University of Birmingham*
Partner Institutions: *University College London, Kings College London and University of Cambridge*

The UKRMP Engineered Cell Environment (ECE) Hub seeks to regenerate and repair damaged organs using two translational strategies (Figure 1). We are using laboratory and animal models of disease to test these strategies.

1. **Developing cell therapies for damaged organs:** we aim to improve transplanted cell performance by understanding of how cells behave in the environment they engraft.
2. **Promoting the body's own (endogenous) repair of damaged organs:** using human stem cells, we are creating automated screening assays to study the behaviour of stem cells and identify signals that promote stem cell expansion and differentiation, optimising repair.

To improve endogenous repair and cell therapies the UKRMP ECE Hub is tackling three translational challenges:

- Understanding and improving the physical properties of aged and injured tissue niches
- Developing artificial environments which act as regenerative signals to support the formation of new tissue and repair damaged tissue
- Discovery and development of new targets to promote the body's own tissue repair mechanisms

Our hub brings together stem cell scientists and tissue engineers with clinician scientists familiar with leading clinical trials and the pathways to translation. We selected three clinical exemplars (liver, joint and lung repair) with maximal potential for tangible clinical gains.

Scientific Achievements

Liver (Forbes, Hay, Carragher, Habib, Franklin)

In the UK, liver disease is the third biggest cause of premature deaths. Liver transplantation remains the only definitive treatment of end stage liver disease and demand far outweighs availability of donor livers. Cell therapies hold some promise: the clinical use of hepatocyte (functional liver cells) transplantation has been used to treat certain metabolic liver diseases but not for more common liver diseases. We are addressing some of the barriers to widespread application of cell therapies, including cryopreservation (freezing and thawing of cells), limited cell engraftment, immune rejection and poor long-term function following transplantation into damaged organs.

We have developed a high throughput screen for proliferation and differentiation of embryonic stem cell derived liver progenitor cells. Using this model, we have screened 1,280 FDA approved drugs, of which 6 show a significant increase in foetal albumin (AFP) secretion (a key function of developing fetal liver) and inhibition of differentiation into metabolically active hepatocyte-like cells. The healthy liver relies on active Wnt/β-catenin signalling during regeneration.

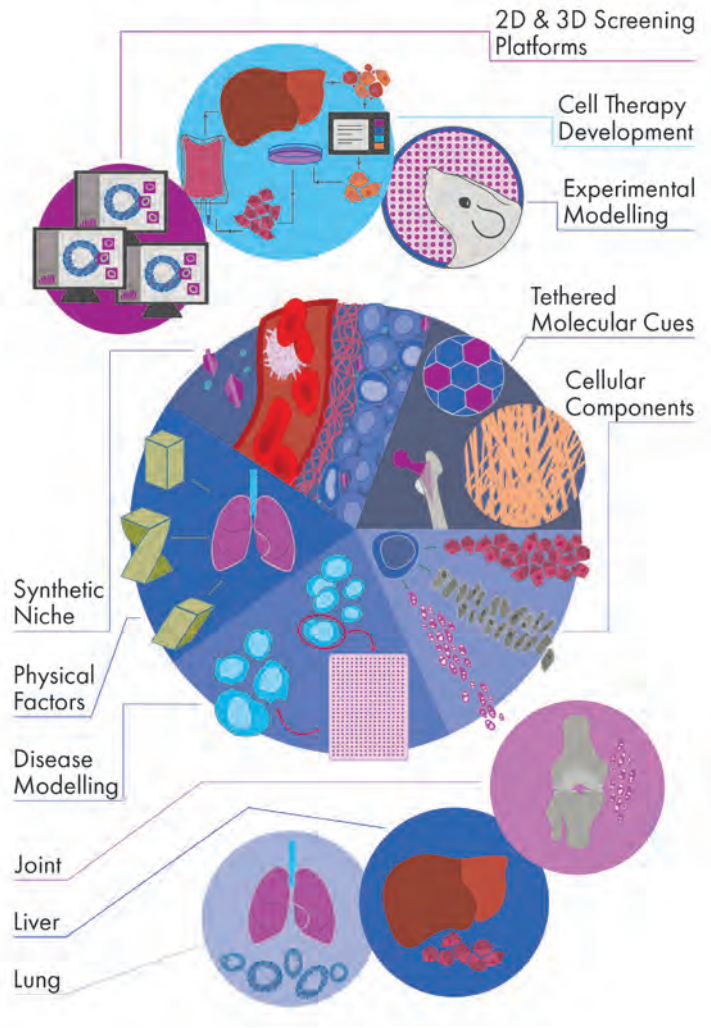


Figure 1: Schematic of the ECE Hub strategy

We have developed materials (nanoparticle and bandage) that deliver regulated Wnt. The activity and reproducibility of the materials has been established and safety and efficacy are being tested in mouse models of liver disease.

The stiffness of damaged tissues affects their ability to regenerate. We have established the stiffness profile of adult liver tissue and assessed culture conditions of different stiffness. We are now assessing the optimal culture conditions for human liver cells to be used prior to transplantation.

Senescence is a cellular stress response, which transmits to neighbouring cells affecting the function of donor cell grafts. We have developed a model of senescence in order to identify therapeutic targets to inhibit this transmitted senescence and improve cell engraftment. These targets are being tested in transplant models (Figure 2).

Joint (El Haj, McCaskie, Birch)

Osteoarthritis (OA) is a major worldwide healthcare burden that can severely impact 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 or 'key-hole' surgery in less severe cases to either clean the site or to encourage natural inflammation, whereby the patient's own cells help repair the damaged tissue. Injectable therapies, containing pre-optimised cells, can be administered at the same time. 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.

We have developed an improved 3D model platform for cartilage formation (chondrogenesis) using human bone marrow stromal cells (BMSCs) to mimic and maintain tissue functions that may be a feature of cartilage repair and regeneration. This model is being optimised by choosing the best biomaterial from three selected by clinical, translational, and regulatory maturity (Figure 3).

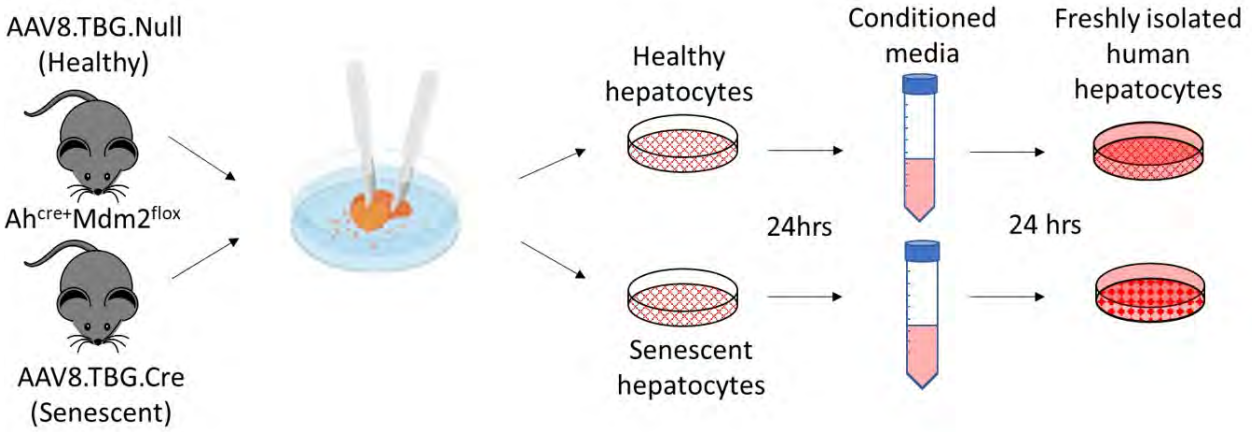


Figure 2: Paracrine Senescence Model

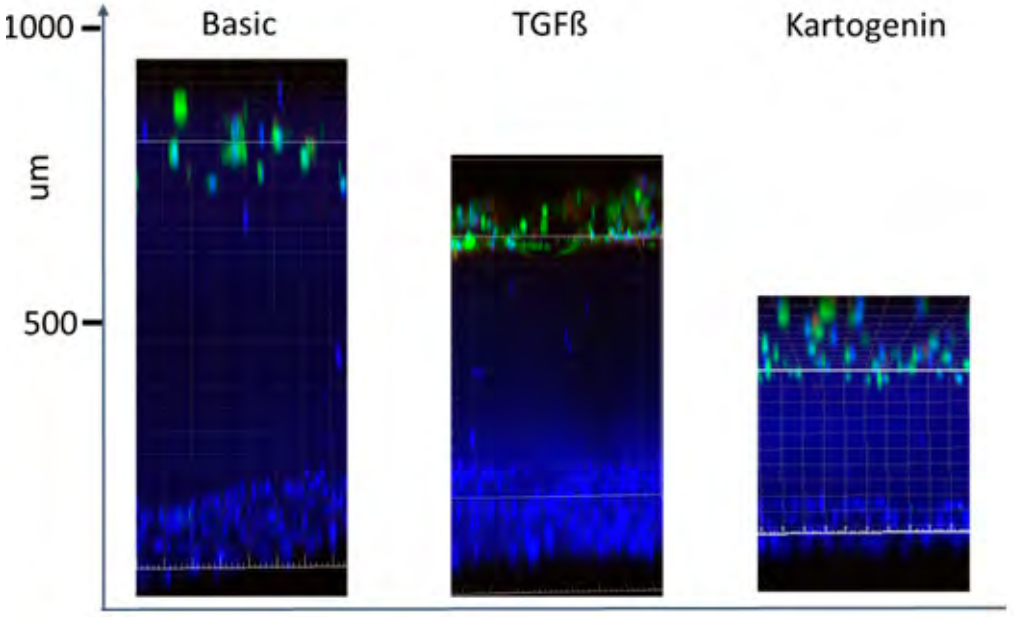


Figure 3: Bone Marrow Stem Cell Migration into hydrogels and differentiation in response to different chondroinductive cues after 7 days.

Using the Wnt-induced osteogenic tissue model (WIOTM) we are screening for complex inductive effects of potential drug targets on both the progenitor proliferation and maintenance as well as differentiation and maturation into cartilage and bone. Finally, based on our publication in Nature (Okuchi Y et al, 2020), we are working towards a patent for a new therapeutic intervention to repair lost or damaged bone.

Lung (Janes, Watt)

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. Lung airways transport air to the alveoli (small air sacs) where gas exchange occurs. The epithelial cells that line the airway are essential for protecting the lungs and respond to insult through a rapid process of repair and regeneration. However, abnormal repair processes can lead to irregular organisation and integrity. Our goal is to find novel factors that influence stem cell activation and differentiation promoting regeneration and repair to restore normal function and protect against further damage.

In order to identify compounds that increase basal cell proliferation and stemness we are working to establish a robust assay for high throughput screening. Cell culture conditions of human bronchial epithelial cells (HBEC) have been optimised. A combination of three inhibitors have been identified as a positive control to increase stemness and proliferation We are currently optimizing automation for a 2D high-throughput screen using 2000 approved drugs and are working towards a 3D screen using lung organoids. In addition, 3D tracheospheres containing 3 lung cell types – basal, ciliated and goblet cells, are being used to assess stem cell growth and differentiation of lung epithelial cells under physiologically relevant conditions (Figure 4). We have also established a robust protocol for measuring stiffness of lung tissue using Atomic Force Measurement along with the elastic characteristics of adult human lung tissue in different diseases (Chronic Obstructive Pulmonary Disease, Idiopathic Pulmonary Fibrosis) and at different stages of disease.

Networking Activities and Partner Projects

The ECE hub is intrinsically collaborative across scientific disciplines. We are developing numerous productive collaborations with industry, including using machine learning to predict drug activity in laboratory models of liver disease. There has been considerable knowledge exchange between laboratories across our Hub despite the challenges faced from the COVID-19 pandemic. Of particular note are: (1) the testing of Wnt particles and bandages (joint and liver), screening platform, and *in vivo* testing (2) the establishment of high-throughput screens and sharing of compound libraries and analysis expertise, and (3) the establishment of stiffness measurement protocols in liver and lung tissues.

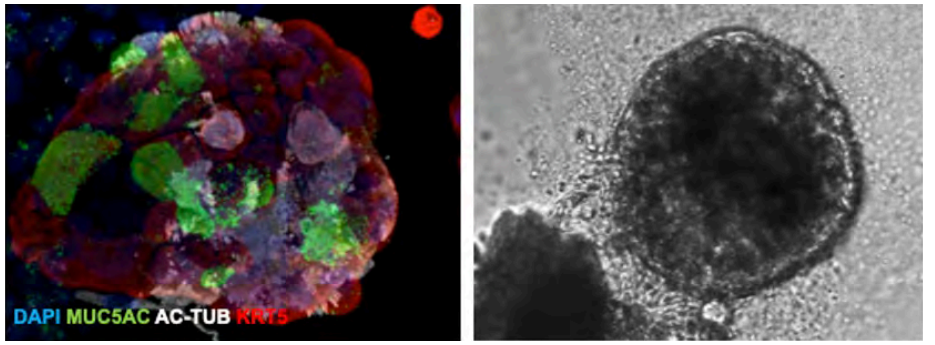


Figure 4: Tracheospheres

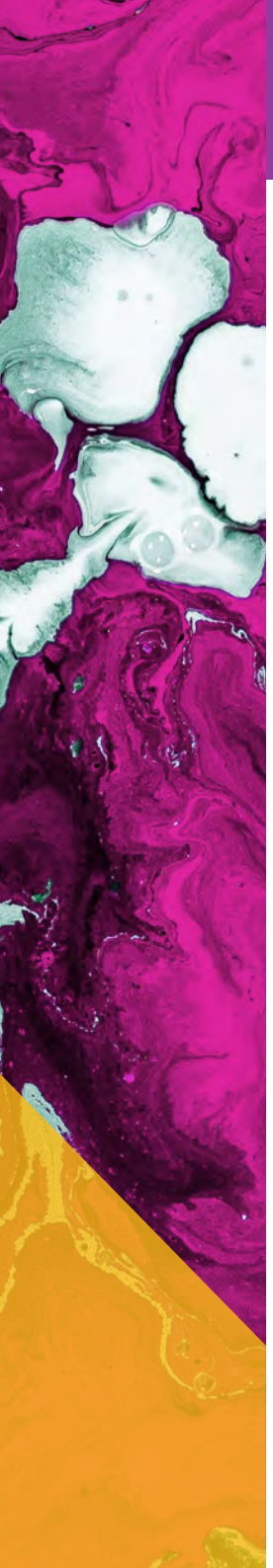
The ECE Hub is holding a workshop on the 'Cutting-edge developments in high throughput screening' in March 2022 at The Frances Crick Institute, London, UK.

Future Directions

We plan to translate our successful programmes via a number of methods, including licencing, industrial partnerships and clinical trial testing. We have achieved this within the previous UKRMP Niche Hub where our ductular transplant work received follow on funding (MRC DPFS) to take it to the point of first-in-human testing. We have numerous collaborations with industry, have licenced materials, and collaborated with industry to exploit our discoveries. For example, Hay and Stem Cell Technologies have developed a hepatic progenitor differentiation system using IP developed during the UKRMP Niche Hub project.

"Our multidisciplinary teams within the UKRMP ECE Hub are making great progress in identifying and developing the tools, drugs and cell therapies to regenerate or repair damaged liver, lungs, and joints."

Professor Stuart Forbes, Director of the Engineered Cell Environment Hub



Engineered Cell Environment Hub case studies

A regenerative cartilage model for drug screening applications

New treatments for osteoarthritis have been limited by the lack of cartilage tissue models that can accurately represent the in vivo environment needed for screening new treatments for therapeutic potential. A new 3D model for cartilage tissue has the potential to enable high-throughput screening, that can help identify treatment candidates with a higher chance of therapeutic success.

Professor Alicia El Haj and Dr Nicola Foster at the University of Birmingham are developing a new 3D model of cartilage tissue that can be used to test new treatments for osteoarthritis. Osteoarthritis is a degenerative joint disease that results from the breakdown of cartilage and is one of the leading debilitating diseases within the adult population. Damaged cartilage has limited capacity for self-repair, so there is an urgent need for new drugs and therapies that can delay the progression of osteoarthritis. At the moment, screening assays for new treatments are carried out in the lab using a single layer of cartilage cells. This 2D model does not accurately represent the cartilage structure and associated support cells that work together in the tissue microenvironment of a living joint. Therefore, many of the seemingly promising treatments identified using traditional assays in the lab do not lead to treatments that can be translated to the clinic for treating osteoarthritis.

The researchers have developed a 3D regenerative model of cartilage which maintains both mature and progenitor cells that make up cartilage in an arrangement that is spatially organised. The team then showed that this model could be transferred to a 96-well plate format, which is needed for screening candidate drugs in high-throughput assays. The model system allows the researchers to screen for new treatments that can induce the formation of cartilage.

The researchers are now exploring ways to scale-up this 3D model with liquid handling systems and automated imaging techniques so they can increase its throughput. The new 3D model is an exciting platform that holds great potential for high-throughput screening to identify drugs that can induce the formation of new cartilage, which can then be used to treat osteoarthritis.

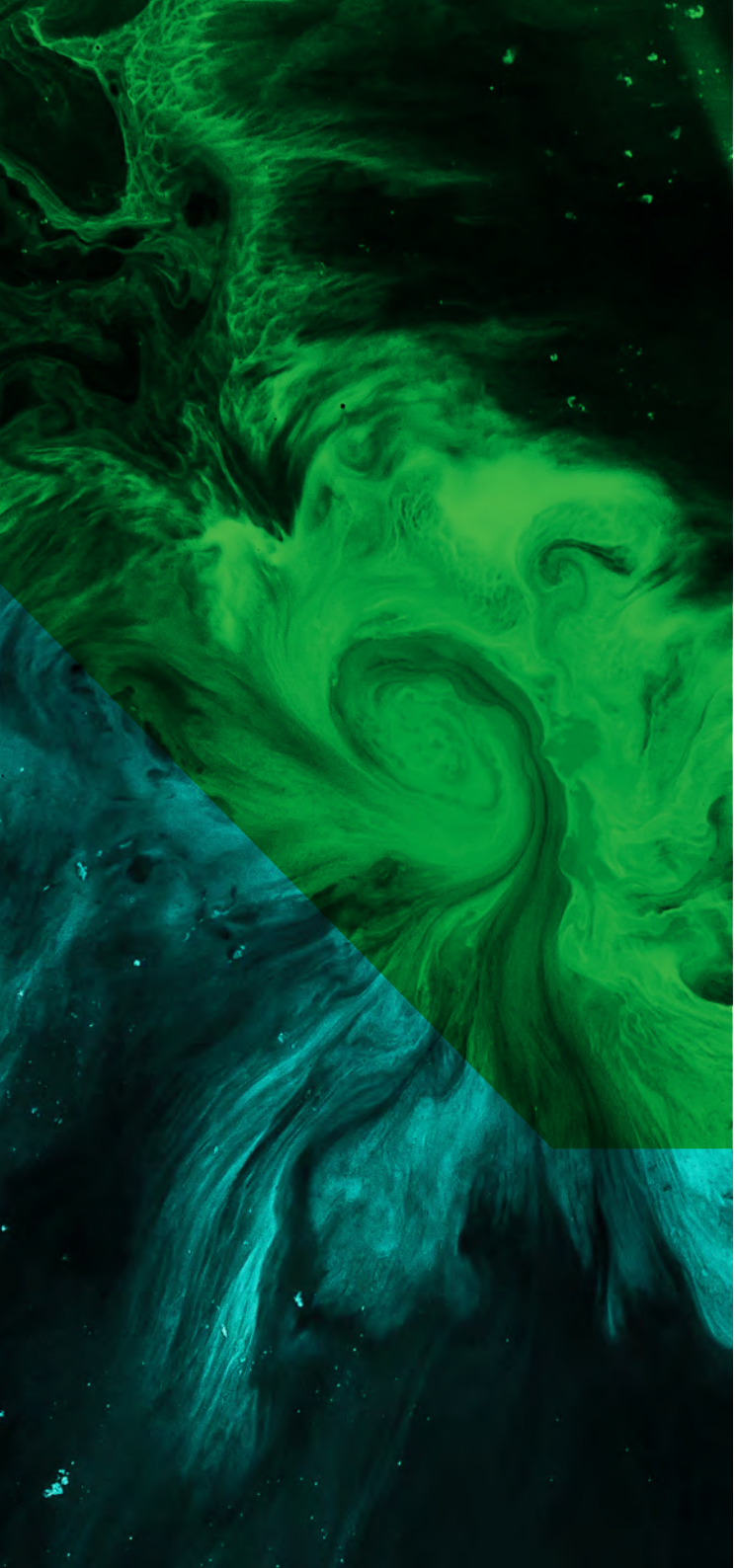
The fate of lung stem cells: a 3D model for screening new drugs

Professor Sam Janes, Dr Yuki Ishii and Jessica Orr are developing 3D lung organoids that contain different cell types that make up lung epithelium tissue. These lung organoids will help the team study epithelial stem cell growth and differentiation under conditions that more closely resemble a living lung. Understanding what type of cell a stem cell will eventually differentiate into, and how this process could be manipulated using the right biochemical signals at the right time, is key to harnessing the power of stem cells to repair damaged tissue.

The team have already established a lab protocol for monitoring cell fate decisions in a 2D assay using a reporter gene system where differentiated cells can be identified and counted. They are now working on transferring this reporter gene system to the 3D lung organoids, so that the team can detect cell differentiation and understand the mechanisms that regulate it. Once this system is established, the team will use the lung organoids in a drug screen with 2,000 FDA-approved compounds, so that any positive hits (i.e. drugs that promote the differentiation of a lung stem cell into new lung epithelium cell) can be accelerated to the clinic.

These lung organoids will provide a valuable tool for identifying different drugs that can regulate stem cells in the lungs. This knowledge in turn can be applied for treating damaged lungs, for example a promising drug identified through this assay could repair damaged lung tissue by inducing stem cells to differentiate into new lung epithelial cells.

3. Hub Networking and Joint Activities



3. Hub Networking and Joint Activities

The three Hubs work closely together to develop collaborations across UKRMP and in addition to participation in regular scientific discussions, they also jointly host events and deliver training for early career researchers.

For example, the 'Regenerative medicine meets mathematical modelling: Discovering symbiotic relationships' workshop (held in Oxford in January 2019) has led to several pump priming and collaborative research projects and reviews, and the 'Safety of Stem Cell Derived Therapies' conference (held in Edinburgh in October 2019), in collaboration with the British Pharmacological Society, brought together international regulators and scientists.

A joint training programme for early career researchers entitled 'Collaboration and Career Development' has offered mentoring, mock interviews, podcasts and curated resources to help researchers develop their careers either within academia or within associated industries.

In addition, the Hubs are developing partnerships with industry and seeking to engage the wider academic and commercial community and promote UKRMP skills and expertise at key scientific meetings, through our web presences and social media.

Website: https://www.ukrmp.org.uk/

Engineered Cell Environment (ECE) Hub:
Contact: Dr Robin Morton, robin.morton@ed.ac.uk
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LinkedIn: https://www.linkedin.com/company/ukrmp-ece-hub

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Smart Materials Hub:
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LinkedIn: https://www.linkedin.com/company/ukrmp-smart-materials-hub/

4. Hub Resources Available to the Community

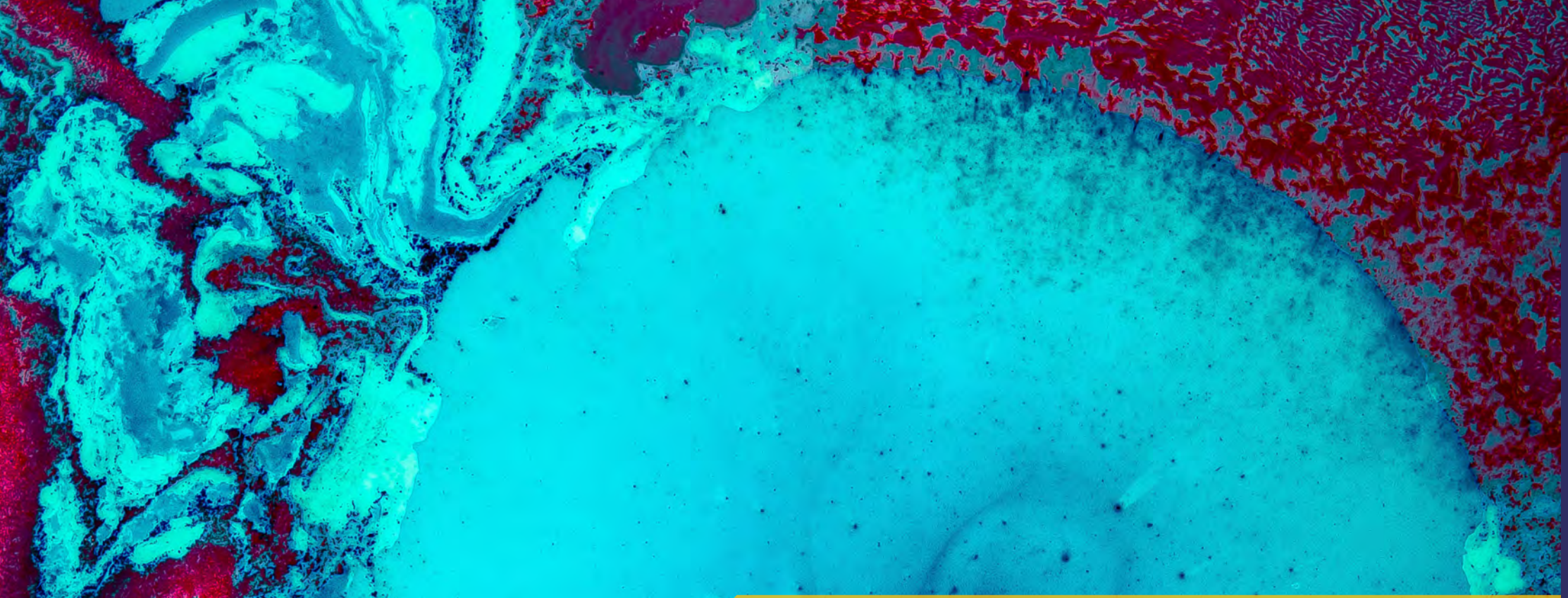
4. Hub Resources Available to the Community

Tools & Resources:

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. Some lines are available as fluorescence reporters.
Immune silent cell lines	hPSC lines which have HLA Class I KO via beta-2-microglobuline.	PSEC	Cedric Ghevaert cg348@cam.ac.uk	We have a number of established lines, or protocols through which the editing can be achieved.
Tools and Reagents	Human bone marrow stromal cells (HBMSCs) – Skeletal Stem and progenitor cells from OA and OP patients for research.	Smart Materials	Professor Richard Oreffo	Disease specific and normal HBMSCs.
Tools and Reagents **Technology**	Synthesis of peptide-modified multi-arm poly-ε-caprolactone	Smart Materials	Professor Molly Stevens	Custom peptide synthesis and synthesis of peptide-polymer conjugates.
	Mineralising Materials	Smart Materials	Professor Alvaro Mata	Elsharkawy et al, Nature Communications 2018, 9(2145).
	Self-assembling hydrogels	Smart Materials	Professor Alvaro Mata	Redondo-Gomez et al, Biomacromolecules 2019, 20(6), 2276-2285.
	Multi-zonal scaffold production	Smart Materials	Professor Molly Stevens	Electrospinning, porogen leaching, and directional freezing.
Technology	Quantification and analysis of protein secondary structure	Smart Materials	Professor Alvaro Mata	Elsharkawy et al, Nature Communications 2018, 9(2145).
	Molecular patterning inside hydrogels	Smart Materials	Professor Alvaro Mata	Aguilar et al, Advanced Functional Materials 2018, 28(15).
	3D printing with self-assembling bioinks	Smart Materials	Professor Alvaro Mata	Hedegaard et al, Advanced Functional Materials 2018, 28(16).

Tools & Resources: (continued)

Resource	Description	Hub	Contact	Further information
Technology (cont)	Filament eletrospinning technology.	Smart Materials	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414.
Equipment	SLA 3D Printing.	Smart Materials	Professor Molly Stevens	Formlabs and Prusa SLA Printers which have been configured to print small (<5 mL) and large (>100 mL) volumes of customised hydrogels and biodegradable polymers.
	Centre for Additive Manufacturing.	Smart Materials	Professor Ricky Wildman	This has been tailored for MSK work untaken in the Hub. https://www.nottingham.ac.uk
	PCL electrospun filament.	Smart Materials	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414.
	Textile equipment (weaving, braiding, twisting).	Smart Materials	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414.



5. UKRMP Immunology Projects

5.1 Immunogenicity test platform – *in vitro* and *in vivo*

Professor Giovanna Lombardi (lead) (*King's College London*),
Dr Joanne Jones and Dr Kourosh-Saeb Parsy (*University of Cambridge*)

Our goal is to develop a platform for testing whether non-self (allogeneic) cellular therapies are likely to be rejected by the immune system when transplanted into patients. Understanding this is key to the success of regenerative medicine.

Using two examples: (i) iPSC-derived hepatocytes (iHeps) and (ii) embryonic stem cell-derived dopaminergic neurones (ES-DA), chosen because they are about to enter clinical trials for the treatment of liver disease and Parkinson's disease respectively, we have performed a series of laboratory (*in-vitro*) and animal (*in-vivo*) studies.

To date, we have shown that iHeps and ES-DA cells do not induce significant immune responses *in-vitro* (even when pre-exposed to inflammatory cytokines, mimicking the *in-vivo* inflammatory response). This is in keeping with our observation that these cells do not express all molecules necessary for immune cell activation.

To better explore immune responses to the cells, we have generated mice with a human immune system by injecting human immune cells into immunodeficient animals. So far iHeps, transplanted under the liver capsule, have been rejected in some animals (within 3 weeks) but not in others, suggesting variable host responses (Figure 1). ES-DA cells (transplanted as day 16 progenitors) survive injection into the mouse brain, and in humanised mice induce a small inflammatory (T-cell) infiltrate (Figure 2). We are currently investigating long-term graft survival and differentiation into mature dopaminergic neurones.

Ultimately our work will include determining whether allogeneic iHeps and ES-DA cells can survive long enough to reverse liver damage and PD motor deficits in our humanised mouse models.

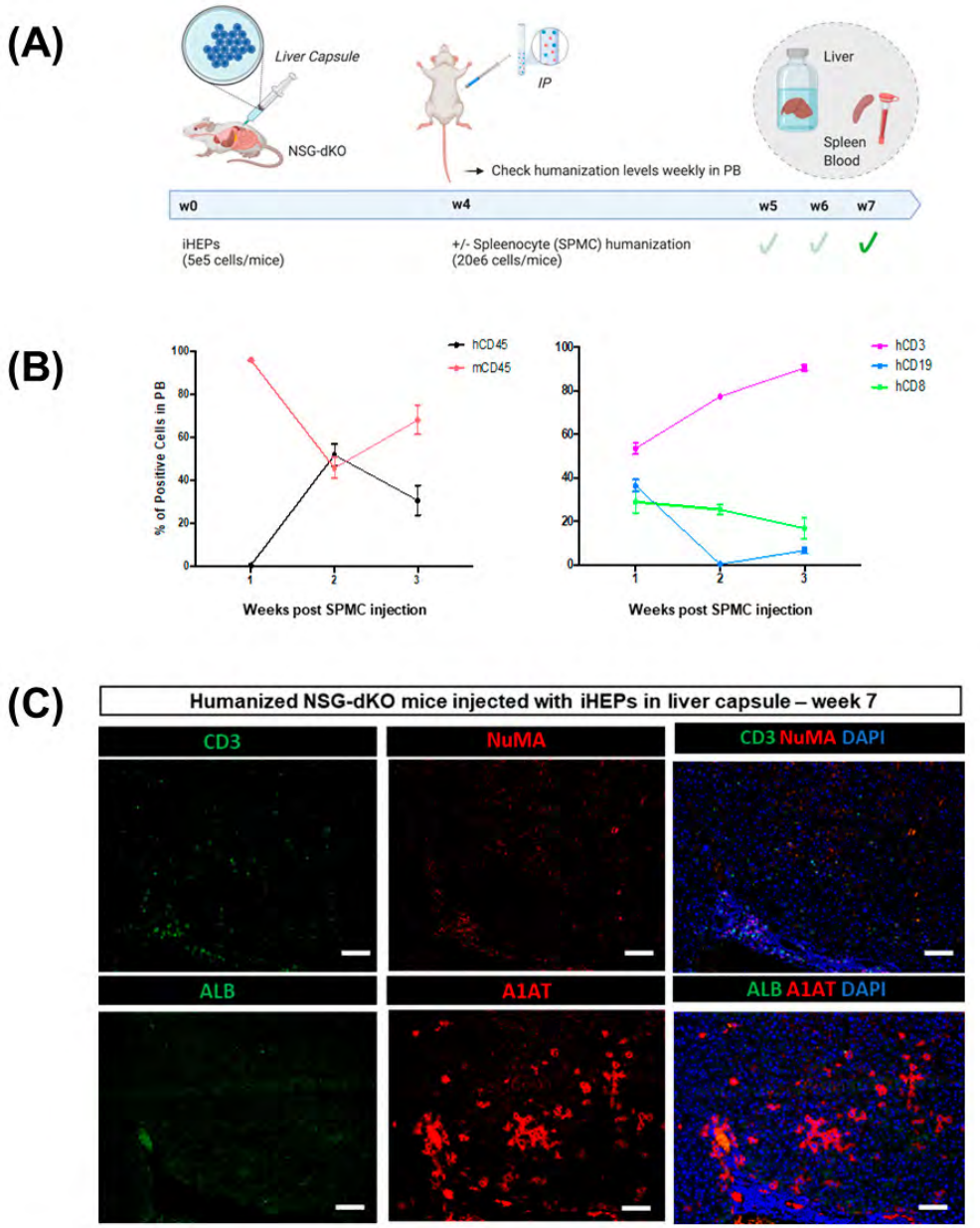


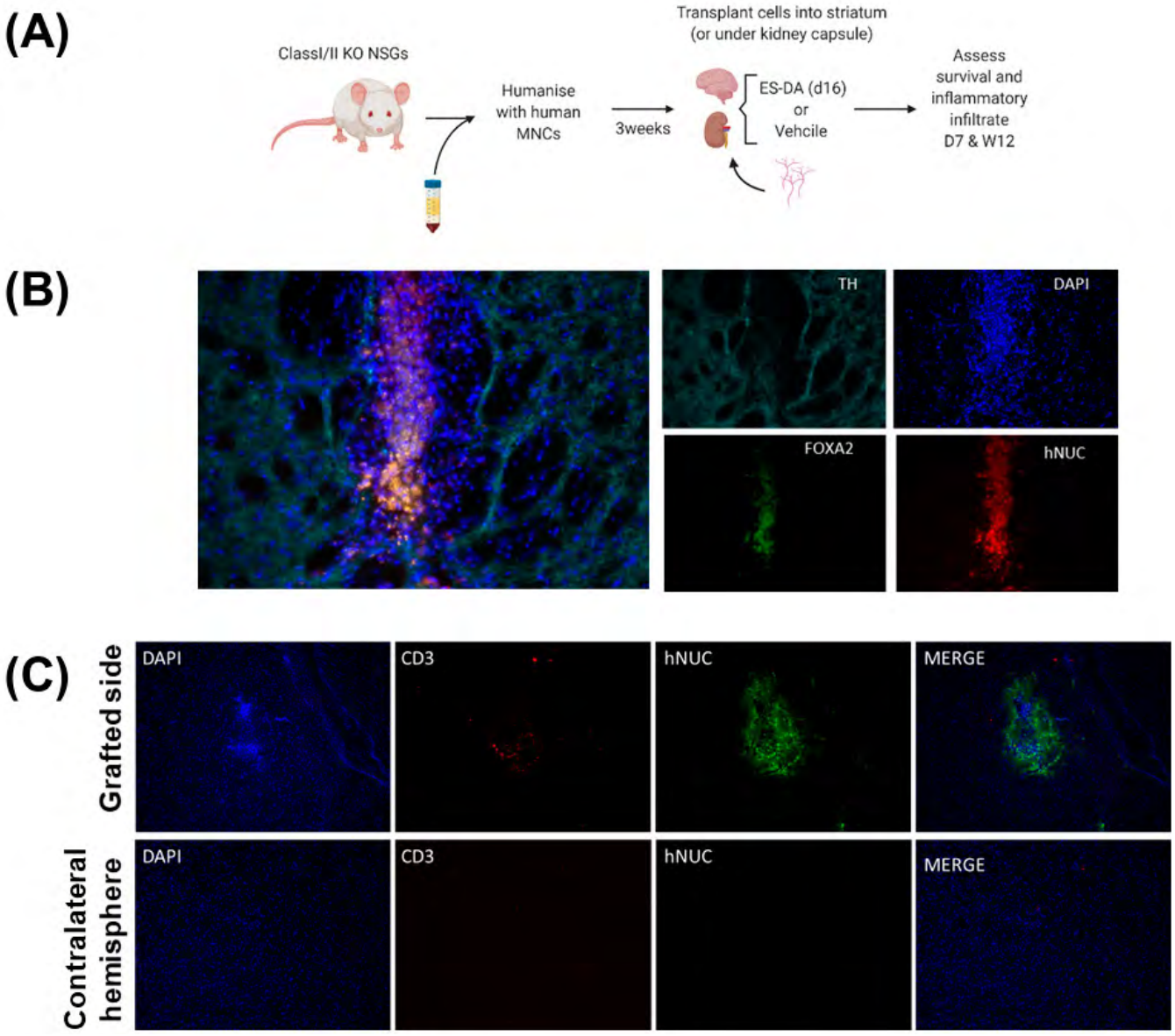
Figure 1 (right): iHEPs injected into the liver capsule of humanized mice as model to study allogeneic immunoresponse of liver cellular therapies in vivo. (A) Schematic of the model. (B) Graphs showing the percentage of positive m/hCD45, hCD3, hCD19 and hCD8 cells measured weekly by flow cytometry in peripheral blood. (C) Immunofluorescence showing human lymphocytes (CD3+, NuMA+) and engrafted iHEPs (A1AT+ or ALB+) 7 weeks after liver capsule injection of iHEPs and SPMC humanization (in non-rejected example shown). Scale bars: 100μm.

Figure 2 (right): Humanised models to assess immunogenicity of allogenic ES-DA cells. (A) Experimental schematic. (B) Early graft survival in humanised NSGs (1 of 3 shown) showing that ES-DA FOXA2 and hNUC positive cells can survive the transplant procedure (also confirmed in ~15 non-humanised NSGs), and in the mouse brain. (C) Infiltration of human immune cells (CD3 and hNUC positive) into the graft at day 7 (1 of 3 experiments shown). Contra-lateral, non-grafted hemisphere shown for comparison. Magnification x10.

Abbreviations: NSG-dKO: NSG-double knock out for HLA-I and HLA-II; SPMCs: spleenocytes; PB: peripheral blood; H/E: Hematoxylin/Eosin; NuMA: nuclear mitotic apparatus protein (human); ALB: albumin (hepatocyte marker); A1AT: alpha-1-anti-trypsin (hepatocyte marker) MNCs: mononuclear cells; DAPI: nuclear stain; hNUC: human nuclear stain; FOXA2: (expressed by DA precursors and mature neurons); TH: tyrosine hydroxylase (expressed by mature neurones); CD3 (T-cell marker).

"Regenerative medicine has the potential to impact the whole spectrum of health care. An important focus of the UKRMP is to drive interdisciplinary research and bring discovery scientists into closer partnerships with end users, companies, and regulatory agencies. This will ensure their work translates into clinical and commercially viable uses and that the UK remains at the forefront of regenerative medicine research."

Dr Robin Buckle, MRC Chief Science Officer



Figures created with BioRender.com.

5.2 Stealth creation using genome engineering

Professor Waseem Qasim (lead) (*University College London*),
Dr Cedric Ghevaert (*University of Cambridge*), Professor Paolo De Coppi (*University College London*)

An attractive proposition for regenerative therapies is the ability to use 'off the shelf' healthy donor cells that evade immune responses. To create immunological 'stealth', strategies are being investigated to prevent expression of HLA proteins. These are the flags on the surface of cells that identify self-tissue and present antigens to alert the immune system during infection. Genome editing involves designing small RNA 'guide' molecules for targeted disruption of genes coding for either the HLA proteins directly, or other genes involved in controlling how and when HLA proteins are expressed. These RNA guides act as navigators for engineered nucleases (for example SpCas9) to cleave and disrupt DNA and can be used in combination for highly efficient multiplexed editing for several genes simultaneously.

Further evolution of the approach has led to RNA-guided delivery of alternative enzymes (notably cytidine deaminases) that can chemically modify single nucleotides at critical locations, and this approach has been exploited to create stop codons in genes targeted for HLA disruption without causing multiple DNA breaks. These emerging tools are already in clinical development for other cellular therapies, providing a ready pathway for further translational development.

For the UKRMP network, HPSC lines have been engineered to remove HLA using both techniques and edited lines are now being investigated for their potential in downstream applications, including for differentiation of hepatocytes and macrophages. Immunological assessments and safety studies are ongoing, including testing of inducible elimination if required, and investigations to map the wider molecular effects of genome editing are underway.

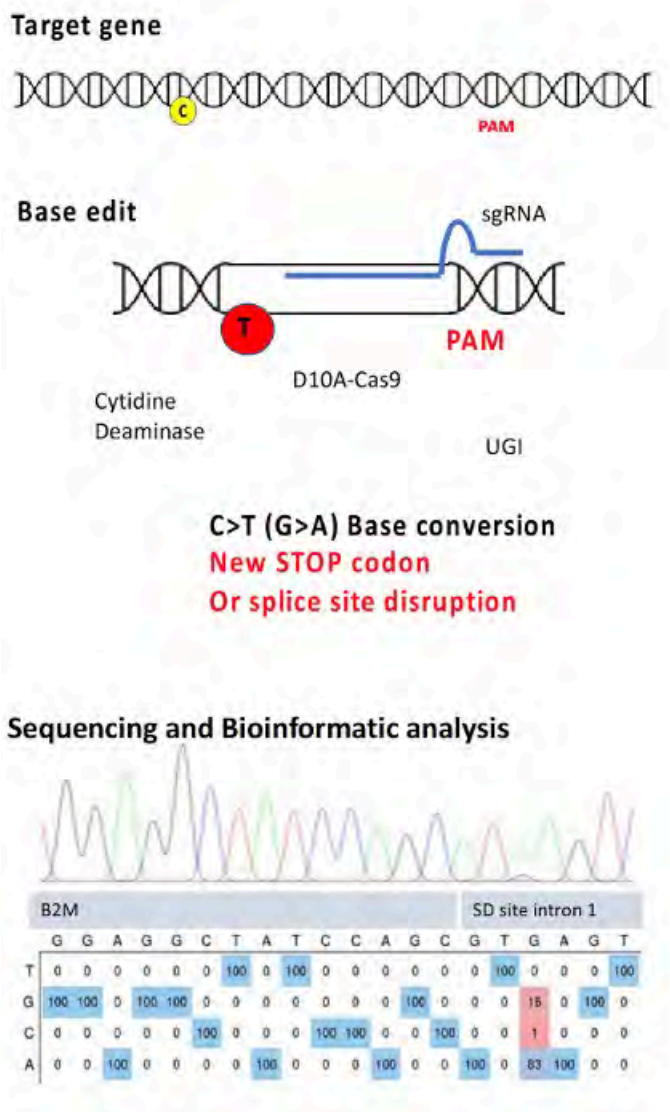


Figure 1: Single guide RNA (sgRNA) designed to target B2M, a conserved aspect of HLA class I proteins having identified a suitable PAM sequence to guide binding of the base editor complex, comprising a modified, non-cleaving, Cas9 mutant fused to deaminase and UGI elements. High efficiency disruption can be quickly confirmed by flow cytometry and verified by sequencing analysis.

5.3 Alveolar regeneration and tissue resident immune cells

Professor Ling-Pei Ho (lead) (*University of Oxford*), Professor Andrew Fisher (*Newcastle University*), Professor James Shaw (*Newcastle University*), and Dr Niwa Ali (*King's College London*)

Aims

Our programme of collaborative studies in Oxford (LPHo), Newcastle (A Fisher, J Shaw) and KCL (A Niwa) investigates the potential impact of tissue-associated immune cells on lung regeneration in chronic disease, focusing on alveolar regeneration in idiopathic pulmonary fibrosis (IPF). IPF is a severe and progressive fibrosing lung disease with limited therapeutic options. Lung transplant affords the only chance of survival beyond 5 years. However, scarcity of organs, surgical risks and limited lifespan of the transplanted organ restrict this approach, and increasing efforts are being made in regenerative medicine approaches like endogenous alveolar regeneration. The pathogenesis of IPF is driven by alveolar epithelial cell injury and dysfunction, with aberrant repair comprising abnormal regeneration of epithelium and overactivity of stromal cells. In IPF, a large number of immune cells, not usually present in normal lungs are found in the interstitium and likely to have an impact on regeneration. Understanding which and how immune cells contribute to normal and aberrant alveolar regeneration is an important step towards the long-term goal of endogenous stem cell proliferation as a therapeutic approach in IPF.

Across the three centres, we are completing work on:

(i) Mapping the tissue immune cells to regenerating alveolar epithelium in human IPF lung samples. Here, we are in the last phase of work - the 32-antibody panel to detect all immune cells and proliferating alveolar epithelial progenitors using single cell mass cytometry imaging has been optimised and validated. Lungs from IPF and healthy donors have been acquired and sectioned. In IPF, areas of end stage

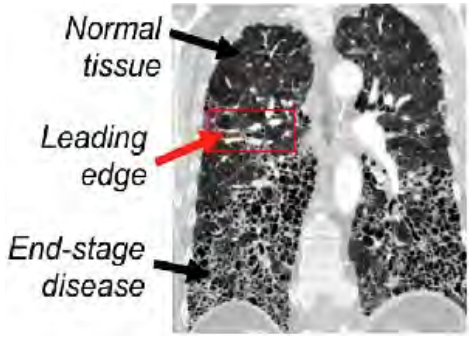


Figure 1: Computerized tomographic image of an IPF lungs showing normal and end stage disease (the latter marked by fibrosis and aberrant regeneration).

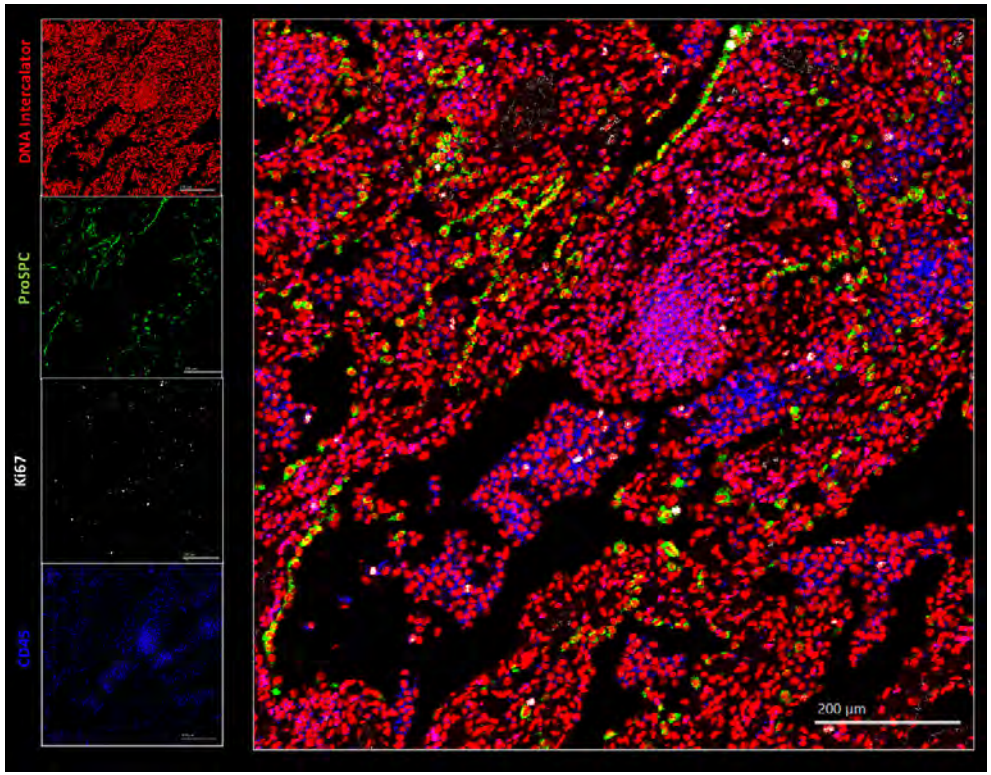


Figure 2: Exemplar of Imaging Mass Cytometry file from an IPF lung sample showing staining for 4 of 32 metal-tagged antibodies stained. CD45+ immune cell (blue), type 2 alveolar epithelial cells (green) are shown amidst nucleated cells (red). Cells are segmented into single cells and an algorithm then extracts information from the staining including the expression of any antibody on every cell and the coordinates of the cell on the tissue section, and presents it as single cell data. This is mapped back onto the image with each cell annotated with its identity. Mathematical spatial statistics are used to examine statistical association between cells of interest; in our case regenerating alveolar epithelium and immune cells of interest e.g. Tregs.

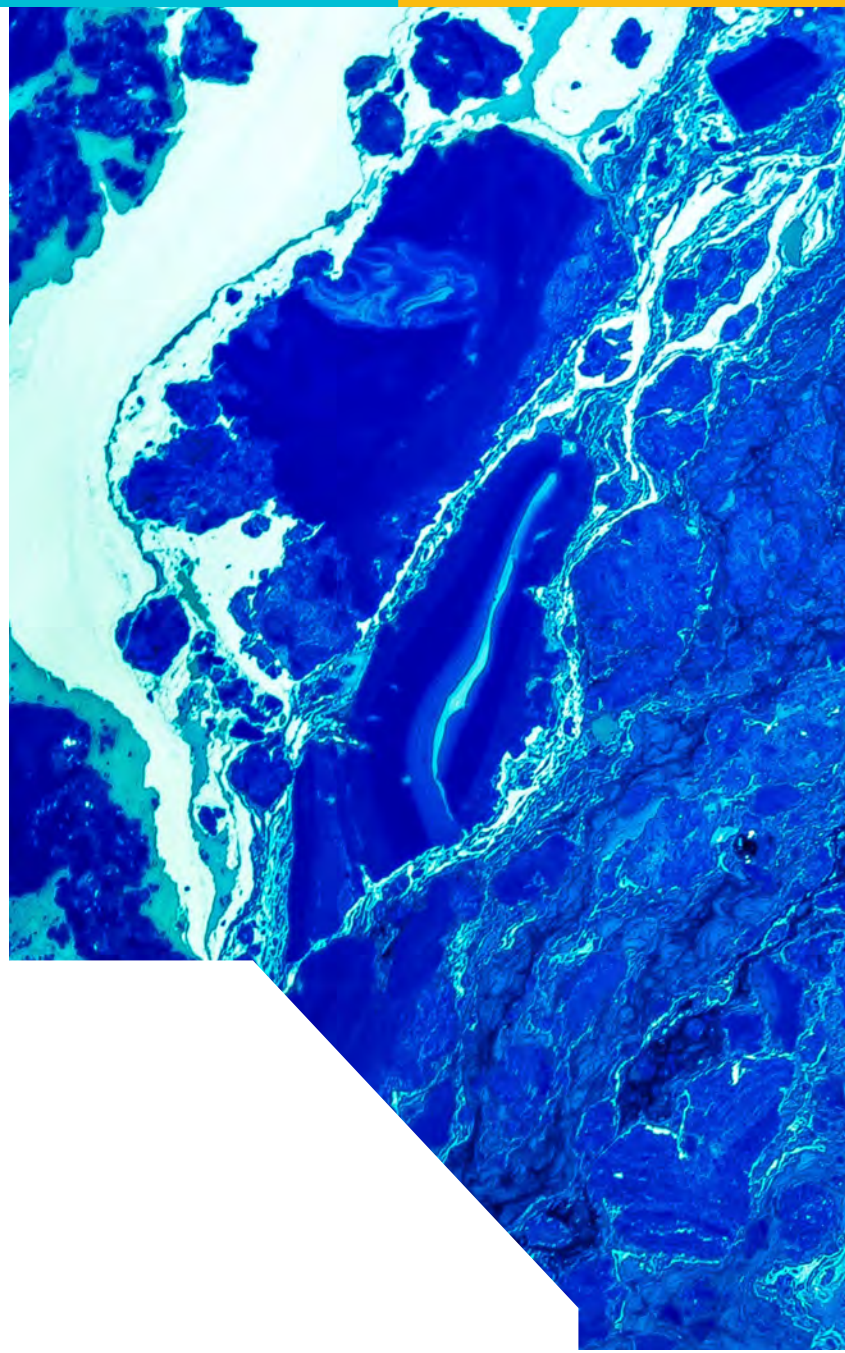
disease, leading edge and 'normal' tissue has been identified and sectioned (Figure 1, page 29). Samples are now being ablated and the study will provide the first ever detailed, spatially resolved atlas of immune cells associated with different areas of near-normal and aberrant alveolar regeneration in chronic lung fibrosis, using cutting edge and comprehensive single cell imaging technology.

(ii) Murine longitudinal studies of immune cellular response in the lungs during injury and normal alveolar regeneration, using multiparameter flow cytometry and single cell transcriptomic analysis. We have identified regulatory T cells (Tregs) and γδ T cells as cells with a potential role in normal alveolar regeneration due to their profile of response during injury and alveolar regeneration. Single cell transcriptomic studies of lung digest from multiple time points representing points of injury, alveolar regeneration and repair have also been completed and awaits RNA sequencing. In a separate model of high alveolar proliferation using neonatal mice (and selective depletion of Tregs at different time points using B6.FoxP3.DTR transgenic mice), our first set of optimised studies suggest that a subset of regulatory T cells (Jag1+ Tregs) is required for normal proliferation of type II alveolar epithelial cells.

Our murine studies suggest that γδ T cells and Tregs have a role in normal alveolar regeneration, and we are poised to examine the spatial location to disease and normal and aberrant alveolar regeneration in human fibrotic lungs. Completion of these studies will represent a significant step in better understanding of immune factors that influence normal and aberrant alveolar regeneration.

"The UKRMP has an essential purpose to address some of the key challenges facing the regenerative medicine field, including those related to immunology and safety. By funding projects that cut across the three scientific themes of the Platform, we are encouraging collaboration to overcome these barriers and successfully translate promising discoveries to the clinic."

Professor Paul Moss, Chair of UKRMP Programme Board



6. UKRMP Strategic Projects

6.1 MICA: Organ-on-a-chip models for safety testing of regenerative medicine products

Professor Hazel Screen (lead) (*Queen Mary University London*),
Professor Martin Knight (*Queen Mary University London*),
Professor Alicia El Haj (*University of Birmingham*)

Better model systems are urgently needed for safety and efficacy testing of regenerative medicine products, prior to clinical trials in people. Our project is focused on the design and development of a series of new 'organ-chips' to provide that function; engineered systems, in which the architecture, functions and surrounding physiochemical environment of a living human organ are recreated.

In collaboration with our industry partner, Emulate, we are using their platform technology within the QMUL-Emulate Organ-Chip centre, to build models of the joint environment, namely cartilage, synovium, bone, tendon and ligament. We have established protocols to isolate and culture multiple cell types from these tissues and are currently developing appropriate 3D matrix niches for each cell type, in which we can control mechanical properties, architecture and cell attachment profiles, to mimic those seen in the relevant joint niche.

We are also investigating the viability and stability of the cell populations in the multiple matrix niches, with data demonstrating that our matrix niche environments are able to maintain cells appropriately.

Initial phenotyping of models confirms they appropriately recapitulate the relevant human organ physiochemical environment, with further validation ongoing. We will progress to explore how each joint model responds to the UKRMP regenerative medicine products.

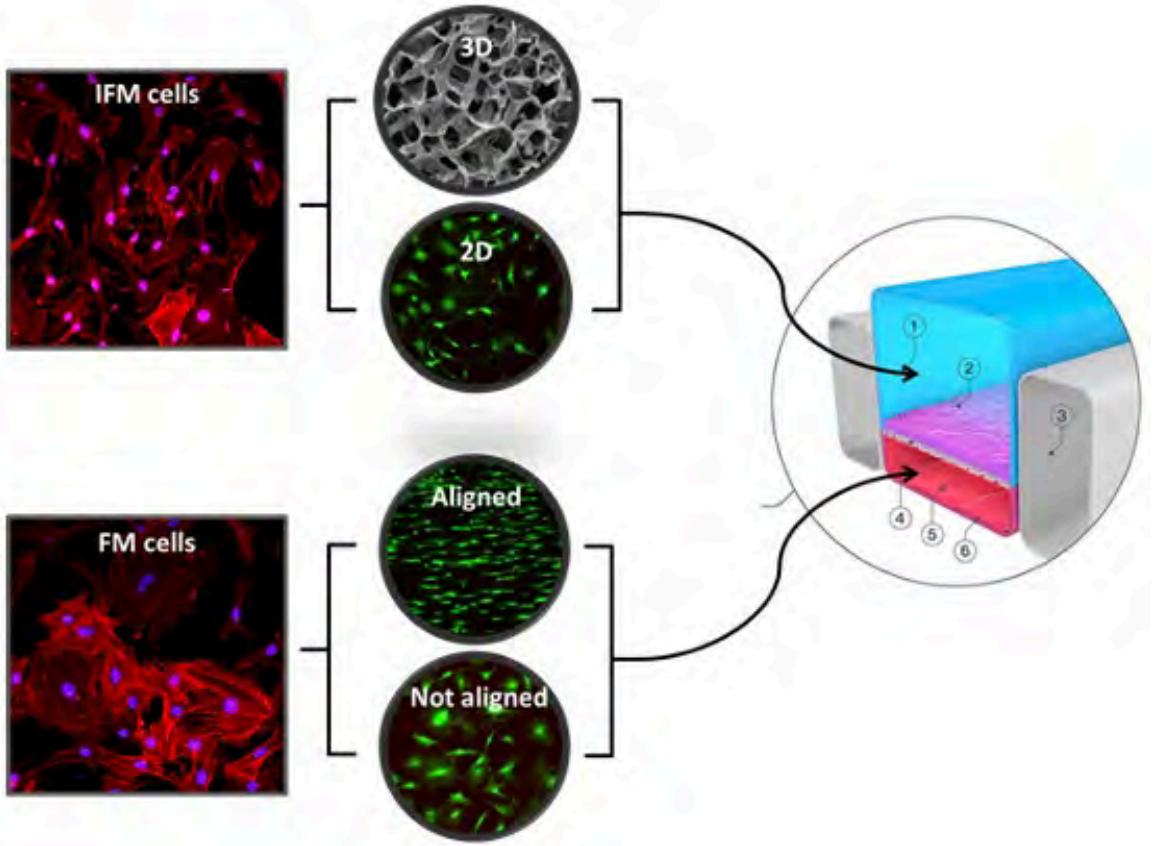
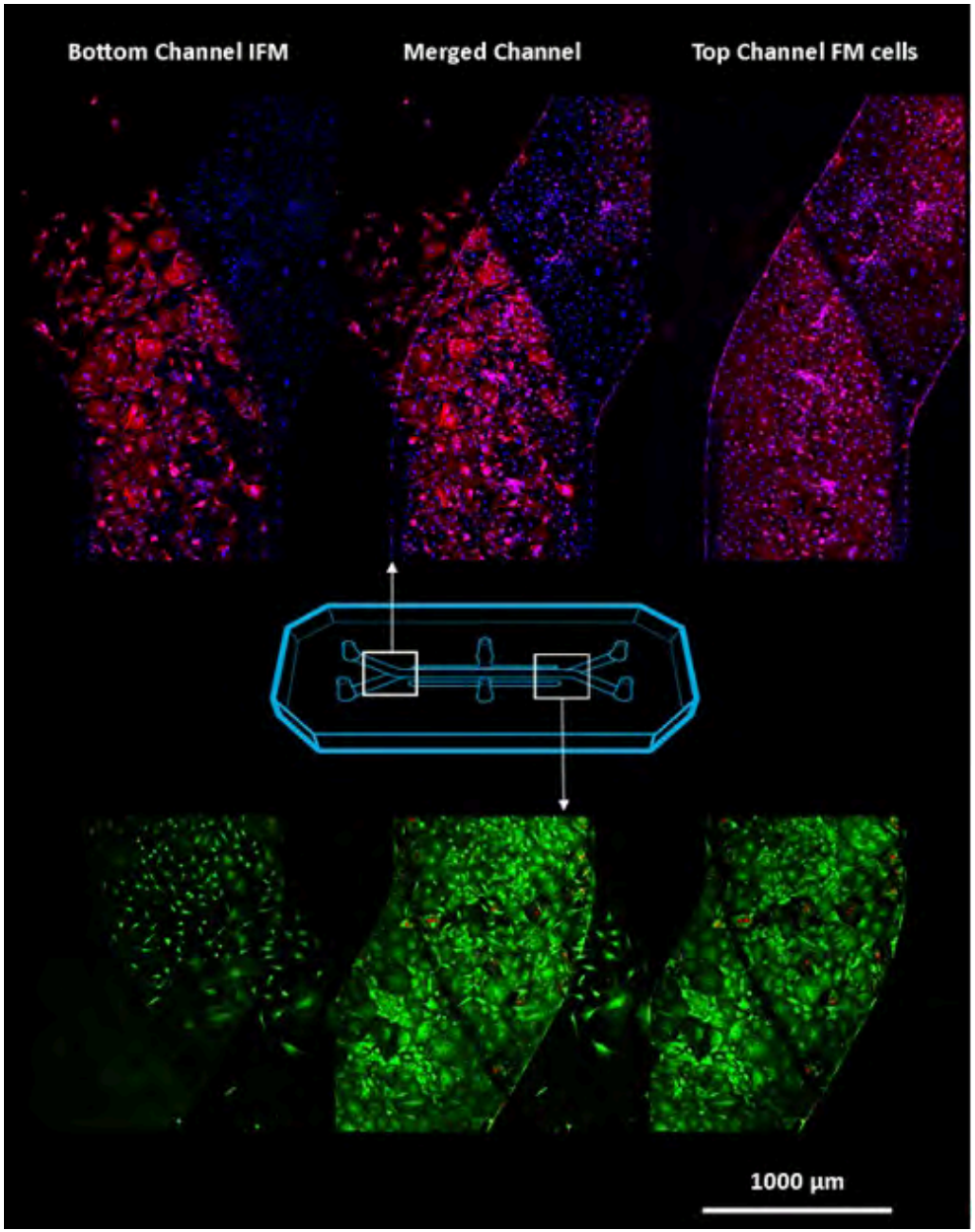


Figure 1 (right). We are building models within the Emulate organ-chip platform. Separate matrix niche environments can be built within each channel, enabling the organ-chip to house different cell populations in custom designed, physiochemically relevant niches. Our new tendon-chip model separates the functionally distinct tenocytes from the surrounding interfascicular cells, to explore how cell cross talk drives tendon disease, and how regenerative medicine approaches can be used to manipulate disease pathways.

Figure 2 (right). We are building organ-chip models within the Emulate platform (organ-chip schematic in middle). Our tendon-chip models separate the functionally distinct tenocytes from the surrounding interfascicular cells, to explore how cell cross talk drives tendon disease, and how regenerative medicine approaches can be used to manipulate disease pathways. Images show the two cell population successfully maintained within the chip environment, maintaining their phenotypic shape differences.



"BBSRC aims to support the development of our basic understanding of stem cell biology and advance new regenerative biology technologies. By contributing funding to flagship initiatives such as the UKRMP, we are enabling UK researchers to design and develop novel treatments that use the abilities of stem cells for replacing damaged, malfunctioning or diseased tissues."

Professor Melanie Welham, BBSRC Executive Chair

6.2 PEG-based hydrogels for iPSCs-derived regenerative therapies for diabetes

Dr Rocio Sancho (lead) (*King's College London*), Dr Eileen Gentleman (*King's College London*), Dr Aileen King (*King's College London*)

Type 1 and late-stage type 2 diabetes is caused by the loss of beta cells in the pancreas resulting in a reduction of insulin levels. Insulin is the only treatment available for diabetes and requires daily management. Promising therapies rely on using induced pluripotent stem cells (iPSC)-derived beta cells, nevertheless the differentiation process is still inefficient. 3D expansion of pancreas progenitor organoids (PPOs) in matrigel provide a good method for increasing such efficiency. However, the use of matrigel is incompatible with any translational cell therapy due to its composition.

Our project focuses on studying hydrogels to understand the molecular and physical cues required to generate iPSCs-derived functional beta cells and provide a safe platform to transplant beta cells that could be translated to human therapy in the future. We have identified the conditions that allow efficient expansion of PPOs. In hydrogels, PPOs cells form organoids (Figure 1) which retain high viability and expression of the key pancreatic differentiation markers (Figure 2).

In the next phase of our project, we will assess the beta cell differentiation potential of hydrogel grown PPOs compared to matrigel (Figure 3). Our results suggest that animal-origin free hydrogels may provide an alternative to matrigel in the generation of beta cells from stem cells.

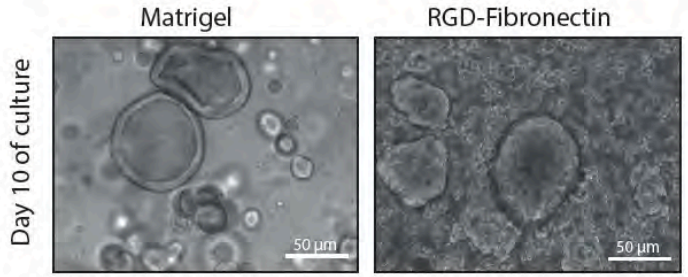


Figure 1. Bright field image of iPSC-derived pancreas progenitors organoids (PPO) grown in Matrigel and PEG-RGD hydrogel after 10 days in culture.

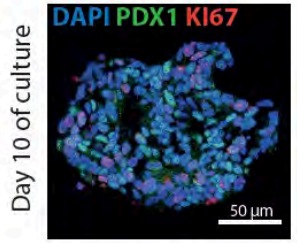


Figure 2. Immunofluorescence staining for Pdx1 and Ki67 on iPSC-derived pancreas progenitors organoids (PPO) after 10 days culture in hydrogels.

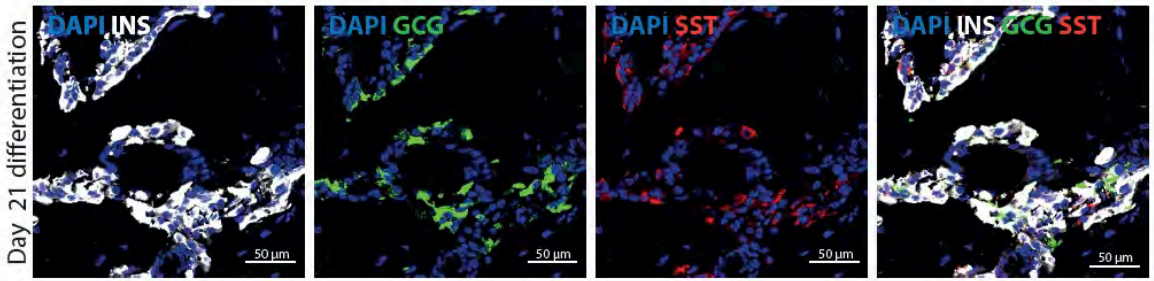


Figure 3. Immunofluorescence staining for Insulin (INS), Glucagon (GCG) and Somatostatin (SST) on matrigel grown PPOs after differentiation to beta cells.

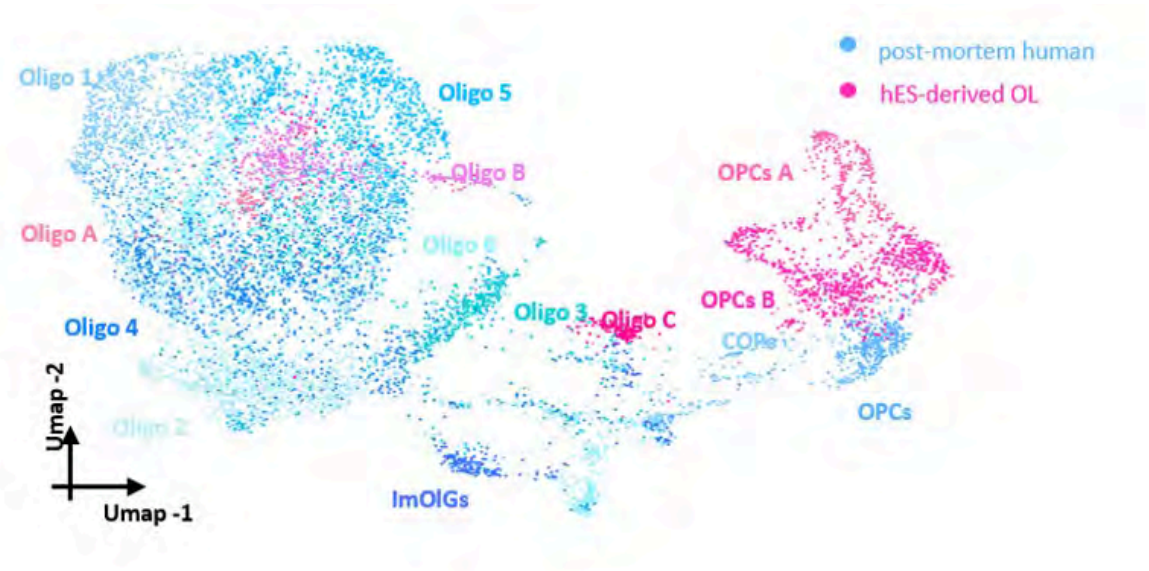
6.3 Do adult human oligodendrocytes remyelinate poorly and can we change this to better treat progressive multiple sclerosis?

Professor Anna Williams (lead) (*University of Edinburgh*),
Professor Robin Franklin (*University of Cambridge*)

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating and neurodegenerative disease of the central nervous system and is the commonest cause of non-traumatic disability in young adults, with a prevalence of around 1 in 500 people. The loss of myelin around axons, leads to the loss of fast saltatory nerve impulse conduction but also to lack of metabolic support normally provided via the myelin sheath from the oligodendrocyte to the axon. Although there is evidence that humans are able to repair the damage caused, through a process called remyelination, this process is inefficient and there is inevitable axon death and neurodegeneration, correlating with increasing patient disability. One way for remyelination to occur is for oligodendrocyte progenitor cells (OPCs) to divide, migrate to the injured site, differentiate into mature oligodendrocytes and contact and form new myelin sheaths around denuded axons.

Therapies that promote the differentiation of OPCs into mature oligodendrocytes have been tested in clinical trials in MS patients showing some promise, but no measurable symptomatic improvement. These therapies have mostly been selected based on screens for compounds to enhance remyelination in rodents and/or early postnatal OPCs. However, recent work has shown that adult rodent OPCs are reluctant to differentiate into mature oligodendrocytes, even when exposed to compounds very effective in promoting early postnatal OPC differentiation. Furthermore, human and rodent oligodendrocytes show differences. This leads to the hypothesis that there will be more effective translation of therapeutics to promote OPC differentiation and remyelination in MS patients if compounds are screened on adult human OPCs.

Figure 1. UMAP plot superimposing hES-derived oligodendroglia (pink) onto previous dataset of human adult oligodendroglia (blue) showing some overlap between OPC populations but with more immature cells in culture compared to adult tissue.



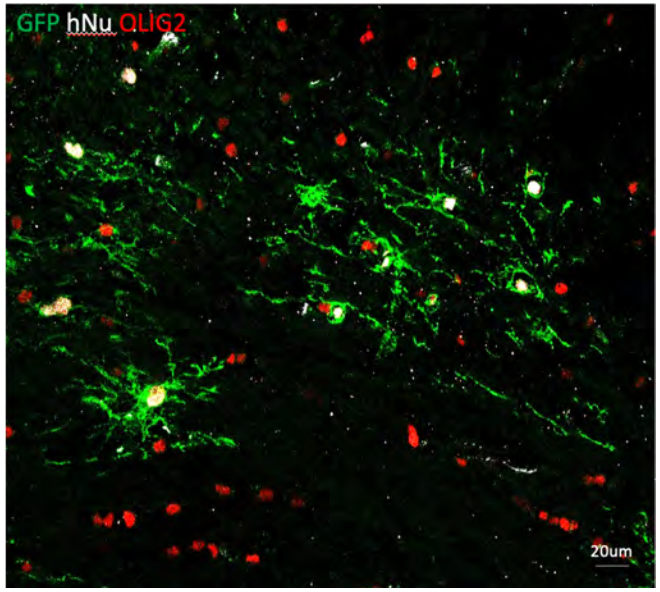


Figure 2: Human oligodendrocyte precursor cells (labelled with human nuclear antigen - hNu, GFP and OLIG2) transplanted into mouse brain where oligodendrocytes are only OLIG2+.

The aim of our project is to try and generate human OPCs that behave like adult OPCs that can be cultured in vitro to use for drug screening for pro-remyelinating drugs. To do this, we first needed to define markers of adult as compared to foetal OPCs, and so we performed bioinformatic analysis on single nuclei RNA sequencing datasets from human foetal and adult brains, subsetting for OPCs. Human OPCs can be generated from human embryonic stem cells (ESCs) in culture, but when we performed single cell RNASeq on these, we found that these cells were immature, with little overlap of transcriptomes with human adult OPCs from post-mortem tissue (Figure 1, page 33) and more overlap with human foetal OPC transcriptomes. Using our panel of markers for immature and mature human OPCs, we are now examining methods of 'aging' our immature hESC derived OPCs. This includes pharmacological manipulation but also by transplantation of these cells into mice (Figure 2, pg 33), forming mouse-human chimeras in which the cells mature long-term and can be extracted later for culture due to a GFP membrane tag (Figure 3). We hope that this work will generate a model of adult human OPCs that can be used for drug screening and discovery as well as disease modelling.

"The regenerative medicine field requires the bringing together of skills, expertise and infrastructure across a range of disciplines. Engineering and physical sciences has a vital role to play in the future direction of the field."

Dr Kedar Pandya, EPSRC Director for Cross Council Programmes

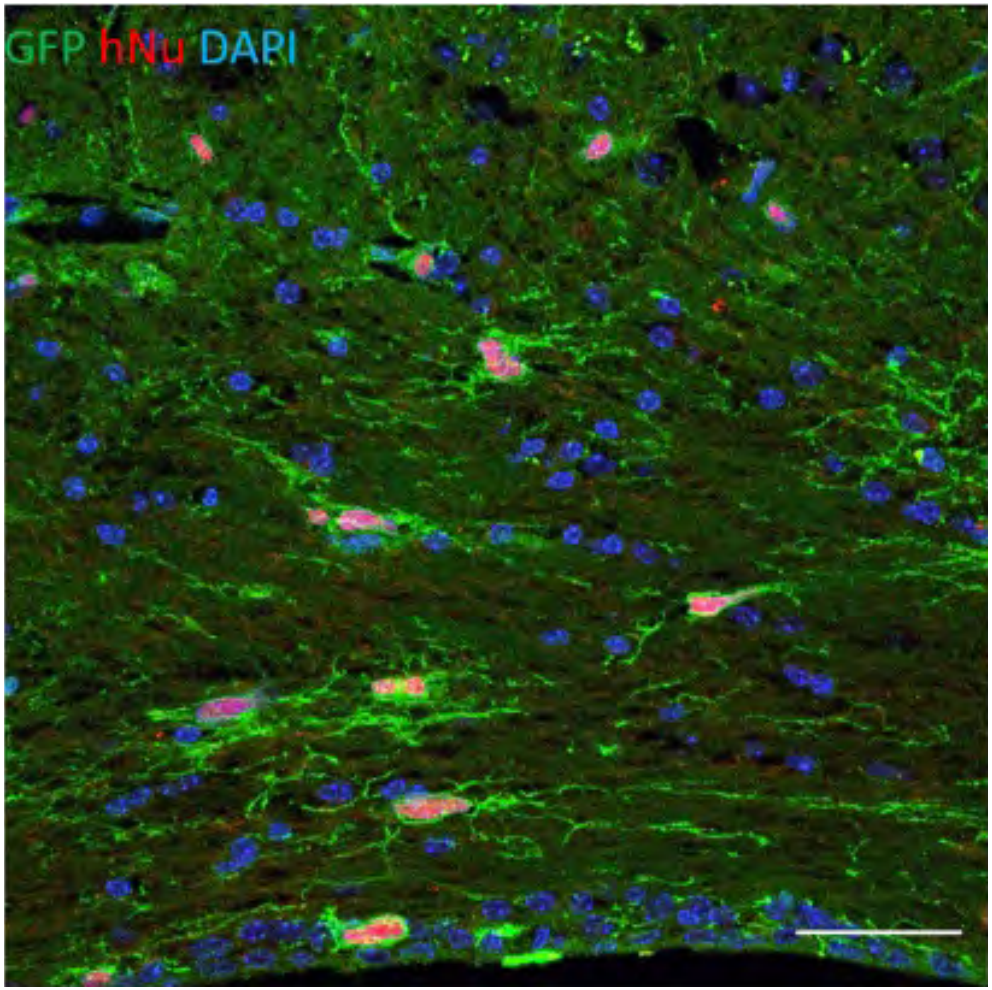


Figure 3. Human oligodendroglia, expressing endogenous GFP (green), fully integrated into the white matter of a human-mouse chimera. Human nuclear marker is in red, DAPI is in blue. Scale bar 20μm.

6.4 Exploiting *in silico* modelling to address the translational bottleneck in regenerative medicine safety

E Antonopoulou, S Finney, C Ashmore-Harris, MR Vieira, VL Gadd, MG Hennessy, A Muench, WY Lu, SJ Forbes, AJ El Haj and SL Waters (lead)

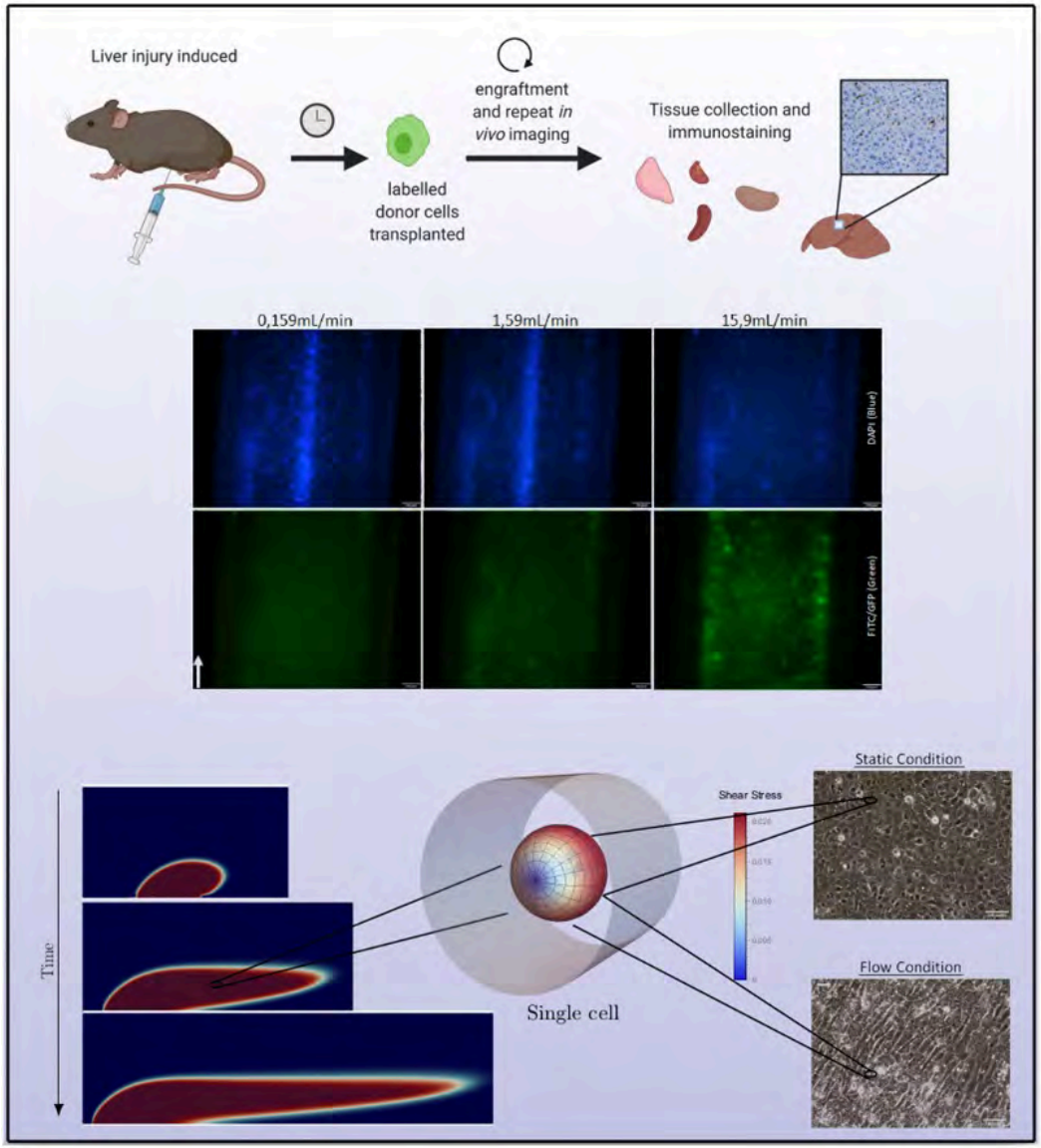
Successful clinical translation of cell therapies requires robust preclinical approaches to assess their safety, toxicity and efficacy. We focus on liver cell therapies, and combine *in silico*, *in vitro* and *in vivo* approaches to determine how the mechanical environment experienced by cells in transit to the injury site impacts cell delivery to, and their ability to engraft at, the site of injury.

In vivo models: Post injection, imaging of the transplanted cell distribution is vital to quantify cell engraftment. We have determined a suite of cell labelling strategies to enable real-time, whole body level *in vivo* imaging of cells, as well as tissue quantification.

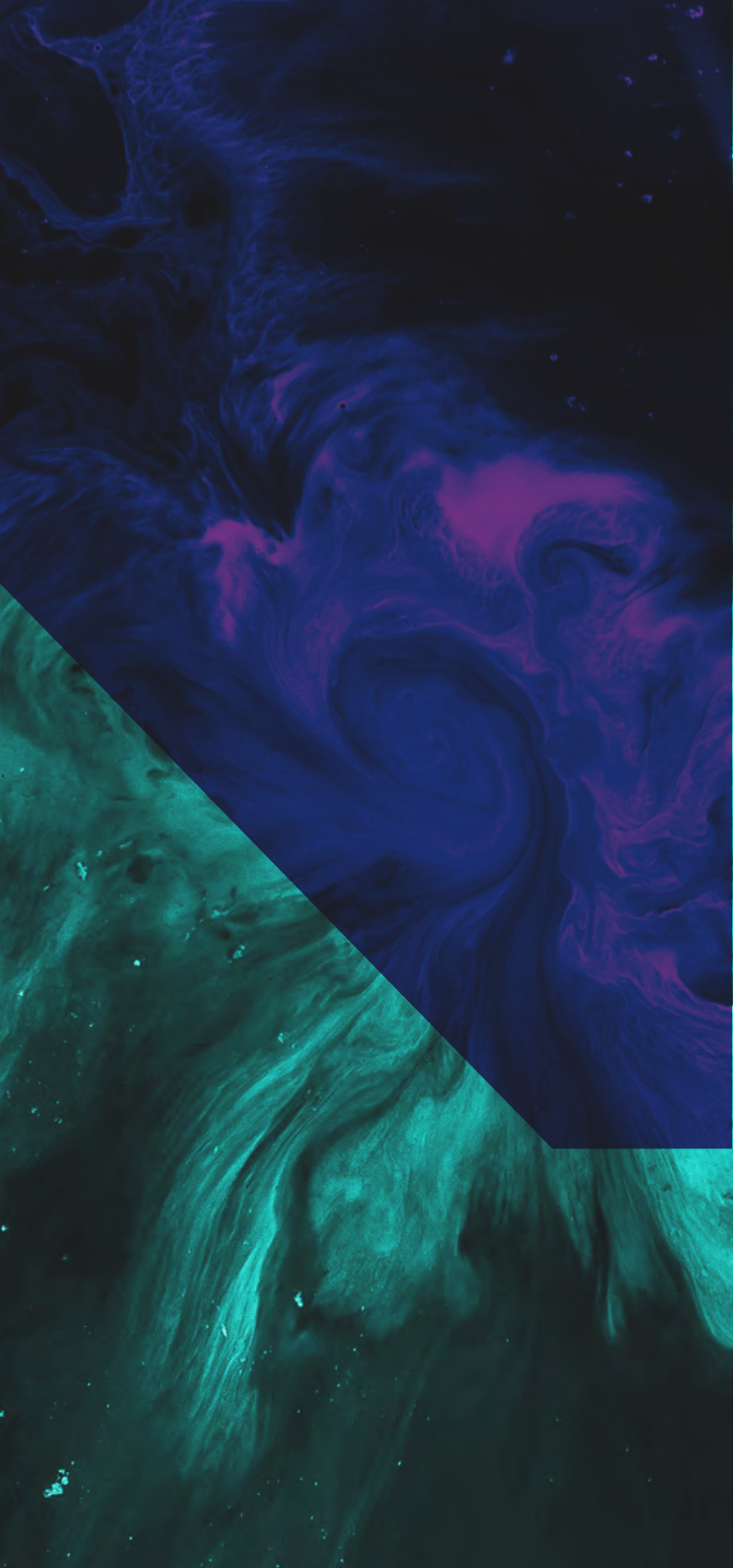
In vitro model: We assess the impact of flow on cell viability and key matrix attachment proteins, such as the family of integrins. Using an experimental model that mimics the physiological flow, we maintain viability and upregulate specific integrin patterns of expression, providing evidence that preconditioning of cells could promote cell engraftment.

In silico models: We solve reductions of the Navier-Stokes equations to determine fluid flow. The transport of a population of transplanted cells is modelled via an advection-diffusion equation, and we determine the fraction of cells reaching the injury site. We also determine the mechanical stress experienced by a single cell translating in a vessel.

Comparison of these complementary data sets enables the stress experienced by the cells in transit to the liver to be related to integrin expression, providing insights into how the mechanical cell environment can be modulated to promote downstream cell engraftment. These insights can be used to guide and optimise novel cell therapy protocols.



7. Annexes



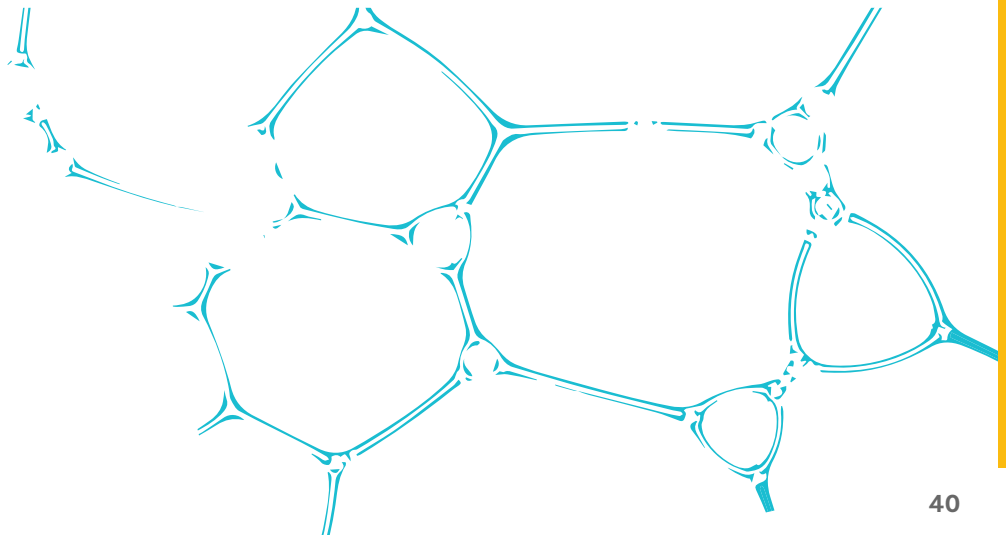
Annex 1 – UKRMP Governances

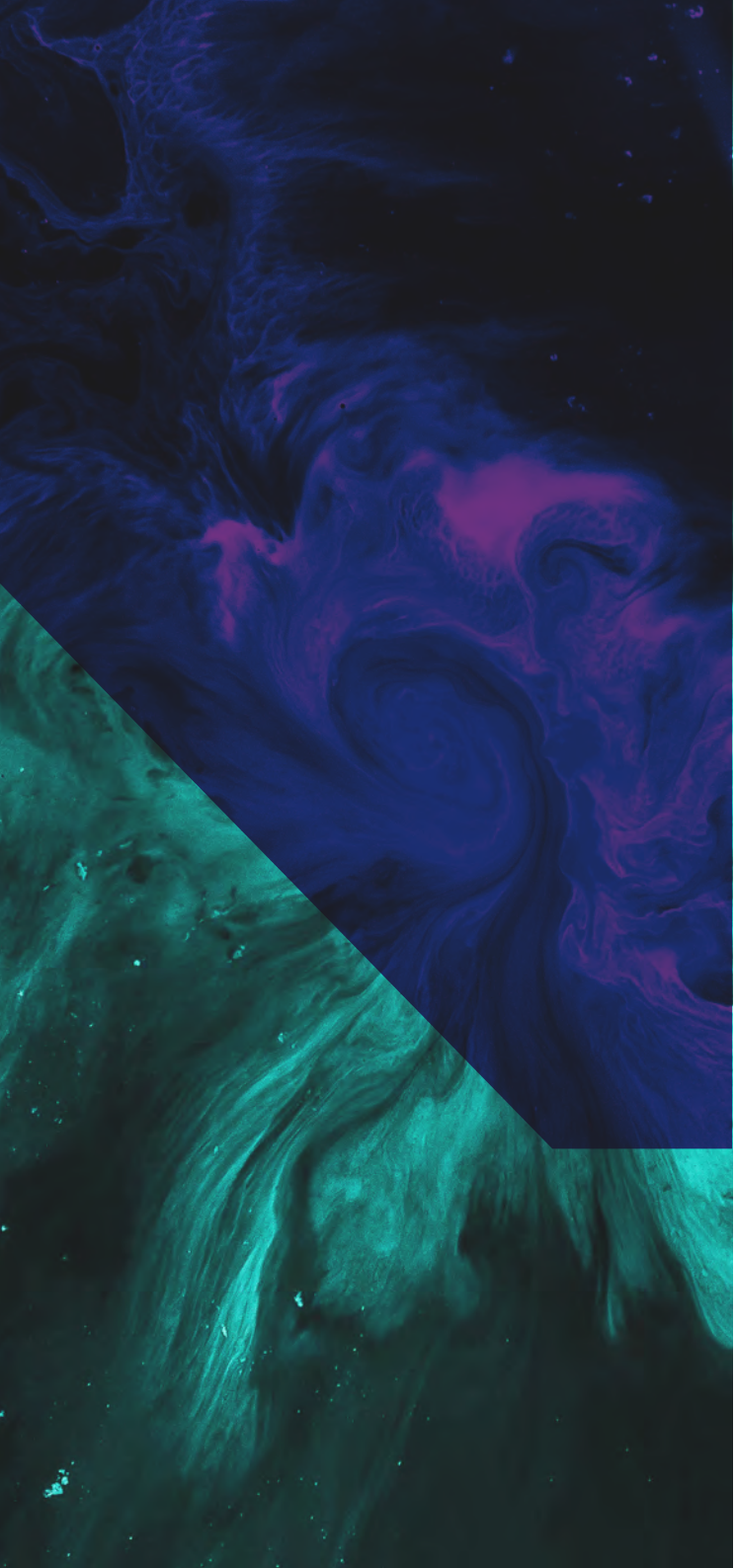
UKRMP Executive Group

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

UKRMP 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 – Gruenthal, UK
- Professor Jöns Hilborn – Uppsala University, Sweden
- Dr Bo Kara – Mereo BioPharma, UK
- Professor Dr Petra Reinke – Berlin-Brandenburg Centre for Regenerative Therapies, Germany
- Professor Anne Rosser – Cardiff University, UK
- Professor Christine Mummery – Leiden University, The Netherlands
- Professor Gerry Graham – University of Glasgow, UK





Annex 2 – UKRMP Awards

UKRMP Hub Awards

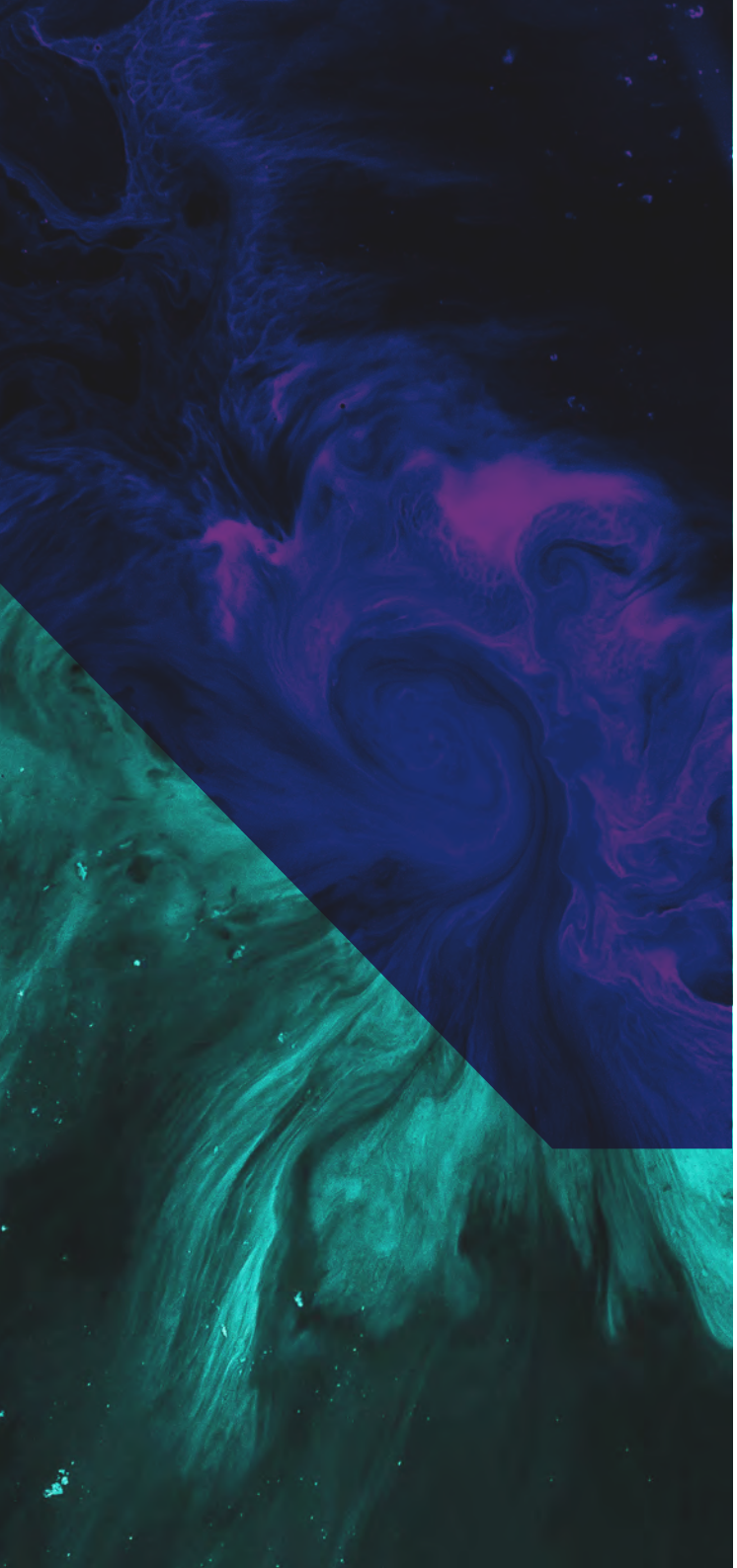
- Professor Roger Barker, University of Cambridge
  The Pluripotent Stem Cells and Engineered Cell (PSEC) Hub - £4.1M
- Professor Stuart Forbes, University of Edinburgh
  The Engineered Cell Environment (ECE) Hub - £4.1M
- Professor Molly Stevens, Imperial College London
  Acellular/Smart Materials –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

UKRMP Immunology Awards

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

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 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



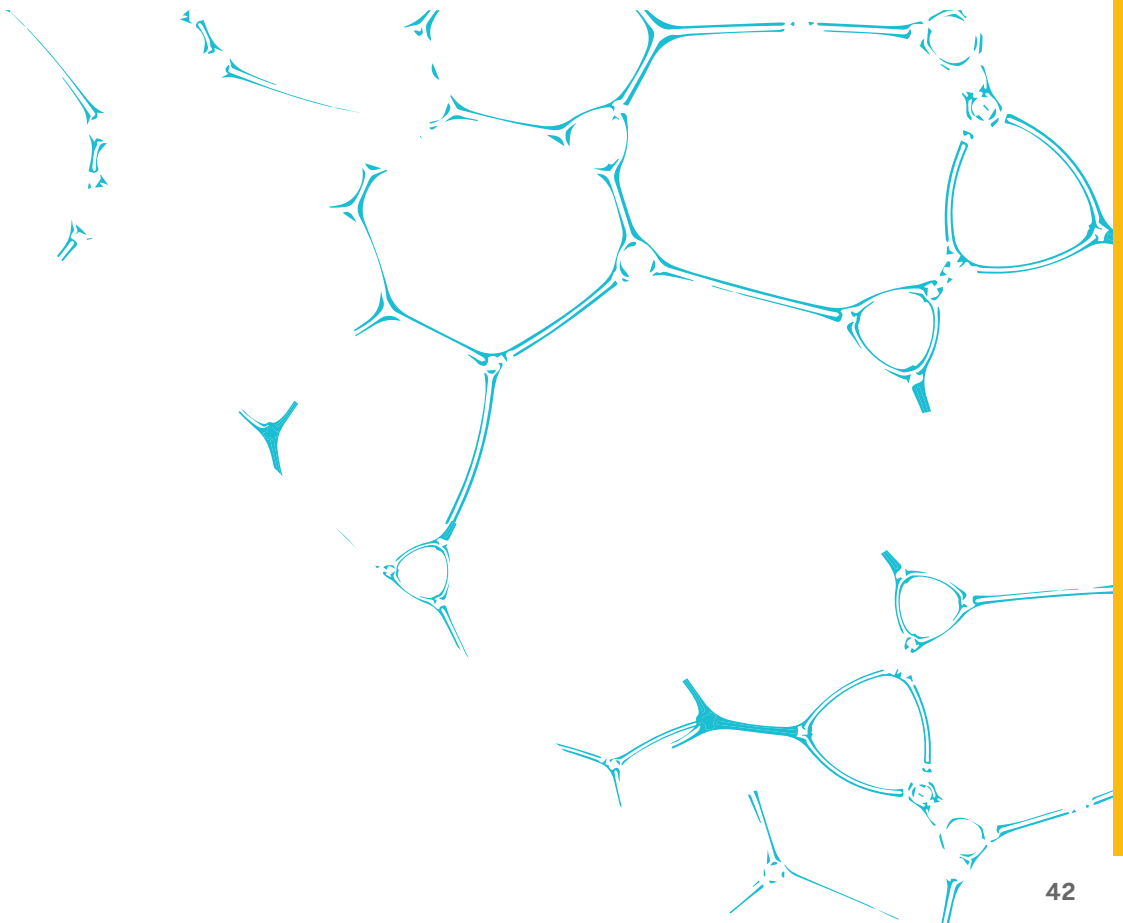
UKRMP Pump-Priming Awards

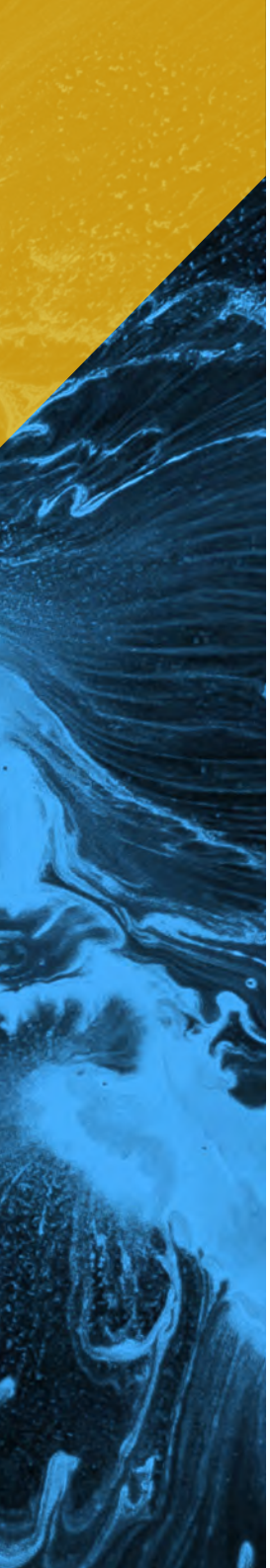
- Professor Molly Stevens, Imperial College London
  ISO testing of target product profiles - £120k

- Professor Cedric Ghevaert, University of Cambridge
  Universal macrophage production for the treatment of liver fibrosis - £144k

- Dr Eileen Gentleman, Kings College London
  Profiling immune cell interactions with thiol-reactive biomaterials - £68k

- Dr Kourosh Saeb-Parsy, University of Cambridge
  Generation of liver-immune double chimeric humanised mouse models: a platform for simultaneous assessment of function and immunogenicity of liver-specific cellular therapies - £117k





Annex 3 – UKRMP Hub Research Teams

PSEC Hub

Principal Investigators:

Professor Roger Barker, University of Cambridge (Director)

Professor Cedric Ghevaert, University of Cambridge (Deputy Director)

Dr Florian Merkle, University of Cambridge

Professor Serena Nik-Zainal, University of Cambridge

Dr Ivana Barbaric, University of Sheffield

Professor Robert Thomas, Loughborough University

Professor Wolf Reik, Babraham Institute

Research Team:

Dr Zoe Hewitt, University of Sheffield (Project Manager)

Dr Amanda Evans, University of Cambridge

Dr Shaline Fazal, University of Cambridge

Mr Imam Mali, University of Cambridge

Dr Venkat Pisupati, University of Cambridge

Dr Amie Waller, University of Cambridge

Miss Cathy Beltran-Rendon, Loughborough University

Dr Preeti Holland, Loughborough University

Miss Gabriele Gelezauskaite, University of Sheffield

Dr Christopher Price, University of Sheffield

Dr Dylan Stavish, University of Sheffield

Mr Owen Laing, University of Sheffield

Mr Theodore Wing, University of Sheffield

Dr Duncan Baker, University of Sheffield/Sheffield Children's NHS Foundation Trust

Associated UKRI/Rutherford Fund Fellows:

Dr Stefan Schoenfelder, is now a Babraham Institute Career Progression Fellow within the Epigenetics Department and co-founder of the biotech/ functional genomics spinout Enhanc3D Genomics.

Dr Wei-Li (William) Kuan is now a Principal Scientist at Talisman Therapeutics, developing iPSC-derived neuronal models to screen drug candidates with therapeutic potential for Alzheimer's disease.

PSEC Alumni:

Dr Yang Cao, Babraham Institute and Dr Benjamin Vallin, University of Cambridge were both Post-Doctoral Researchers associated with our linked UKRI/Rutherford Fund Fellows. With these fellowships having ended, they are no longer associated with our Hub. Dr Cao continues to work at the Babraham Institute with Dr Stefan Schoenfelder whilst Dr Vallin has now moved to Oxford, to work with Professor Richard Wade-Martins at the Oxford Parkinson's Disease Centre.

Dr Maria Rostovskaya, alumnus Post-Doctoral Researcher, Babraham Institute, has now been awarded a Researcher Co-I position at Babraham Institute, working towards an independent fellowship.

Dr Moyra Lawrence, alumnus Post-Doctoral Researcher, University of Cambridge is now an Independent Research Fellow at CIRA, Japan.

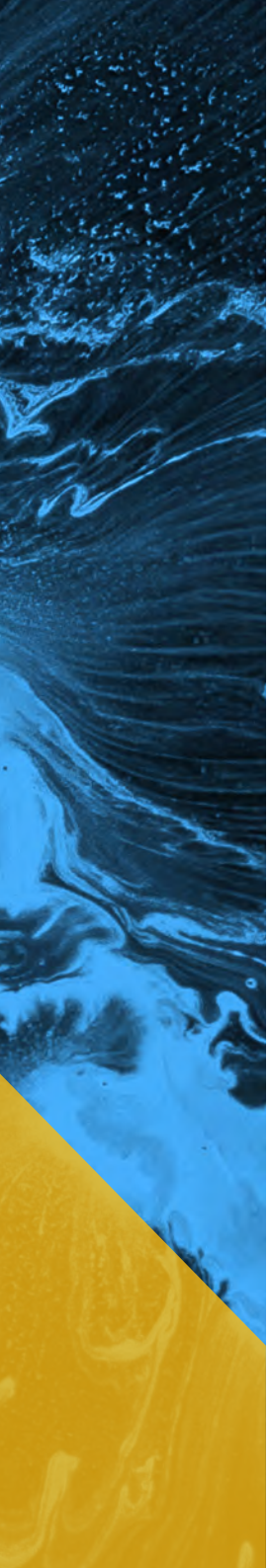
Dr Minjung Song, alumnus Post-Doctoral Researcher, University of Cambridge now Senior Scientist at Crescendo Biosciences.

Dr Hanif Ghanbar, alumnus Post-Doctoral Researcher, Loughborough University.

Dr Marta Milo, alumnus co-PI, University of Sheffield now Research Data Science Lead, Biostatistics & Combinations in Oncology R&D at AstraZeneca.

Dr Mark McCall, alumnus co-PI, Loughborough University now Quality Site Lead at Norbrook Laboratories Ltd, Belfast.

Mrs Mercy Suchanek (Danga), alumnus Research Assistant, University of Cambridge now Procurement Manager at Oncologica UK.



PSEC Alumni (continued):

Miss Antigoni Gogolou, alumnus Research Technician now PhD candidate at the University of Sheffield.

Mr Thomas Mattimoe, alumnus Research Technician, University of Sheffield now PhD Candidate at Centre for Genomic Regulation, Barcelona after being an R&D Scientist at Stem Cell Technologies.

Dr Ferdinand von Meyenn, alumnus UKRI/Rutherford Fund Fellow, Kings College London now Assistant Professor at ETH Zurich.

Smart Materials Hub

Professor Molly Stevens, Imperial College London (Director)

Professor Felicity Rose, University of Nottingham (Deputy Director)

Professor Andrew Carr, University of Oxford

Professor Jonathan Jeffers, Imperial College London

Dr Bohwon Kim, Imperial College London (Programme Manager)

Professor Alvaro Mata, University of Nottingham

Associate Professor Lisa White, University of Nottingham

Professor Ricky Wildman, University of Nottingham

Associate Professor Pierre-Alexis Mouthuy, University of Oxford

Professor Richard Oreffo, University of Southampton

Dr Nicholas Evans, University of Southampton

Dr Jon Dawson, University of Southampton

Professor Stuart Forbes, University of Edinburgh

Professor Mark Bradley, University of Edinburgh

Professor Robin Ali, King's College London

Professor Rachel Williams, University of Liverpool

Professor Manual Salmeron-Sanchez, University of Glasgow

Professor Alberto Saiani, University of Manchester

Associate Members:

Dr Eileen Gentleman, King's College London

Professor Julian R Jones, Imperial College London

Professor Matthew Dalby, University of Glasgow

Dr Mathis Riehle, University of Glasgow

Dr Eoghan M Cunnane, University of Limerick

Associated UKRI/Rutherford Fund Fellows:

Dr James Armstrong is now a UKRI Future Leaders Fellow, leading a research group based in Translational Health Sciences at the University of Bristol seeking to develop biotechnologies for organoid engineering.

Dr Marco Cantini is now a Lecturer at the University of Glasgow, working within the University's Advanced Research Centre to develop dynamic biointerfaces and viscoelastic hydrogels for the regulation of stem cell fate.

Hub Research Teams (PDRA's)*:

Dr Jonathan Wojciechowski, Imperial College London

Dr Tao Yang, Imperial College London

Dr Karen Marshall, University of Southampton

Dr Robert Owen, University of Nottingham

Dr I-Ning Lee, University of Nottingham

Dr Abshar Hasan, University of Nottingham

Dr Emma West, King's College London

Dr Victoria Gadd, University of Edinburgh

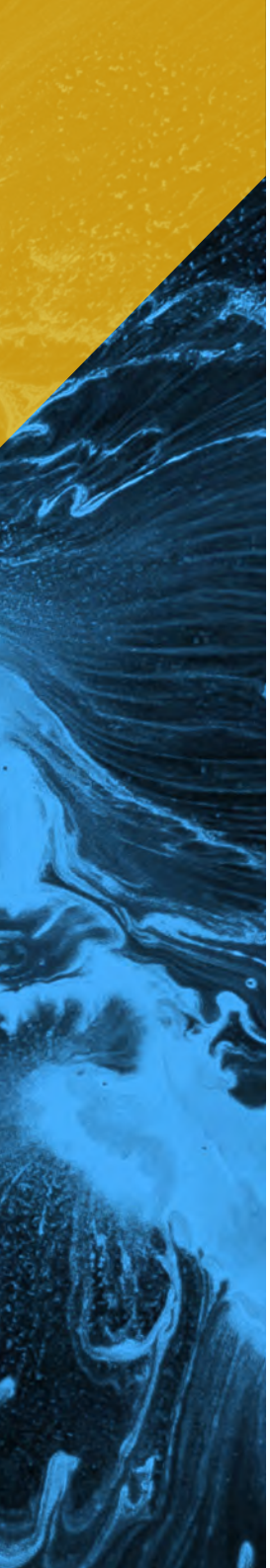
Dr Vineetha Jayawarna, University of Glasgow

* UKRMP post-docs only

Smart Materials Alumni:

Dr Axel Moore, alumnus Post-Doctoral researcher at Imperial College London, is now Research Scientist at the University of Delaware in the Department of Biomedical Engineering, USA.

Dr He Liang, alumnus Post-Doctoral researcher at the University of Liverpool, is now Product development scientist at 4D Biomaterials.



ECE Hub

Principal Investigators:

Professor Stuart Forbes, University of Edinburgh (Director)
Professor Alicia El Haj, University of Birmingham (Deputy Director)
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 Neil Carragher, University of Edinburgh
Professor David Hay, University of Edinburgh
Dr Shukry Habib, Kings College London
Professor Fiona Watt, Kings College London
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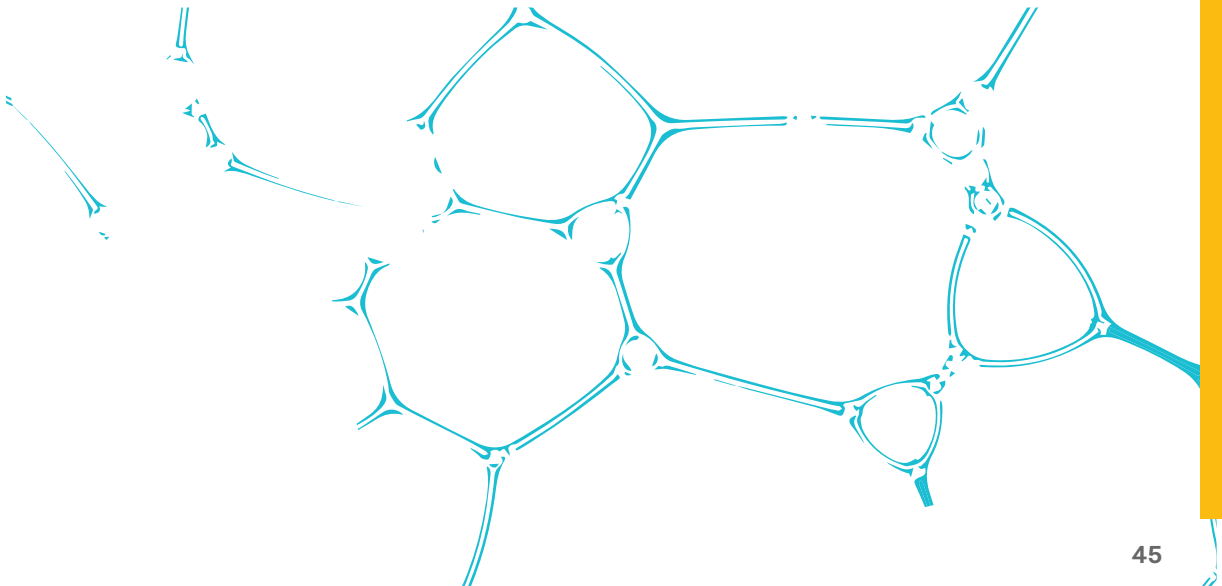
Dr Rawiya Al Hosni, University of Cambridge
Dr Victoria Gadd, University of Edinburgh
Dr Cecilia Rocchi, University of Edinburgh
Dr Josephine Barnes, University College London
Dr Masahiro Yoshida, University College London
Dr Yuki Ishii, University College London
Dr Angela Imere, University of Birmingham
Mr Joshua Reeves, Kings College London
Ms Tjasa Bensa, Kings College London
Dr Rebecca Hughes, University of Edinburgh
Mr Mantas Jonaitis, University of Edinburgh

Associated UKRI/Rutherford Fund Fellows:

Dr Elaine Emmerson, University of Edinburgh
Dr Marko Nikolic, University College London



Annex 4 – Hub publications since previous report (2019)

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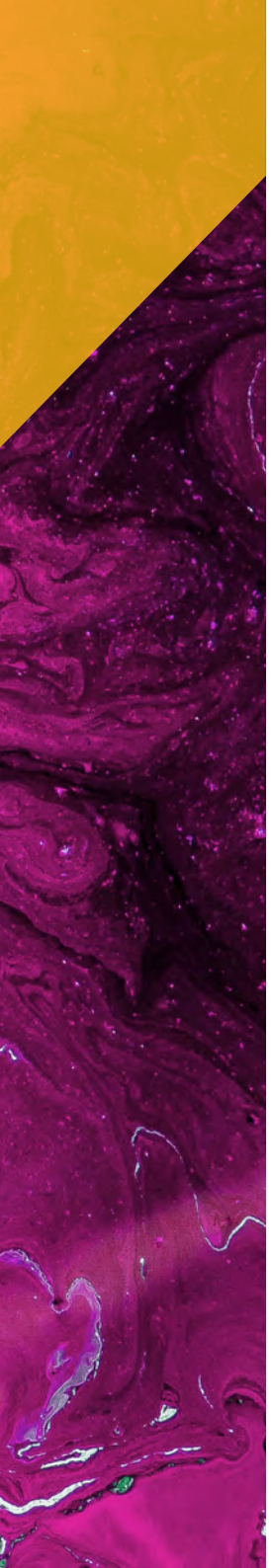

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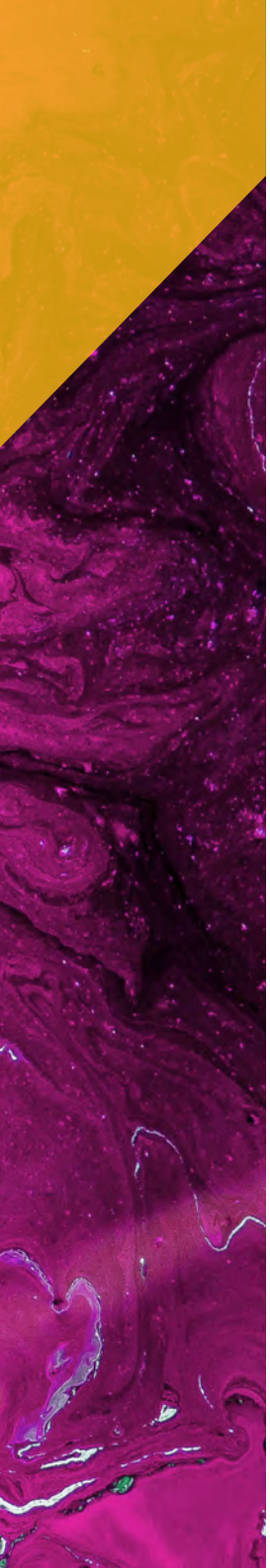

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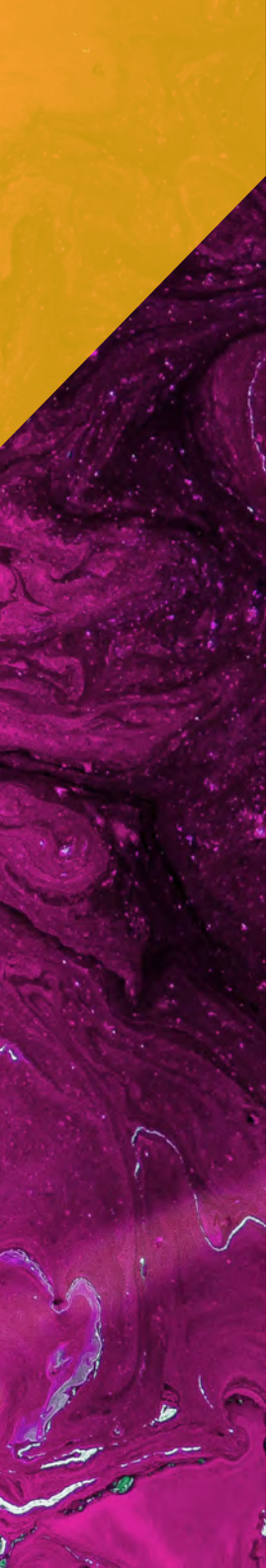

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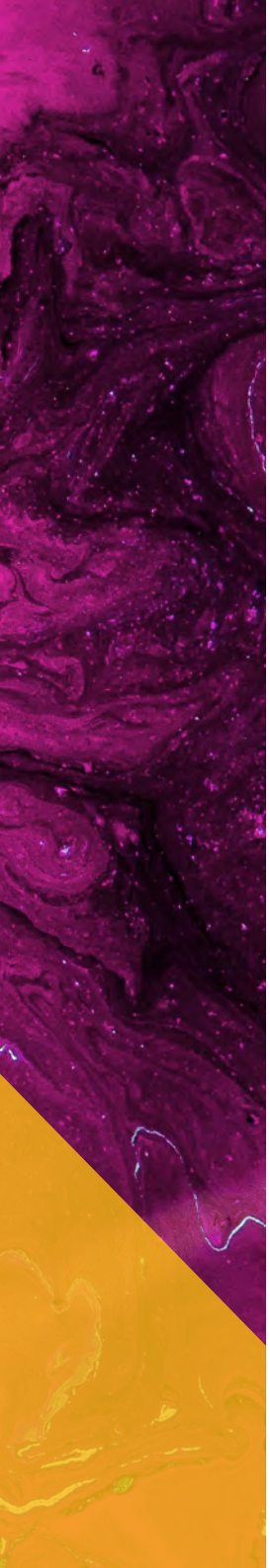

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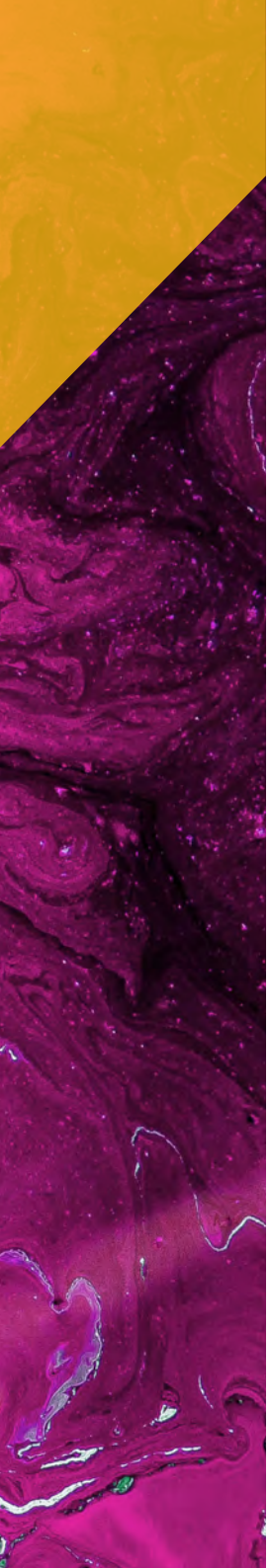

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