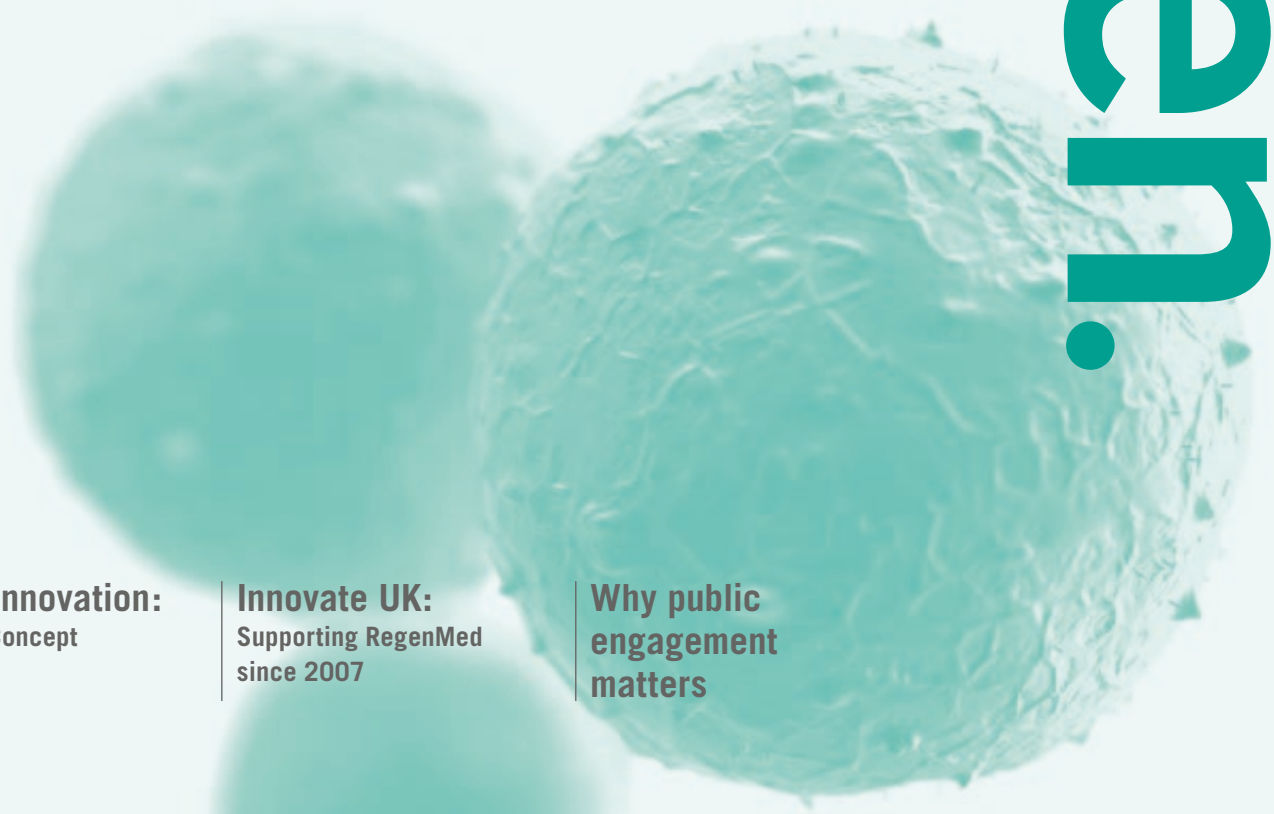
regen.
Issue 07 | 2016

> “The UK continues to be among the best places in the world to develop, manufacture and sell therapies utilising the principles of regenerative medicine.



Smart innovation:
Proof of Concept projects

Innovate UK:
Supporting RegenMed since 2007

Why public engagement matters

Building the regenerative devices industry

TRANSLATING REGENERATIVE DEVICES
Regener8

Contents

Foreword

It's been nearly nine years since we created Regener8 to bring together academics, industry and clinicians as a network for regenerative medicine in the north. During those years, we've had to adapt to a constantly changing landscape.

Professor John Fisher, Regener8 Executive Director

> **"Global trends predict a market growth of 100% over the next 10 years and I believe the UK can compete – both in technology development and as a manufacturing base – to build a potential £1 billion industry in the UK by 2025, creating new and enabling technologies and companies and developing and growing markets and companies through enhancements to medical technologies and devices.**

The UK regenerative medicine strategy, the Cell Therapy Catapult, the Nurse Review, an increased emphasis on internationally excellent collaborative research and impact deliberations about the role of cities and regions, developments in market place regulation and in the global community and the emerging importance of developing countries such as China and India have all impacted on the development of Regener8.

Acellular scaffolds and regenerative devices have emerged as key areas in the global regenerative medicine landscape, offering opportunities for more rapid and cost-effective translation and adoption. Regener8 has strategically focused on regenerative devices and through support from EPSRC Innovation and Knowledge Centre in Medical Technologies has extended its reach with membership across the UK and is now recognised as the UK network for regenerative devices.

While regenerative medicine is still an emerging scientific field, the novel technologies emerging from the regenerative devices sector is further ahead, with increasing numbers of products and devices undergoing clinical trials and entering the clinic and market to meet the needs of an active, healthy, ageing population.

Global trends predict a market growth of 100% over the next 10 years and I believe the UK can compete – both in technology development and as a manufacturing base – to build a potential £1 billion industry in the UK by 2025, creating new and enabling technologies and companies and developing and growing markets and companies through enhancements to medical technologies and devices.

To realise its share of this predicted market, the UK must not only continue to invest in research and basic science, advance and improve existing technologies and create new disruptive technologies; critically, it must also remove barriers and reduce risk in their translation, develop cost-effective solutions that can be readily adopted by existing service providers and continue to attract investment in the private sector to develop technologies.

The first phase of the Medical Technologies IKC in Regenerative Devices proved that this is possible, leveraging £120 million investment from the private sector to develop new technologies. And that's not the end of the story in terms of economic value: those technologies will continue to create further economic value over many years to come. The second phase of IKC will continue to support research and technology development across the UK and Regener8 will continue to be supported as the UK national network.

Regenerative devices is an exciting and dynamic sector, with many new products now resulting from the convergence of medical devices with life sciences to deliver novel enhanced patient interventions. In addition, there are companion technologies which help us stratify the patient population to high levels of precision and reliability: new diagnostics, data analytics and advances in imaging. As products become more complex, the number of stakeholders multiplies too, to handle intricacies in regulation and reimbursement, different health service provisions and different patient needs on a global scale.

The technologies and products that successfully reach the clinic will be those that address all of these aspects – world-leading science is essential, but is not enough to deliver successful translation and patient outcomes. By bringing all these stakeholders together at an early stage, Regener8 is enabling a community approach to navigating the non-linear pathway towards innovation translation, and thereby underpinning continued development of the UK regenerative devices sector. The renewal of funding for the IKC allows us to support Regener8 to continue this critical role. In this issue of regen, we showcase some of the many people, technologies and collaborations within the IKC and Regener8 community that are helping the UK realise its potential in the global regenerative devices market. ■

Translation – at the heart of what we seek to do

The UK continues to be among the best places in the world to develop, manufacture and sell therapies utilising the principles of regenerative medicine.

Recent initiatives such as the Advanced Therapies Taskforce – chaired by George Freeman, UK Minister for Life Sciences and Ian McCubbin of GSK – have sought to examine the conditions and actions required to anchor Advanced Therapy (ATMP) manufacturing in the UK. As noted by Professor John Fisher in his Foreword, Regener8's strategic focus is on regenerative devices as a further essential component of the UK's regenerative medicine offering.

Regenerative devices – regenerative therapies that can be delivered to the market and the patient as Class III medical devices (or human tissue products) – are likely to be translated and adopted more rapidly than advanced therapies due to their device classification and lower overall risk rating. As such, they will be able to provide the quick(er) wins still needed by the regenerative medicine industry to verify the overall value proposition. Such wins are, however, close to realisation – with the translational achievements of Tissue Regenix, Azellon, Videregen, Cytori Therapeutics, Orthox, Locate Therapeutics, TiGenix, Osteopore, Neotherix, Xeltis, Organovo and NHS Blood and Transplant, for instance, making a non-exclusive roll of honour.

Regener8, together with its wider network partners at the Medical Technologies IKC in Leeds and across the UK, will continue to provide advice and sector-relevant examples, make connections and – through EPSRC and other funders – establish proof of concept (PoC) through collaborative projects for regenerative device applications. The UK has a rich pool of talent in academic, clinical and industry settings and it is vital that these are brought together – through themed workshops and conferences such as the Regener8 Annual Meeting (now in its 9th year) – to share information and realise opportunities. We are looking forward to making new connections through this year's meeting. We want to understand the particular barriers to translation experienced by our members (which is what we hope all connections will become) and together with our matrix of experts, help find solutions and the means to overcome these barriers.

For this year's conference, Regener8 has restated its tagline to "Translating Regenerative Devices". Translation is at the heart of what we seek to do: translational research must result in better, more effective, stratified and affordable products and treatments. We must not forget that the priority for the patient is for our research to be brought to them as effective treatments as soon as possible.

In this issue 7 of regen, you will find news of key players in the RegenMed landscape as well as case studies from PoC projects supported or assisted by Regener8 and the IKC. We have included a feature for the first time this year in which stakeholders occupying various roles and positions of responsibility give their assessment of the challenges and opportunities ahead for RegenMed. This makes for a fascinating commentary on the reasons for optimism and the work still to be done in our field.

Regener8 and its partners continue to recognise the need to both ensure a succession of skilled and appropriately trained people to enter the medical technology and regenerative medicine sectors at all levels and to create an interest, understanding and trust in what we do. We are therefore very pleased to include articles on public engagement and responsible innovation in this issue.

Through our positions of influence at numerous levels, Regener8 and the Medical Technologies IKC can provide advocacy, particularly for the regenerative device stream of the regenerative medicine sector. Our membership, events and programmes bring together the right players at the right level of engagement to strengthen the translation of regenerative devices. ■

Professor Mike Raxworthy
Regener8 Operations Director

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Mike Raxworthy
Regener8 Operations Director

2016
IKC–Regener8 Conference:

Building the Regenerative Devices Industry

01 July 2016

Horizon Conference Centre, Leeds

We are looking forward to welcoming delegates to the IKC–Regener8 Annual Conference and 2016's theme: Building the Regenerative Devices Industry. This year we have organised the meeting with our partners at the Medical Technologies IKC and so will attract an audience reached by both organisations.

We have introduced another first this year in inviting submissions from Regener8 members and the wider network for a community sourced session. This will focus on challenges facing the translation and application of regenerative medicine and how collaboration may enable these to be tackled.

We are also pleased to welcome sessions on Regenerative medicine at the frontline, led by the Defence Science and Technology Laboratory (Dstl) of the UK Ministry of Defence and on Monitoring biomarkers to improve treatment of chronic wounds, led by the National Physical Laboratory (NPL). In both cases, delegates will be hearing new concepts able to extend the reach of regenerative medicine.

I am confident that new ideas and exciting possibilities will be opened up by Professor Boris Chichkov from the Laser Zentrum Hannover in his keynote presentation on laser printing of 3D scaffolds, nanoparticles and living cells.

We also expect the case studies from translational projects (those establishing proof of concept and those progressing from proof of concept) to once again be among the highlights of the meeting and are pleased to give these prominence. Finally, we have planned a panel with experts dealing with questions on the translation of medical technologies to the market.

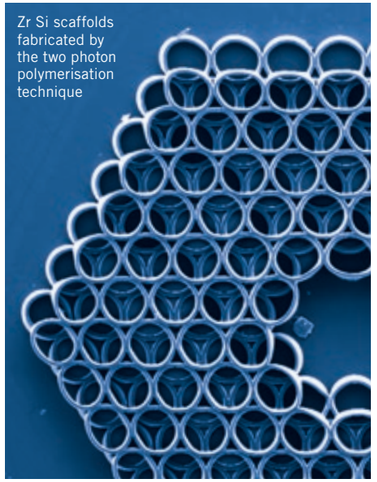
Of course, the IKC Regener8 meeting will be an opportunity to catch up with events and news from our community in more informal ways and I d encourage the many Early Career Researchers attending to use the opportunity afforded by the networking sessions to meet more experienced practitioners – maybe around their posters – and get that advice and direction on what questions really need answering! ■

Mike Raxworthy
Regener8 Operations Director

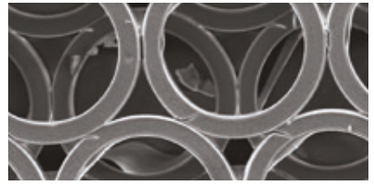
2016
IKC–Regener8 Conference

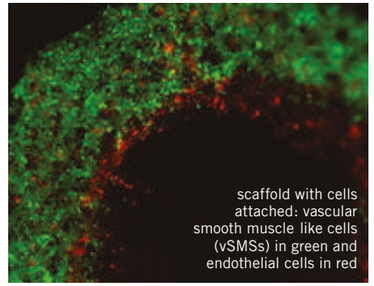
3D laser printing of scaffolds and living cells

Laser-based techniques can be used to generate highly precise 3D scaffolds with sub-micron resolution, and for printing biological cells into 3D patterns, explains our keynote speaker, Professor Boris Chichkov, of Laser Zentrum Hannover.



Zr Si scaffolds fabricated by the two photon polymerisation technique





scaffold with cells attached: vascular smooth muscle like cells (vSMSs) in green and endothelial cells in red

Fundamental understanding of interactions between different cells and their environment is essential for cell-based therapies in regenerative medicine. Common *ex vivo* cell studies in two-dimensional cell culture have significant limitations and are not appropriate to simulate complex interactions in 3D tissues and cell microenvironments in vivo, since cell behaviour differs dramatically in 3D. To bridge the gap between common cell culture conditions in vitro and animal models, 3D cell systems are essential.

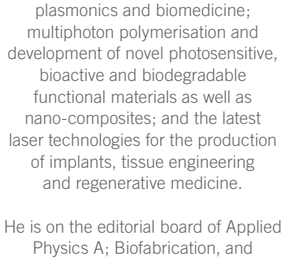
For the scaffold generation, we use a two-photon polymerisation (2PP) technique, which allows the writing of CAD structures directly into the volume of photosensitive polymer solutions. The polymerisation occurs only in the laser focus zone and can achieve resolutions below the diffraction limit down to the sub-100-nanometer range. Scaffolds from different biomaterials like organic-inorganic Sol-Gel-Composites such as zirconium-hybrids, biodegradable polymers such as polylactic acid (PLA), polycaprolactone (PCL), polyethylene glycol (PEG), and hydrogels such as gelatin, hyaluronic acid, chitosan, alginate, gellan gum or hydrogel blends, have all been generated with this technique.

For arranging cells in 3D patterns, we use laser-assisted bioprinting (LAB) based on the laser-induced forward transfer process, which can print different cell types, including primary cells and stem cells embedded in hydrogels (which mimic extracellular matrix). This method has enabled the generation of 3D stem cell grafts, skin tissue, and cell patterns for studying cell-cell interactions.

Both 2PP and LAB techniques are capable of advancing 3D cell culture towards CAD-defined and precisely arranged 3D cell models and 'organ-on-chip' systems. These innovative 3D cell models could provide new insights in understanding cell behaviour, tissue functions and their regeneration. Printed tissue – for example, skin – can be used for analysing the effect of agents such as pharmaceuticals or cosmetics *ex vivo*; and, by applying human primary cells, it has potential to be used instead of animal tests. ■

Introducing
this year's international keynote speaker

Professor Boris Chichkov
Head of the Nanotechnology Department at Laser Zentrum Hannover e.V and W3 Professor of Physics at Leibniz Universität Hannover

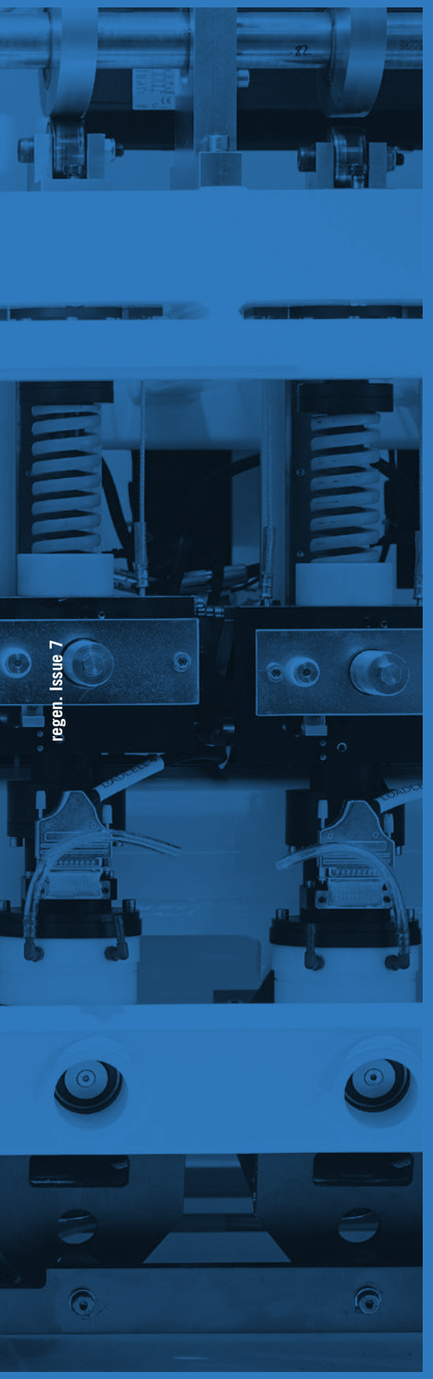


Prof Chichkov has a PhD in Physics from the Moscow Institute of Physics and Technology (MIPT) and the P.N. Lebedev Physical Institute of the Russian Academy of Sciences, where from 1981 to 1995, he was a scientific employee, as well as assistant professor at MITP from 1987-88.

He joined the Laser Zentrum Hannover e.V. in 1995 and was head of its Strategy Group from 2001-2004. During this time (1997-2000) he was also associate professor at the Institute for Quantum Optics, University of Hannover.

Prof Chichkov now applies his wealth of expertise in Physics to regenerative medicine. His research areas include application of lasers in micro– and nanotechnology for photonics, plasmonics and biomedicine; multiphoton polymerisation and development of novel photosensitive, bioactive and biodegradable functional materials as well as nano-composites; and the latest laser technologies for the production of implants, tissue engineering and regenerative medicine.

He is on the editorial board of Applied Physics A; Biofabrication, and Materials Science and Engineering C: Materials for Biological Application.



2016
IKC–Regener8 Conference
Invited speakers and session chairs

Professor John Fisher CBE FREng FMedSci FIMechE FIPEM CEng, is Director of the Institute of Medical and Biological Engineering (iMBE) and Deputy Vice Chancellor at the University of Leeds. He is Director of the following EPSRC research centres: IKC Innovation and Knowledge Centre in Medical Technologies, Centre for Innovative Manufacturing in Medical Devices, Centre for Doctoral Training in Tissue Engineering & Regenerative Medicine and is Executive Director of Regener8. John s research interests include pre clinical simulation and testing in joint replacements and regenerative devices and he holds a grant portfolio of £50m. He has started four spin out companies, collaborates and consults with companies across the globe, has published over four hundred journal papers and supervised over 100 PhD students.

Professor Eileen Ingham holds a chair in Medical Immunology at the University of Leeds with an international reputation in the fields of biocompatibility of medical implants. She is inventor on 8 patent families, has published 280 peer reviewed papers and has supervised around 70 PhD/MD research students. She is co founder and Deputy Director of the Institute of Medical & Biological Engineering (iMBE) at Leeds and has a long standing collaboration with the NHS National Blood & Tissue Services to whom she has licensed platform technologies for the decellurisation of allografts. She is an academic founder of spin out company Tissue Regenix Group PLC, which is commercialising acellular biological scaffold technology.

Professor Jennifer Southgate began her career at the Imperial Cancer Research Fund (ICRF) in London. From 1992 she led the Biology of Normal and Malignant Epithelial Cells research group at St James s University Hospital. In 1999, she was appointed Chair of Molecular Carcinogenesis as Director of the Jack Birch Unit, a research unit sponsored by York Against Cancer. Her research focuses on cellular regulation of tissue homeostasis in health and disease and developing cell and tissue culture systems for normal human urothelium.

Mr Ramnath Subramaniam is a Consultant Paediatric Urologist at Leeds Teaching Hospitals NHS Trust and Honorary Clinical Associate Professor at University of Leeds. His main clinical areas of specialisation are minimally invasive surgery and reconstructive paediatric urology. He is currently Chairman for Education and Training in Europe under the umbrella of European Society of Paediatric Urology. His research interests include bladder tissue engineering in collaboration with the Universities of York and Leeds, and biomaterials in reconstructive lower urinary tract surgery.

Dr Paul Rooney is Research and Development Manager at the National Blood Service. He is a registered Clinical Scientist and runs the Tissue Development Laboratory which performs validations on existing tissue grafts and processes and is involved in new tissue graft development. After his PhD he spent 20 years in academic research into connective tissues, particularly bone and cartilage. Paul holds an Honorary Lectureship from Manchester University, and is Honorary Associate Professor at the University of Leeds. He has published more than 60 scientific articles on connective tissue research and is associated with some £7 million in research grants.

Professor Mike Raxworthy is Operations Director of Regener8. A biomedical scientist with PhD from the University of Leeds, he has nearly 30 years' experience leading R&D in the medical device and pharmaceutical industries, and became involved in tissue engineering in 1996. He has an MBA from Warwick Business School and is founder and CEO of Neotherix Ltd, spun out from Smith & Nephew in 2007, which produces bioresorbable regenerative scaffolds for tissue repair. He was awarded an RAEng Visiting Professorship in Medical Technology Innovation and Translation at the University of Leeds in 2015.

John Wilkinson joined the MHRA from Eucomed, the European medical technology industry association, where he was Chief Executive. His earlier experience includes Director General of the Association of British Healthcare Industries and a number of roles in the medical devices industry, both in the UK and the USA, with Becton Dickinson and the BOC Group.

Dr Steve Bloor has over 20 years' experience in the medical device and regenerative medicine industry having worked within both start up and multinational medical companies. Dr Bloor has a proven track record of innovation leadership and senior management including Vice President R&D at Covidien and Chief Scientific Officer for TSL (AIM listed SME) with direct responsibility for R&D, Regulatory, Clinical and Compliance functions. Dr Bloor founded Videregen Ltd in 2011 to develop and commercialise advanced organ replacement technologies.

Dr Itoro Udofia is the Head of Medical Device Operations and Training at BSI. He has over fifteen years' experience working with orthopaedics devices, as a Technical Specialist working in medical devices and as Head of the Orthopaedics and Dental devices team. Itoro s academic research includes biomedical engineering, biotribology and computational modelling of orthopaedic devices. He worked as a research consultant with leading orthopaedic manufacturers in product development and testing, publishing numerous scientific papers and has delivered presentations and workshops at international conferences on European medical device regulations.

Dr Simon Chandler is Director, New Business & Partnership at IP Group. He works closely with IP Group s university partners to identify, validate and accelerate the commercial exploitation of new healthcare technologies through the formation of spin out technology companies. Before joining IP Group he held commercial positions within the biotechnology and pharmaceutical industries. He has worked to develop entirely new market sectors for cutting edge genomics technologies at both Bio Rad laboratories and Applied Biosystems, and to develop the early stage advanced therapeutics/biotechnology business in Europe for Covance Laboratories.

Phil Brown is Director, Technical and Regulatory at the Association of British Healthcare Industries (ABHI). He has worked in the fields of Regulatory Affairs, Quality Assurance and Compliance for global medical device companies for over 25 years, including roles at Smith & Nephew, Genzyme Biosurgery, D Target, Quintiles and Wright Medical, where he was responsible for Regulatory Affairs, Quality Assurance, Reimbursement and Compliance across the EMEA region.

Dr Stephen Simpson is Director of Research, Arthritis Research UK (ARUK). He is responsible for leading the development and effective implementation of research at the charity, including new areas of research translation and partnership funding. Stephen was formerly Director of Life Sciences at Science Foundation Ireland (SFI), where he led the core objectives of the Foundation in delivering research excellence in the life sciences, and sustaining economic relevance and growth of Irish research. He was also editor of the international journal Science for eight years.

Dr Frances Henson is Senior Lecturer in the Department of Veterinary Medicine, University of Cambridge and a Research Fellow in the Division of Trauma and Orthopaedic Surgery, Department of Surgery, University of Cambridge. Her research interest is in the healing of joint surface defects in both man and animals, both from the molecular control of bone and cartilage healing to in vivo experiments assessing efficacy of novel treatments.

Dr Chaozong Liu is a non clinical senior lecturer at UCL Division of Surgery & Interventional Science, the Royal National Orthopaedic Hospital. His research is directed toward biomedical devices development for enhancing treatment of musculoskeletal disorders. Core activities include: (1) scaffold innovation for musculoskeletal tissue regeneration; (2) Customized medical devices for intervention of orthopaedic disorders. (3) Biomedical device surface processing for enhancing in vivo service functions.

Paul F. McMillan is Ramsay Professor of Chemistry at University College London. He graduated with Chemistry BSc from Edinburgh University (1977) and his PhD degree (geochemistry) at Arizona State University (1981). There he studied the structure of aluminosilicate glasses using Raman spectroscopy. In 2000 he moved to London to a UCL Chair in Solid State Chemistry, held jointly with the Royal Institution. He also began to expand his research interests into biophysics and biology, including Raman spectroscopy for biomedical applications.

Dr Abi Spear is a Principal Scientist in the Medical Sciences programme at the Defence, Science and Technology Laboratory (Dstl), an agency of the Ministry of Defence. Abi studied Biochemistry at the University of Oxford and has a PhD from the London School of Hygiene and Tropical Medicine. Her research focuses on the molecular and cellular biology of trauma. She recently received a Frontiers Innovator award from the Wellcome Trust.

Dr Alex Knight completed a PhD in Molecular Biology at the MRC LMB in 1994, followed by post docs at the Whitehead Institute and the University of York. He is currently a Principal Research Scientist at the National Physical Laboratory and is Chief Investigator and Project Manager for the NIHR i4i RegeniTherix project. His research at NPL includes point of care diagnostics, super resolution microscopy, and the application of metrology to the life sciences.

Dr Thomas Baboolal s research is focused on the role of mesenchymal stem cells (MSCs) in cartilage, bone and soft tissue repair. In particular, he focuses on how by understanding MSC biology, repair of these tissue can be better augmented using devices or biological therapeutics. Thomas is involved in all facets of research from basic science to clinical translation including medical device trials. ■

For the first time, we offered the Regener8 community a unique opportunity to present at the 2016 conference. Applications were invited from members which showcased a challenge or project involving the translation of university and industry research in regenerative therapies and devices, and where the solution involved a collaborative approach between academia, industry, clinicians, regulatory and/or IP experts.

The two selected proposals are outlined here.

Community-sourced showcase

Regenerative medicine at the frontline

Dr Abigail Spear, Dstl

What's the challenge?

Severe trauma, whether sustained in a civilian or military context, constitutes a complex 'disease state', requiring a multifaceted approach to treatment in order to improve survival and recovery. Regenerative therapies hold great promise in the treatment of severe trauma at all stages of the patient care pathway. Deploying molecular and cellular regenerative strategies far forward, however, presents its own logistical challenges in an austere military environment. The 'product' needs to balance potentially cutting-edge bioengineering with a delivery system that is light, easy to carry, simple to administer and to store.

Two example technologies

A wound bandage loaded with stem cells that can be kept at room temperature for up to a week without loss of viability. Growth factors released from these bandages upon application aim to speed up wound healing.

An injectable macroporous scaffold that can deliver controlled pores on demand, capable of transducing mechanical cues for platelet aggregation and cellular integration to minimise progressive cell death.

Who's involved?

The Defence, Science and Technology Laboratory (Dstl) conducts, funds and collaborates on medical research for military applications.

The Royal Centre for Defence Medicine (RCDM) – Defence clinical academics experienced in research and forward trauma management formulate the question and potential solutions.

Newcastle University, Faculty of Medicine – researchers here are developing the stem cell bandage.

University College London – researchers here are investigating an injectable macroporous scaffold for haemorrhage control and tissue regeneration.

What's next for this field?

Dstl and RCDM have been working together to identify research gaps with respect to regenerative medicine research for military applications and wish to actively engage with industry and civilian academia to help drive regenerative research in trauma. ■

> **"There are new opportunities for regenerative medicine in Defence that many in the sector haven't yet considered. While the military applications might seem a very specific market, technologies developed would rapidly cross over to treating civilian trauma."**

2016
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Conference

Cryogenic SEM image of scaffold and hydrogel at ×2,500 magnification. The sample has been fractured while frozen to view the interaction between scaffold fibres and the surrounding hydrogel phase, leaving some scaffold fibres visibly protruding from the hydrogel, and holes where other fibres have been pulled from it.

Community-sourced showcase

Monitoring biomarkers to improve treatment of chronic wounds

Dr Alex Knight, NPL

The technology

The RegeniTherix™ system is a multi-faceted device to treat chronic wounds: a bioresorbable tissue scaffold enables cells to colonise the wound bed; a hydrogel layer absorbs biomarkers present in the wound; and a simple diagnostic test enables the clinician to identify the biomarkers and thereby determine the state of the wound and decide appropriate treatment.

The hydrogel is thermoreversible: a gel at skin temperature, it becomes a liquid at low temperatures, allowing easy application to the wound and subsequent testing using lateral flow diagnostic assays.

What's the potential impact?

The annual cost of care for patients with diabetic foot ulcers – the most common type of chronic wound – in England alone is £650 million, including the cost of amputation where ulcers cannot be healed.

Who's involved?

National Physical Laboratory (NPL) – the government laboratory is leading the project, using their expertise in point-of-care diagnostic devices.

Leeds Teaching Hospitals Trust – first-in-man trials of the device will take place at one of the UK's largest health trusts.

Neotherix – the UK-based SME manufactures the tissue scaffold and the hydrogel.

Complement Genomics – the project's other industrial partner works on identifying relevant wound biomarkers.

What's next for the research?

The consortium has won both Innovate UK (as Technology Strategy Board) and now NIHR i4i funding to develop and take the device into clinical trials – initially with patients suffering from diabetic ulcers – and these start later this year. Work is also underway to further refine the panel of biomarkers. ■

> **"Combining the diverse expertise of all the partners has enabled us to create a multi-faceted device with real clinical potential. Having a knowledge base of wound biomarkers and their association with different wound states, including healthy healing, subclinical infection and inflammation, will enable us to apply the technology to a range of chronic wound types."**

National focus

Supporting RegenMed since 2007

Dr Michael Sullivan,
Lead Technologist - Regenerative Medicine, Innovate UK

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Tissue engineering, the science of creating and manufacturing organs and tissue to replace damaged or diseased tissue, is highly complex.

To succeed it requires an exquisite understanding of basic biology and physiology and a multidisciplinary approach that includes chemistry, materials science and many other disciplines.

Tissue engineering, the science of creating and manufacturing organs and tissue to replace damaged or diseased tissue, is highly complex. To succeed it requires an exquisite understanding of basic biology and physiology and a multidisciplinary approach that includes chemistry, materials science and many other disciplines.

While surgery used to be all about excision and removal, the emergence of replacement surgery to aid repair, healing and regeneration has developed from the findings that skin and bone tissues could be grafted from one site to another in the same patient. Then came reconstructive surgery and finally whole organ transplant surgery that was enabled by the discovery, development and use of the selective T-cell immunoregulatory agent ciclosporin. The use of ciclosporin helped make solid organ transplant a routine procedure but there is a shortage of donor organs. Currently, just in the UK, there are over 7,000 people on the national transplant waiting list and, during the last financial year, over 1,300 people either died whilst on the waiting list or became too sick to receive a transplant (NHSBT figures). A potential solution is the delivery of alternative suitable organs, tissue and cells through tissue engineering and regenerative medicine.

Innovate UK has provided long term support to the area of regenerative medicine and advanced therapies for UK businesses. Since its formation in 2007, Innovate UK has supported work to address translation and commercialisation challenges in this area and since 2009, through our Regenerative Medicine Programme, the Biomedical Catalyst, and a number of other funding streams, Innovate UK has supported over 120 advanced therapy and regenerative medicine projects with over £54 million in grants.

These projects have focused on the development and validation of therapeutic products towards clinical application, support for underpinning tools and technologies to evaluate toxicity/efficacy and assist manufacturing, and the evaluation of novel supply chains and business models. These investments will have allowed more than ten therapies to advance into clinical trials for the first time, and have allowed companies to raise further investment as a direct consequence of the programme.

Innovate UK established the Cell and Gene Therapy Catapult in 2012 (funding of £70 million for 2012-17) to support the growth of this emerging industry sector and establish the UK as a global centre. The Cell and Gene Therapy Catapult is based at Guy’s Hospital in London, a pioneering healthcare centre of excellence. The Catapult provides access to technical, regulatory, clinical and financial expertise and infrastructure, enhancing the UK’s key strengths in this area, and enabling the UK to be a global leader in the development and rapid commercial exploitation of cell therapies.

To build engineered tissue or organ requires a three-dimensional structure or scaffold that is used to support cells as they grow and develop. Skin, blood vessels, bladders, trachea, esophagus, muscle and other types of tissue have been successfully engineered; and some of these tissues have already been used in treating human disease. We have provided support for a number of pioneering UK companies such as Collagen Solutions, Videregen, Locate Therapeutics, Neotherix, The Electrospinning Company, Tissue Regenix, NuVision Biotherapies, Jellagen, Oxford Biomaterials, Orthox, Xiros, and Azellon that are developing the use of biomaterials or synthetic materials as scaffolds in regenerative medicine and tissue engineering to enhance positive clinical outcomes for patients. The outstanding challenge remains the routine translation of the science of regenerative medicine and tissue engineering into clinical therapies.

The 2016/17 financial year sees the introduction of a simpler Innovate UK competition process with each of our four sectors running two broad sector-themed competitions in the year. In addition we will run two open competitions where companies can apply regardless of sector or technology area. ■

More details can be found in our Delivery Plan that can be downloaded from **www.gov.uk/government/publications/innovate-uk-delivery-plan-2016-to-2017**

Details of current and forthcoming funding competitions run by Innovate UK can now be found at **www.gov.uk/government/collections/innovation-grants-for-business-apply-for-funding**

Common approaches to industrialisation across the advanced therapy sector

Recent analysis by the Alliance for Regenerative Medicine shows that the advanced therapy sector continues to grow year on year with over 669 global clinical trials. Out of the $1.2 billion raised this year across the broader sector, over $48 million in finance has been raised by the tissue engineering industry.

Dr Stephen Ward,
Chief Operating Officer,
Cell and Gene Therapy
Catapult (CGT)

“

The currently available supply chain methodologies are often inefficient, cost prohibitive and unscalable.

At CGT we are investing in our Seamless Freight programme with collaborators to ensure that the entire end to end supply chain is controlled and reproducible through better product tracking, product movement and thawing control.

In the UK, the advanced therapy sector is continuing to grow both the number of companies and their supply chains. Annual analysis by the Cell and Gene Therapy Catapult (CGT) has shown an almost doubling of clinical trials since 2013 in the UK.

Across the advanced therapy technologies, what are the pan industry challenges? A key driver is the ability to manufacture products reliably and cost effectively at scale. The CGT is approaching from two directions. Firstly, to invest in process and analytical systems that can generate processes that deliver products at a cost that is affordable to healthcare providers. Secondly, to provide access to large scale GMP facilities with a capacity to deliver products for pivotal clinical trials and early commercial supply. There is a strong translational manufacturing base in the UK and the CGT large scale manufacturing centre, online in early 2017 will help grow a UK based global industry. It will be a CGT supported and controlled environment which enables multiple collaborators to retain control of their process without the capital investment of building their own facility.

To secure a sustainable commercial future, cell therapy processes need to become more reproducible, so batch failure rates are reduced; more robust, to allow manufacturing to be performed at more than one site and as already mentioned, more cost efficient. To achieve this, a systematic Quality by Design (QbD) approach to process deconstruction and reconstruction is essential. The CGT QbD platform covers the entire end to end manufacturing cycle and ultimately identifies the critical process parameter (CPP) operating space in which the product critical quality attributes (CQAs) are maintained – in line with the target product profile (TPP) and within a defined risk management strategy which ensures whole bioprocess robustness.

Underpinning this process industrialisation, is the need for far better analytical and characterisation platforms. Understanding the impact of process changes on product functionality and safety is a critical growth area for the sector. These methodologies can also be used to develop better control systems and reactive production processes, so successful QC release is hard wired into the process and not tested in at the end of the batch. Specifically for tissue engineering products once cells are on scaffold, it can be difficult to test and characterise the various drug components with suitable sensitivity and precision.

The currently available supply chain methodologies are often inefficient, cost prohibitive and unscalable. At CGT we are investing in our Seamless Freight programme with collaborators to ensure that the entire end to end supply chain is controlled and reproducible through better product tracking, product movement and thawing control.

The tissue engineering bioprocessing community is in good company with the rest of the advanced therapy sector in that we are all facing a number of challenges in moving from clinical stage to commercially appropriate products. Nevertheless, we can be optimistic in that an approach that focuses on consistent quality, defined specifications and up front development that drives down end to end manufacturing costs will be necessary and sufficient, to ensure wide clinical adoption of these remarkable therapies. ■

Opening innovation to make it more responsible

In the age characterised by an almost religious faith in ability of technological progress to resolve grand social challenges and increase economic wellbeing, it is not surprising that many old ideas about innovation receive strong momentum under new and catchy labels.

The notion that innovation is essentially a collaborative endeavour spanning multiple constituencies has received renewed attention with the concept of Open Innovation. This concept highlights, with equal importance, knowledge generated outside an organisation and knowledge produced within organisational borders. Innovative organisations are advised to tap into a rich pool of externally available knowledge and, at the same time, pay serious attention to internally generated knowledge that resists commercialisation through existing business models or current market channels.

Similarly, the old debates about the role of science and technology in society have received a significant boost under the label of Responsible Innovation. In particular, advances in emergent technologies such as nanotechnology, genetically modified organisms, synthetic biology, robotics and information technology have triggered calls for innovation to become a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products.

It is intriguing that both concepts have rarely been integrated, despite the fact both emphasise the importance of collective actions and engagement. This may well be explained by different intellectual roots and a degree of ambiguity that still characterises both open and responsible innovation. Open innovation unquestionably resonates with innovation practitioners, policy-makers and management academics, yet its meaning is often creatively stretched beyond the original propositions.

For some, open innovation is an umbrella term for all collaborative activities, including partnering with companies, engaging with universities, interacting with governments and integrating users into the process of innovation. For others, open innovation is limited to approaches where any IP protection is considered less of a strategic issue. Sometimes open innovation is reduced to IT-enabled crowdsourcing and distributed problem solving.

Responsible Innovation even more lacks clarity in concept and especially in practice. It is very often misunderstood for individual adherence to well-defined rules and norms. Combining high-level aspirations for collective governance of emerging technologies through institutionally negotiated frameworks with pleas for individual reflexivity inevitably creates problems when organisations and individuals aspire to put responsible innovation into practice.

The emerging ecosystem of regenerative medical devices is a perfect environment in which to open innovation processes in order to increase participation and inclusivity and consequently strengthen responsiveness to the interests of different constituencies. It is populated by scientists from different disciplinary backgrounds, new organisational entities with the mission of commercialising technology, policy-makers concerned with costs of health, entrepreneurs eager to explore emerging opportunities, established companies with intent to strengthen competitive advantage, medical regulators concerned with safety and efficacies, managers of national health services, clinicians that use technologies and patients who should benefit from any innovation. Multiple interests and values in such a diverse and complex ecosystem could create circumstances where individually responsible people produce irresponsible outcomes on the level of the entire system.

Open innovation approaches especially those enabled by ICT could be effectively used to facilitate collective anticipation about the evolution of medical technologies in general and regenerative devices in particular. Multiple constituencies should be included in different technology foresights and strategic planning, which will increase the likelihood of identifying the most relevant clinical needs, emerging dilemmas, and unintended (and sometimes undesirable) impacts of innovation. Additionally, crowdsourcing techniques and innovation platforms could be used to facilitate wide participation of different constituencies in the very process of innovation by contributing to generating ideas, evaluating the proposed ideas and co-developing innovative and responsible solutions. ■

Krsto Pandza,
Professor of Strategy & Innovation,
Leeds University Business School

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The emerging ecosystem of regenerative medical devices is a perfect environment in which to open innovation processes in order to increase participation and inclusivity and consequently strengthen responsiveness to the interests of different constituencies.

N8 and the life sciences Northern powerhouse proposition

The North of England has a rich heritage of technological and medical innovation. City leaders across the North have recently endorsed Health and Life Sciences as one of four key economic sectors that will form the cornerstones of the Northern Powerhouse.

This region contains

- eight world class research-intensive universities
- over 15 million people
- Five of the UK's top 10 urban areas
- With a regional GVA of over £300 billion, the North would be the 10th largest economy in the EU, were it a country

"The Northern Powerhouse is home to 1,000 health and life science businesses, supporting around 38,000 high skilled jobs and contributing £10.8 billion to the UK economy each year

N8 and the life sciences Northern powerhouse proposition

Dr Peter Simpson,
Director of N8 Research Partnership

"Other great N8 facilities include the WELMEC Centre of Excellence in Medical Engineering, EPSRC Centre for Innovative Manufacturing in Medical Devices (MeDe), and Sheffield's Medical Advanced Manufacturing Research Centre (MAMRC). The region also hosts two NIHR Diagnostic Evidence Co-operatives, which support development of in vitro diagnostics.

Is there evidence to be confident about the role of Health and Life Sciences in future economic growth? Actually, yes. For example:

- 30% of clinical trials throughout England are conducted in the North, accounting for 37% of the UK's clinical trial participants
- The Northern Powerhouse is home to 1,000 health and life science businesses, supporting around 38,000 high skilled jobs and contributing £10.8 billion to the UK economy each year
- A pharmaceutical manufacturing hotspot is located in this region, including AstraZeneca's largest manufacturing site – which alone contributes 1% of the UK's export value of all goods
- Eli Lilly, Actavis, Fujifilm Diosynth and Medimmune are part of the internationally leading biologics manufacturing cluster in the North
- Major technology innovators in this region include Waters Corporation, Life Technologies
- One of the UK's largest clusters of orthopaedic, medical device and surgical companies is in this region, home to Smith and Nephew, Surgical Innovations, Reckitt Benckiser, JRI Orthopaedics, Swann Morton and DePuy Synthes
- The North has a growing SME sector

In addition, the North has world class life sciences research facilities and expertise. These include the world class N8 universities that work in partnership with internationally renowned research centres in the region.

MedTech is a notable regional strength. In Leeds, the Institute of Medical and Biological Engineering (iMBE) is a world-class bio-engineering research institute, whilst N8, Regener8 and the IKC in Medical Technologies have developed a successful platform of innovation and partnership with business.

Other great N8 facilities include the WELMEC Centre of Excellence in Medical Engineering, EPSRC Centre for Innovative Manufacturing in Medical Devices, and Sheffield's Medical Advanced Manufacturing Research Centre (MAMRC). The region also hosts two NIHR Diagnostic Evidence Co-operatives, which support development of in vitro diagnostics.

In business and research, then, the North of England has shown it can succeed in the life sciences arena. But the field remains highly globally competitive – how can we build that success further? Universities have a major role to play.

The N8 Research Partnership is the UK's best established university partnership. N8 works on regionally coherent innovation for growth agenda by

- promoting collaboration
- establishing innovative research programmes of international prominence
- driving economic growth

In Life Sciences, N8 is translating national leadership expertise in biotechnology into a new Bioeconomy programme for analytical innovation through academic-business collaboration.

Strategic investment is needed.

For the North, and the UK as a whole, cross-sectoral partnerships and innovative funding will be critical to retain and build on our strengths. N8 has already been highly active in bridging academia-business gaps through providing an innovation forum for the establishment of collaborations. Our colleagues at Northern Health Science Alliance support multi-centre clinical development projects, while BioNow and AHSNs seek to simplify business relationships and NHS innovation. Greater funding for this comprehensive support network will ease the way for new collaborative endeavours.

Overall, the North is working together to an unprecedented extent, across politics, business organisations, and the academic sector. We have a strong, investable proposition that combines fantastic science, with a skilled work force, and outstanding quality of life. Let's keep up that momentum! ■

Risky business?

Innovation in cutting-edge technologies involves unavoidable barriers and risks as well as abundant opportunities.

We asked colleagues in our network what they believed the biggest opportunities or challenges would be over the next few years for the Regenerative Medicine sector, and how these might shape or contribute to building a healthy regenerative devices industry. Their responses provide an illuminating snapshot of opinions from experts across the board – covering research, translation, intellectual property, regulatory affairs, investment and market development.

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The field continues to evolve, with cellular immunotherapy now accounting for over 40% of the current clinical trials and 60% of the estimated $10Bn raised globally in 2015 in Regenerative Medicine. This illustrates the speed and volume of investments available on the back of truly exciting clinical data. However, the rise and eventual bankruptcy of companies like Dendreon provides unfortunate but valuable lessons that must be studied and learned from in order to prevent recurrence in the future.

Dr Paul Kemp,
Intercytex

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There is an exciting opportunity ahead in using regenerative approaches as a prophylactic treatment before serious tissue failure occurs. This type of early intervention would significantly improve patient well being and considerably reduce subsequent healthcare costs; however, several challenges need to be addressed. We need a concerted effort to promote diagnostics and screening programmes to identify those patients at high risk and develop minimally invasive approaches to tissue regeneration. We then need to convince healthcare authorities of the benefits of this type of proactive approach.

Dr Ifty Ahmed,
Associate Professor,
Advanced Materials Research Group, University of Nottingham

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Opportunities to improve the success of regenerative medicines targeting conditions such as vascular disease, diabetes and age related disorders, will increase with a better understanding of the impact these conditions have on the pathology of the stem cell niche. This could underpin the development of innovative ‘smart matrices’ that provide the protection and spatial cues required to establish a functional cell niche.

Dr Cathy Prescott,
Biolatris Ltd

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For regenerative medicine to fulfil its potential of revolutionising patient care, regulatory bodies and healthcare institutions must embrace emerging products. Yet specific challenges facing the adoption of regenerative medicine need addressing. These include accessibility of tissue and cells, lack of standardisation protocol and safety criteria, ambiguity over translational routes, restricted clinical trials, scale up and manufacturing difficulties, inadequate health technology de risking process, concern over IP protection, and the risk of insufficient investment and return. Overcoming such barriers must be seen as the new challenges – and opportunities – for the regenerative medicine community.

Dr Aram Saeed,
Lecturer in Drug Delivery and Tissue Engineering,
University of East Anglia

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Exciting clinical effects of modified immune cell therapy have reinvigorated commercialisation prospects for the whole Advanced Therapies sector, leading to significant, renewed interest in regenerative therapies combining living cells and biomaterials. The UK Government's Expert Panel in regenerative therapies reported on NICE's decision framework as being applicable to these therapies, which is encouraging news for both developers and investors alike. Biomaterial based innovations potentially offer very substantial patient benefits but will require quantifiable clinical improvement to demand adaptable payment methods.

Dr Tim Allsopp,
Neusentis Regenerative Medicine
Co ordinator IMI EBiSC Project,
(Pfizer Ltd)

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The advent of new fabrication techniques such as 3D printing has great potential for regenerative medicine, but represents a huge potential challenge to the current regulatory paradigm. Many biomaterials and scaffolds are regulated as medical devices and have a clear and well established route to the marketplace, but the routine preparation of individualised products via a customisable technology platform may be beyond the scope of the current provisions for custom made devices.

Alison Wilson,
Cell Data Services

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To induce or accelerate the regeneration of damaged and diseased tissues is a compelling goal in medicine. The pace of design and effectiveness of implantable devices that can nurture endogenous processes of repair, or ensure the delivery, retention and activity of exogenous cargos of cells is quickening, and approaches in treating musculoskeletal diseases exemplify how this is being achieved. But with osteoarthritis (OA), the structural severity of disease does not always correlate with the pain of the condition, or its treatment. Designing future approaches with this disconnect in mind may enhance the impact of regenerative therapies for conditions like OA.

Dr Stephen Simpson,
Director of Research & Programmes,
Arthritis Research UK

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Smart biomaterials are getting even smarter but so must we. It's vital that we find the most effective way of exploiting novel materials to drive tissue regeneration without pushing up the costs of the therapeutics or increasing the risk of failing to clear regulatory hurdles. Overcoming these challenges will give us the chance to do some really interesting science along the way.

Professor Anthony Hollander,
Head, Institute of Integrative
Biology, University of Liverpool

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Recent advancements in nuclease based genome editing such as CRISPR/Cas9 could have significant impact by increasing the applications for cellular therapy. Clinical data supporting in vivo repair of faulty or deleted genes is likely in the foreseeable future and the FDA has approved clinical studies for Haemophilia B and Mucopolysaccharidosis Type I. Despite this exciting potential, regenerative medicine has largely failed to deliver on the significant investment to date. Commercially successful products and companies remain rare exceptions. Business models are still a major challenge especially for ex vivo cell therapy companies, where allogeneic rather than autologous approaches are needed to address scalability concerns.

Dr Simon Graindorge,
Director, IP Group

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The quality of the UK's supply of higher level skills which enable the exploitation of technological breakthroughs in the regenerative device subsector will be essential for our future competitiveness in global markets. Harnessing the higher education sector's capabilities in business led research and innovation will help address this challenge and enable the UK to capture a sizeable market share.

Dr Jo Dixon Hardy,
Director of Medical Technologies
Innovation, University of Leeds

Smart innovation:
Proof of concept projects

A total of 48 Proof of Concept projects have been funded to date through the IKC, and a growing number of these are co-funded through a collaboration with Arthritis Research UK (ARUK).

Successful applicants receive up to £100k to progress their projects for 12-24 months. In addition, each project is allocated a highly experienced project manager, to ensure the project remains on track, on time and on budget. Project managers provide practical support as well as advice and guidance to help the project teams navigate the challenges of bringing a new technology or device to market. This includes guidance on IP issues, clinical trials support, licensing, next steps beyond the proof of concept stage, and using the Regener8 network of industrial contacts to make introductions to companies best suited to commercialising the technology.

Professor Jenny Southgate

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PABM was well-tolerated and became incorporated into the host tissues.

Case Study

Urinary tract application for bladder-derived natural acellular matrix

A biomaterial produced from pigs’ bladders could improve surgical outcomes for a common congenital condition that affects boys.

Hypospadias is a birth defect of the urethra which results in the urinary opening appearing along the shaft or at the base of the penis instead of at the tip.

Treatment requires surgery, but with very little ‘spare’ tissue to reconstruct the urethra and relocate the opening, these procedures often fail. Salvage operations, which may include taking graft material from inside the cheek, can result in additional scarring or holes (fistulas), which make a successful outcome increasingly difficult to achieve.

A team led by Professor Jenny Southgate at the University of York is investigating whether their biomaterial could be used in the initial surgery as a scaffold for new tissue formation to help repair the defect.

The material, called PABM (porcine acellular bladder matrix), is prepared by stretching the bladder as thinly as possible so that all the cells can be removed, using a decellularisation technique developed by the University of Leeds and commercialised through spin-out company, Tissue Regenix. The remaining collagen matrix is soft and pliant, but also very strong, making it particularly suitable for reconstructive surgery. Because collagen is very well conserved between species it can be used as a donor material without triggering an immune response from the recipient.

The PABM material was tested in pigs, which were monitored over several months to see how well it integrated and promoted cellular ingrowth. It was also compared with another dermis-derived biomaterial which is commercially available.

“PABM was well-tolerated and became incorporated into the host tissues,” says Professor Southgate. “Our results showed it performed better than another material used for comparison purposes, and we think it could be useful to treat hypospadias.”

The team is continuing to work with Tissue Regenix to develop routes to market for PABM. A second Proof of Concept study is also underway to find out if PABM could also be used in bladder reconstructive surgery. ■

Project Manager:
Dr Graeme Howling, IKC
Funding: IKC

Case Study

Pre-clinical trial of a novel patient specific biphasic synthetic scaffold for the treatment of osteochondral defects

Repairing large osteochondral defects in knee joints is a big challenge for surgeons. Conditions such as osteoarthritis or damage caused by sporting injuries can require whole joint replacement – a painful and costly operation.

Around 2.36 million working-age people need treatment for knee osteoarthritis in the UK each year, so improved, cost-effective, and personalised treatments could bring huge benefits.

A veterinary surgeon at the University of Cambridge is working with engineers at the University of Newcastle on a new technique to repair osteochondral defects larger than 2.5cm^2.

The team has developed a device based on a two-phase scaffold developed at Newcastle University, with the bulk of the structure made from a macro and micro porous bioceramic which has an integrated biopolymer top surface.

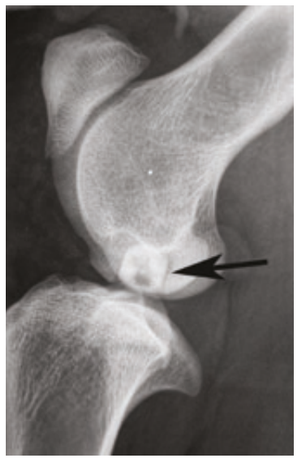
The combination of materials offers an excellent match for the mechanical properties of both cartilage and subchondral bone. Data taken from the patient’s x-rays and CT scans is used to 3D print the implants, which are custom-made to fit the precise contour of each joint.

Dr Frances Henson, who is leading the project in Cambridge, explains: “Because the deep holes caused by these defects pass through two very different types of tissue, we need this two-part scaffold to enable us to secure the implant and to encourage the remaining tissue to heal.”

The Proof of Concept study will enable the team to investigate the performance of the implant in sheep to analyse whether the technology can progress to a ‘first in man’ clinical trial.

“We monitor the sheep extremely closely to gather data about the implant, but also to look after their welfare,” says Frances. “We’re using gait analysis, force plates and even – for the first time in this sort of study – telemetry to track their movements 24 hours a day. This technology enables us to gather valuable data and will also contribute to our goal of using few animals in these studies.” ■

Lateral x-ray view of sheep knee with osteochondral plug in place (arrow)



Dr Frances Henson

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Project Manager:
Prof Mike Raxworthy, Regener8
Funding: IKC/ARUK

Dr Jayesh Dudhia

“For knee surgery, partial replacement is preferred wherever possible as patients recover much faster, but failure rates can be high because it’s difficult for surgeons to visually identify sub-clinical disease elsewhere in the joint.

Case Study

The application of Raman arthrospectroscopy for intra-operative mapping of early articular cartilage degeneration

Dr Jayesh Dudhia from the Royal Veterinary College, is developing a device for surgeons to identify the early onset of osteoarthritis in articulating joints.

Dr Dudhia’s previous research with collaborators discovered a biomarker of sub-clinical cartilage degeneration that can be detected using Raman spectroscopy – a technique which directs a laser at matter and analyses how the light scatters to characterise its chemical composition.

Alongside chemists Professor Paul McMillan and Dr Steve Firth from UCL, the team is using Proof of Concept funding to develop an arthroscopic probe to provide objective information about cartilage health to inform surgical decisions in real-time. A test using an experimental instrument has already been successfully trialled in four patients undergoing minimally invasive knee assessment.

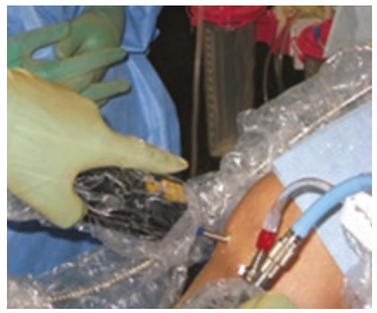
“For knee surgery, partial replacement is preferred wherever possible as patients recover much faster, but failure rates can be high because it’s difficult for surgeons to visually identify sub-clinical disease elsewhere in the joint,” says Jayesh. “Remedial surgery is expensive in term of time and resources so getting it right first time would be better for the patient and less expensive for the NHS.”

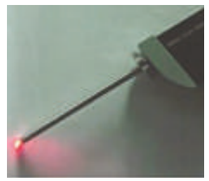
The team intends to translate the technology into a ‘traffic light’ system that will give surgeons the information necessary to assess cartilage health.

“We need to process the complex information from the light spectra into a quantifiable, simple signature first,” says Jayesh. “We’re currently looking at the spectra to separate the true signal from the background noise.”

The team is in talks with a UK company which has the technology to amplify the signal at least tenfold. “We’ve come much further in 12 months than I could ever have anticipated,” says Jayesh, “and there are other potential applications in regenerative medicine and tissue engineering, where the non-destructive nature of the technology would be extremely useful. It’s exciting to be combining biology, chemistry and physics for a clinical problem in a way that’s not been done before.” ■

Professor Paul McMillan





Project Manager:
Dr Graeme Howling, IKC
Funding: IKC/ARUK

Case Study

Development of an arthroscopic device for enhanced joint repair

An arthroscopic device is showing promise as a simple, inexpensive and one-step method of harvesting and mechanically releasing autologous mesenchymal stem cells (MSCs) into the knee joint to aid repair of damaged cartilage.

The device, developed by Dr Thomas Baboolal and Professor Dennis McGonagle from the University of Leeds, is based on the discovery that MSCs are found in relative abundance in the adjacent synovium. They believe the device could replace the technique of subchondral drilling which allow stem cells from the bone marrow to enter the joint. It may also render obsolete the expensive procedure of tissue extraction and culture expansion.

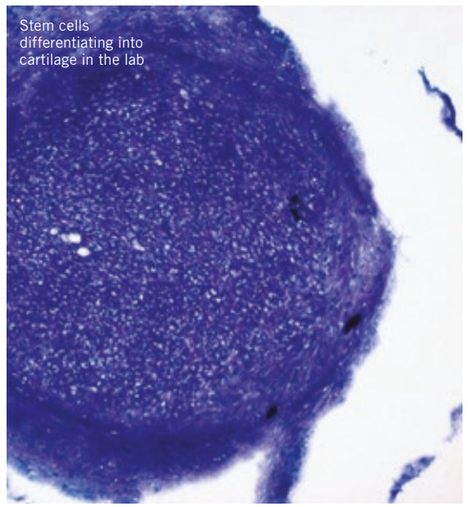
Says Thomas: “Since MSCs with good intrinsic cartilage forming capabilities are abundant in the synovium, it makes sense to use these to aid repair, especially as synovium and cartilage cells come from a common progenitor cell – they’re pre-programmed to form joint tissues.”

The device has been shown to work in vitro, and is currently being tested in patients, for which the released cells will be removed and quantified in the laboratory. The team are about to start a Leeds Musculoskeletal Biomedical Research Unit supported safety and efficacy trial which will leave the released MSCs in the patients’ joints and evaluate cartilage repair.

“I trained as a basic research scientist, adds Thomas, “so to be involved in translating knowledge, designing a device and seeing this being tested in patients is amazing – as is being named on my first patent!”

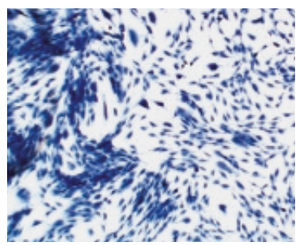
Professor McGonagle added: “It’s very exciting to see such as simple, inexpensive solution potentially emerging from twenty years of stem cell research in Leeds.”

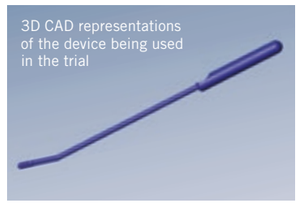
The team is also working with Dutch researchers, to see if the device, by increasing stem cells at injury sites, can boost the effectiveness of a technique called ‘joint distraction’, in patients too young to be suitable for joint replacement surgery. ■



Stem cells differentiating into cartilage in the lab

Growing stem cells harvested from a patient using the device





3D CAD representations of the device being used in the trial

Dr Thomas Baboolal

“Since MSCs with good intrinsic cartilage forming capabilities are abundant in the synovium, it makes sense to use these to aid repair, especially as synovium and cartilage cells come from a common progenitor cell – they’re pre-programmed to form joint tissues.

Project Manager:
Dr Graeme Howling, IKC
Funding: Welmec/IKC

Dr Chaozong Liu

Case Study

Measuring the efficacy of a functionally biomimetic osteochondral scaffold for large osteochondral defect repair

A biomimetic PLGA-titanium scaffold developed by a team from UCL may offer the first effective repair of large osteochondral defects (OCDs).

Whether caused by trauma such as sports injuries, or through slow cartilage deterioration, left untreated, OCDs can progress to affect the subchondral bone and lead to osteoarthritis – for which the only treatment is joint replacement.

Dr Chaozong Liu, Professor Gordon Blunn and Mr Andy Goldberg from UCL and the Royal National Orthopaedic Hospital, in collaboration with Oxford MEStar Ltd and Collagen Solutions Plc, are currently preparing for an in vivo trial using a sheep condyle model, with proof of concept funding from Arthritis Research UK and IKC. A previous ex vivo study showed the scaffold to have excellent mechanical stability, with its unique structure encouraging the formation of hyaline cartilage.

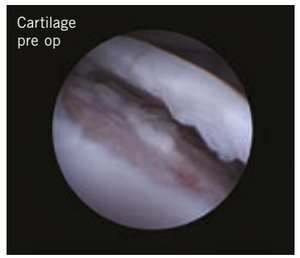
An unusual stroke of luck has also given them a tantalising glimpse of how the scaffold could perform in the clinic, through a collaboration with Professor Noel Fitzpatrick, star of the Channel 4 TV series, Supervet.

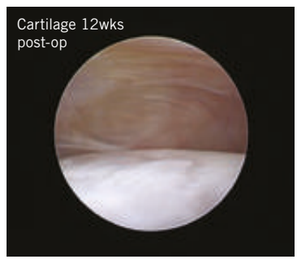
Known for his use of cutting edge technologies to help pets in his care, Prof Fitzpatrick used the UCL scaffold in November 2015 to treat a large OCD in a pet dog. He reported back recently with scans revealing the cartilage had regenerated well, matching the curvature of the joint perfectly.

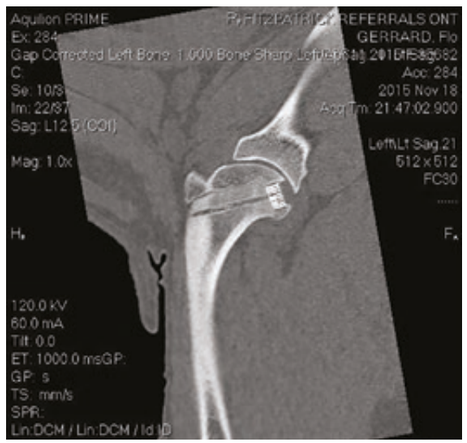
"We're confident our scaffold has the potential to address this unmet clinical need," says Dr Liu who leads the project. "We've shown it has the strength needed to bear the physical load of the joints and its patented biomedical structure encourages consistent cartilage fill and a smooth articular surface. We're very happy with progress."

Having secured ethical approval, the team is assessing the preclinical performance of the scaffold using tissue from patients undergoing join replacement surgery. Ultimately the team hopes to run a clinical trial at the Royal National Orthopaedic Hospital in Stanmore. ■

> "We're confident our scaffold has the potential to address this unmet clinical need
>
> We've shown it has the strength needed to bear the physical load of the joints and its patented biomedical structure encourages consistent cartilage fill and a smooth articular surface. We're very happy with progress.







Scan of affected area (image courtesy of Prof Noel Fitzpatrick)

Project Manager:
Dr Sarah Odoi, ARUK
Funding: IKC/ARUK

MedEN8+

Assessing collaborative research and innovation potential in medical technologies/medical engineering in the north of England (MedEN8+)

An EPSRC Institutional Award to the University of Leeds has allowed the collaborative research and innovation potential to be explored in five areas of medical engineering technology that border on the Medical Technologies IKC and Regener8 existing core strengths in implants, biomaterials and regenerative devices.

The areas chosen were:

- Digital Health
- Diagnostics
- Imaging
- Surgical Delivery Technologies
- Rehabilitation

Our team conducted scoping and mapping activities to review academic and industry strengths across the UK with a particular concentration on those found in the "N8+ region (ie the geography covered by the N8 universities defined to include the work of non N8 universities such as Bradford, Hull, Salford and others where relevant). The work involved user led definition of clinical needs and, in parallel, the mapping and classifying of academic capabilities and industry strengths.

From this work we are now seeking to understand the potential for new collaborations to address any poorly met clinical needs identified in the first stage of the exercise. This scoping work will now feed into a series of thematic collaborative workshops to which key academics, industry and clinicians will be invited and which will run before October 2016.

Proposals for collaborations will be developed using the Medical Technology IKC methodology for defining and testing the strength of technology opportunities and successful proposals will be further developed as funder ready applications. ■

Further information on this initiative can be obtained from Professor Mike Raxworthy, Regener8 Operations Director via **m.j.raxworthy@leeds.ac.uk**

image courtesy of Neotherix Ltd

Why public engagement matters

Why should the regenerative devices sector care about public engagement and involvement in research?

Here are four reasons:

One
Public engagement in schools will inspire the next generation of scientists and engineers to fill the skills gap we face in the sector and help to keep it vibrant.

Two
Public engagement events for the wider public helps us be accountable for the public money that funds a proportion of our research in the sector.

Three
Such events ensure that the public continues to support our research, because they understand what the sector can offer them, as potential future patients.

Four
Involving patients in research makes our research better, by improving recruitment to studies and ensuring our devices meet the needs of the end user.

And perhaps the future will see a fifth reason: involving the public as 'citizen engineers' to help us collect and analyse data to improve medical innovations.

If you're still not convinced, take a look at how researchers in the Institute of Medical and Biological Engineering (iMBE) at the University of Leeds view the benefits of public engagement.

Dr Dawn Groves
Postdoctoral Research Assistant

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There are strict ethical processes that cover how patients are recruited to take part in research, to ensure informed consent, but directly engaging with patients can also be extremely useful in making a research project a success.

For my PhD, I needed to recruit patients with advanced osteoarthritis, who were waiting for a total hip replacement. It was only through speaking directly to patients, to the clinical staff who worked with them and the Patient and Public Involvement (PPI) Group at Leeds Musculoskeletal Biomedical Research Unit (LMBRU), that I was able to recruit successfully to the study. I got invaluable advice on where to approach patients, the best methods to use and what kind of wording would gain their interest and provide the information they'd need to make a decision.

I now work with Dr Sophie Williams to manage iMBE's implant retrievals lab, which collects joint replacements that have been removed from patients for use in specific research projects. We're revising our ethics procedures and will definitely be asking the advice of the PPI group at LMBRU about our new information materials – the importance of getting input from patients and the public can't be overstated.

Dr Marlène Mengoni
Research Fellow

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Public engagement activities can sometimes provide unexpected benefits for your research. My work in developing an interactive app, to display 3D medical images and outcomes of computational models has led to me looking at new ways to share data across iMBE. I now take the lead on data management for iMBE and beyond.

I work in silico biomechanical research, developing computational models of musculoskeletal tissue. I wanted to find an interactive way to present this to the public, and developed an app based on some visualization tools I'd created during my PhD. However, I soon realised that it was very cumbersome, not at all user-friendly for non-experts, and needed a new platform.

With funding from the Wellcome Trust, I worked with a team of early career researchers and academics to transform my idea into an interactive touchscreen app. In its first year, the app was used at 10 national public engagement events, reaching 8,000 people.

Dr Claire Brockett
University Academic Fellow

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One important aspect of public engagement is in breaking down preconceptions. Through the Inspiring the Future scheme, I've given talks about my career to local schools, particularly in disadvantaged areas, but the pupils are only told in advance that the engineer, Dr Brockett, will come into the class. They're usually very surprised to see a woman! Most students have no idea that women regularly get PhDs, that jobs like mine exist, or what medical engineering involves.

I studied for a Postgraduate Certificate in Practical Science Communication as I felt it was important to gain some formal training on how to 'do public engagement' well and I'm now the iMBE lead on public engagement, helping to organise our displays at science festivals and the workshops we run in schools.

We also are starting to involve more ideas from patients and the public in our research. As an academic, it's easy to lose sight of the fact that patients are the ultimate end user and beneficiary of your research, especially if you have no direct contact with them through your work. Most input into research projects comes from industry, other academics or clinicians, but getting feedback from patients on research proposals can bring in new and interesting ideas which improve your original plans. ■

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World-leading science is essential but not enough to deliver successful translation and patient outcomes. By bringing together all stakeholders at an early stage, Regener8 is enabling a community approach to navigating the non-linear pathway towards innovation translation.

The renewal of funding for the IKC allows us to support Regener8 to continue this critical role.

Professor John Fisher,
Regener8 Executive Director

Membership benefits

Membership of Regener8 is free and it's easy to sign up. Regener8 members benefit from the following:

Collaborative projects

Regener8 works with members to identify specific projects, form consortia and broker funding. In some cases we can project manage where appropriate.

Regener8 members also have access to a greater pool of expertise and resource as a result of the strategic alliance between Regener8 and the Medical Technologies Innovation and Knowledge Centre (IKC). The IKC focuses on the commercialisation of medical technology, facilitating collaborations between companies, engineers, scientists and clinicians. Working in collaboration with Regener8 and IKC provides the opportunity to: speed up route to market; ensure products and services are fit for purpose; reduce the risk of late-stage failure; and access resources to support innovation for new product development.

Access to world-class technology

Regener8 has close links with other networks across the UK and the N8 universities (Durham, Lancaster, Leeds, Liverpool, Manchester, Newcastle, Sheffield and York), research institutes and clinical centres of excellence in regenerative medicine throughout the UK.

Early career researchers

Regener8 has a dedicated membership stream to support Early Career Researchers (ECRs) which is open to all ECRs working in relevant regenerative medicine and medical technology fields. Events (such as the 'How to Choose and Secure Your Dream Career' workshop) and visits to Regener8 member companies and other organisations are core benefits of membership. Networking with other ECRs and co-operation with ECR groups in allied organisations (MeDe Innovation, Medical Technologies IKC, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine) are also available to members.

Regener8 website

The Regener8 website www.regener8.ac.uk typically attracts over 1,000 unique visitors per month and has referrals on key partner websites. Regener8 members are featured on the Regener8 website with a profile, logo web link and contact details. Regener8 members can update and edit their personal or organisation details at any time, simply by logging into the site. Regener8 members can also post their own news and events to the website.

The site also features a fully searchable Expertise Directory to find Regener8 members by location and area of expertise.

E-newsletter

Our regular e-newsletter contains news and events from members and the wider regenerative medicine community and is distributed to over 900 named individuals. If you'd like to receive the Regener8 e-newsletter, you can sign up via the website.

regen magazine

regen is the annual magazine for Regener8 members and the wider regenerative medicine community. Copies are distributed at Regener8 events and it is also available online on our website. Advertising packages are available.

Member events

The online events calendar on the Regener8 website is regularly updated with events that we think will be of interest to the regenerative medicine community.

Annual conference

We hold an annual conference, featuring respected academic, clinical and industry speakers from the translational regenerative community. Now established as one of the leading RegenMed events in the UK, the Regener8 annual conference offers networking and sales opportunities through the exhibition packages available.

Marketing and PR opportunities

Members can share their news on the Regener8 website, through the e-newsletter and in regen magazine.

For more information and to sign up as a Regener8 member, visit **www.regener8.ac.uk**

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