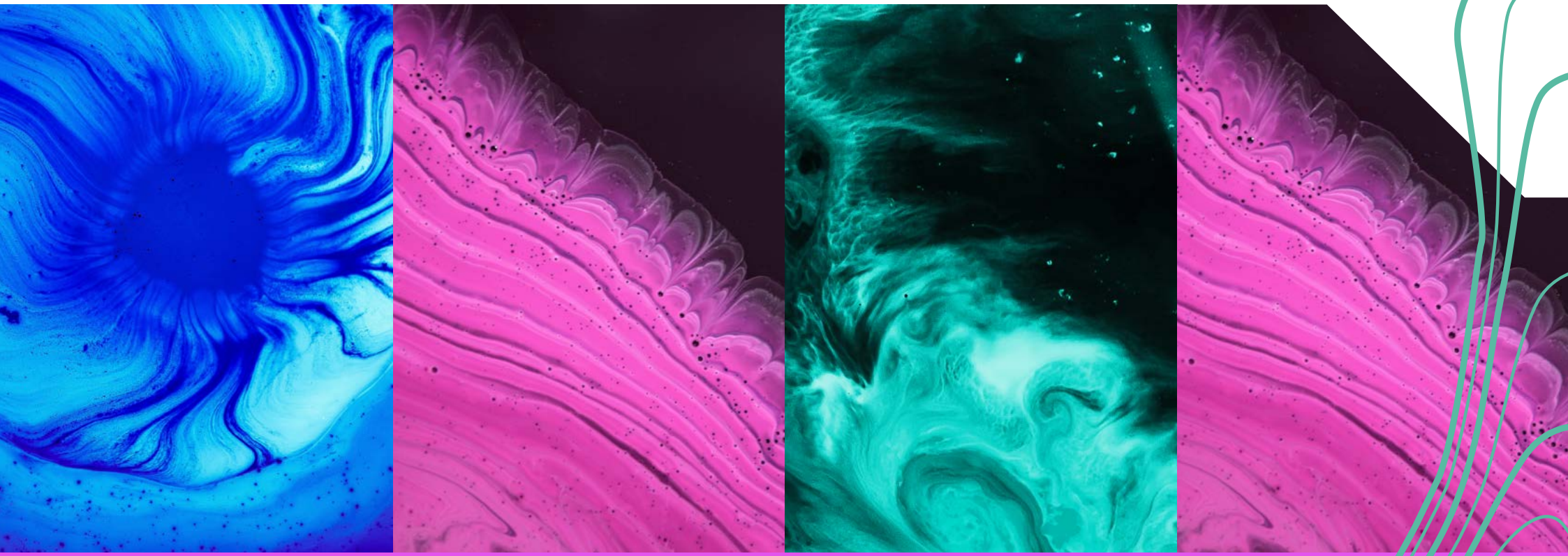
EPSRC, BBSRC and MRC

UK Regenerative Medicine Platform

End Report

2024



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1. Introduction

1 Introduction

The UK Regenerative Medicine Platform (UKRMP) is a £42m national initiative that brought 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), Engineering and Physical Sciences Research Council (EPSRC) and Medical Research Council (MRC), the UKRMP completed its second and final phase of funding in 2024. Eleven years of continuous strategic investment focussed on building a truly interdisciplinary agenda has helped address critical roadblocks to progress and established the UK at the forefront of the international regenerative medicine landscape. This final report aims to celebrate the exciting outcomes of the initiative, focusing on its recent second phase which began in 2018.

The overall mission of UKRMP was to overcome hurdles in bringing innovative regenerative medicine therapies to patients. Specifically, UKRMP had three aims:

- To establish several interdisciplinary research hubs with the critical mass and expertise to address the key knowledge gaps in the translation of stem cell biology and regenerative medicine towards application;
- To provide novel tools, platform technologies and engineering solutions needed for therapeutic development; and
- To create a world-leading and fully connected national programme to pull through excellent discovery science in support of the commercial development and clinical delivery of regenerative medicine products.

UKRMP was delivered in two phases. The first tranche of funding (£25m) between 2013-2018 drew together the major players in UK regenerative medicine and supported five interdisciplinary and complementary research hubs, as well as five disease-focused projects.
The five UKRMP1 hubs were:

- Cell behaviour, differentiation and manufacturing Hub (Director: Peter Andrews, University of Sheffield)
- Engineering and exploiting the stem cell niche Hub (Director: Stuart Forbes, University of Edinburgh)
- Safety and efficacy, focussing on imaging technologies Hub (Director: Kevin Park, University of Liverpool)
- Acellular approaches for therapeutic delivery Hub (Director: Kevin Shakesheff, University of Nottingham)
- Immunomodulation Hub (Director: Fiona Watt, King's College London)

Introduction

Starting in 2018, the second phase (£17m) represented an evolved and consolidated structure of three interdisciplinary research hubs that captured and built on the strengths of the previous funding period. Each hub had its own broad but distinctive focus, supported by a dedicated research team and connections to commercial and clinical end-users. As such, every UKRMP2 hub provided a UK 'centre of expertise' for their specific thematic area:

- The Pluripotent Stem Cells and Engineered Cells Hub (Director: Roger Barker, University of Cambridge) aimed to advance regenerative medicine by overcoming the key outstanding hurdles to translate human pluripotent stem cell based cellular therapies into standard clinical practice.
- The Engineered Cell Environment Hub (Director: Stuart Forbes, University of Edinburgh) aimed to facilitate the regeneration and repair of damaged organs with a particular focus on the role of the stem cell graft environment or "niche" within the body.
- The Smart Materials Hub (Director: Molly Stevens, Imperial College London) aimed to develop the next generation of bioactive scaffolds and biomatrices for clinical applications.

Collectively, the UKRMP hubs have provided a central source of expertise and knowledge – generating new tools, protocols and resources that can be utilised by other research groups in both academia and industry. **Chapter 3** provides a detailed list of resources made available to the community by UKRMP2 and we encourage researchers to take full advantage of these.

A key element within UKRMP2 was the cluster of cross-cutting projects to help accelerate the research undertaken in each hub towards clinical application. In 2018, UKRMP provided £2.5m of funding for new projects that specifically focused on the immunological issues of regenerative medicine. Furthermore, four strategic research projects were supported in 2019, two co-funded with the Juvenile Diabetes Research Foundation (JDRF) and the Multiple Sclerosis (MS) Society. The establishment of new projects like these brought new researchers into the platform to add capability and further foster collaboration within UKRMP2, furthering the effort to address translational bottlenecks in regenerative medicine.

The fascinating, leading-edge research and impactful outcomes of the UKRMP2 hubs and projects are summarised in this report. Several case studies highlight particularly exciting outcomes within each hub while comprehensive publication lists are provided in **Annex 1**.

We hope this report will be valuable to the community in bringing fully into view the activities and outputs across the Platform over the past decade. We also look forward to seeing the established collaborations continue to drive progress in the coming years, effectively bridging the gap between bench and the clinic to bring to fruition the much-anticipated transformative impact of regenerative medicine on human health.

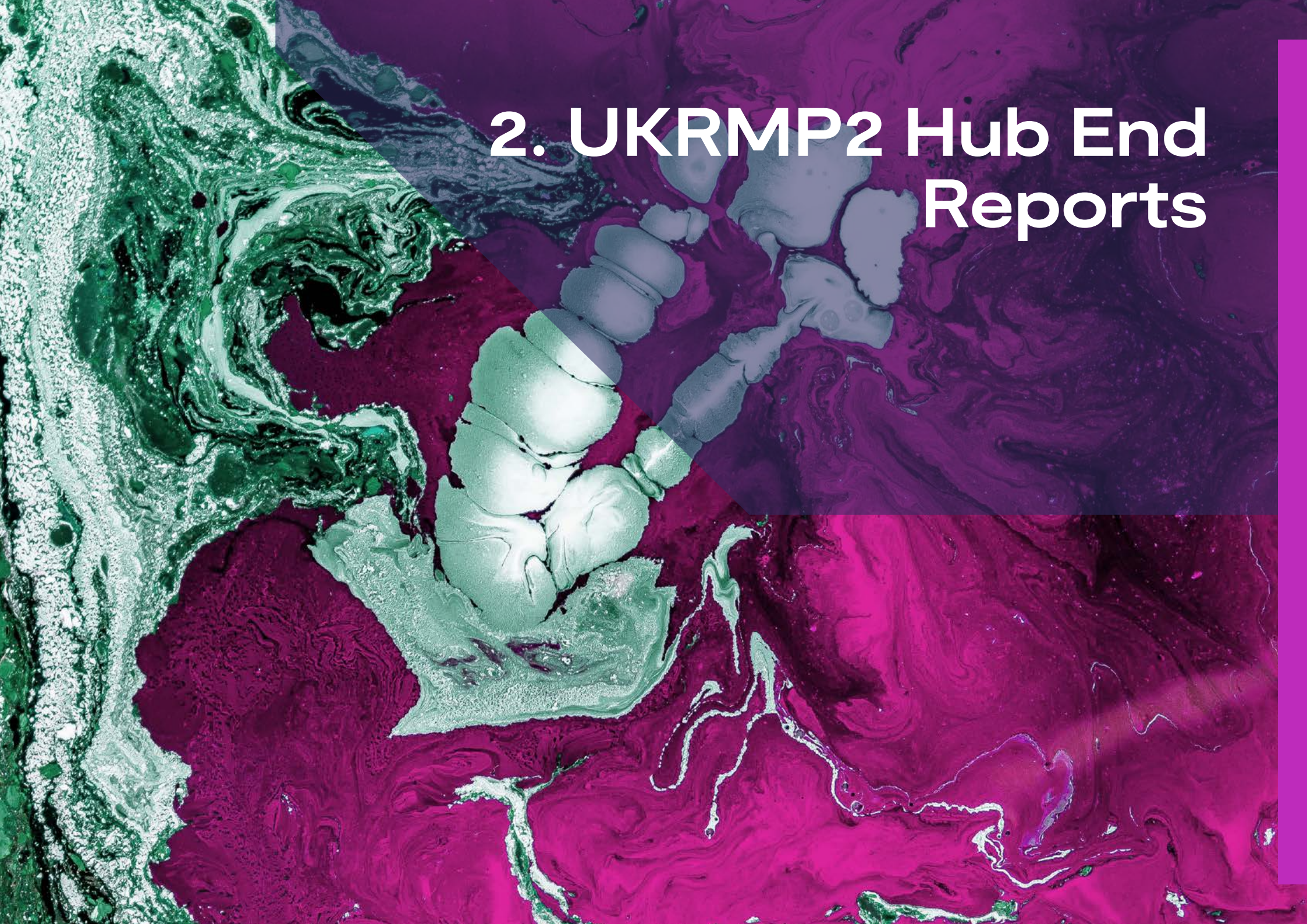
UKRMP Executive Group:

Rob Buckle (UKRI MRC)

Philippa Hemmings (UKRI EPSRC)

Paul Moss (University of Birmingham)

Sadhana Sharma (UKRI BBSRC)



2. UKRMP2 Hub End Reports

2.1 Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

Who are PSEC and what do we do:

The PSEC executive management team consisted of its director Prof. Roger Barker (University of Cambridge) and its project manager Dr Zoe Hewitt (University of Sheffield) and included representatives from each of the partnering institutions, who also led the three research programme themes. Theme 1, the largest workstream, was led by Prof. Ivana Barbaric (University of Sheffield) with Prof Wolf Reik (Babraham Institute) initially acting as deputy before Dr Florian Merkle (University of Cambridge) took over, Theme 2 was led by Prof. Robert Thomas (Loughborough University) and Theme 3 by Prof Cedric Ghevaert (University of Cambridge), who was also the deputy PSEC director.

The overarching aim of the hub was **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 the research, PSEC used two principal clinical exemplars that sat at different stages along the therapeutic pipeline: hPSC-derived dopaminergic (DA) neurons that are being developed for transplantation into the brain of people with Parkinson's to replace the cells they have lost to the disease process and hPSC-derived megakaryocytes (MK), which make a component of blood called platelets that are needed for normal clotting, which are being developed to treat some people with low platelet counts (thrombocytopenia). Over the course of the programme, these exemplars were expanded to include hPSC-derived cells of the immune system (Macrophages), nerve cells in the gut (Enteric Neurones) and heart muscle cells (Cardiomyocytes) through linked projects.

The three themes of the research programme each had specific aims which also crosslinked to enhance the progress and impact for the field (Figure 1).
These aims were:

- To define and understand the biological significance of commonly acquired (epi)genetic changes in hPSCs which occurs over time as these cells are grown in the lab. This includes understanding what this means for cells that are then derived from these genetically different stem cells.
- To develop predictive models for hPSC manufactured products so they can be made more efficiently but still at the level needed for clinical use.
- To develop a translational pipeline from lab to clinic through which we can genetically engineer cells to make them perform better or to stop them being rejected once implanted into a patient, but without that genetic manipulation having consequences through effects on genes that were not suppose to have been edited!

Over the course of the award, PSEC successfully leveraged over a million pounds of additional funding to support the delivery of these scientific aims, with their direct research outputs enabling further funding awards in excess of 3.5 million pounds. The hub produced more than 80 peer reviewed publications, influenced international guidelines on stem cell research and clinical application, provided high quality resources and tools for the community, positively influenced the regenerative medicine careers of over 40 staff, collaborated with at least 20 external partners (mostly from industry) and hosted or co-hosted 10 high quality partnership dissemination events with industry and key stakeholders including the Cell and Gene Therapy Catapult, The British Society for Gene and Cell Therapy, The Canadian Stem Cell Institute, The British Pharmacological Society and The Tissue Engineering and Regenerative Medicine International Society (TERMIS).

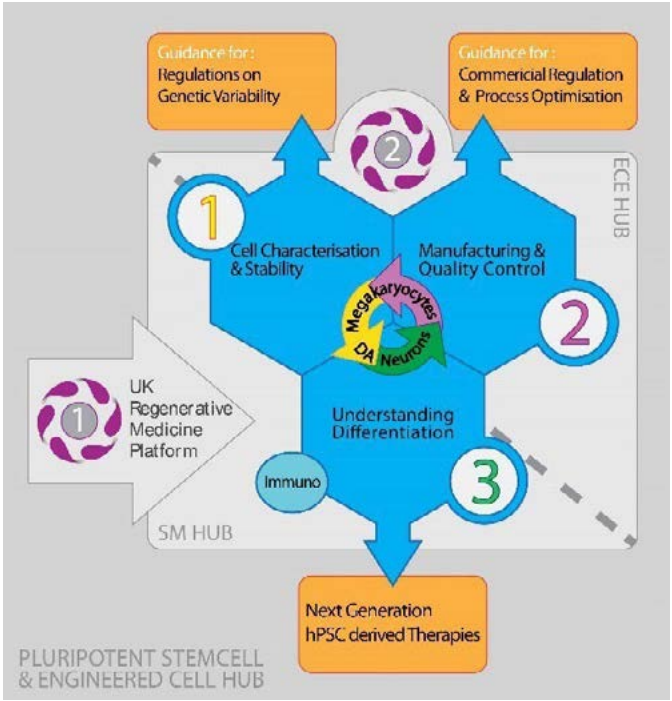


Figure 1: PSEC infographic depicting the internal

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

Key Scientific Contributions

Over the duration of the award, PSEC has been able to contribute significantly to the Regenerative Medicine field. Our key scientific contributions are highlighted, but not limited to:

- Developing an understanding of which genetically variant cells posed a potential risk for cell therapy (i.e. identify which cells that have been grown in the lab for many years have changed their genetic make up such that they may not behave as expected when being developed as a clinical therapy). This work led by the **Barbaric group**, in partnership with WiCell (USA), first produced an updated catalogue of the recurrent genetic changes detected in long term cultures of many different types of human PSCs (Figure 2). This analysis revealed striking changes in the emergence of recurrent genetic variants over time, in part because of changes in standard lab practices on growing such cells. This work provided an insight into the most common genetic changes with growing hPSC in the lab and allowed us to focus our research on designing improved strategies for their reliable detection and for minimising their occurrence.
- Identifying strategies for minimising the occurrence of these common, possibly dangerous, genetic variants. Again, within the **Barbaric group** we have analysed how these common genetic changes affects the behaviour of hPSCs and this led us to identify culture conditions that favour the emergence of particular variants. This provided critical information on how to prevent these genetic changes from emerging as well as what might be happening in the cell which allowed it to grow better than less genetically altered cells. By identifying a molecular mechanism of such competitive interactions, we were able to devise new culture conditions to minimise the dominance of recurrent variants in expanding hPSC cultures, which will have major benefits for all groups growing such cells.
- Through industrial collaboration, with Broken Strings Biosciences, the **Barbaric team** have been able to produce an atlas of where in the genome, these changes tend to occur and possibly why.
- Collaborating across the hub (**Barker**, **Ghevaert** & **Barbaric**) and externally with academic partners and through associated studentships (**Barbaric/Oh**), we have shown that these genetic variants don't just change how the cells grow in the lab, but also affect their ability to turn into different cell types which is clearly critical in any work looking to translate such cells to patients.
- As an alternative approach to assessing the significance of genetic variants in these cells and what culture conditions favour them, the **Merkle group** has developed novel culture strategies and bioinformatic tools to do this using a computational approach. This has allowed us to test more than 30 different culture conditions and identify which conditions favour the development of genetic variants and which tend to prevent this from happening.
- Work within the **Reik group** identified recurrent changes in the epigenome, which consists of a series of factors (e.g. chromatin) that sits on the DNA and controls gene expression. Whether these recurrent changes in the epigenome map on to those seen in the genome is still unclear.
- Within our manufacturing theme, the **Thomas group** have developed a novel statistical method, which has allowed us to identify predictors in the manufacturing process which are critical for the efficient translation of lab-based approaches to clinical production. This work has attracted significant interest from industry as it has the potential to greatly reduce the time needed to manufacture new hPSC products.
- These techniques developed by the **Thomas group** have now been used within the industry to support clinical development of several products including megakaryocyte (MK) differentiation.

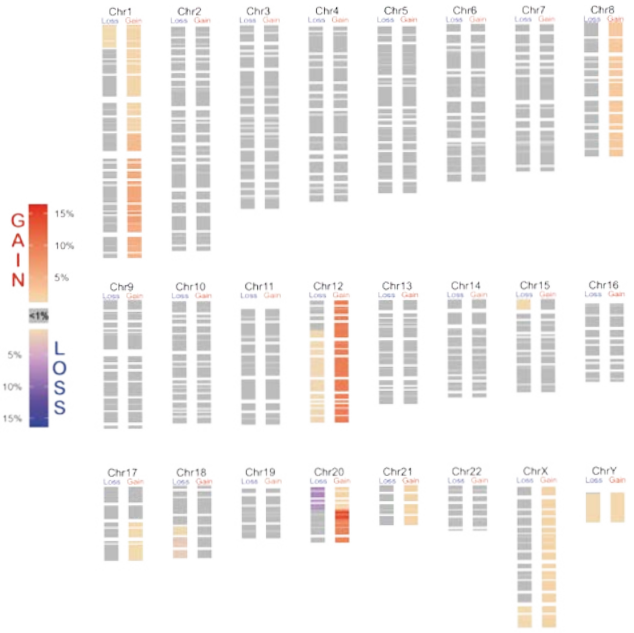


Figure 2; Heatmap summarising the most frequently detected karyotypic aberrations in hPSCs. Image adapted from Stavish et al (2024) Stem Cell Reports

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

- The **Ghevaert group** systematically optimised the process for genome editing of hPSCs (both knocking-in and knocking-out gene targets of interest) which led to collaborations with academics, industry, and government organisations, including work on COVID19.
- The **Barker group** have developed a platform for testing the immunogenicity of hESC-derived dopaminergic neurons, in partnership with the **Jones group** and "UKRMP Immunogenicity Platform" immunology project and have shown that such DA precursors behave similarly to their human foetal counterparts. Namely these cells seem not to drive a major immune response which would mean that in the clinic, long term immunosuppression would not be needed in patients grafted with such cells. We have also manipulated these cells to make them less immunogenic (e.g. by knocking out a major immune molecule MHC-Class I) and then seeing what effect this had on them turning into the dopamine cells we need to treat people with parkinson's. To date knocking MHC class 1 out has no major effects on this (Figure 3).
- In addition to this work directly influencing the ongoing STEMPD clinical trial for the treatment of Parkinson's, being led by the **Barker group**, it has also highlighted the significant technical challenges when trying to assess immune responses in animal models models that have been given the human immune system (so called humanised mice). This work has laid the foundations for ongoing research with grant applications submitted to further these initial findings.

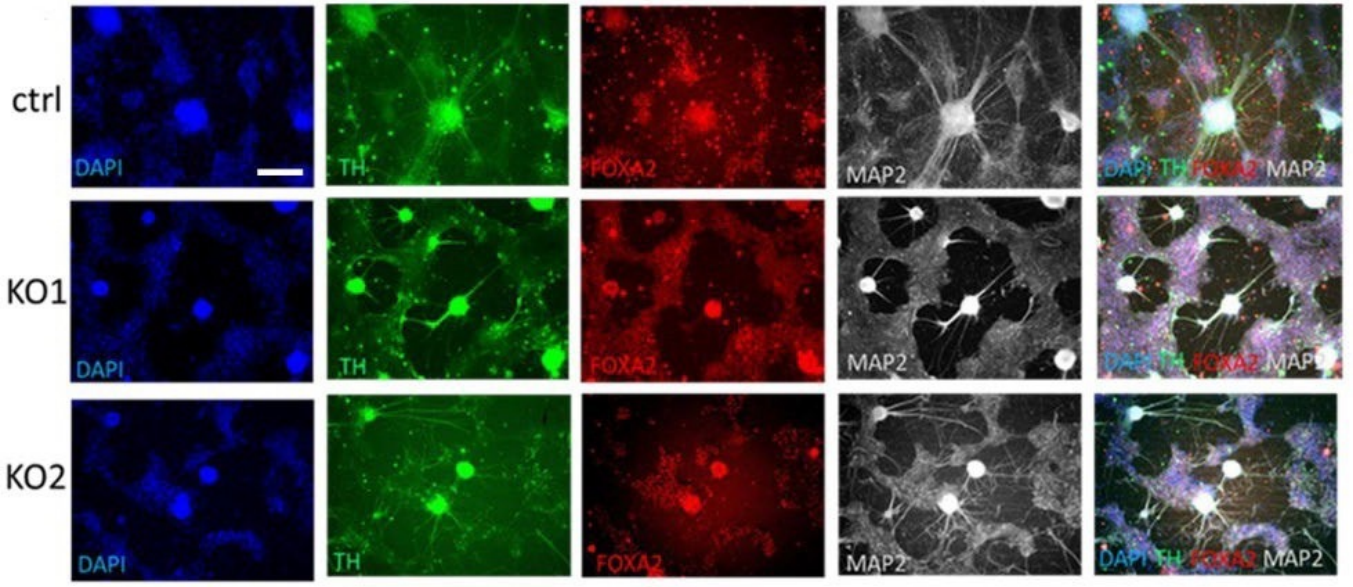


Figure 3: Immunofluorescence analysis of day 45 mesDA neurons showing representative images of RC17 control (ctrl), MHC-I knockout clones (KO1 and KO2. The floor-plate marker FOXA2 is shown in red, the dopaminergic neuronal marker TH in green and the mature neuronal markers MAP2 and TUJ1 are shown in grey. The merged images are used for visualization of the co-localisation of the markers.

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

Networking activities:

Networking has been a central pillar in the success of PSEC. As a team we have driven many activities to broaden our network and support the wider UK Regenerative Medicine field including:

- Working jointly within UKRMP to host collaborative events between hubs and projects, such as the "Regenerative medicine meets mathematical modelling: Discovering symbiotic relationships" workshop (Oxford Jan 2019), the "Collaboration and Career Progression" training programme held virtually in 2021 and several Mentoring and Mock interview events over the years to support the ECR career progression pipeline.
- Exhibiting jointly at events to promote the UK regenerative medicine landscape more broadly, these have included the Tissue and Cell Engineering Society (Virtual Conference 2021) and the Till and McCulloch Meeting (Virtual conference 2021) which led to the establishment of the "MRC/ Canadian Stem Cell Network (SCN) Exchange Programme" and recently relaunched its second round of funding.
- Working with external organisations such as the Canadian SCN has been an integral part of our Hub. In addition, we have also worked closely with the British Pharmacological Society to jointly run a workshop on the "Safety of stem cell-derived therapies" (Oct 2019), with the Cell and Gene Therapy Catapult, to address issues relating to "IP and freedom to operate" (Jan 2020) and with The British Society for Gene and Cell Therapy (BSGCT) to engage with industry as therapies progress to clinic (Jun 2023).
- Working internationally to promote best practice such as with the International Society for Stem Cell Research (ISSCR) where Barbaric led the working group on genetic stability contributing heavily to the new "Standards for Use of Human Stem Cells in Research". These efforts have been expanded further as PSEC leads on an international effort to develop a White Paper following an event in May 2024 which brought together specialists, including those in hPSC biology, genetic stability, cancer, natural human genomic variation and artificial intelligence, to determine how we can predict the functional significance of genetic variants for applications of hPSCs in the future.

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

Regen CTC

A sustainable future:

PSEC researchers at all levels have engaging collaboratively across the UKRMP network, with industrial partners and academic groups to develop ongoing research partnerships to support the development of cell-based therapies. This has resulted in significant ongoing grant income (>£3.5Million) that will continue to progress the Regenerative Medicine field.

However, as an alternative sustainability strategy, PSEC has worked with facilitators from the Commercialisation and Impact Team at the University of Sheffield, and established a spin out company in September 2022, Regenerative Cell Therapy Consulting (Regen CTC) Limited to support early translational scientists to navigate the road from bench to clinic.

Our market discovery, undertaken via the UKRI Lean Launch Programme, identified a significant knowledge gap when it comes to institutional support to translate Regenerative Medicines to the clinic. Regen CTC has brought together a network of academics, with real world experience of doing just that, established as a team under UKRMP, which aims to help fill this gap, and support a growing industry.

PSEC Principal Investigators:

- Prof Roger Barker, University of Cambridge (Director)
- Prof Cedric Ghevaert, University of Cambridge (Deputy Director)
- Dr Florian Merkle, University of Cambridge
- Prof Serena Nik-Zainal, University of Cambridge
- Prof Robert Thomas, Loughborough University
- Prof Ivana Barbaric, University of Sheffield

PSEC Alumni:

- Dr Annabel Curle, alumnus associate PhD Student now Post-Doctoral Researcher at the University of Cambridge.
- Dr Sarah Howlett, an associated Post-Doctoral Researcher continues within the Barker/Jones laboratories supporting the Parkinson's projects (including the STEM-PD Trial) at the University of Cambridge.
- Dr Cathy Beltran-Rendon, alumnus associate PhD Student and Post-Doctoral Researcher at Loughborough University, now Bioprocess Engineer with Safi Biotherapeutics.
- Dr Katie Glen, alumnus Post-Doctoral Researcher at Loughborough University became Associate Director of Research and Development at Safi Biotherapeutics and Director of Advanced Bioprocess Services.
- Miss Gabriele Gelezauskaite, as an associated PhD Student, is continuing with her studies at the University of Sheffield.
- Dr Zoe Hewitt, alumnus Project Manager, University of Sheffield now, Co-Founder, Chief Executive Officer, and Lead Quality Management Specialist Consult at Regenerative Cell Therapy Consulting.
- Dr Owen Laing, alumnus associate PhD Student, University of Sheffield now Post-Doctoral Researcher, University of Sheffield.
- Dr Theodore Wing, alumnus associate PhD Student and Post-Doctoral Researcher, University of Sheffield.
- Dr Duncan Baker, University of Sheffield/ Sheffield Children's NHS Foundation Trust continues as a senior cytogeneticist.
- Dr Christopher Price, alumnus Post-Doctoral Researcher, University of Sheffield now Senior Scientist at Stem Cell Technologies, Vancouver.
- Miss Swetha Sirinivasaraghavan, alumnus Research Assistant, University of Cambridge, now PhD Candidate in Canada.
- Dr Dylan Stavish, alumnus Post-Doctoral Researcher, University of Sheffield now Senior Scientist at Stem Cell Technologies, Cambridge.
- Dr Shamma Qarin, alumnus associate PhD Student now holds a position at Insmed Incorporated.
- Dr Preeti Holland, alumnus Post-Doctoral Researcher, Loughborough University.
- Dr Venkat Pisupati, alumnus Post-Doctoral Researcher, University of Cambridge.

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub

- Dr Amie Waller, an associated Post-Doctoral Researcher continues within the Ghevaert Laboratory supporting the MK clinical trial activities at the University of Cambridge.
- Dr Amanda Evans, alumnus Post-Doctoral Researcher, University of Cambridge, now retired.
- Dr Shaline Fazal, alumnus Post-Doctoral Researcher, now Laboratory Manager at University of Cambridge.
- Mr Iman Mali, University of Cambridge, alumnus Research Assistant, now PhD Candidate at University of Cambridge.
- Prof Wolf Reik, alumnus Co-I, Babraham Institute is now Director of the Altos Cambridge Institute of Science.
- 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 now a Cell and Gene therapy bioprocess development scientist, at GSK.
- 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.
- Dr Antigoni Gogolou, alumnus Research Technician now Postdoctoral Researcher 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.

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 head of biology at the Alborada Cambridge Drug Discovery Institute.
- Dr Ferdinand von Meyenn, alumnus UKRI/Rutherford Fund Fellow, Kings College London now Assistant Professor at ETH Zurich.

Pluripotent Stem Cells and Engineered Cells Hub Case Studies

Immune test for stem cell therapies

The host immune response is one of the biggest barriers to the effective, long-term clinical translation of regenerative medicines such as stem cell therapies. Developing a platform for testing whether a treatment will cause a host immune reaction will make it more efficient to progress these therapies through the clinical pipeline. It can also give researchers and clinicians a better idea of how they expect patients to respond to stem cell transplants.

Dr Annabel Curle at the University of Cambridge is working on a cross-cutting immunology project to develop a platform to measure the ability of stem cells to provoke an immune response, known as their immunogenicity. The platform would measure the immunogenicity of stem cells ***in vitro***, by co-culturing the stem cells with different types of immune cells and then running functional assays, to see how the immune cells respond. These assays include studying gene expression changes, to understand the likelihood of immune rejection after a transplant or a graft.

Dr Curle and her team (in the Jones and Barker labs, Cambridge) carried out the tests on dopaminergic neuron progenitor cells (DA-NPCs), a type of human stem cell-derived product that has recently entered clinical trials for people with Parkinson's. Parkinson's is a neurodegenerative disease caused by the progressive loss of neurons that produce dopamine. It is hoped that transplanting DA-NPCs that can go on to develop into replacement neurons that produce dopamine can improve motor function, and thereby slow or halt the movement-related symptoms of Parkinson's. However, it is vital to first test whether a transplant might provoke an unwanted immune response and Dr Curle's platform to measure the immunogenicity of these cells would allow the researchers to do this.

The results were intriguing. Dr Curle found that these DA-NPCs did not provoke any significant immune cell activation in the assays, but instead that the DA-NPCs possess immunoregulatory qualities, suppressing T-cell activation (T-cells being the cell type responsible for cell-mediated rejection). These results showed that aggressive immunosuppression may not be required following the transplantation of these stem cell-derived neural cells. It also meant that researchers may not need to genetically modify stem cell therapies to reduce immunogenicity in the 'next generation' of stem cell products, as the platform offers an opportunity to anticipate how we may expect patients to respond to these therapies.

The project demonstrates how platforms such as the one being developed by Dr Curle are necessary to comprehensively investigate the immunogenicity of stem cell therapies, to ensure their clinical safety and efficacy. The PSEC Hub of UKRMP brings together the multidisciplinary expertise and infrastructure required to do this, in order to accelerate progress towards translating the benefits of stem cell therapies for patient benefit.

"The platform has offered great opportunities for me as an early career researcher to present my work and network with the regenerative medicine community"

Dr Annabel Curle,

University of Cambridge UKRMP PSEC Hub

Genetic variation and its effects on stem cell populations

Studying how stem cell populations behave in prolonged culture conditions has led to new insights into how they differentiate, which may be linked to their underlying genetic variation. Building on previous research, these advances in knowledge can help suggest new approaches for removing genetically variant cells from stem cell culture for research and future clinical applications.

Cardiomyocytes, or heart cells derived from human stem cells are a powerful tool for modelling disease and developing stem cell-based therapies. Producing cardiomyocytes requires stem cells to be cultured for prolonged periods of time. Unfortunately, this extended culture predisposes the stem cells to acquire genetic changes, such as the gain of an extra arm of chromosome 1, known as +1q. These genetic changes in turn can alter the signalling pathways that are responsible for controlling the way the stem cells differentiate into cardiomyocytes.

Pluripotent Stem Cells and Engineered Cells Hub Case Studies

Dr Theodore Wing at the University of Sheffield is studying genetic changes in stem cells to understand more about the cellular signalling processes. The team found that genetic changes in the cells with a +1q defect caused the abnormal activation of a pathway called the Wnt signalling pathway. They also showed that abnormal Wnt signalling has long-lasting impacts on the stem cell, and their ability to form specialised cell types such as cardiomyocytes, as well as the function of these cells once differentiated.

The research has emphasised the concerns surrounding the presence of genetic variation on stem cell-based therapies, with even extremely small contaminations of mutant cells significantly impacting the ability of genetically normal cells to form functional cardiomyocytes. The team will use these insights to develop new approaches to investigate cell culture conditions and how they impact genetic variation in stem cells, thereby improving ways to grow human stem cells safely for research and clinical applications.

"Being a member of PSEC and UKRMP has allowed me to present my work, to meet and engage with fellow researchers in a wide range of fields. This has greatly helped me to see the broader scope of the generation of potential regenerative medicine therapies and has aided me to see where my work fits in with this picture and how to tailor my research to the greatest benefit"

Dr Theodore Wing

University of Sheffield, UKRMP PSEC Hub

Support for translating regenerative cell therapies

As with all medicines, advanced therapy medicinal product (ATMPs) like cell therapies must be evaluated in clinical trials before they can be routinely administered to patients. For these complex medicines the clinical translation journey is often a long and demanding process, as ATMPs have to be shown to be consistent, safe and effective before they can be administered to patients enrolled in these clinical trials. Regen CTC, a spin-out established in 2022 by UKRMP experts, provides bespoke support for researchers as they navigate this translational journey.

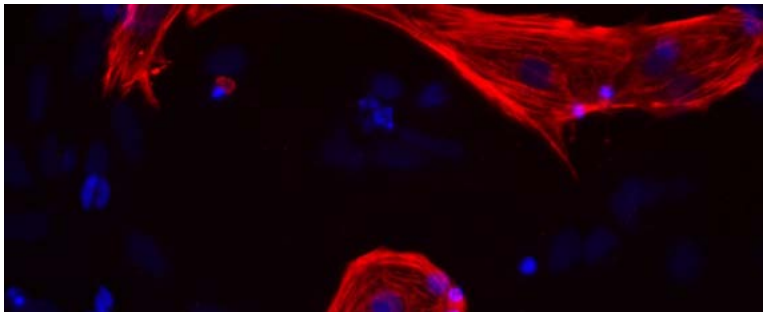
The process of translating cell therapy products into patient treatments is a steep learning curve for many researchers embarking on clinical development. These areas include developing quality management systems, establishing or partnering with clean room (Good Manufacturing Practice (GMP)) facilities, process development of research protocols and the development of key quality indicators. The PSEC executive team, led by Dr Zoe Hewitt at the University of Sheffield undertook a market discovery journey, supported by the commercialisation team at the University of Sheffield, and identified that there was a significant and immediate need for this kind of guidance. As a result, the team launched a spin-out company called Regen CTC in 2022, which provides clients with access to a network of UK experts with real world experience of translating human pluripotent stem cell derived cell therapies to the clinic.

With the ability to access a large network of UK academic specialists through the UKRMP network, the team can facilitate a variety of activities, helping to share best practise and knowledge. For example, early implementation of document and quality management systems have enabled therapy developers to capture critical information early in the translational journey. This in turn ensures that public funding is maximised and that the products being developed are more robust and hence attractive to investment opportunities as they progress.

"The PSEC executive have supported me to undertake this discovery journey and establish Regen CTC. The UKRMP network more broadly has also been supportive, both as key opinion leaders and as potential clients of the services we offer. The market discovery journey presented a fantastic opportunity to promote the UKRMP internationally and its reputation, as the background to Regen CTC, has provided our company with an incredible platform from which to grow"

Dr Zoe Hewitt, Project Manager

UKRMP PSEC and Co-Founder and CEO of Regen CTC



2.2 Engineered Cell Environment (ECE) Hub

The UKRMP Engineered Cell Environment (ECE) Hub sought to regenerate and repair damaged organs (liver, joint and lung). Our hub brought together stem cell scientists and tissue engineers with clinician scientists familiar with leading clinical trials and the pathways to translation.

The Hub Director was Professor Stuart Forbes (University of Edinburgh, Liver theme) and the Deputy Director Professor Alicia El Haj (University of Birmingham, Bone and Joint theme). Professor Sam Janes (University College London) lead our Lung theme. Other partner institutions were Kings College London and the University of Cambridge.

The ECE Hub sought to promote tissue regeneration and repair in liver, lung and joints using two translational strategies:

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

We used laboratory and animal models of disease to test these strategies (Figure 1).

To improve endogenous repair and cell therapies the UKRMP ECE Hub tackled 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

We selected three clinical exemplars - liver, joint and lung repair – with maximal potential for tangible clinical gains.

We continue to work to translate our findings into the clinic and have been successful in securing follow-on funding to refine our small molecule hits, initiate clinical trials and further understand the stem cell niche and how to improve both engraftment of exogenous cells and promote endogenous repair. Two of our technologies have been patented, there have been 4 related spin-out companies and many of our tools have been made available through publication. We have patented a new therapeutic intervention (WO2021156519A1, El Haj & Habib) a tissue regeneration patch to repair lost or damaged bone. A first in human cell therapy study for biliary disease is planned for 2025. We have published a novel single cell trajectory inference applied to image-based Cell Painting data, the first time this has been used for drug screening. The ECE Hub have had 160+ publications in journals including Nature, Nature Medicine, Nature Materials and Cell Stem Cell.

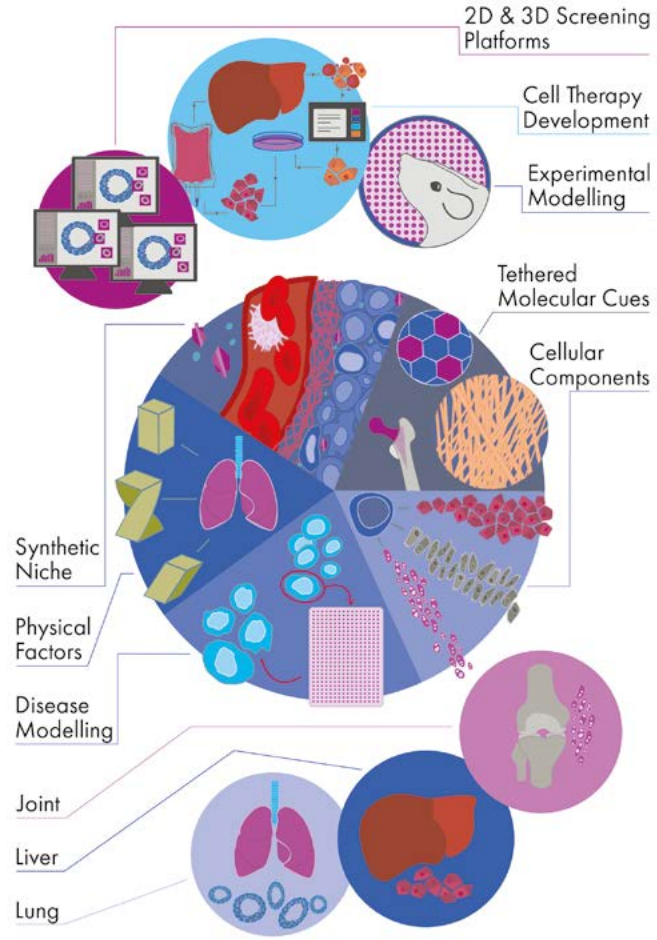


Figure 1. Schematic of the ECE Hub Strategy.

Engineered Cell Environment (ECE) Hub

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 use of hepatocytes (functional liver cells) to treat metabolic liver disease has been demonstrated in the clinic. 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.

Improving endogenous liver repair

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 (Hay/Carragher), of which 6 showed a significant increase in foetal albumin (AFP) secretion (a key function of healthy liver) and inhibition of differentiation into metabolically active hepatocyte-like cells. We also established a novel 384-well high content Cell Painting assay using HepaRG cells and a multiparametric image-based phenotypic signature to classify compound hits promoting liver cell progenitor and differentiation phenotypes (Carragher). Importantly, small molecule hits that promoted differentiation in screening assays were replicated in human primary hepatic progenitor cells. Optimised hepatocyte progenitor cell media are being developed for potential GMP use for cell expansion prior to first in human transplant testing.

A chemically defined cell growth media and recombinant proteins to promote differentiation of hepatic progenitors has been developed (Hay). The definition of the cell culture niche improves the quality of engineered liver tissue products, allowing the team to automate manufacture of liver tissue so that the technology could be scaled for use *in vivo*. As a result of this work, a patent was granted exclusively licensing the technology to Biolamina. The growth media is commercially available through Stem Cell Technologies and is being used in the development of new products for Prof Hay's spinout Stimuliver.

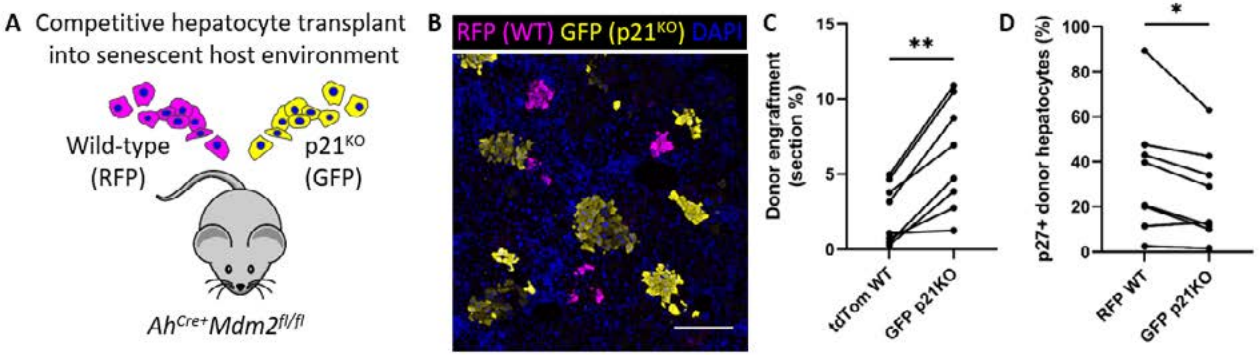


Figure 2. Paracrine senescence model.

We developed materials (nanoparticle and bandage) that deliver regulated Wnt (Habib). The activity, reproducibility and safety and efficacy have been tested in mouse models of liver disease.

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 (Forbes). These targets are being tested in transplant models (Figure 2).

Joint (El Haj, McCaskie, Birch, Habib)

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 aimed to understand how the progenitor cells within the cartilage and bone tissues in the joint can be recruited and instructed to promote.

We have developed an improved 3D model platform for cartilage formation (chondrogenesis) using human progenitor cell lines to mimic and maintain tissue functions such as asymmetric division, migration and differentiation which are key features of cartilage and improve cell engraftment (El Haj).

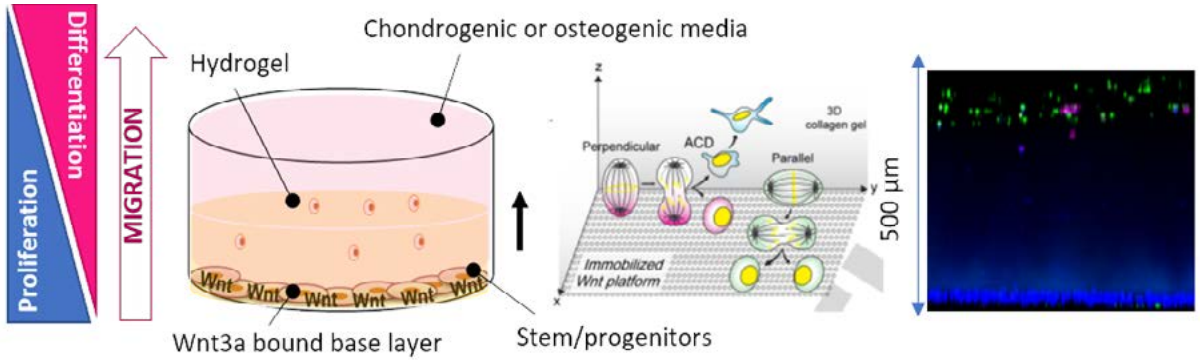


Figure 3. 3D chondrogenic and osteogenic models for regenerative platforms and translation to therapy for cartilage and bone repair (Loundes et al 2019; Okuchi et al, 2020).

This model is being optimised by choosing the Centre for Drug Screening in collaboration with Professor Neil Callagher to identify potential drug candidates for regenerative therapies. In addition, the approach of using key agonists in novel shear gel delivery systems is being translated to our mouse injury models to test for clinical relevance and potential use for cartilage repair (Figure 3). Using the Wnt-induced osteogenic tissue model (WIOTM) we screened 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 (McCaskie/Birch). Finally, based on our publication in Nature (Okuchi Y et al, 2020), we have patented a new therapeutic intervention to repair lost or damaged bone (El Haj/Habib).

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 was 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 have established a robust assay for 2D and 3D high throughput (lung organoid) 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. In addition, 3D tracheospheres containing 3 lung cell types – basal, ciliated and goblet cells, were used to assess stem cell growth and differentiation of lung epithelial cells under physiologically relevant conditions (Figure 4). We selected our most promising compound to be tested in a mouse model. We successfully demonstrated that treatment with the compound induced the expression of targets crucial for proliferation in both the trachea and lungs *in vivo*.

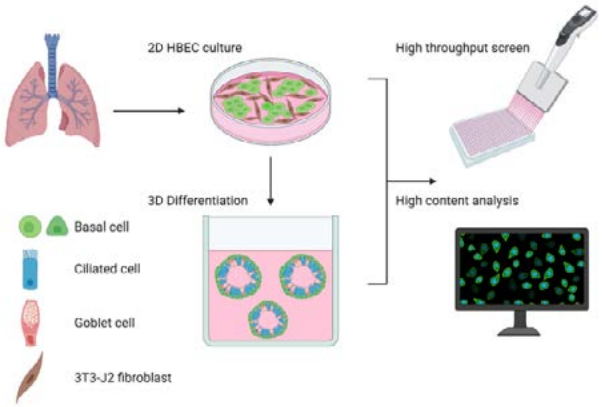


Figure 4. 2D and 3D Lung organoid screens.

Engineered Cell Environment (ECE) Hub

Collaboration

The ECE hub was intrinsically collaborative across scientific disciplines. We developed 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:

- The testing of wnt particles and bandages across therapeutic area, screening platforms and *in vivo* testing.
- The establishment of high throughput screens (lung, liver and joint), sharing of compound libraries and analysis expertise.

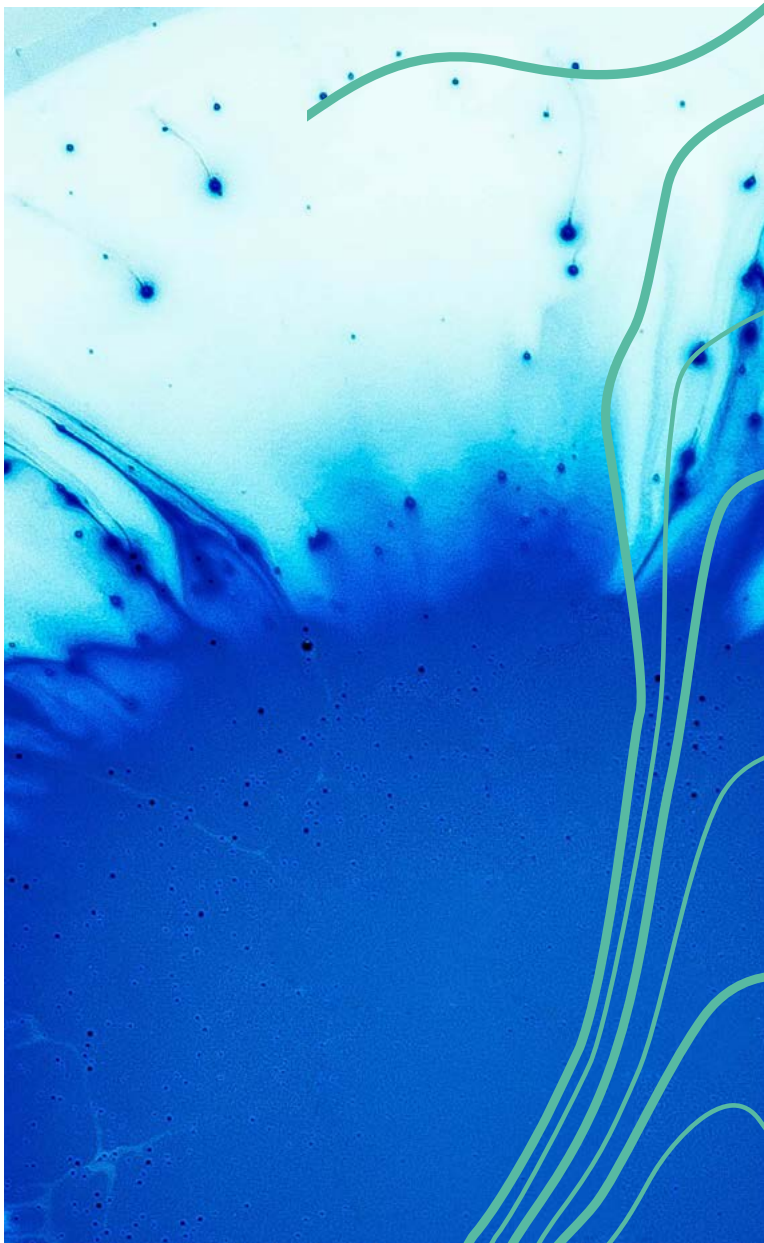
Networking

The ECE Hub worked closely with other hubs to develop collaborations across and outwith the UKRMP network. 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 project and reviews.

In March 2022 we held a cross-hub High Throughput Screening workshop at The Frances Crick Institute in London, with talks from both industry and academia. Four early career participants pitched new high throughput models to a panel of academic and industry experts.

In addition, the Hubs developed partnerships with industry and sought to engage the wider academic and commercial community, promoting UKRMP skills and expertise at key scientific meetings, including the very successful UKRMP Regenerative Medicine 2023 conference in Edinburgh.

Hubs also interacted through annual scientific meetings and a joint training programme for early career researchers "Collaboration and Career progression", which helped hub members develop in their careers in the biotechnology industry and academia.



Engineered Cell Environment (ECE) Hub Case Studies

New regenerative cartilage model reveals potential novel drug targets for osteoarthritis therapy

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 her team 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.

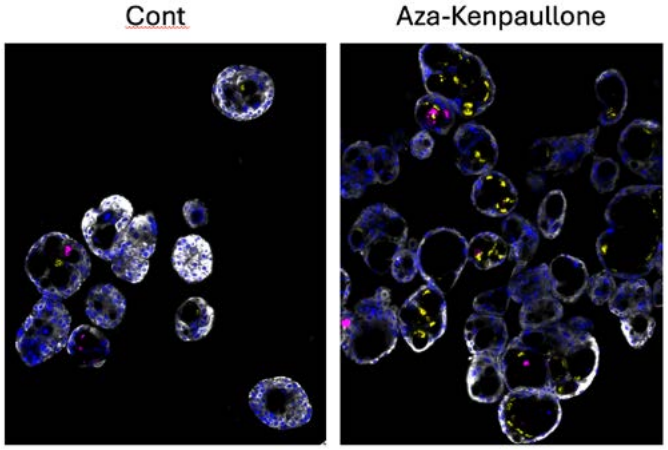
The researchers have developed a 3D regenerative model of cartilage which maintains both mature and progenitor cells that make up cartilage in an arrangement that is spatially organised. The model system allows the researchers to screen for new treatments that can induce the formation of cartilage. The next step would be to scale up the model and transfer the model to a 96-well plate format to enable screening candidate drugs in high-throughput assays. This is exactly what they did, in collaboration with Professor Neil Carragher and the Drug Screening Centre at Edinburgh University, using liquid handling systems and automated imaging techniques.

A 57 candidate library was then screened for potential compounds which promote different cellular processes such as proliferation, differentiation and migration of cartilage progenitor cells. The high-throughput system would allow the researchers to observe these processes taking place, in response to various potential compounds. The team identified several drug targets for further validation, which appear to promote the cartilage repair process. These results showcase how the platform has potentially enabled the future development of a new drug for treating osteoarthritis.

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

Failure to repair damage to lung epithelia can lead to severe lung disease, and once this happens, there are no treatment options to reverse the damage or repair lung function. Activating stem cells in lung epithelium offers a promising approach for developing new therapies to tackle this problem but requires a deeper understanding of how cell fate decisions are regulated in airway epithelium.

Professor Sam Janes, Dr Yuki Ishii and Dr Jess Orr use 2D and 3D patient-derived airway cell cultures to investigate stem cell proliferation and differentiation. 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.



Validation of a screen hit compound as an inducer of airway stem cell proliferation in 3D tracheoshpere assay. KRT5: white, ACT:yellow, Muc5AC:Magenda, DAPI:blue.

The team have already established a 384-well plate format assay to screen compounds for their effects on airway cell proliferation. They have performed this higher-throughput screen, testing around 1400 compounds-including 1276 FDA-approved compounds, and identified several 'hit' compounds. These are compounds that appeared to increase the number of primary airway epithelial cells. Next, the team validated these hit compounds in multiple patient-derived cell cultures to confirm that they do indeed increase cell proliferation

and that the compounds had a concentration-dependent response. The researchers also showed that the hit compounds increased 3D lung organoid size. The team are currently developing a mouse model of lung regeneration to validate these hit compounds *in vivo* and are also investigating the cell signalling mechanisms that may be involved.

The group have also created a reporter gene system to monitor airway epithelial differentiation in live cell cultures. They have validated these bioluminescence-based reporter constructs in patient-derived air-liquid interface and lung organoid cultures. The reporter constructs are being made available on the Addgene platform, so that they can benefit the wider academic community.

These new methodologies are valuable tools for identifying drugs that can regulate the stem cells of the airway epithelium. Promising drugs identified through these assays could be developed into therapeutics to accelerate the repair and regeneration of damaged airway epithelium.

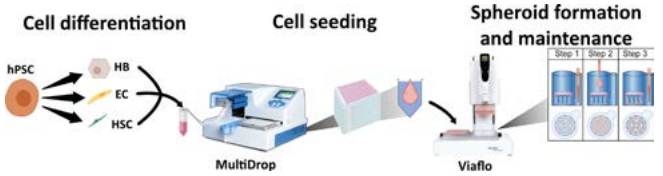
From liver in a dish to implantable human liver tissue: stem-cell derived liver models allow researchers to recreate human liver biology

Engineered human liver tissue derived from human stem cells has the potential to build more predictive human disease models, and ultimately treat human liver disease. Produced at scale from a renewable cell source, the engineered liver tissue could improve human drug development and repurposing, and in the future may provide an alternative source of human tissue to treat failing human liver function.

The liver is the largest solid organ in the human body, with an important role in human health. It is responsible for over 500 functions, including processing digested food and the detoxification of foreign substances. Liver physiology and disease is often studied in the laboratory using cells derived from donor organs or liver cancer cell lines. However, both these sources of cells have inherent disadvantages; the former eventually runs out while the latter can have chromosomal abnormalities.

Professor David Hay and his team at the University of Edinburgh have been using human stem cells to grow liver tissue in the lab. These cell populations are capable of indefinite growth under carefully maintained conditions in the lab, and the team have developed reliable methods for building human liver tissue using these cells. These engineered liver tissues appear to behave in a similar way to the liver found in the human body. As such the tissue could be used to better model and ultimately treat human liver disease. The team have developed automated 2D and 3D systems to produce the engineered human liver tissue at scale.

The close similarity between the engineered liver tissue and actual liver tissue is due to the use of chemically defined cell growth media and recombinant proteins in the cell culture system. The definition of the cell culture niche has improved the quality of the engineered liver tissue product, allowing the team to automate its manufacture so that the technology could be scaled for use *in vivo*. As a result of this work, a patent was granted exclusively licensing the technology to Biolamina, the commercial provider of the extracellular matrix that the cells grow on. In addition, these successful outcomes attracted further investments from Novo Nordisk Foundation, Old College Capital, and Export & Investment Fund of Denmark as well as non-dilutive grant funding from Innovation Foundation Denmark, resulting in the formation of a spin-out company called Stimuliver.



"Funding from the UKRMP1 Niche and UKRMP2 ECE hubs, along with the UKRMP Disease/Systems Focussed Programme award as PI, allowed me to develop our interdisciplinary research (Biology, Chemistry, Engineering and Medicine) to the point of translation. We are currently building a prototype liver implant for the clinic and have currently secured >€3 million euros of investment and non-dilutive grant funding"

Professor David Hay

University of Edinburgh, UKRMP ECE Hub

2.3 Smart Materials Hub

Director: Professor Molly Stevens
University of Oxford and Imperial College London

Deputy Director: Professor Felicity Rose
University of Nottingham

Partner Institutions: University of Oxford, Imperial College London, University of Nottingham, University of Southampton, University of Edinburgh, King's College London, University of Glasgow, University of Manchester, University of Liverpool

The core goals of the UKRMP Smart Materials Hub 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 foster partnerships with manufacturing, commercial, and regulatory bodies to ensure the effectiveness of our translational process
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.

The Hub has made significant progress over the past five years, achieving exciting early scientific success with contributions from all 9 institutions. Scientific outputs from these institutes include 12 granted international patents and several more pending applications and over 180 peer-reviewed journal articles.

The Hub is now well-positioned to enter the next phase of development, in which we will continue to evaluate efficacy of our materials in disease models of the eye, liver and musculoskeletal system.

The Hub has continued to strengthen links across the UK and international research communities, collaborating with the Scientific Advisory Board (SAB) and regulatory authorities to deliver transformative and sustainable technologies in the regenerative medicine industry.

Working closely with the Safety and Immunology (SI) panel and the Manufacturing, Commercial and Regulatory (MCR) panel, the Hub continues to develop Target Product Profiles (TPPs) with high potential to maximise research translatability, addressing future clinical, industrial and regulatory needs. Regular progress review meetings have continued within each clinical exemplar, and key activities for the target applications are as follows.

Scientific Achievements

New materials for the musculoskeletal system

The collaborative research team from Southampton, Imperial, Nottingham and Glasgow (Marshall, Wojciechowski, Yang, Mata, Hasan, Vineetha, Oreffo, Stevens & Salmeron-Sanchez) have been investigating the development of innovative acellular materials based on 3D printed nylon, titanium and polycaprolcatone (PCL) scaffolds. These scaffolds were functionalised with biomimetic proteins, minerals and/or growth factors present in the bone microenvironment to enhance bone formation by skeletal cell populations. PCL scaffolds, coated with various materials, were supplied to the Southampton team for in vitro assessments followed by a subcutaneous implant study and a femur defect model in mice. Based on the results of these studies, the team selected PCL-900 octetruss scaffolds coated with LaponiteTM and BMP-2 (Bone morphogenetic protein 2) for use in an ovine femoral condyle defect model (large animal) at Nottingham.

The Nottingham team (Owen, Rose & Wildman) has developed highly defined porous microparticles based on pentaerythritol triacrylate (PETA) to support cell infiltration in vitro and is currently exploring tissue infiltration into defect sites in vivo and their potential to promote bone formation. The materials were tested at an ISO 10993 certified contract research organisation, and the team confirmed that the results aligned with their in-house cytotoxicity assessments.

The Imperial team has engineered 3D scaffolds using remote acoustic stimulation for deep zone cytoarchitecture (Armstrong & Stevens) (Figure 1).

They have also developed an electrospun osteochondral implant (FiHy$_{TM}$) and conducted extensive in vitro assessments for both cartilage and bone repair in collaboration with the University of Pennsylvania (Moore & Stevens).

The Oxford team (Carr & Mouthuy) has successfully completed essential in vitro and in vivo studies on BioPatch and BioYarn. BioPatch is a synthetic degradable electrospun patch that promotes the rapid regrowth of tendon tissue, and BioYarn is made of synthetic degradable nanofibers that mimic a normal tendon, aimed at enhancing the repair of rotator cuffs. The Oxford team has confirmed that BioPatch has shown very encouraging results both in vitro and in vivo studies, involving small and large animal models. The team is now working with the Oxford Innovation team to develop sustainable strategies and secure funding for further research.

Additionally, the team has commenced a pilot in vitro degradation study for BioLig, synthetic degradable nanofibers, and collaborations with the Glasgow and Southampton team are underway to explore design variants.

The Southampton team (Dawson & Oreffo) is working on developing injectable nanoclay gels (Figure 2) 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. The team is investigating how to apply this technology for dental bone reconstruction within a newly awarded EPSRC Impact Acceleration Account project.

The Nottingham team (Hasan & Mata) has been working on the development of a new technology for remineralisation of dental enamel. The team are now collaborating with Radboud University in the Netherlands to test the mineralising coating for practical dental applications.

The team are also moving this technology forward by conducting in-depth experiments to compare the performance of the product with commercially available alternatives. A spin-out company, Mintech-Bio, has been established to commercialise this technology.

New materials for the eye

The Liverpool team (Robinson, Bilir, Levis & Williams) is continuing to develop the biosynthetic corneal endothelial graft with a new formulation of hydrogels. They have assessed the cell compatibility of the hydrogels using a human corneal endothelial cell line and primary porcine endothelial cells. Work will continue within the recently awarded MRC DPFS project to enhance the mechanical properties of the hydrogels and develop a sterilisation method.

The Imperial team (Cunnane, Barron, Zhong, Fernandez-Debets & Stevens) has developed 3D scaffolds with a patterned microstructure designed to polarise photoreceptor cells for retinal repair. The team has also optimised the electrospinning polymer scaffold fabrication process and successfully manufactured scaffolds that resemble the native human Bruch's membrane. A pilot study was conducted to evaluate the biocompatibility of the chosen hydrogel formulation for the photoreceptor scaffolds. A subretinal scaffold delivery system has been designed and tested in an ex vivo porcine eye model. The King's team (Kalargyrou, Lanning, Pearson & Ali) is continuing to evaluate the biocompatibility of these scaffolds through an assessment of the inflammatory and gliotic response of the implanted retina in mice.

Work is progressing to assess the transplantation of photoreceptor and retinal pigment epithelium (RPE) containing scaffolds in a rabbit model.

New materials for liver regeneration

The Nottingham team (Lee & White), in collaboration with the Edinburgh team (Gadd, Ashmore-Harris & Forbes), has made significant progress in designing materials to enhance liver cell engraftment and regeneration (Figure 3). They have achieved controlled release of vascular endothelial growth factor (VEGF), IL-10, IL-1ra and Etanercept in vitro. The Nottingham team is continuing to investigate how to prolong the release of immunomodulatory factors from the microparticles, which are made with poly (lactic-co-glycolic acid) (PLGA) and galactose (Gal). Meanwhile, the Edinburgh team has established the biodistribution and dosage of microparticles in vivo and is currently investigating how co-transplanting microparticles with hepatocytes improves cell engraftment in mouse models.

Future directions

The Hub has successfully secured £31 million in follow-on grants from various funding bodies, enabling us to further advance the development of novel materials that mimic the natural extracellular matrix and support innovative treatments for a wide range of diseases and injuries. At the same time, we acknowledge the need to address complex ethical, regulatory, and practical challenges as the field of regenerative medicine continues to evolve.

In line with our vision of nurturing the next generation of regenerative medicine scientists, the Hub remains committed to fostering collaboration between academia, medical practice, industry, and research funders. Our dedication lies in promoting interdisciplinary research excellence among these diverse groups, with the goal of facilitating a future where regenerative medicine thrives.

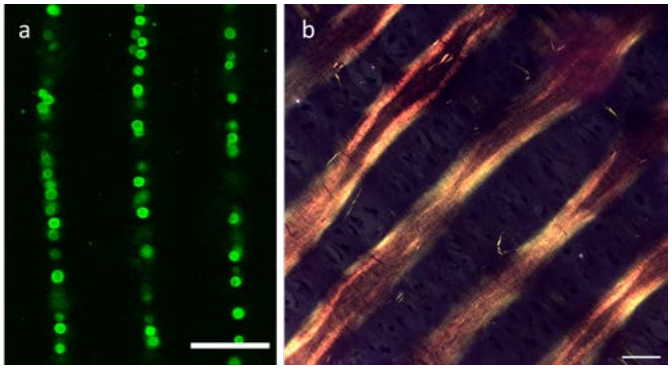


Figure 1. Acoustic cell patterning can be used to engineer hyaline cartilage with deep zone cytoarchitecture (a) High-magnification confocal fluorescence microscopy shows the patterned chondrocytes, labelled with a fluorescent membrane stain (green) for visualization. The patterned features were predominantly single-cell width, which is analogous to the cellular organization of deep zone articular cartilage (scale bar = 100 μm). (b) The patterned cartilage was stained with picrosirius red and imaged using a polarized microscope (scale bar = 50 μm). J Armstrong et al., Advanced Healthcare Materials, DOI: 10.1002/adhm.202200481

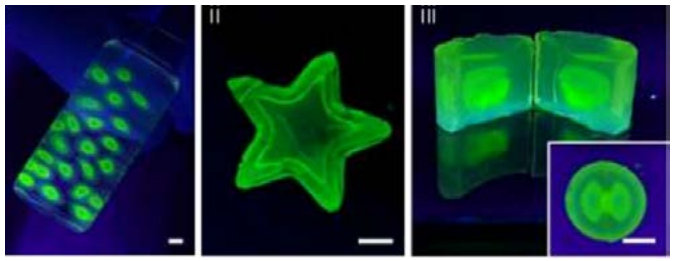


Figure 2. Assembly of 3D protein patterning within nanoclay colloidal gels. The system supports the assembly and patterning of structures of a range of size and shapes as defined by the initial casting (scale bar = 200 μm). R. Ramnarine et al., Advanced Materials, DOI: 10.1002/adma.202304461

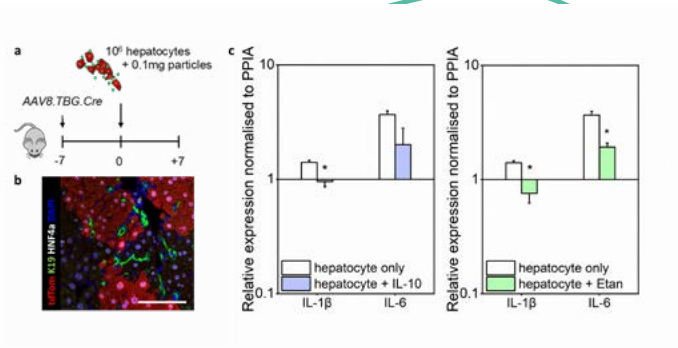


*Figure 3: IL-10 and etanercept encapsulated Gal-MPs reduce inflammation in vivo. IL-10 encapsulated Gal-MPs and etanercept encapsulated Gal-MPs were separately delivered, each with hepatocytes, in the AhCreMdm2flox mice model (a). Successful hepatocyte engraftment requires the optimal level of host injury and inflammation to support donor cell expansion in AhCreMdm2flox mice. Image stained with tdTom (transplanted hepatocytes), K19 (biliary cells) HNF4a (hepatocytes) and DAPI (nuclei), scale bar = 100 μm (b). Hepatocytes transplanted with IL-10 MPs showed down regulation of IL-1β compared to hepatocytes alone. Hepatocytes transplanted with etanercept MPs showed down regulation of IL-1β and reduced expression of IL-6 compared to hepatocytes alone. Error bars display mean ± S.D of pro-inflammatory gene expression of harvested liver homogenate. N=3. *p<0.05, significant.*

Smart Materials Hub Case Studies

3D printed scaffolds for repairing bones

Non-union bone fractures are typically treated using a bone graft to promote regeneration. However, bone grafts are complicated by the fact that the graft has to come from the patient, which may cause issues at the site of harvesting, or a donor, which may cause immune rejection. A 3D scaffold that could promote bone repair and then be bio-reabsorbed once sufficient bone regeneration has taken place would offer an ingenious alternative to repair non-healing fractures and critical-sized bone defects.

Non-union bone fractures occur when fractured bones fail to heal and mend after an extended period of time. These fractures can cause prolonged pain for patients, often lasting for months or even years. The clinical 'gold standard' for treating these non-union fractures is using an auto- or allo- graft, using either the patient's own bone or bone from a donor. However, these approaches come with their own challenges, for example sourcing donor bone tissue for grafts, and the risks of immune rejection by the host.

The Smart Materials Hub are developing an inventive approach to this problem. The project is a collaboration between the teams of Professor Dame Molly Stevens at the University of Oxford and Imperial College London, Professors Richard Oreffo and Jon Dawson at the University of Southampton, Professor Manuel Salmeron-Sanchez at the University of Glasgow, and Professors Felicity Rose and Alvaro Mata at the University of Nottingham. Together, the teams of researchers are developing a bio-resorbable 3D printable scaffold material using stereolithography (SLA) techniques.

This approach uses photochemical processes by which light causes chemical monomers and oligomers to cross-link together to form polymers. The approach would enable high-throughput and consistent manufacturing, and demonstrate a first in class bio-resorbable SLA 3D printable material for bone repair.

To do this, the team focused on key components of the project; developing a bio-resorbable 3D printable scaffold, coating the scaffold material to promote bone regeneration, and assessing the coated scaffolds *in vitro*, and *in vivo* using small to large animal models. The team tested three different bioactive coatings to promote bone regeneration and narrowed down the choice to a coating called Laponite, a nanoclay which strongly adsorbs a protein called bone morphogenetic protein 2 (BMP-2). BMP-2 is a key growth factor, known to stimulate the production of bone tissue however, excessive concentrations can have undesired effects. The team observed that the Laponite/BMP-2 coated scaffold promoted significant bone formation, as well as being biocompatible and well-tolerated in animal studies.

As next step, the team will take the scaffold forward for testing according to the International Organisation for Standardisation (ISO) standard and manufacturing according to Good Manufacturing Practice (GMP). These are crucial steps towards the clinical translation of the scaffold as a 3D printable material for bone regeneration. With ISO-certification, the researchers hope that the scaffold can be translated clinically as potential 3D printable material for bone regeneration.

"For a project focused on translation, the Smart Materials Hub and wider UKRMP have been incredibly resourceful. From the beginning of the project, we have had structured targeted product profiles for the materials/devices we have been developing, with consistent feedback from the Manufacturing Commercial and Regulatory (MCR) Panel. This has allowed us to make considered changes and design choices to the material to lower the safety risks of the material and improve its likelihood towards translation"

Dr Jonathan Wojciechowski

Imperial College London, UKRMP Smart Materials Hub

Smart Materials Hub Case Studies

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.

Professor 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.

To address this challenge, the team have developed a nanoclay gel that can support stem cell growth and colonisation. They have characterised the cellular response to the 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 have been instrumental for progressing the clinical translation of the technology, in collaboration with Renovos Biologics, a Southampton-based spinout company recently launched by the team. Importantly, Renovos Biologics has been granted a breakthrough device designation for the application of this technology for spinal fusion operations.

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 collaborative project to explore the early immune response to nanoclays as a springboard for bone repair processes.

3. UKRMP2 resources available to the community

Pluripotent Stem Cells and Engineered Cells (PSEC) Hub Resources

Resource	Description	Hub	Contact	Further Information
Genetically variant 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 fluorescently-labelled.
Reference cell line	Reference human induced pluripotent stem cell line and its gene-edited derivatives.	PSEC	Florian Merkle **fm436@medschl.cam.ac.uk**	Deeply genotypically and phenotypically characterised human induced pluripotent stem cell line and accompanying data, available from our collaborators at **https://www.jax.org/jax-mice-and-services/ipsc**.
Immune silent cell lines	hPSC lines which have HLA Class I KO via beta-2- microglobulin.	PSEC	Cedric Ghevaert **cg348@cam.ac.uk**	We have a number of established lines or protocols through which the editing can be achieved.
Database	Karyotyping database.	PSEC	Ivana Barbaric **i.barbaric@sheffield.ac.uk**	Database of over 20,000 hPSC karyotypes and associated metadata (e.g. ES/iPSC, culture conditions, sex etc) that can be searched for potential association of genetic changes with different parameters.
Database	Database of structural and sequence genetic variants in hPSCs.	PSEC	Florian Merkle **fm436@medschl.cam.ac.uk**	Searchable online database of genetic variants in readily-available human embryonic stem cells (https://hscgp.broadinstitute.org/).
Code	Computational methods for measuring pool balance.	PSEC	Florian Merkle **fm436@medschl.cam.ac.uk**	Annotated code to estimate the fractional abundance of cell lines within a pool from sequencing data.

Engineered Cell Environment (ECE) Hub Resources

Resource	Description	Hub	Contact	Further Information
Hepatocyte Differentiation media system	Cell growth media and recombinant proteins to promote differentiation of hepatic progenitors.	ECE	Commercially available through Stem Cell Technologies **https://www.stemcell.com/**	A chemically defined cell growth media and recombinant proteins to promote differentiation of hepatic progenitors.
Implantable human liver tissue	Prototype liver implant for the clinic	ECE	**https://www.stimuliver.bio/**	Spin out company Stimuliver are building a prototype liver implant for the clinic
High content 'Cell Painting' assay and Single Cell Morphological Trajectory Inference Assay	Hight content screen for expansion or bi-potent differentiation into hepatocyte-like and billary-like cells	ECE	**https://doi.org/10.1101/2023.11.15.567184**	A novel 384-well high content 'Cell Painting' assay using Hep-aRG™ cells and single-cell dif-ferentiation trajectory analysis based on morphological signa-ture of hepaRG progenitor ex-pansion or bi-potent differentia-tion into hepatocyte-like and bil-lary-like cells.. Published in Gra-ham et al., BioRxiv.
Hepatocyte progenitor differentiation hit NXP900	A screening hit compound which promotes hepatocyte progenitor differentiaton	ECE	Professor Neil Carragher **N.Carragher@ed.ac.uk**	Hepatocyte progenitor differentiation hit NXP900 was discovered in the University of Edinburgh and licensed to Nuvectis Pharma in 2021. The compound is currently in phase 1 dose escalation studies in oncology: **https://clinicaltrials.gov/study/NCT05873686**.
Mouse models of liver Injury (AhCreMdm2fl/fl and AAV8.p21+CCl4)	Mouse models of senescence-driven liver injury	ECE	Professor Stuart Forbes **stuart.forbes@ed.ac.uk**	A mouse model senescence-driven liver injury using AhCreMdm2fl/fl mice and a sec-ond independent model of exper-imental cell cycle arrest (AAV8.p21 overexpression. Pub-lished in Gadd et al. 2024, In Re-vision).
Bile Duct cell therapy product	Bile duct cell therapy product	ECE	Professor Stuart Forbes **stuart.forbes@ed.ac.uk**	An editable lentiviral luciferase reporter construct that was used to create promoter-reporter constructs for basal, mucosecretory and ciliated cells.
3D Wnt model of the chondrogenic niche	A 3D model for cartilage formation (chondrogenesis)	ECE	Profesor Alicia El Haj **a.elhaj@bham.ac.uk**	A 3D model for cartilage formation (chondrogenesis) using human progenitor cell lines to mimic and maintain tissue functions.
Wnt platform Strategies to demonstrate cartilage repair	Ligands and materials of interest to validate their effects on repairing the osteochon-dral injury	ECE	Professor Andrew McCaskie **awm41@cam.ac.uk**	In vivo studies using selected ligands and materials of interest to validate their effects on repair-ing the osteochondral injury. We aim to publish this work.
Organ-on-a-Chip model of of the Musculo-skeletal system	Organ-on-a-Chip model of of musculo-skeletal sys-tem for de-veloping re-generative therapies	ECE	Professor Alicia El Haj **a.elhaj@bham.ac.uk**	An organ-on-a-chip Wnt platform model approach using a microfluidic device in collaboration with EMULATE.

Engineered Cell Environment (ECE) Hub Resources

Resource	Description	Hub	Contact	Further Information
Wnt-bandages which promote bone repair.	A tissue re-generation patch to re-pair lost or damaged bone	ECE	Professor Alicia El Haj **a.elhaj@bham.ac.uk**	Wnt-bandages which promote bone repair. Patent P6125GB00 (El Haj & Habib) a tissue regeneration patch to repair lost or damaged bone based on our publication in Nature Materials. The basis of this work has been published in Okuchi Y et al, 2020.
Lung High Throughput Screen and Validation Assays	A high throughput assay for screening for modulators of proliferation.	ECE	Professor Sam Janes **s.janes@ucl.ac.uk**	A high throughput assay for screening primary airway epithelial cells for modulators of proliferation.
Lentiviral luciferase reporter construct lung differentiation screen	Lentiviral lu-ciferase re-porter con-struct for 3D lung differen-tiation screen	ECE	Available on Addgene (215326-215329)	An editable lentiviral luciferase reporter construct that was used to create promoter-reporter con-structs for basal, mucosecretory and ciliated cells.

Smart Materials Hub Resources

Resource	Description	Hub	Contact	Further Information
Tools and Reagents	Human bone marrow stromal cells (HBMSCs) – Skeletal Stem and progenitor cells from OA and OP patients for research	SM	Dr Janos Kanczler	Disease specific and normal HBMSCs
	Synthesis of peptide- modified multi-arm poly- caprolactone	SM	Professor Molly Stevens	Custom peptide synthesis and synthesis of peptide-polymer conjugates..
	Mineralising Materials	SM	Professor Alvaro Mata	Elsharkawy et al, Nature Communi-cations 2018, 9(2145)
	Self-assembling hydro-gels	SM	Professor Alvaro Mata	Redondo-Gomez et al, Biomacromolecules 2019, 20(6),
	Multi-zonal scaffold produc-tion	SM	Professor Molly Stevens	Electrospinning, porogen leaching, and directional freezing Steele et al, Biomaterials, 2022, 286(121548)
	Poly--lysine hydrogels	SM	Professor Rachel Williams	Levis et al, Investigative Ophthalmology & Visual Science, 2023, 64(8)
	Poroelastic electrospun fibres (FiHy™) for cartilage regeneration	SM	Professor Molly Stevens	Moore et al, Acta Biomaterialia, 2023, 167(69-82)
	Electrospun polymer fibres for retinal regeneration	SM	Professor Molly Stevens, Professor Robin Ali, Professor Rachael Pearson	
	HealiOst – bioactive osteogenic coating	SM	Professor Manuel Salmeron-Sanchez	
	A mouse model senescence-driven liver injury using AhCreMdm2fl/fl mice	SM	Professor Stuart Forbes	

Smart Materials Hub Resources

Resource	Description	Hub	Contact	Further Information
Technology	Quantification and analysis of protein secondary structure	SM	Professor Alvaro Mata	Elsharkawy et al, Nature Communi-cations 2018, 9(2145)
	Molecular patterning inside hydrogels	SM	Professor Alvaro Mata	Aguilar et al, Advanced Functional Materials 2018, 28(15)
	3D printing with self- assembling bioinks	SM	Professor Molly Stevens	Formlabs and Prusa SLA Printers which have been configured to print small (<5 mL) and large (>100 mL) volumes of customised hydro-gels and biodegradable polymers.
	Filament electrospinning and braiding technology	SM	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414
	Centre for Additive Manufacturing	SM	Professor Lisa White	
Equipment	SLA 3D Printing	SM	Professor Ricky Wildman	This has been tailored for MSK work untaken in the Hub. **https://www.nottingham.ac.uk**
	PCL electrospun filament	SM	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414
	Textile equipment (weaving, braiding, twisting)	SM	Associate Professor Pierre-Alexis Mouthuy	Savic et al. Mater Sci Eng C Mater Biol Appl 129, 2021, 112414

4. UKRMP2 Immunology Project End Reports

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

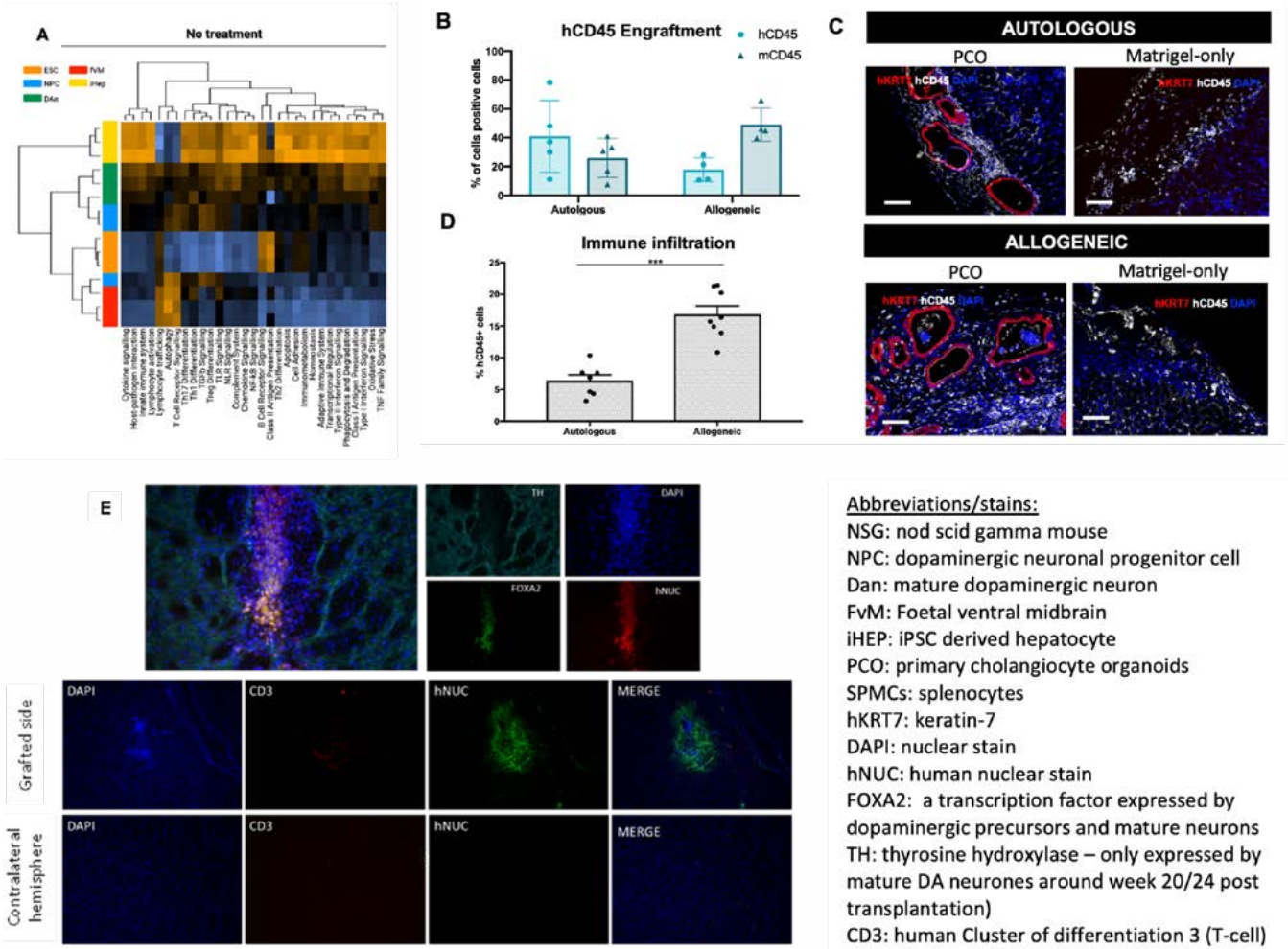
Professor Giovanna Lombardi (lead) *(King's College London)*
Dr Joanne Jones and Professor Kourosh-Saeb Parsy *(University of Cambridge)*

Our goal was to develop a platform for testing immune responses to advanced cellular therapies to assess their likelihood of rejection when transplanted into patients. Understanding this is key to the success of regenerative medicine.

Using: (i) iHEPs and primary cholangiocyte organoids (PCO; allogeneic vs autologous, *in-vivo*), and (ii) embryonic stem cell-derived dopaminergic neurones (ES-DA), chosen because they are about to enter clinical trials for the treatment of liver/bile-duct 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). This is in keeping with our observation that these cells do not express all molecules necessary for immune cell activation. We also performed an immune targeted bulk transcriptional screen on different cell types, throughout their differentiation states and compared to previously tolerated cell (dissociated foetal ventral midbrain – fVM – tissue) (Figure A). To better explore immune responses we generated mice with a human immune system by injecting human immune cells into immunodeficient animals. Interestingly, allogeneic PCOs survived under the kidney capsule but caused significantly higher immune infiltration compared to autologous cells (Figures B-D). ES-DA cells (transplanted as day16 progenitors) survived injection into the mouse brain, and in induced only a small inflammatory infiltrate (Figures E,F), confirming their low immunogenicity.

Figure (A) cluster analysis of molecules expressed cells at various stages of differentiation, (B) Percent positive m/hCD45 cells in spleen of autologous and allogeneic mice at endpoint (C) Immunofluorescence showing hCD45+ and engrafted PCOs (hKRT7) 6 weeks after kidney capsule injection and 3 weeks after humanisation in autologous and allogeneic mice. Matrigel-only injection in contiguous kidney capsule as control. Scale bars: 100µm. (D) Percent hCD45+ cells in autologous and allogeneic mice under kidney capsule at endpoint. (E) Early ES-DA graft survival in humanised NSGs (F) Infiltration of human T cells into the graft at 1 week. Contra-lateral, non-grafted hemisphere for comparison.



Abbreviations/stains:
NSG: nod scid gamma mouse
NPC: dopaminergic neuronal progenitor cell
Dan: mature dopaminergic neuron
FvM: Foetal ventral midbrain
iHEP: iPSC derived hepatocyte
PCO: primary cholangiocyte organoids
SPMCs: splenocytes
hKRT7: keratin-7
DAPI: nuclear stain
hNUC: human nuclear stain
FOXA2: a transcription factor expressed by dopaminergic precursors and mature neurons
TH: thyrosine hydroxylase – only expressed by mature DA neurones around week 20/24 post transplantation)
CD3: human Cluster of differentiation 3 (T-cell)

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*)

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive fibrosis and regions of abnormal alveolar regeneration. The causes and functional consequences of abnormal alveolar regeneration is not fully understood. Our work focuses on characterising the alveolar regenerating niche in situ, in human IPF lung tissue, and identifying immune cells that are co-located with normal and abnormal areas of alveolar regeneration.

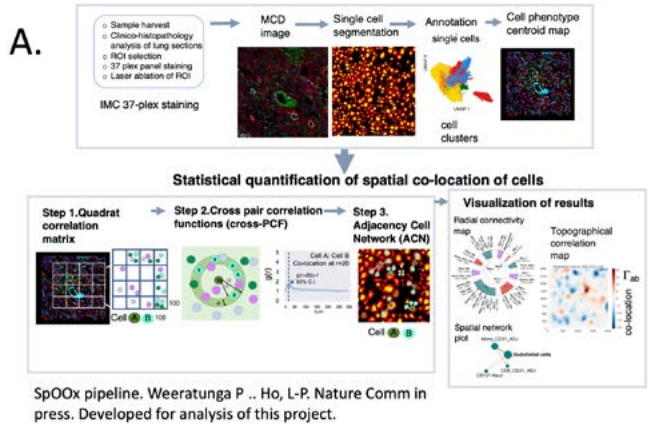
Normal alveolar regeneration is primarily the responsibility of Wnt-II- enriched AT II cells. However in IPF and after severe injury (like in severe COVID pneumonitis), a group of metaplastic KRT5+ basal cells appear after the loss of these AT II cells. Recent studies in murine lungs show that a complex mixture of intermediate ATII stem cells emerges after injury, which may also be present in human IPF lungs. These intermediate ATII stem cells may be the pre-requisite to bronchiolization and irreversibly damaged alveolar epithelium.

It is not clear why ATII cells in IPF lungs fail to regenerate appropriately but the diseased microenvironment that surrounds these progenitors is likely to play a major role. Our programme of work examines the cellular composition of the regenerating alveolar niche and physical interaction between immune cells and the alveolar stem cells and its intermediates. Understanding this immune tissue microenvironment is a pre-requisite to delineating how immune cells influence alveolar regeneration, and eventually our vision of manipulating immune cells to enhance normal endogenous regeneration for IPF patients.

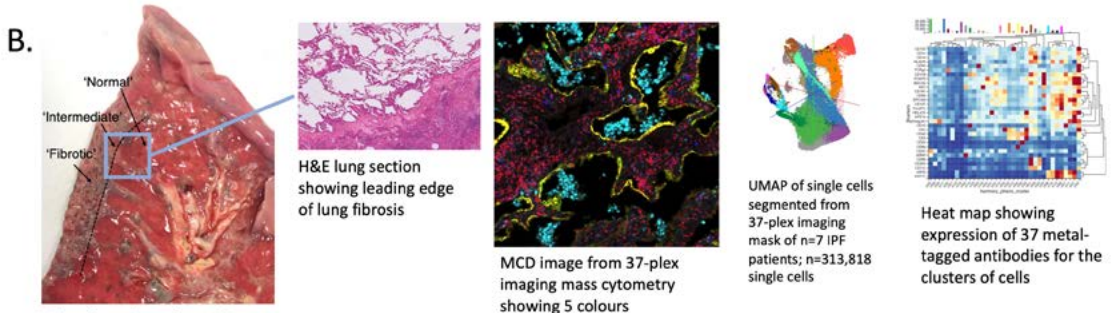
We use single cell resolution imaging of lung tissue with 37-plex antibody panel staining (performed in University of Newcastle) to decipher the co-location between highly annotated immune cells and structural cells in the regenerating alveolar niche in IPF lungs. We developed a suite of mathematical tools in collaboration with colleagues at Oxford Mathematical Institute and the MRC WIMM Centre for Computational Biology for this task (Weeratunga P Nature Communication in press).

Combining these advanced methods and expert histopathopothologist-led analysis of lung tissue, we were able to spatially isolate the regenerating alveolar niche and about to complete a high resolution temporo-spatial map for these niches. We combine these findings with single cell transcriptomic data to examine receptor ligand signalling. We expect a final report of this before the end of the year.

The work is led by Prof Ling-Pei Ho and is a collaboration between University of Oxford (MRC Translational Immune Discovery Unit, MRC WIMM Computational Biology; The Oxford Mathematical Institute) and University of Newcastle (Prof Andrew Fisher, Andrew Filby and Jim Shaw, Institute of Cellular Medicine). Outcomes have been recently published in a **preprint**. We acknowledge funding from UKRMP, MRC, NIHR BRC, Chinese Academy of Medical Science Oxford Institute, the Wellcome Trust, and Medical Sciences Division, University of Oxford for various parts of the project.



SpOOx pipeline. Weeratunga P .. Ho, L-P. Nature Comm in press. Developed for analysis of this project.



Unique lung tissue from IPF patients undergoing lung transplantation, showing typical macroscopic areas of advancing fibrosis

H&E lung section showing leading edge of lung fibrosis

MCD image from 37-plex imaging mass cytometry showing 5 colours
CD3 Red, CD68 Cyan, CD20 - Blue

UMAP of single cells segmented from 37-plex imaging mask of n=7 IPF patients; n=313,818 single cells

Heat map showing expression of 37 metal-tagged antibodies for the clusters of cells

5. UKRMP2 Strategic Project End Reports

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

Professor Hazel Screen (lead), Professor Martin Knight *(Queen Mary University London)*, Professor Alicia El Haj *(University of Birmingham)* Dr Simon Grossemy, Brenda Sanchez, Dr Clare Thompson (*Queen Mary University London)*

Background

Better model systems are urgently needed for safety and efficacy testing of regenerative medicine products, prior to clinical trials in people. An organ-chip is a bioengineered system, in which the architecture, functions and surrounding physiochemical environment of a living human organ are recreated. We focus on developing physiologically and pathologically relevant 3D matrix niche environments for joint-chip models, to provide improved models systems for product testing.

Methods and Results

Bone, synovium, cartilage, tendon, ligament and muscle models are under development to provide joint-chips. Development of each tissue necessitate knowledge of resident cell populations and of extracellular matrix biophysical parameters, to recreate appropriate niche environments within the chip to maintain each cell population and enable users to drive the model towards healthy or pathological status. We have established protocols to generate a range of hard and soft 2D and 3D environments within microfluidic organ chips to support this broad model creation, and have used these approaches to develop at least one chip model of each tissue.

We have also optimised approaches to integrate vasculature within each model. In cartilage, synovium and tendon, we have recreated joint inflammation within the chips and explore the associated pathways.

Our tendon model has offered particular challenge, owing to poor knowledge of resident cell populations and their management. Building on our previous studies indicating two distinct cell niche environments: the collagen-rich fascicular matrix containing fascicular matrix (FM) cells, and the soft proteoglycan-rich interfascicular matrix containing interfascicular matrix (IFM) cells[1], we have generated approaches to spatially separate the cell populations to explore their phenotype. We have demonstrated that IFM cells do not grow in classic cell culture, but must be grown on softer substrates if they are to be retained for appropriate organ-chip studies (fig 1).

We have established approaches to maintain IFM cells and build a tendon model incorporating both populations, showing that the model can capture the cytokine response of IFM cells to FM cell inflammatory insult, and demonstrating that this can be diminished with the addition of steroids.

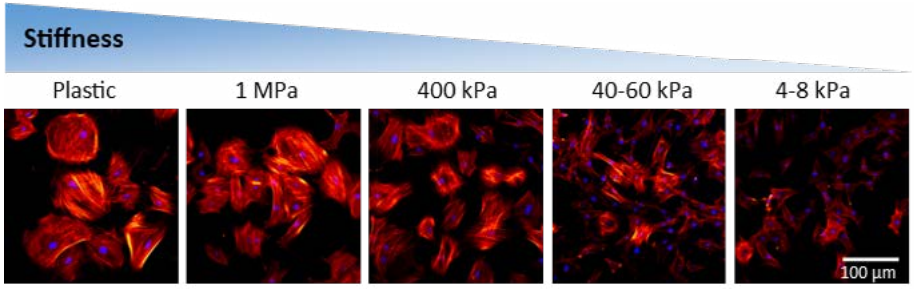


Figure 1: Tendon IFM cells cultured on a range of substates ranging from cell culture plastic to surfaces mimicking adipose tissue stiffness (4-8kPa). IFM cells stop proliferating and dedifferentiated on hard surfaces. Our measures of IFM tissue stiffness report values of 2-4kPa. IFM cell morphology and gene expression is best recapitulated on the equivalent 4-8kPa culture surface.

We have recently tested the first ECE Hub target, kartogenin, within our tendon model. Kartogenin has been identified as beneficial in supporting cartilage healthy growth and inhibiting chondrocyte response to inflammatory stimuli[2]. Preliminary analysis of data indicates that kartogenin also drive tendon FM cells towards chondrocytic matrix production and augments the response of IFM and FM cells to inflammatory insult, indicating care may be required in its use at a whole joint level.

Conclusions

Our new joint-chip models enable studies into the physiological and pathological behaviour of each joint tissue to better understand drivers of disease, as well as providing a platform in which to test the safety and efficacy of potential regenerative medicine targets, ultimately helping address the bottlenecks in translating new therapies to clinic.

References

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2. *Hou M, Zhang Y, Zhou X, Liu T, Yang H, He F, Zhu X (2012) Kartogenin prevents cartilage degradation and alleviates osteoarthritis progression in mice via the miR-146a/NRF2 axis. Cell Death Dis. DOI: 10.1038/s41419-021-03765-x*

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

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

The primary cause of Type 1 and late-stage Type 2 diabetes is the loss of beta cells in the pancreas, resulting in reduced insulin levels. The management of diabetes requires daily insulin administration. Promising therapies revolve around the use of beta cells derived from induced pluripotent stem cells (iPSCs). However, the differentiation process still suffers from its inefficiency. To enhance this efficiency, a viable method involves the three-dimensional expansion of pancreas progenitor organoids (PPOs) within a 3D scaffold such as Matrigel. Unfortunately, the use of Matrigel proves incompatible with any translational cell therapy due to its variable composition and animal origin.

Our project focuses on studying hydrogels to understand the molecular and physical cues required to generate iPSC-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, PPO cells form organoids which retain high viability and expression of the key pancreatic differentiation markers.

We tested different functionalized hydrogels for their ability to sustain PPO growth and performed RNAseq analysis to identify the molecular pathways activated in each condition. In addition, we optimized a protocol to differentiate the hydrogel-expanded PPO organoids into beta-like cells (Fig. 1). All the conditions resulted in a differentiation similar or slightly higher than Matrigel; however, the GSIS response was concomitant with an immature beta cell phenotype.

Preliminary experiments are ongoing to address whether the cells could fully mature after transplantation in normoglycemic mice. These results demonstrate that hydrogels are an alternative platform that sustains the growth and differentiation of PPOs into beta cells and pave the way for optimization to achieve iPSC-derived beta cells for future therapies.

Co-funded by:

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

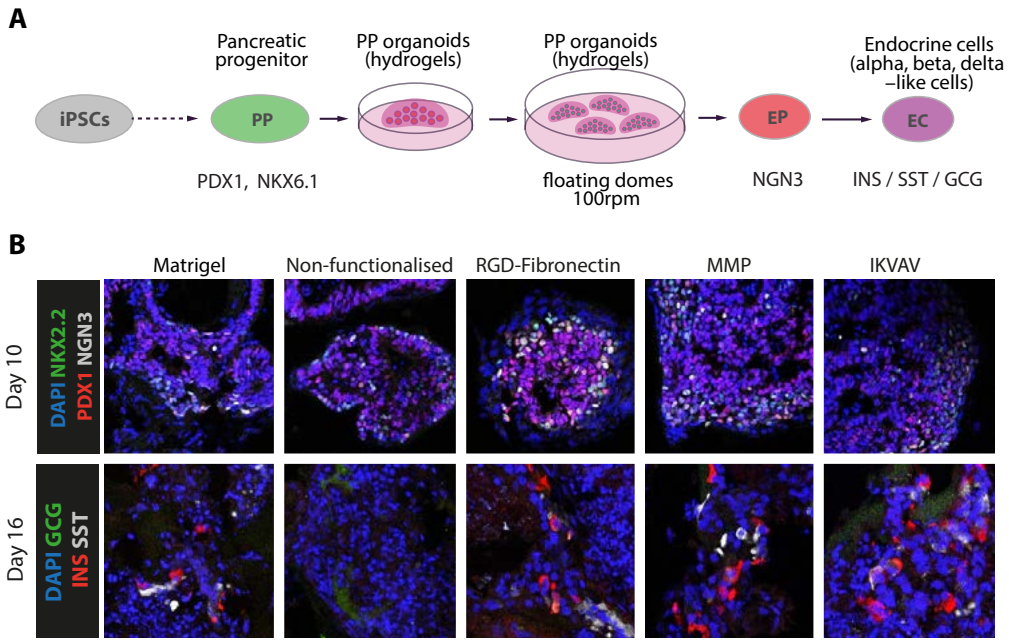


Figure 1. (A) Schematic representation of the PPOs to endocrine cells differentiation protocol. (B) Immunofluorescence characterization of PPOs grown in different 3D hydrogels after Day 10 (Ngn3 endocrine progenitor stage) or Day 16 (endocrine cell stage). Antibodies anti-Insulin (INS), CGC (Glucagon), SST (Somatostatin), NGN3 (Neurogenin 3), PDX1 and NKX2.2 were used.

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

Professor Anna Williams, Dr Laura Wagstaff, Nadine Bestard-Cuche (*University of Edinburgh*), Professor Robin Franklin (*University of Cambridge*)

Co-funded by:

MS Society

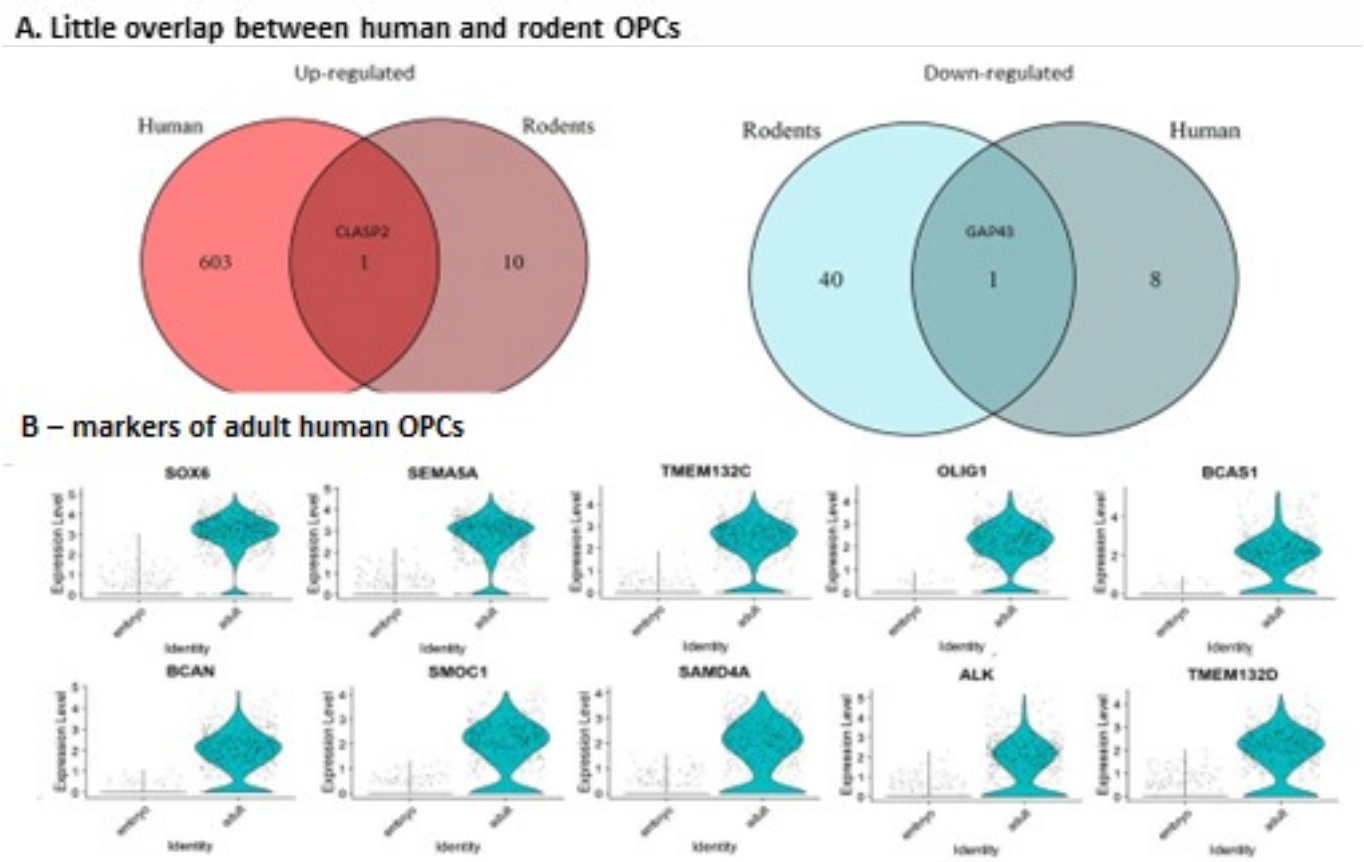
Our aim was to generate human oligodendrocytes in the laboratory which are adult-like (rather than foetal) to better test therapeutics to improve their function, to improve the ability to translate such therapies successfully to adult multiple sclerosis (MS) patients, to improve remyelination and provide neuroprotection in the neurodegenerative phase of MS.

We addressed three challenges:

1) Do adult human oligodendroglia in health and in MS express markers of ageing similar to those in aged rat?

2) How can we model aged adult human oligodendroglia in vitro that well reflect these adult human brain tissue cells, including the correct oligodendroglial subtypes?

3) Does the drug metformin rejuvenate the response of human adult oligodendrocyte precursor cells (OPCs) to pro-remyelinating compounds leading to better myelin protein formation *in vitro* and better myelination and remyelination *in vivo*, with an appropriate proportion of oligodendroglial subtypes?



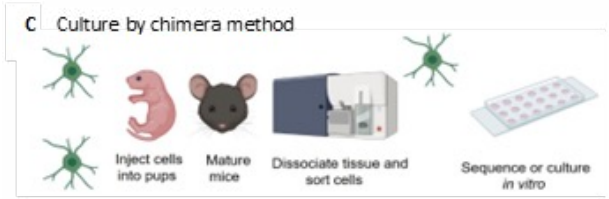
In summary, by comparison with our and publicly available datasets, we have identified markers of human adult OPCs, and found that these are different from rodent ones focussing our work onto human cells (A,B) (Seeker et al., 2023, MacNair et al., 2023).

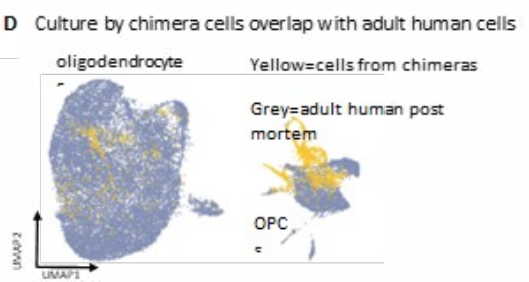
Do adult human oligodendrocytes remyelinate poorly and can we change this to better treat progressive multiple sclerosis?

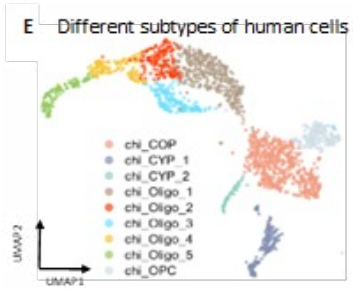
Professor Anna Williams, Dr Laura Wagstaff, Nadine Bestard-Cuche (*University of Edinburgh*), Professor Robin Franklin (*University of Cambridge*)

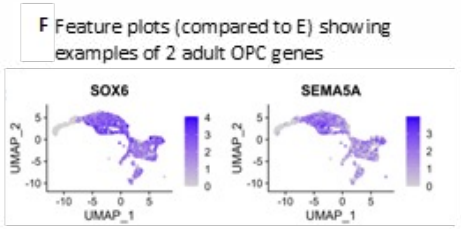
We have tested a variety of culture systems for human OPCs, and found that human embryonic stem (ES) cell-derived OPCs in monocultures are much more like foetal OPCs, in organoids, are more mature, with different subtypes, but very few in number and if transplanted into mice (chimeras, (C)) show much more similarity to adult human OPCs (D) (Kazakou, Wagstaff et al., in preparation). These also show different subtypes of relevance to remyelination in MS (E) (Jaekel et al., 2019, MacNair et al., 2023) with markers relevant to adult cells (F). This gives us a robust system to test potential remyelination therapeutics in adult/older human oligodendrocytes rather than young rodent ones which will improve the choice of effective drugs to better translate to clinical benefit in adult MS patients. However, this is clearly not high throughput. We have further developed a method of extracting these cells following incubation and successfully culturing them *in vitro*, where they retain low responsiveness to pro-remyelination drugs, as expected with adult-like OPCs, and which is more high-throughput (G).

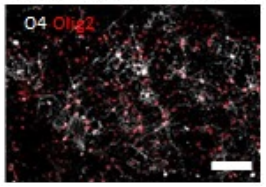
We have tested the responsiveness of OPCs in all of these systems to metformin (and selected other pro-remyelinating drugs). Metformin increases human OPC functional activity in terms of increased myelin formation (G,H), and enhanced metabolic activity (mitochondrial response (I) and other metabolic functions) but this enhanced metabolic response is also present in the neuronal axons, in the chimeric mouse model. This is of great interest as metformin is now being tested in MS clinical trials in the Multiple Sclerosis Society UK's UK-wide OCTOPUS trial for progressive multiple sclerosis, a trial platform extending over 10y in an adaptive trial design and in a second MS Society-funded trial in the earlier phase of relapsing-remitting MS, combining metformin with clemastine. The role of metabolism in neurodegeneration is very much of interest to the neuroprotection field for all neurodegenerative diseases and this work has allowed us to gain a recent Progressive MS Alliance project grant investigating neuronal metabolism in MS and MS model (collaboration between Dr Don Mahad and AW).

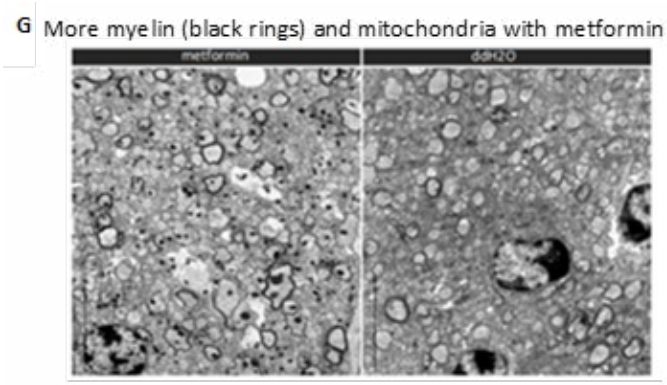


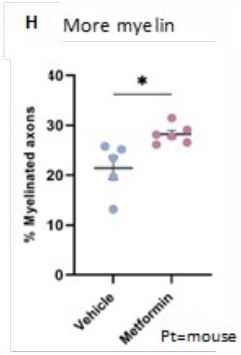


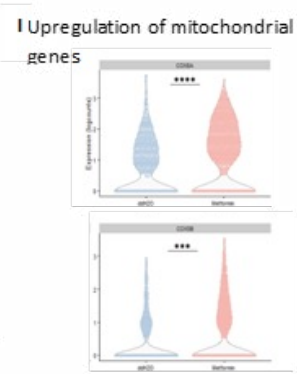












Exploiting in silico modelling to address the translational bottleneck in regenerative medicine safety

AR Alipio, MR Vieira, MC Arno & AJ El Haj, *University of Birmingham*, C Ashmore-Harris, WY Lu, VL Gadd & SJ Forbes, *University of Edinburgh*, E Antonopoulou, SM Finney, MG Hennessy, A Muench & SL Waters (lead), *University of Oxford*

Successful clinical translation of cell therapies requires robust preclinical approaches to assess their safety, toxicity and efficacy as well as an understanding of the injured tissue niche. We focus on liver cell therapies, and combine *in silico*, *in vitro* and *in vivo* approaches to understand how the level of senescence in the injured liver influences the multicellular interplay of different spatiotemporally activated pro-inflammatory and pro-regenerative responders, tissue regeneration and injury resolution, alongside how the mechanical environment experienced by cell therapies in transit through the vasculature to the injury site impacts their delivery to, and ability to engraft at, the site of injury.

***In vivo*-in silico models:** We perform detailed quantitative histological and mRNA expression characterisation of the key players in the regenerative response and report this for a moderate level of senescence induced hepatic injury, utilising the AhCreMdm2flox/flox mouse model (Fig. A1). We next derived a complementary ordinary differential equation model to capture the dynamics of the key cell players in the injury response (Fig. A2). We show that the mathematical model is able to predict the host response to moderate injury via qualitative comparison of the model predictions with the experimental data. We then use the model to predict the host response to mild and severe senescence induced injury, and test these predictions *in vivo*, obtaining good qualitative agreement. Both *in silico* and *in vivo* we find a dose and time dependent tissue regeneration response with initial polarisation of macrophages towards an inflammatory state, facilitation of immune cell migration to the injury niche through activation of endothelial cells and tissue remodelling as a result of myofibroblast activation and collagen-I deposition. This is followed by a regenerative phase, including a macrophage phenotypic switch towards a pro-regenerative phenotype, a reduction in activated endothelial cells and clearance of activated myofibroblasts and excess collagen-I.

***In vitro*-in silico model:** Using a 3D *in vitro* model that mimics physiological flow, we assess the impact of flow on cell viability and key matrix attachment proteins, such as the family of integrins (Fig B1). Exposure to fluid flow reveals significant changes in integrin gene expression across different cell types, in contrast to those cells not subjected to shear stress (Fig. C), which ultimately can impact ECM adhesion and cell engraftment. We assess the impact of an adhesive coating at the cell membrane on increasing cell adhesion to extracellular matrix components and cell-cell interactions (Fig. B2). 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 model a single hydrogel-coated cell translating in a vessel to quantify the impacts of the geometric confinement and coating on the experienced mechanical cues (Fig. B3). We demonstrate the importance of cell size, showing that an increase in coating thickness may or may not have a dampening effect on the cell deformation due to the confinement.

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.

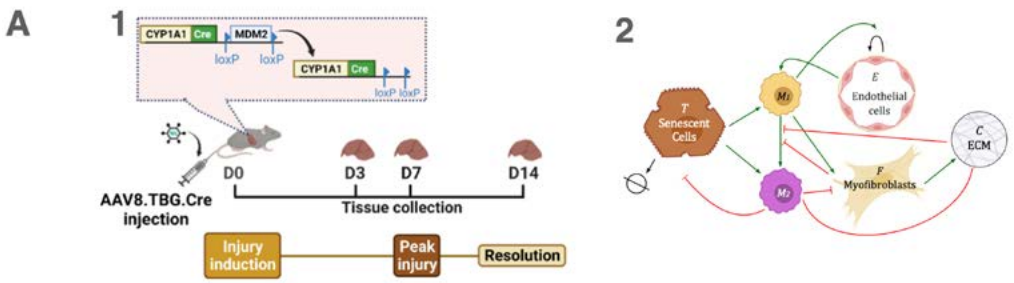


Figure A. A1: Induction of senescence marker expression in Mdm2 mice by AAV8.TBG.Cre dosing. Inset demonstrates Cre recombinase expression mediated loss of Mdm2 in hepatocytes as a result of injection of hepatotropic AAV8.TBG.Cre. Timepoints for tissue collection and analysis are indicated by days since injury induction. A2: Schematic of the in silico injury model with variables and their interactions are presented. Green arrows indicate promotion and flat head red arrows indicate inhibition.

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

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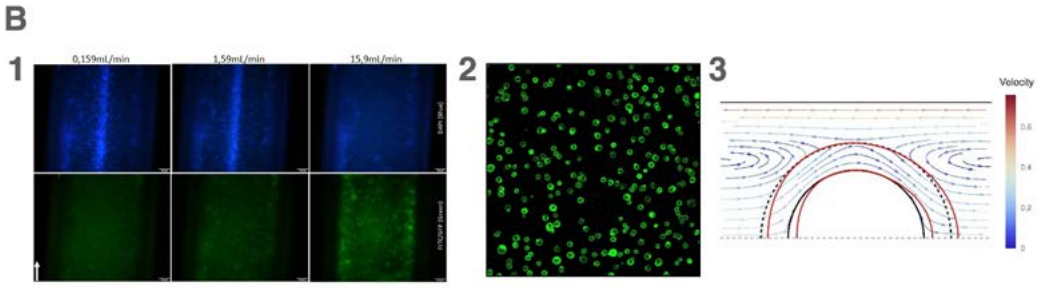

Figure B. B1: Live Cell Imaging. Mouse hepatic progenitor cells (HPC) in transit under flow conditions (bottom to top direction) treated with LIVE/DEAD® dyes. Left 0.159mL/min; middle 1.59mL/min; right 15.9mL/min, 4x magnification, Olympus cell Sens software. Top: NucBlue Live reagent stains cells nuclei, DAPI (blue) detection (excitation/emission: 360/460 nm) Bottom: NucGreen Dead reagent stains dead cells nuclei, FITC/GFP (green) detection (excitation/emission: 504/523 nm). B2: HPCs coated with hyaluronic acid (green) through bio-orthogonal azide-alkyne click chemistry. B3: In silico model of an individual hydrogel-coated cell translating along the centre-line of a cylindrical tube. The arrows are velocity streamlines with the deformed cell and coating surfaces shown in red.

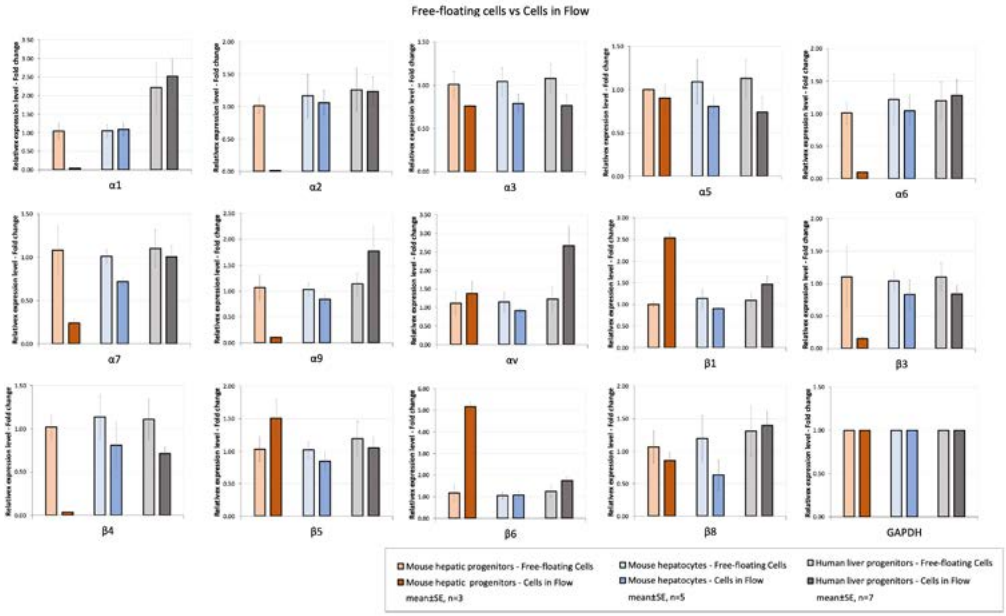

Figure C Relative expression. Gene expression levels of endogenous beta and alpha integrins (Itgb, Itga) in mouse hepatic progenitors (HPC), mouse hepatocytes and human liver progenitor cells under flow conditions (1.59mL/min). Analysis of integrins mRNA expression are presented relative to GAPDH mRNA and normalised to cells not subjected to flow (free-floating) as a baseline control (2-ΔΔCq). All values are mean±SE (standard error), n=3,5,7 replicates per group, respectively.

6. Annexes

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Patents

1. US/2019/0247542 - Polymer-clay composite and organoclay. Publication date: 15.08.2019. Grant date: 16.11.2021. Applicant: University of Southampton. Inventors: Richard Oreffo, Jonathan Dawson, David Gibbs, Jons Hilborn, Dmitri Ossipov. Related patents: US/2017/0043058 (Granted: 02.04.2019), EP3134470, WO/2015/170075, EP4242257, ES2949440.

2. WO/2020/058724 – Structured gels. Publication date: 26.03.2020. Applicant: University of Southampton. Inventors: Richard Oreffo, Jonathan Dawson, Nicholas Evans, Roxanna Sharon Ramnarine Sanchez. Related patents: US/2022/0096715, EP3852808.

3. WO/2021/161290 – Materials chemistries and microtopographies and uses thereof. Publication date: 19.08.2021. Applicant: University of Nottingham. Inventors: Morgan Alexander, Amir Ghaemmaghami, Paul Williams, Simon Avery, Andre Hook, Felicity Rose, Chris Denning. Related patents: EP4103677.

4. WO/2018/083500 – Additive Manufacturing. Publication date: 11.05.2018. Applicant: University of Nottingham. Inventors: Christopher John Tuck, Belen Begines Ruiz, Yinfeng He, Ricky Darren Wildman, Richard James Mackenzie Hague. Related patents: CN110167743 (Granted: 12.10.2021), EP3525110, IL266475 (Granted: 01.02.2023), US/2019/0263058 (Granted: 23.11.2021).

5. WO/2023/233155 – Micron-scale 3D objects for the modulation of cell phenotype from pro to anti-inflammatory states. Publication date: 07.12.2023. Applicant: University of Nottingham. Inventors: Morgan Alexander, Ricky Wildman, Amir Ghaemmaghami.

6. WO/2021/156607 – Drug formulations. Publication date: 12.08.2021. Applicant: University of Nottingham. Inventors: Yifeng He, Ricky Wildman, Clive Roberts, Derek Irvine, Giuseppe Mantovani, Richard Hague, Christopher Tuck, Vincenzo Taresco. Related patents: CN115666530.

7. US/2018/0133364 – Materials and methods for tissue regeneration. Publication date: 17.05.2018. Grant date: 16.01.2024. Applicants: University of Glasgow, Georgia Tech Research Corporation. Inventors: Manuel Salmeron-Sancez, Matthew J. Dalby, Andres J. Garcia. Related patents: EP3302590, WO/2016/189094, ES28824575.

8. WO/2023/041529 – Composition for 3D tissue culture. Publication date: 23.03.2023. Applicants: University of Glasgow, Imperial College Innovations Limited, Cellink Bioprinting AB. Inventors: Oana Dobre, Sara Trujillo-Muñoz, Matthew John Dalby, Manuel Salmeron-Sanchez, Lilian Ouyang, Molly Stevens, Adel Itedal Namro Redwan, Volodymyr Kuzmenko, Erik Gatenholm, Hector Martinez. Related patents: EP/2022/789868.

9. US/2019/0060517 – Scaffold for cardiac patch. Publication date: 28.02.2019. Applicants: Tecnologias Avanzadas Inspiralia S.L., University of Manchester, Institul de chimie macromoleculara Petru Poni, Ustav experimentalni akademie ved ceske republiky verejna vyzkumna instituce. Invenotrs: Guillame Saint-Pierre, Miguel Herrero Gomez, Sandra Martinex Creispera, Alberto Saiani, Catherine Merry, Kate Meade, Jean-Baptiste Guildbaud, Aline Fiona Miller, Constentin Ciobanu, Evzen Amler. Related Patents: EP2897659, US20150246157 (Granted: 20.11.2018), ES2599705, WO/2014/044321, JP2015532845 (Granted: 31.03.2017), PL2897659.

10. US/2019/0135897 – Crystal structures comprising elastin-like peptides. Publication date: 09.05.2019. Applicant: Queen Mary University of London. Inventors: Sherif Ahmed Abdelsalam Elsharkawy, Maisoon Al-Jawad, Alvaro Mata Chavarria, Esther Tejeda-Montes, Roxanna Sharon Ramnsarine Sanchez. Related patents: EP3436474, WO/2021/168183, US/2022/0363734 (Granted: 23.04.2024).

11. WO/2020/058456 – Self-assembling graphene oxide-protein matrix. Publication date: 26.03.2020. Applicant: Queen Mary University of London. Inventors: Yuanhao Wu, Wen Wang, Alvaro Mata Chavarria. Related patents: EP3852821, US/2021/0346570.

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13. US/2016/0229104 – Electrospun filaments. Publication date: 11.08.206. Grant date: 17.08.2021. Applicants: ISIS Innovation Ltd, Oxford University Innovation Ltd. Inventor: Pierre-Alexis Mouthuy. Related patents: CN105658850 (Granted: 29.03.2019), EP3047057, WO/2015/040399.

14. EP3349814 – Non-gelling soluble extracellular matrix with biological activity. Publication date: 25.07.2018. Applicants: University of Pittsburgh Commonwealth Sys Higher Education, University of Nottingham. Inventors: Stephen F. Badylak, Timothy Joseph Keane Jr, Lisa Jane White. Related patents: US/2019/0060521 (Granted: 11.08.2020), WO/2017/049167, ES2873519, US/2020/0360565.

15. WO/2022/229653 – Decellularized tiddue hydrogels. Publication date: 03.11.2022. Applicant: Univesity of Nottingham. Inventors: Lisa White, Joshua Jones. Related patents: EP4329833.

16. US/2018/0318212 _ Composition comprising diacid derivatives and their use in the treatment of collagenic eye disorders. Publication date: 08.11.2018. Grant date: 05.11.2019. Applicants: University of Liverpool. Inventors: Rachel L. Williams, Colin E. Willoughby. Related patents. EP3370736, WO/2017/077300.

17. EP3496760 – Opthalmic compositions. Publication date: 19.06.2019. Applicant: University of Liverpool. Inventors: Victoria Kearns, Helen Cauldbeck, Steve Rannard, Rachel Williams, Maude Le Hellaye. Related patents: US/2019/0175742 (Granted: 19.03.2024), WO/2018/029477, ES2910987.

18. WO/2023/194587 – Hydrogels. Publication date: 12.10.2023. Applicant: University of Liverpool. Inventors: Rachel Williams, He Liang, Hannah Levis, Vito Romano.

19. WO/2023/237898 – Novel treatment. Publication date: 14.12.2023. Applicant: University of Liverpool. Inventors: Rachel Williams, Jyle Doherty, Hala Dhowre.

20. WO/2019/243375 – Single particle automated raman trapping analysis. Publication date: 26.12.2019. Applicant: Imperial College of Science, Technology and Medicine. Inventors: Molly Stevens, Jelle Penders, Isaac Pence. Related patents: CA3104027, CN112585448, EP3811052, US20210262915, JP2021527818 (granted 30.08.2023), DK3811052 (granted 11.09.2023), FIEP3811052, ES2960707, IN202117001782.

21. WO/2021/019253 – ultrasound-triggered liposome payload release. Publication date: 04.02.2021. Applicants: Imperial College Innovation Ltd, The Chancellor, masters and scholars of the University of Oxford. Inventors: Valeria Nele, James P. Armstrong, Molly M. Stevens, Carolyn Schutt Ibsen, Michael D. Gray, Constantin C. Coussios. Related patents: CA3149618, EP4007608, CN114728067, JP2022544752, US20220249669.

22. WO/2023/217767 – Scaffold supported organoid farms for controlled high-throughput in vitro organoid aggregation and regional orgaonid patterning. Publication date: 16.11.2023. Applicants: Imperial College Innovation Ltd, Institut für molekulare biotechnologie GMBH, Christopher Lawrence Grigsby. Inventors: Christopher Lawrence Grigsby, Kaja I. Ritzau-Reid, Richard Wang, Ruoxiao Xie, Daniel Reumann, Jürgen Knoblich, James P. Armstrong, Jonathan Yeow, Molly M. Stevens.

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