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A decade of progress: Achievements and future challenges for regenerative medicine research in the United Kingdom

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ABSTRACT

The final United Kingdom Regenerative Medicine Platform (UKRMP) conference held in Edinburgh's iconic McEwan Hall between 8th and November 10, 2023 saw a gathering of nearly 200 international delegates presenting exceptional science and celebrating a decade of this initiative. The UKRMP had the core mission to break down the major barriers to clinical translation of regenerative medicine products. UKRMP2 was established as three hubs that worked closely with industry and regulators: 1) Pluripotent Stem Cells and Engineered Cells, 2) Engineered Cell Environments, and 3) Smart Materials. In this meeting report, we outline the original aims of UKRMP, examine how it achieved critical mass, summarise the major developments that the UKRMP hubs delivered, and examine some unresolved challenges that still lie ahead in the field of regenerative medicine.

1. Introduction

In the early 1990s 'Regenerative Medicine' was first used as a term to describe a future branch of medicine that, at the interface with engineering, would restore tissue function after damage by disease, trauma, or time. Twenty years later it was still heralded as being capable of transforming global human health, but whilst our repertoire of approaches to creating tissues *in vitro* had seen tissue engineering principles applied to an encompassing range of cell types, tissues, and organ systems, little progress had been made with regards to translating these products to the clinic and achieving real clinical impact. Following a strategic review of regenerative medicine in the UK led and published by the MRC between 2010 and 2012,[1] the United Kingdom Regenerative Medicine Platform (UKRMP) was established by the Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC), and Engineering and Physical Sciences Research Council (EPSRC), as a new approach to target the translational challenges of regenerative medicine.

The goal of this initiative was to prioritise collaborative, cross-disciplinary research, combining academics, industry, and clinicians to create a 'push-pull' dynamic that would accelerate translation. As a new scheme, UKRMP set out to achieve this with three aims.

1. To establish interdisciplinary research hubs with the critical mass and expertise to address key knowledge gaps in the translation of stem cell biology and regenerative medicine towards application.
2. To provide novel tools, platform technologies, and engineering solutions needed for therapeutic development.

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3. 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.

1.1. Building UKRMP as a critical mass

The UKRMP was delivered in two phases. The first phase (2013–2018) saw a £25 million investment supporting five interdisciplinary, complementary research hubs focusing on: Cell Behaviour, Differentiation and Manufacturing (Peter Andrews, University of Sheffield); Engineering and Exploiting the Stem Cell Niche (Stuart Forbes, University of Edinburgh); Safety and Efficacy, focusing on Imaging Technologies (Kevin Parks, University of Liverpool); Acellular approaches for Therapeutic Delivery (Kevin Shakesheff, University of Nottingham); and Immunomodulation (Fiona Watt, King's College London). By focusing the UK regenerative medicine research community into five national hubs, the UKRMP's critical mass was born. Hubs were locally managed by an academic executive team supported by a project manager with scientific oversight provided by a hub-appointed Advisory Board. As a UKRI managed strategic programme, progress of the hubs was proactively reviewed and shaped by guidance from a UKRI appointed international Programme Board, currently chaired by Paul Moss (University of Birmingham), which has been critical for driving the overall focus and coherence of the programme over its two phases. The second phase (2018–2023) represented an evolved and consolidated structure of three cross-discipline research hubs that captured and built on the strengths of the previous funding period with a further £17 million investment. The Pluripotent Stem Cell and Engineered Cell (PSEC) hub (Roger Barker, University of Cambridge), Engineered Cell Environment (ECE) hub (Stuart Forbes, University of Edinburgh) and Smart Materials hub (Molly Stevens, Imperial College London) each had its own broad but distinctive focus, supported by a dedicated research team with commercial and clinical end-user collaborations. A key element of UKRMP2 was the introduction of independently funded, cross-cutting themes (safety, immunology, manufacturing) and specific strategic projects to address common translational bottlenecks. UKRMP's mission was to advance regenerative medicine by overcoming the hurdles to the translation of innovative concepts towards clinical testing. Collectively, the hubs and associated projects have delivered a central source of expertise and knowledge, and have worked to generate novel tools, protocols, and resources that could be utilised by other research groups in both academia and industry. By working with other UK funded initiatives such as the Cell and Gene Therapy Catapult, UK Stem Cell Bank, and both UK (Medicines and Healthcare products Regulatory Agency (MHRA)) and international regulatory agencies, an integrated UK ecosystem for advanced therapy development has been created.

1.2. Pluripotent Stem Cells and Engineered Cell (PSEC) hub

The overarching aim of the PSEC hub was to deliver a platform of technologies and expertise that could efficiently and safely facilitate the translation of any new human pluripotent stem cell (hPSC) based therapy to the clinic. As a consequence, PSEC focused on cross-cutting challenges as themes (immunology, manufacturing and safety) and used disease exemplars to develop and validate tools. Directed by Roger Barker (University of Cambridge), clinical lead of the recently initiated first-in-human STEM-PD clinical trial,[2] the hub also brought together Deputy Director Cedric Ghevaert (Second Generation Products lead) and Florian Merkle at the University of Cambridge, Ivana Barbaric (Genetic Stability lead) at The University of Sheffield, Wolf Reik at the Babraham Institute and Robert Thomas (Manufacturing lead) at Loughborough University. STEM-PD is exploring a human embryonic stem cell (hESC)-derived dopamine neuron (DAn) progenitor cell product to treat people with moderately advanced Parkinson's Disease using a relatively small number of implanted cells. The STEM-PD product acted as one of the two exemplar products used by the PSEC team. The contrast to the second exemplar, iPSC-derived megakaryocytes for treatment of thrombocytopenia, highlights the breadth of the challenges being faced by the field in terms of required manufactured cell yield (10^6 vs 10^{11} per patient dose) needed for this therapy to be translatable and competitive. These two exemplars therefore present very different manufacturing challenges and approaches (adherent vs suspension), as well as different translational hurdles.

The UKRMP2 PSEC hub evolved from the Cell Behaviour, Differentiation and Manufacturing hub (also referred to as Pluripotent Stem Cell Platform (PSCP)), and focused its efforts on understanding three key bottlenecks in generating translational products for therapy using resources developed during UKRMP1.

1. **(Epi)Genetic stability:** In UKRMP1, PSCP aimed to define the nature and frequency[3] of recurrent (epi)genetic changes in undifferentiated hPSCs → while in UKRMP2, PSEC sought to elucidate the functional consequences of these changes both within the hPSC population and in the behaviour of hPSC-derivatives. Furthermore, through an affiliated UKRI Innovation/Rutherford Fellowship, **Stefan Schoenfelder** (Babraham Institute), sought to examine higher-order chromatin structures and regulatory sequence variation in human iPSC self-renewal and differentiation.
2. **Manufacturing:** To build new process development models to overcome some of the hurdles inherent in the manufacturing of hPSC cell products (hESC-DAn for PD) → adherent and suspension cell products, models that predict and facilitate manufacturing of cells for clinical use.
3. **Second generation products:** Generate hPSC-DAn cells from different hPSC sources → using GMP (Good Manufacturing Practice)-compliant forward reprogramming and genetic engineering approaches (and tested using tools from 1 and models from 2) as well as less immunogenic megakaryocytes.

Work in the (epi)genetic stability theme (**Ivana Barbaric, Florian Merkle, Wolf Reik**), used hPSC culture and bioinformatics tools to develop key resources. In collaboration with WiCell (https://www.wicell.org/), they produced a comprehensive catalogue of recurrent genetic aberrations detected in long-term hPSC cultures and identified changes in trends of recurrent abnormalities associated with a field-wide shift to feeder-free conditions.[4,5] They revealed likely pathogenic single nucleotide variants and mechanisms underlying genetic instability, which can be reviewed on a user-friendly web-based genome browser ([4,5]; https://hscgp.broadinstitute.org/). Understanding how different variants affect hPSC behaviour and cell fate in culture, and how culture conditions favour the emergence of certain variants, let the team build upon the mechanistic understanding for how the presence of variant cells detrimentally affects neighbouring normal cells.[6] The team developed novel, high-throughput methods to systematically optimise culture conditions to reduce selective pressures and reduce the emergence of culture-acquired mutations (unpublished). Furthermore, by mapping double strand breaks in hPSC genomes, the team generated a detailed map of the specific sites vulnerable to genome damage. Finally, they determined epigenetic changes that can be corrected,[7] and began elucidating the effects of different genetic variants on differentiation to mature cell products in terms of efficiency and functionality, including retinal pigment epithelium[8] and cardiomyocytes.[9]

Building upon the findings of the genetic stability teams, the manufacturing theme (**Robert Thomas**) developed methods to support rapid process development for cell therapy manufacture. They modelled the selective growth advantage of variants to predict and control outgrowth in specific manufacturing processes or associated QC assays, then modified manufacturing conditions to accelerate or slow this competitive growth advantage of variant lines.[10] A statistical clustering

analysis tool was developed to identify data-driven target populations from process data; identification of early predictors of manufacturing process control through correlations with critical quality attributes in end-product target profiles. This work has attracted significant interest from industry as it has the potential to greatly reduce the time needed to develop optimal culture conditions for any hPSC derived product. Another key output from the manufacturing team has been research using the clinical exemplars to assess and support the development of manufacturing platforms which can scale readily from bench to commercial manufacture. This directly contributed to iPSC-derived megakaryocyte precursor scale up and generated data that will support a first-in-human clinical trial application and commercialisation, establishing two new companies in cell therapy manufacturing operating across the US and UK.

Finally, theme 3 (**Cedric Ghevaert and Roger Barker**) aimed to bring forward second generation products, taking lessons from PSCP and the exemplar products: iPSC-megakaryocytes and hESC-DAn. These activities were highly collaborative, involving academics and industry partners from within and outside the hub, with the affiliated UKRI Innovation/Rutherford Fellow **Wei-Li Kuan** (Cambridge), and the associated immunology platform projects. Immunogenicity is considered a crucial addition to the standard preclinical pipeline for cell therapy products. Protocols developed by the Ghevaert lab for specific CRISPR editing of hPSCs were utilised to develop immunologically inert cell products which have to some extent been characterised *in vitro*. Alongside immunogenicity, genetic editing to enhance cell functionality has been explored. This knowledge was transferred to develop cell lines to study diseases (e.g. SARS-CoV-2 and its interaction with platelets/megakaryocytes) by genetically editing putative genes responsible for disease phenotype.

By focusing on these cross-cutting themes, the hub aimed to influence the international regenerative medicine field by developing guidelines and informing a regulatory framework for use by authorities overseeing clinical translation of hPSC-derived therapies. Much of the research undertaken within PSEC has been incorporated into the 2023 ISSCR standards for the use of human stem cells in basic research.[11] In addition, PSEC have provided generic tools to support cell therapy developers such as optimised protocols for robust gene editing.[12,13]

1.3. Engineered Cell Environment (ECE) hub

The overarching aim of the ECE hub was to facilitate regeneration and repair of damaged organs, using the liver, joint and lung as clinical exemplars, with a particular focus on the role of the stem cell environmental niche *in vivo*. Outputs from the ECE hub built upon research undertaken by the "Niche" hub during UKRMP1. An intrinsically collaborative interdisciplinary team was directed by Stuart Forbes (University of Edinburgh, Liver theme lead), with Deputy Director, Alicia El Haj (University of Birmingham, Joint theme lead), Sam Janes (University College London (UCL), Lung theme lead) and partners from King's College London and the University of Cambridge.

The ECE hub had two translational strategies.

1) **Development of cell therapies for damaged organs:** Successful cell therapies require a better understanding of the biology of transplanted cells and their engraftment environment. Approaches spanned clinical applications with key molecules (e.g. Wnt, known to play crucial roles in stem cell maintenance, renewal and differentiation[14]) to improve transplanted cell performance. Importantly, clinical platforms were aligned to GMP cell therapy manufacturing facilities with expertise in translation to clinical trials.
2) **Promotion of endogenous repair of damaged organs:** Human stem cells were utilised *in vitro* to create high content 2D and 3D screens to allow study of their behaviour and identify signals promoting stem cell expansion and differentiation, allowing optimisation of endogenous repair and subsequent validation *in vivo*. FDA (Food and Drug Administration)-approved compound libraries were used to identify potential drugs and biological agents that support stem cell expansion and direct lineage commitment.

To improve endogenous repair and cell therapies, the ECE Hub had three objectives spanning the liver, joint and lung: to understand the physical properties of aged and injured tissue niches, to develop artificial niches to control stem cell behaviour, and to create high content phenotypic screens, allowing discovery of novel targets for endogenous repair.

The liver theme (**Stuart Forbes, David Hay, Neil Carragher, Shukry Habib, Robin Franklin**) focused on addressing some of the barriers to potential widespread application of cell therapies for treatment of liver disease, including cryopreservation, limited engraftment, immune rejection, and poor long-term function. UKRMP2 has contributed to progress in these challenge areas through the development of a high throughput screen for proliferation and differentiation of hESC-derived liver progenitor cells. Using this model, 1280 FDA-approved drugs were screened, 6 of which 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. In addition, a novel 384-well high content 'Cell Painting' assay[15] was established, using HepaRG™ cells (terminally-differentiated human hepatocellular carcinoma cells) and a multiparametric image-based phenotypic signature to classify compound hits promoting liver cell progenitor and differentiation phenotypes. Importantly, small molecule hits that promoted differentiation in screening assays have been replicated in human primary hepatic progenitor cells and, in collaboration with industry, optimised media are being developed for GMP use for cell expansion prior to first-in-human transplant testing. They have also developed Wnt-delivery materials (nanoparticles, bandages) and tested them for activity, reproducibility, safety and efficacy in mouse models of liver disease. A model of senescence[16] has also been produced to identify therapeutic targets to inhibit transmitted senescence and improve cell engraftment; assessment of these targets in murine transplant models is underway. Additionally, through collaboration with industry, they use machine learning to predict drug activity in laboratory models of liver disease.

The remit of the joint theme (**Alicia El Haj, Andrew McCaskie, Mark Birch**) was to develop bone and cartilage repair and regeneration strategies to address early-stage osteoarthritis. Research focused on understanding the niches within the bone marrow and joint as these act as both a source of cells for therapies and a target for non-cellular, molecular, and scaffold-based approaches to support endogenous healing. Work aimed to enhance endogenous targeting (including via bone microfracture) and cell therapy (chondrocyte implantation) for joint repair in the pursuit of improved quality and quantity of bone/cartilage repair. Intra-hub collaboration facilitated the development of reproducible, high throughput, 3D Wnt models of cartilage formation, utilising the human Y201 bone marrow stromal cell line and GelMA (gelatin methacryloyl). This model, measuring asymmetric division, migration, and differentiation, has been used by the Centre for High Throughput Drug Screening in collaboration with the Carragher lab, to identify potential drug candidates (ENZO library, 56 compounds) for regenerative therapies, with several compounds now undergoing validation for clinical use. In addition, the approach of using key agonists in novel shear gel delivery systems[17] is being translated to mouse injury models to test for clinical relevance and potential use for cartilage repair. Also, a 3D Wnt-induced osteogenic tissue model (WIOTM)[18,19] is being used to screen for complex inductive effects of potential drug targets on both progenitor proliferation and maintenance as well as differentiation and maturation into cartilage and bone. Finally, based on the WIOTM, a new therapeutic intervention (a transplantable bandage) to repair lost or damaged bone,[18] has been patented.

In the lung theme (**Sam Janes, Fiona Watt, Marko Nikolić, Robert Hynds**), the primary focus was repair and regeneration of damaged

airway epithelium in respiratory diseases. The complexity of the lungs versus other tissues (e.g. 80 different cell types and states in human lungs[20] versus 25 in the liver[21]) means developing repair and regenerative strategies is an elusive challenge.[22] The Janes and Hynds groups focused on identifying novel factors that influence epithelial stem cell activation and differentiation, aiming to promote regeneration, repair, and allow restoration of normal epithelial function or protection against further damage. They developed robust, high throughput 2D[23] and 3D screens using human bronchial epithelial cells (HBECs). The 2D model comprised HBECs transduced with reporter genes, while 3D tracheospheres containing basal, ciliated, and goblet cells, were used to assess epithelial differentiation under physiologically relevant conditions. In collaboration with the Carragher lab, the 2D model has been used to screen compounds from ENZO (176 compounds) and Prestwick (1276 compounds) chemical libraries, identifying candidates of interest that were subsequently validated *in vitro* and are currently being tested *in vivo* in a mouse model of lung regeneration.

Two UKRI Innovation/Rutherford fellows were aligned with the ECE hub; **Marko Nikolić** (UCL) and **Elaine Emmerson** (University of Edinburgh). Nikolić contributed to an improved biological understanding of the lung epithelium during human development[24] and in postnatal health and disease,[25–27] and Emmerson developed therapeutics to regenerate salivary glands injured by irradiation in head and neck cancer patients, with focus on interrogating cell-cell interactions within the salivary gland niche.[28–31]

1.4. Smart Materials hub

The overarching aim of the Smart Materials hub was to develop new material technologies that enhance the safety and efficacy of regenerative medicine products. Evolving from the Acellular Approaches for Therapeutic Delivery Hub of UKRMP1, the vision of the phase 2 hub directed by Molly Stevens (Imperial College London) with Deputy Directors Felicity Rose (University of Nottingham) and Richard Oreffo (University of Southampton), was to fulfil the need for material systems that not only deliver cells safely, but also provide cues for differentiation and organisation of hierarchical and vascularised tissues. The hub aimed to initially develop a platform of innovative, smart, and acellular technologies (**Molly Stevens, Felicity Rose, Lisa White, Ricky Wildman, Jonathan Dawson, Nicholas Evans, Mark Bradley, Manuel Salmeron-Sanchez, Rachel Williams, Alberto Saiani, Alvaro Mata, Pierre-Alexis Mouthuy, Andrew Carr**) that advanced the role of materials from supportive (e.g., augmenting cell survival and function) to smart, by innately providing cues for cell differentiation and organisation through their design. Specific design parameters were defined by the clinical needs and these technologies were subsequently deployed in three important clinical areas with defined aims.

1) **Musculoskeletal System:** Develop a range of smart bio-responsive materials including gels, 3D printed scaffolds, electrospun materials, and drug delivery systems to solve unmet clinical need in bone, tendon and ligament, and cartilage repair.
2) **Eye:** Develop new 3D structured, injectable, and surface functionalised materials for application in corneal repair and in the posterior chamber of the eye for effective cell transplantation and tissue repair.
3) **Liver:** Develop immune interactive materials combined with new drug delivery strategies to enhance liver cell engraftment following cell transplantation (in collaboration with the ECE hub).

Materials developed were taken through a robust, gated pipeline to pre-clinical testing to maintain a sharp focus on translation. Three strategic gates fully informed by expert panels in manufacturing, regulation, immunology, and safety considerations were used to assess i) efficacy, ii) safety, and iii) commercial viability and regulatory amenability of developed technologies, with the panels identifying which technologies should be prioritised for clinical translation.

The standout scientific developments were only possible through the core UKRMP ethos of collaboration. A strong example of this collaborative force was the musculoskeletal team (**Richard Oreffo, Andrew Carr, Pierre-Alexis Mouthuy, Molly Stevens, Mark Bradley, Felicity Rose, Lisa White, Alvaro Mata, Manuel Salmeron-Sanchez, Jonathan Dawson, Nicholas Evans**) that spanned Southampton, Imperial, Nottingham, Oxford, and Glasgow and systematically screened a range of innovative, acellular material systems for repairing the musculoskeletal system. These were 3D printed from different material types (nylon, titanium, biodegradable polyesters) and functionalised with a range of bioactive coatings (biomimetic protein, mineral, growth factors) found within native bone. Through a series of *in vitro* and *in vivo* studies, these were advanced through the strategic gated pipeline, ultimately fully progressing a 3D printed, polycaprolactone, octetruss-design[32] scaffold decorated with a nanoclay/BMP-2 coating.[33] This nanoclay delivery system,[34] which is being commercialised by Renovos Biologics Limited (a University of Southampton spin-out founded during UKRMP1), integrated the knowledge gained on achieving local drug delivery to aid tissue regeneration from UKRMP1 into the surface functionalisation of a new, fully evaluated 3D-printed biomaterial in UKRMP2. The final scaffold design demonstrated robust bone repair in an ovine femoral condyle defect model.

Additional materials developed for the musculoskeletal system include 3D printed microparticles for bone repair that are capable of guiding cell response solely through their designed, defined cell-scale geometry, which were advanced through external biological evaluation of medical device safety testing (ISO 10993-5) at a certified contract research organisation prior to commencing the final *in vivo* stage of preclinical development.[35] Several approaches were undertaken to develop materials for cartilage repair. **James Armstrong** (Imperial College and subsequently University of Bristol), one of the two UKRI/Rutherford Fellows aligned with the hub, used acoustic cell patterning to recapitulate native hyaline cartilage cytoarchitecture with a view to creating mechanically anisotropic grafts for articular cartilage regeneration.[36] Fibre reinforced hydrated networks (FiHy™) were developed into osteochondral implants that approach the physiological poroelasticity of cartilage and these have undergone extensive *in vitro* assessment for both bone and cartilage repair.[37] **Marco Cantini** (University of Glasgow, UKRI/Rutherford Fellow) researched how we can engineer materials that mediate cell response and differentiation through their physical and chemical properties alone[38], with a view to repairing damaged cartilage[39] without growth factors. For other tissues in the musculoskeletal system, technology to remineralise enamel has been spun-out (Mintech-bio) and is currently in development with international collaborations (Nottingham/Radbound) to deliver practical applications in dentistry. Research at Oxford has led to a suite of electrospun products (BioPatch/Yarn/Lig) for tendon and ligament repair.[40] The team have demonstrated the potential of the devices *in vitro* and *in vivo* (in small and large animals), as well as the ability to manufacture in a GMP facility. These products are continuing their translational journey, with some awaiting approval for human trials.

Development of materials for the eye (**Rachel Williams, Hannah Levis, Robin Ali, Rachael Pearson, Molly Stevens**) can be divided into corneal and retinal applications. A family of peptide hydrogels based on poly-ε-lysine (pεK) has been developed that have excellent transparency, high water content, and appropriate mechanical properties for surgical handling whilst supporting the attachment and growth of a monolayer of primary corneal endothelial cells and the ingrowth of corneal stromal cells.[41,42] Through a collaboration between Liverpool and Imperial, these materials have been 3D printed and using site-specific chemistry, have been post-modified with biomolecules such as peptides, proteins and antibody fragments to tailor the surface properties for optimal cell behaviour. This biosynthetic corneal endothelial graft will continue towards clinical translation through an MRC DPFS project, developing appropriate sterilisation methodologies (led by Levis). For the retina, 3D printed moulds that micropattern hydrogels

to create scaffolds that polarise photoreceptor cells for retinal repair have been developed through collaboration of Stevens, Ali and Pearson. In parallel, they used electrospinning to create a polymer scaffold that resembles the native Bruch's membrane. Biocompatibility assessments of these scaffolds is underway and provides a significant advance in the use of biomaterials for retinal repair.[43]

For the liver (**Stuart Forbes, Lisa White**), the collaborative relationship between Nottingham and Edinburgh initiated in UKRMP1 to provide materials that enhance liver cell engraftment during transplantation has deepened. Formulations have advanced to ones that undergo targeted biodistribution to the liver through their chemistry by incorporating galactose into PLGA (poly lactic-*co*-glycolic acid) microparticles to specifically target receptors only found on hepatocytes.[44] Furthermore, these smart microparticles achieve controlled release of pro-healing and immunomodulatory growth factors and drugs (Vascular endothelial growth factor (VEGF), Interleukin (IL)-10, IL-1 receptor antagonist, Etanercept) and have undergone *in vivo* assessment.[45] This is one example of several advanced drug delivery systems that were developed in the Smart Materials hub by Nottingham and Imperial. Furthermore, one of the spin-outs from Imperial (Sparta Biodiscovery) has pioneered a standalone instrumentation for Single Particle Automated Raman Trapping Analysis (SPARTA) that has been successfully applied to many advanced drug delivery systems developed by researchers within the hub.[46]

1.5. Cross-hub achievements

Successful clinical translation of cell therapies and biomaterials requires robust preclinical assessment of immunogenicity, safety, toxicity, and efficacy – considerations outlined in our previous roadmap for regenerative medicine.[47] Therefore, within UKRMP2, cross-cutting safety, manufacturing, and immunology themes spanned the hubs. For the safety and manufacturing themes target product profiles (TPPs) were employed, especially within the Smart Materials hub (aided by advisors Anne Roques and Alison Wilson), collating input from researchers, industry leaders, clinicians, and regulators to fully define the objectives and requirements of new technologies being produced for clinical translation. This ensured research choices made were not in conflict with the regulatory requirements for clinical translation. Within these TPPs, safety requirements were defined and external testing, in accordance with ISO standards, was performed for selected new technologies.

Three independent immunology projects were introduced to form the immunology theme: an immunogenicity test platform – *in vitro* and *in vivo* (**Joanne Jones, Kourosh Saeb-Parsy** (University of Cambridge) and **Giovanna Lombardi** (King's College London)), stealth creation using genome engineering (**Waseem Qasim** (UCL)), and alveolar regeneration and tissue resident immune cells (**Ling-Pei Ho** (University of Oxford)). The immunology theme was a major contributor to the PSEC and ECE outcomes. Three cell types (hESC-DAn progenitors (PSEC), iPSC-hepatocyte-like cells and iPSC-cholangiocytes (ECE)) were assayed for immunogenicity *in vitro* and *in vivo*, including in a humanised mouse model[48] developed within UKRMP2. A specific mechanism of immunomodulation for the iPSC-derived hepatocyte-like cells was determined to be via the tryptophan/IDO-1 pathway[49] alongside the hESC-DAn which were found to be immunosuppressive,[50] further adding to the strong literature around immune interaction of hPSC-derived products. From this, several review articles[51–53] have highlighted the need for immune considerations to be made and early discussions to be had on the use of genetically modified "universal" or "immunologically inert" cell products for therapies. Another collaborative review, between UKRMP and the Canadian Stem Cell Network described the current *in vitro* and *in vivo* landscape for modelling the neuroimmune axis.[54] While great strides have been made in developing the optimal pre-clinical immunogenicity assay for any hPSC cell product, there is clearly still an urgent need for better models by which to study the human rejection/immune response to such therapies in its entirety - both in terms of the repertoire of cells and their contributions as well as how this changes over time.

To accelerate research reaching the clinic, new researchers were brought into UKRMP2 to specifically address translational bottlenecks in regenerative medicine via strategic projects. Their research included: development of an organ-on-a-chip model (for the joint) for safety testing of regenerative medicine products (**Hazel Screen**, Queen Mary University London), development of hydrogels for iPSC-derived regenerative therapies for diabetes (**Rocio Sancho** and **Eileen Gentleman**, King's College London), investigation of remyelination of oligodendrocytes to better treat multiple sclerosis (**Anna Williams**, University of Edinburgh), and use of *in silico* modelling alongside *in vitro* and *in vivo* approaches to address regenerative medicine safety in the liver (**Sarah Waters**, University of Oxford) (see Fig. 1).

Collaboration has always been a key tenet of UKRMP, with inter- and intra-hub, and academia-industry relationships actively nurtured and encouraged. Reflections in the closing moments of the final platform meeting in Edinburgh identified that one of UKRMP's greatest successes was how it had brought individuals together from different disciplines to address regenerative medicine challenges, and that it was these successful collaborations that ultimately had resulted in quicker translation of therapies to the clinic. Future successes will depend on existing relationships being maintained and new ones being forged, and early career researchers (ECRs) involved in UKRMP will be instrumental in these. Within UKRMP, ECRs were offered a plethora of career development opportunities, including affiliated independent UKRI/Rutherford research fellowships in UKRMP2, workshops on grant/fellowship writing and incorporation of mathematical modelling into regenerative medicine research,[38] mock fellowship interviews, pump priming funding through sandpit events, and travel partnerships with the Canadian Stem Cell Network (established and funded by the MRC). UKRMP's cross-hub focus on the development of these future leaders has already aided the transition of 39 researchers to academic and translational roles within regenerative medicine, and has also influenced UKRI's interpretation of impactful research and contributions which can not always be measured via scientific publications alone. Overall, there can be no doubt that UKRMP was a highly productive and collaborative initiative (Fig. 2), with 31 industrial partners and 15 academic institutions, producing over 250 peer-reviewed publications and 6 patents filed. Over £50 million in follow up grants and awards has been achieved based on data produced within UKRMP, providing opportunity for many collaborations to continue beyond UKRMP. In addition, the establishment of 14 spin-out companies contributes significantly to the vibrate biotechnology sector within the UK providing routes of translation for UKRMP research (https://www.ukrmp.org.uk/). Furthermore, the translational impact of the initiative is also clear, with work done under UKRMP1/2 influencing clinical trials, including STEM-PD (NCT05635409[2]) and MAcrophage Therapy for liver CirrHosis (MATCH; ISRCTN 10368050[55,56]).

2. Future of UK regenerative medicine

UKRMP research has changed the landscape of regenerative medicine within the UK and within a short time has made significant impacts in many areas. However, there is still much to be done, not least moving the work from the preclinical space into clinical application. Importantly in this respect, our pre-clinical workflows have been shown to be robust and brought with them greater knowledge on how to effectively engineer and control different cell types and environments in complex 2D and 3D environments that recapitulate aspects of the native (diseased) tissue and the host response to it. With these foundations in place, when different pathologies emerge as the major contributors to the global burden of disease, we are well positioned to apply these systems as needed. Our approaches can be further refined, e.g., through better quality control in the generation and genetic engineering of hPSCs, better understanding of the host response to cells and materials in both

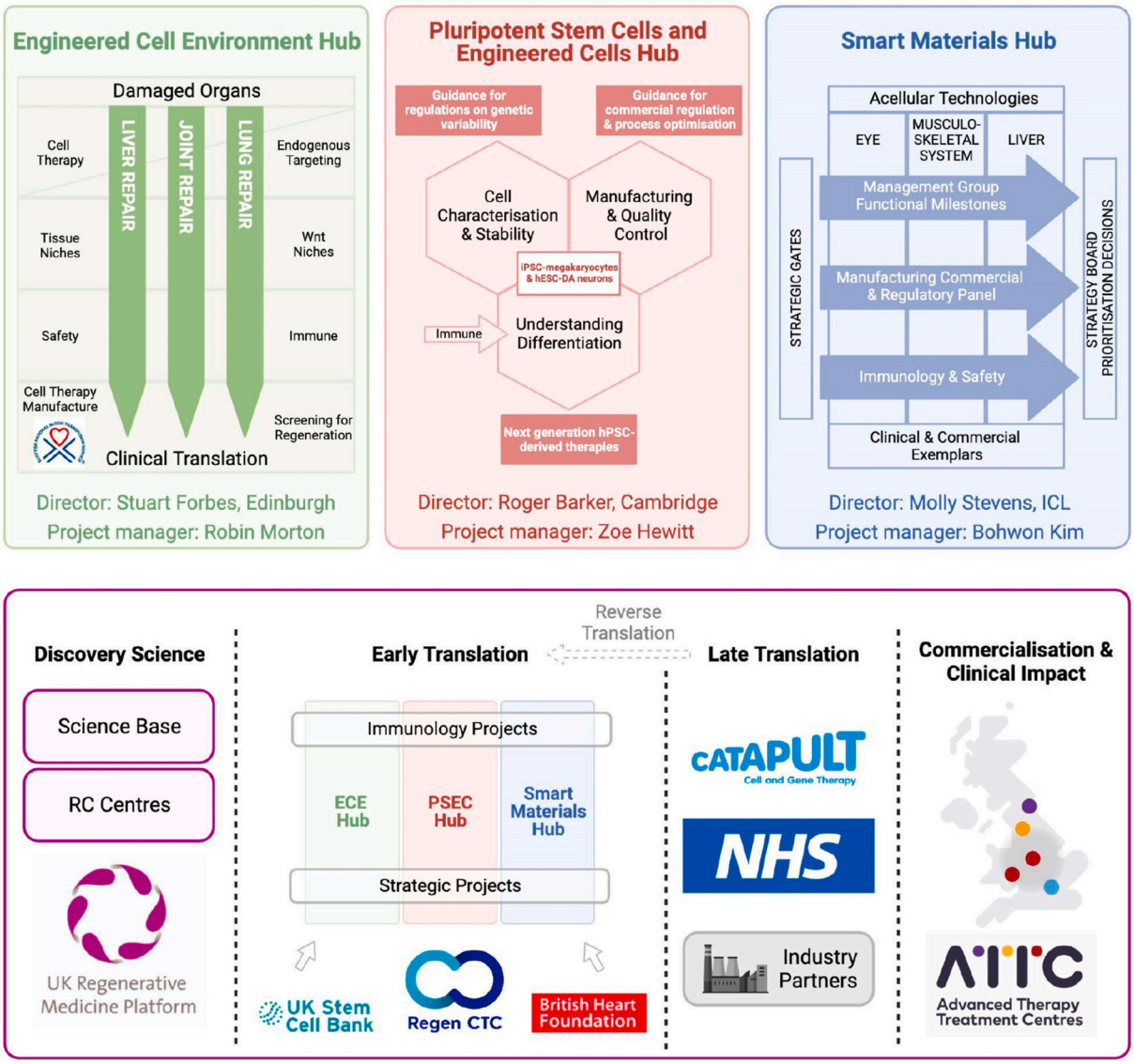

Fig. 1. Overview schematic of the UKRMP2 hub structure and activity.

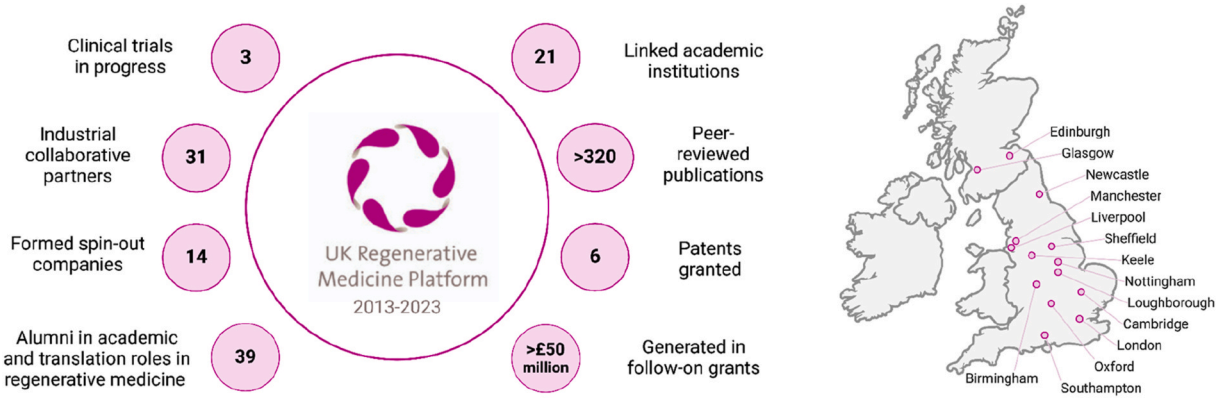

Fig. 2. Achievements of the UKRMP Hubs across both phases and geographical breadth of UKRMP.

healthy and diseased contexts[57], and/or better mechanistic understanding of cell responses to the properties of the materials we use to harness and control these therapeutically. What's more, advances in computational power and artificial intelligence will aid our ability to determine these underlying biological and molecular mechanisms. However, non-scientific barriers (e.g., regulation, manufacturing and supply chain, treatment cost) are perhaps where the most work is needed to begin to see the benefit of these technologies *en masse*.

Most regenerative medicine strategies will be classed by regulators as advanced therapy medicinal products (ATMPs). Currently, gaining approval is a slow and expensive process resulting in very high treatment prices where approval is ultimately granted. Greater involvement of the regulators at early stages of research and participation in policy development for how these products are regulated, such as PSEC's involvement in defining recent ISSCR standards, will offer opportunities to streamline these processes. Where treatments require manipulation of the patients' own cells, very few hospitals have the necessary supporting infrastructure and GMP capability to routinely deliver these treatments. Furthermore, manufacture, sterilisation, transport, and storage of products that contain fragile and sensitive biological material will require some level of redesigning of medical product supply chains, likely towards a point-of-care manufacturing model. Until these challenges are addressed, the regulatory and practical barriers mean that our regenerative medicine strategies will struggle to be adopted into national healthcare systems, risking further contributing to the current inequality in healthcare. Therefore, as regenerative medicine products become increasingly efficacious and available, perhaps one of the largest unanswered questions in the field is how we can maintain the human right of access to the highest attainable standard of health without discriminating by socioeconomic background.

Success within UKRMP2 has facilitated over £50 million in follow-on funding, enabling the further development of innovative cellular and material therapies that recapitulate and regenerate native tissue to treat a wide range of diseases and injuries as the global burden of disease continues to grow. The next decade will see the progression of our discoveries and technologies through safety and efficacy trials and into the clinic, bringing about a paradigm shift in treatment options for patients. Underpinning this, the future of UK regenerative medicine is dependent on the network of researchers, clinicians, and companies that UKRMP has nurtured in the previous decade. The collaborative and interdisciplinary framework of UKRMP has led to a whole new generation of early career researchers in this field who recognise the translational challenges of regenerative medicine products and the need for interdisciplinary approaches to achieve this goal. This legacy is perhaps one of UKRMP's greatest achievements, and means that as the initiative concludes, the future of regenerative medicine in the UK is in a very healthy state with exciting future prospects.

CRediT authorship contribution statement

Annabel J. Curle: Writing – original draft. **Josephine L. Barnes:** Writing – original draft. **Robert Owen:** Writing – original draft. **Roger A. Barker:** Funding acquisition, Writing – review & editing. **Alicia El Haj:** Writing – review & editing. **Stuart J. Forbes:** Funding acquisition, Writing – review & editing. **Cedric Ghevaert:** Writing – review & editing. **Richard OC. Oreffo:** Writing – review & editing. **Felicity RAJ. Rose:** Writing – review & editing. **Molly M. Stevens:** Funding acquisition, Writing – review & editing. **Zoe Hewitt:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ZH and RAB are co-founders of Regen CTC, a company established under UKRMP. MMS is a founder of Sparta Biodiscovery and ROCO is a co-founder and shareholder in Renovos with a license to IP indirectly related to part of the current manuscript.

Data availability

No data was used for the research described in the article.

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