MeDe Innovation

EPSRC Centre for Innovative Manufacturing in Medical Devices

Annual review 2017

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WELCOME

MeDe Innovation was created by the Engineering and Physical Sciences Research Council (EPSRC) to lead the UK in the innovative manufacture of implants, biomaterials and new regenerative devices for the treatment of musculoskeletal disease and related disorders.

Our definition of 'manufacturing' spans the entire value chain, from creative idea and patient need, right through to manufactured products and services delivered to the patient and the market. We aim to advance knowledge and technology towards creating lasting social value, as well as supporting UK manufacturing in growing its share of a global market that will be worth $75 billion by 2020.

With an ageing population that expects to be more active for longer, we must deliver 21st century products and services and personalised interventions that last for 50 active years after 50®. This requires an exceptional underpinning research base, the right collaborations and the vision to see how new advancements in different technologies can be combined into new multifunctional products and services to address clinical and industry challenges. We must also develop people who are equipped with the right skills and experience to deliver.

Four years into our funding, we have many successes to celebrate. We've built a strong community from which we can draw together the best collaborations possible to address specific challenges in research translation and delivery of social and economic benefits.

Our core partnership of five universities – Leeds, Sheffield, Newcastle, Bradford and Nottingham – now collaborates with 48 universities around the world. Our 17 original industrial partners have now grown to 37. These relationships deliver mutual benefits in terms of research advances and commercial success and have leveraged a further £64m of funding and investment, of which £38m are new external grants awarded in the last four years.

Through our international partnerships with both universities and companies we can offer our staff, and those of our partners, greater opportunities for skills development at all professional levels. These events, conferences, training workshops, research collaborations and secondments are ensuring that people and businesses can thrive.

Our work with DePuy Synthes is just one example of this success. Through this partnership, we have delivered experimental and computational simulation systems for artificial joints that are unrivalled, and our natural knee simulator, developed in collaboration with Simulation Solutions for tissue sparing interventions, is a world first. Our long-standing relationship has seen DePuy Synthes expand its new research, development and technical centre in Leeds, securing approximately 500 jobs including 70 industrial R&D positions.

All of these achievements directly match the key elements of the government's Industrial Strategy on science, research and innovation which seeks to enable the UK to harness its world-leading science base to drive economic growth. They are also directly contributing to the EPSRC's aim to "combine with others in the multidisciplinary approaches required to solve the national and global problems of our age."

Professor John Fisher CBE
Director, MeDe Innovation

The Centre has created a critical mass of research and academic capacity, which currently comprises:

25 core academic staff

6 support staff

44 PDRA researchers

61 Doctoral PhD students

PEOPLE, EVENTS AND TRAINING

POST-GRADUATE SECONDMENTS

Six successful applicants have been awarded up to £1,500 to undertake secondments in academic laboratories, companies, hospitals or government bodies.

The placements covered a variety of topics and aims: some researchers aimed to enhance their own projects or secure access to specific facilities, while others looked more broadly at developing new collaborations and gaining insight into clinical or industrial needs. Due to demand a second call has taken place, with four further secondments awarded from three universities.

2016 SANDPIT AWARDS

MeDe Innovation's popular Sandpit events offer early career researchers the opportunity to use their expertise in larger, collaborative projects, through which they gain valuable experience of preparing proposals and understanding of the grant application process.

Two projects were awarded £5k grants following the 2016 event:

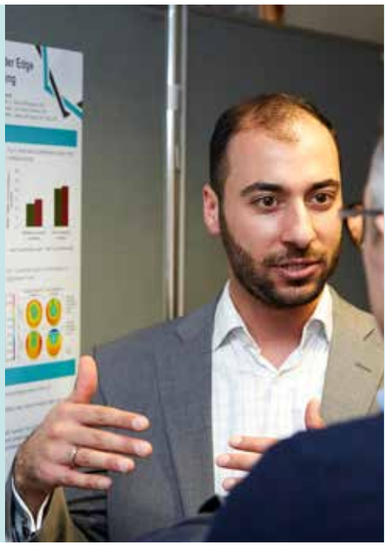
- Maria Katsikogianni, University of Sheffield
  Innovative manufacturing of composite materials with enhanced osteogenic and antibacterial properties
- Dimitrios Vgenopoulos, University of Bradford
  Shape memory sutures coated with silver particles for antimicrobial properties.

ASK THE EXPERT

This year saw the launch of our 'Ask the Expert' series of events, hosted by MeDe Innovation co-investigators, in which experts from industry, academia or the clinic speak about the particular challenges they face in their field.

Professor Will Shu from the University of Strathclyde joined Professor Kenny Dalgarno at Newcastle University to present the first event, addressing challenges in biofabrication. The meeting was sold out, with 50 attendees, and representatives from eight organisations outside the consortium.

A further four events are planned next year.



4TH ANNUAL CONFERENCE

The keynote presentation at MeDe Innovation's 4th Annual Conference was delivered by Professor Noel Fitzpatrick, the world-class orthopaedic-neuro veterinary surgeon and star of the Channel 4 documentary series *Supervet*.

Professor Fitzpatrick's presentation, 'One medicine for man and animal – working together toward a new era for custom implants and regenerative scaffolds,' launched a packed programme including 14 presentations from MeDe Innovation researchers and invited speakers.

National leadership in the medical devices arena rests on the ability to work across academic, industrial, regulatory and clinical fields to ensure the latest innovation management practice. With that in mind, we were pleased to welcome more than 200 delegates from 35 different organisations to the event, held at the University of Bradford.

Professor Noel Fitzpatrick, Fitzpatrick Referrals

> I found the keynote speech particularly engaging and thought provoking, and Professor Fitzpatrick showed a real interest in the range of research being presented – there was a good mixture of topics."
>
> GRACE STEVENSON, TISSUE REGENIX PLC

The Centre has grown its funding through the development of research and innovation activities, actively seeking external funding to deliver the translation of research.

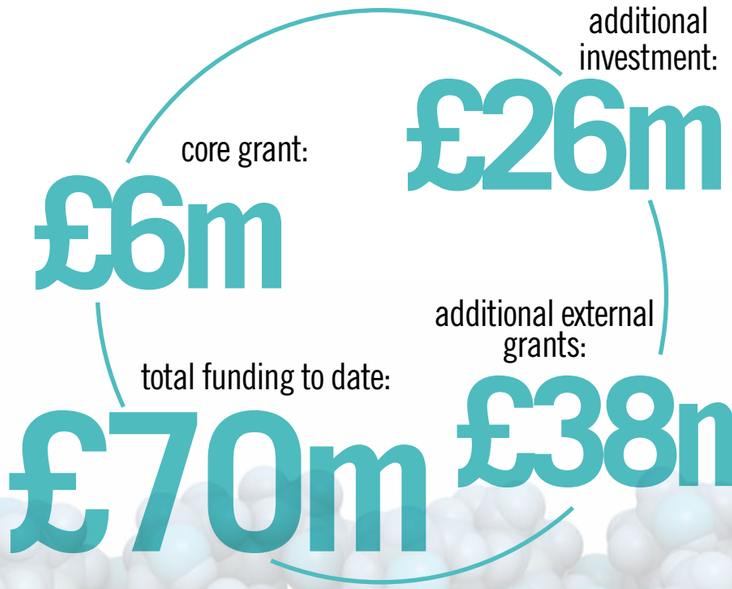
INCOME

The success of our approach is evident: from a core grant of £6m, our total funding to date has now exceeded £70m.

As a powerhouse for innovative manufacturing research, we attract resources and funding from a variety of sources, including the public sector, universities, charities and industry and we have been successful in aligning over £64m of investment and new funding to the strategic goals of the Centre.

To date, our collaborative approach to developing research projects has seen us be successful in securing £38m in new external research awards to support the Centre's ongoing research activities.

We will continue to work intensively with our partners to jointly respond to funding opportunities and to strengthen and expand the distinctive collaborative approaches that underpin the Centre's success.



ASSETS

On top of our extensive facilities and specialised equipment, the Centre has also established a suite of research methods, experimental and computational models and research tools – all of which enable us to increase our research activities with industry.

A full inventory can be found on our website, but these include:

- Additive manufacture for synthetic and biological materials
- Nonwoven manufacture of biological and synthetic materials
- New bioprocesses for acellular scaffolds
- Macro and micro scale polymer processing
- Nanocomposite manufacture and processes
- Virtual models predicting function in artificial and natural joints, which can be used as predictive design tools
- Pre-clinical experimental simulation and testing of joint replacements, natural joints and scaffolds
- Multiphase material characterisation methods
- Mechanical and tribological testing clean rooms
- Advanced metrology methods, high resolution micro CT and microscopy for synthetic, biological and composite materials
- Models for in situ, in patient manufacture
- A national implant retrieval bank for joint prostheses
- Advanced clinical MRI patient imaging and gait analysis
- ISO accredited test facilities for joint replacements.

MeDe Innovation is engaged at every stage of the innovation and translation pipeline, from initial ideas and concepts, through developing methods, technologies and intellectual property, to collaborating with device manufacturers and clinicians to deliver new products.

INNOVATION PIPELINE

Our focus has always been on supporting continuous innovation: establishing and nurturing an innovation pipeline that enables ideas to flourish and supports researchers to develop those ideas through different Technology Readiness Levels (TRLs) towards commercial development.

To date, there are more than 90 projects in our portfolio, progressing from TRL 1 to TRL 5 and beyond.

Through our network, we are able to support innovation in a wider sense too, through sharing information about available funding opportunities, and promoting Knowledge Transfer Partnerships and CASE awards to encourage collaboration. We support academic and industry secondments, to stimulate knowledge sharing throughout the sector and work with businesses to translate knowledge through an extensive range of consultancy work and contracts. Our Early Career Researcher Network is vital to the early-stage process: developing the next generation of researchers in medical device manufacture is essential if we are to continue to produce innovative ideas and projects.

Initiatives such as our Sandpit events, and post-graduate secondments have provided valuable opportunities for our ECRs to develop projects, but equally important is our ECR Forum, which links members together to share ideas and form partnerships through workshops, presentations and virtual networking.

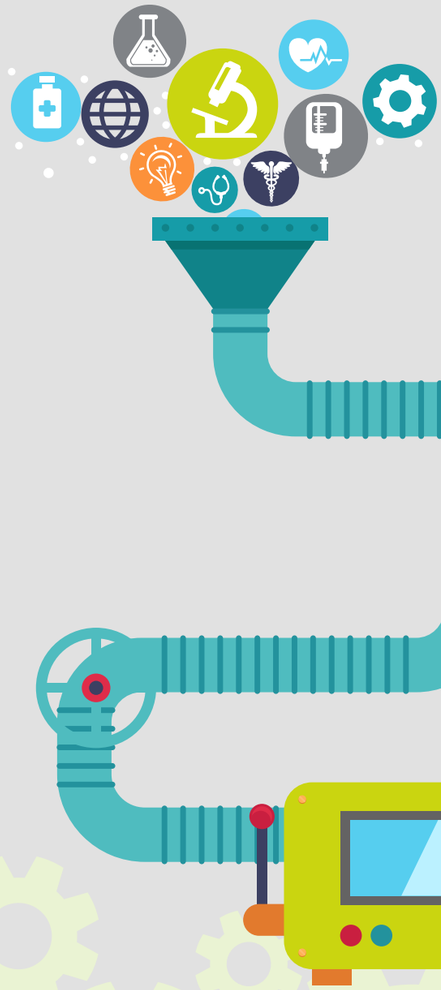
> **Collaborative working with industry is absolutely fundamental to accelerating the development of new technologies and getting them into clinical use safely and efficiently.**
>
> **PROFESSOR JOHN FISHER**

The career progression of our highly trained researchers, moving on to new positions in industry, regulatory bodies and other research centres and universities is a key part of our successful innovation and translation.

Further along the innovation pipeline, we've been able to accelerate the commercial development of several of our technologies and apply the very latest innovation management practice through collaboration with the Medical Technologies IKC.

Cambridge researcher Dr Frances Henson, for example, is progressing new methods of repairing large osteochondral defects in knee joints. Funded by an IKC proof of concept grant, Dr Henson has developed a two-phase scaffold made from a macro and micro porous bioceramic which has an integrated biopolymer top surface. The materials were developed through a MeDe Innovation project led by Professor Kenny Dalgarno at the University of Newcastle.

In another project, based at UCL, Dr Chaozong Liu is working to repair large osteochondral defects using a functionally biomimetic scaffold made from a titanium and polymer matrix. The project received initial funding via a MeDe Innovation feasibility award, before progressing to proof of concept stage with funding from the IKC and Arthritis Research UK. Further support from Innovate UK will now enable Dr Liu to take the technology forward into a clinical trial.

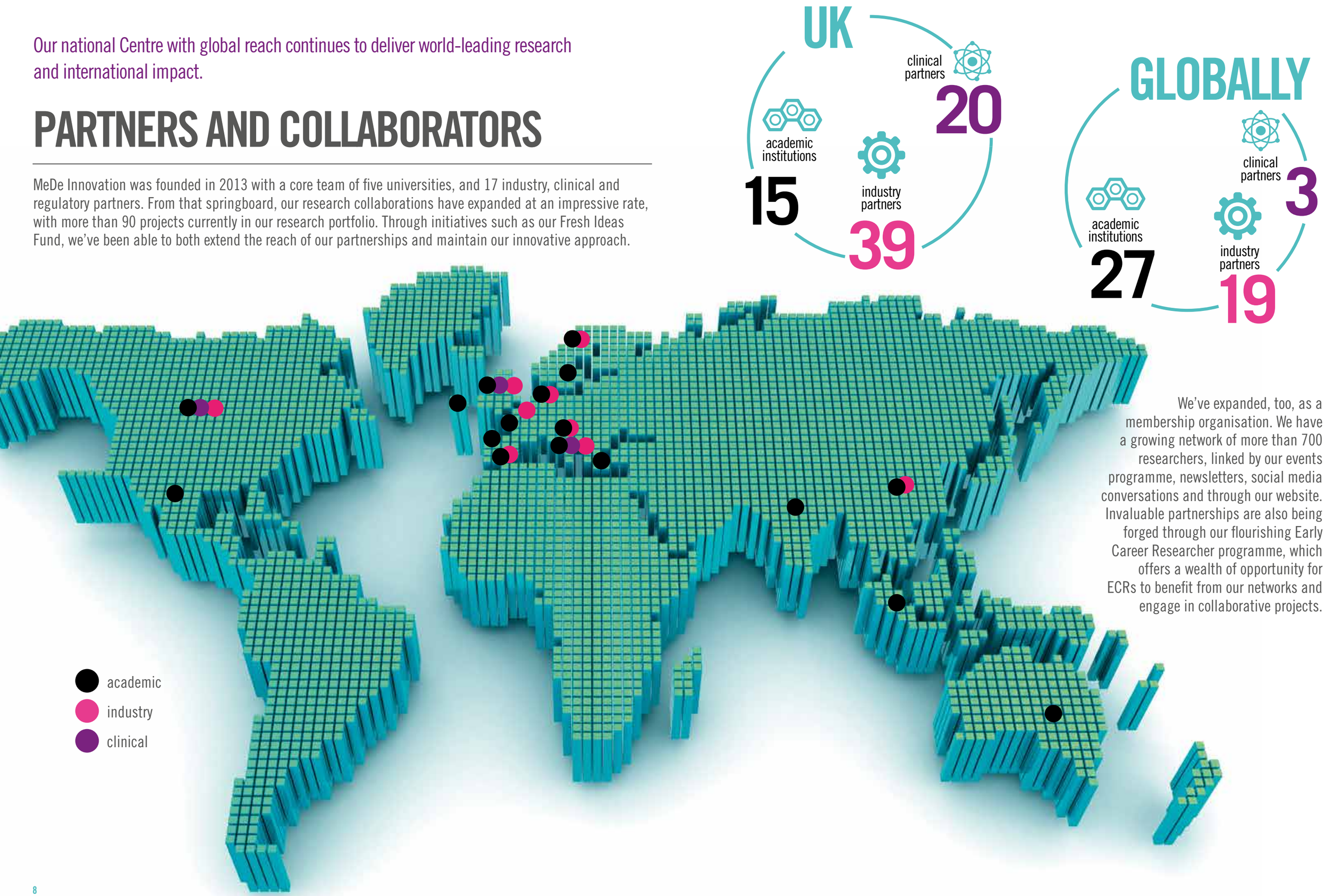


Our industry partners have also been instrumental in progressing MeDe Innovation projects beyond Technology Readiness Level 3, by supporting design development and manufacture and creating commercial value. These include development projects by our partners DePuy Synthes, Invibio, NHS Blood and Transplant, Tissue Regenix Group plc, Biocomposites, Simulation Solutions, Mathys AG, Ceramisys and Surgical Dynamics.

Our national Centre with global reach continues to deliver world-leading research and international impact.

PARTNERS AND COLLABORATORS

MeDe Innovation was founded in 2013 with a core team of five universities, and 17 industry, clinical and regulatory partners. From that springboard, our research collaborations have expanded at an impressive rate, with more than 90 projects currently in our research portfolio. Through initiatives such as our Fresh Ideas Fund, we've been able to both extend the reach of our partnerships and maintain our innovative approach.



We've expanded, too, as a membership organisation. We have a growing network of more than 700 researchers, linked by our events programme, newsletters, social media conversations and through our website. Invaluable partnerships are also being forged through our flourishing Early Career Researcher programme, which offers a wealth of opportunity for ECRs to benefit from our networks and engage in collaborative projects.

MeDe Innovation researchers are tackling challenges that by their nature are global. Our success in developing solutions to these challenges depends on the strength and quality of our international collaborations, from academic research to clinical implementation.

INTERNATIONAL ENGAGEMENT

We are building research capacity and capability through our international co-operations, adding to the extensive MeDe Innovation UK network. Our research collaborations now extend across Europe, North America, Asia and Australia.

Of particular note are our strong and growing networks in China. Engagement with the RCUK Science Bridges China programme, in collaboration with the University of Bradford, has led to a joint annual conference, Early Career Researcher workshops and a range of ECR research exchanges. We've also established a joint Engineering School with Southwest Jiaotong University in Chengdu, China. Led by Professor Zhongmin Jin, formerly Professor at the University of Leeds, this will form the basis of future research and training initiatives and a pipeline for future international researchers.

In industry, our work continues to have international impact. Working with Simulation Solutions, our expertise in both virtual simulation methods and pre-clinical experimental simulation has been translated into simulation equipment that is being sold all over the world.

In addition, MeDe Innovation researchers have both led and contributed to two new draft international standards and protocols for the pre-clinical testing of joint replacements, with MeDe Innovation academic Dr Louise Jennings chairing the international committee for testing standards for joint replacements.

IN INDUSTRY, OUR WORK CONTINUES TO HAVE INTERNATIONAL IMPACT. WORKING WITH SIMULATION SOLUTIONS, OUR EXPERTISE IN BOTH VIRTUAL SIMULATION METHODS AND PRE-CLINICAL EXPERIMENTAL SIMULATION HAS BEEN TRANSLATED INTO SIMULATION EQUIPMENT THAT IS BEING SOLD ALL OVER THE WORLD

CASE STUDY

Science Bridges China

Our Science Bridges China platform has seen considerable growth and deepening of relationships – it has become 'people bridges' to the mutual benefit of the UK and China. I believe that the involvement of MeDe Innovation over the past few years has provided a step change in bringing more top level UK and Chinese groups together, addressing exciting and highly relevant healthcare technologies of particular relevance to ageing populations.

PROFESSOR PHIL COATES

The Science Bridges China programme, founded by Research Councils UK in 2009, works to encourage international academic collaboration and links with clinicians and business.

Professor Phil Coates, MeDe Innovation Executive Board member and Director of the Polymer IRC at the University of Bradford, directs the RCUK Science Bridges China Advanced Materials for Healthcare platform. He has established the UK-China Advanced Materials Research Institute with leading Chinese partners, a virtual platform designed to foster collaboration between researchers, co-directed by Professor Guangxian Li, Senior Executive Vice-President of Sichuan University.

To date, three Joint International Research Laboratories have been formed between Bradford and Sichuan University, the Changchun Institute of Chemistry, Chinese Academy of Sciences and Beijing University of Chemical Technology. A number of events have been organised by the Institute, including a research workshops and over 40 ECR research exchanges. The platform has led to significant funding in collaborative programmes in China and the UK, led by Chinese partners and the University of Bradford, which draw in other leading groups from around the world.

MeDe Innovation has become a significant presence in this platform. A Newton Early Career Workshop was held in China in December 2016, designed to address the growing healthcare needs of ageing populations in China and the UK.

One key output from the workshop – notable for its sheer energy and desire to develop collaboration – was the competitive award of 13 researcher exchanges, each lasting up to one month, sponsored by MeDe Innovation, the University of Bradford and Chinese partners.

Chinese and UK researchers attending the workshop were able to bid for the opportunity to undertake an exchange visit to a MeDe Innovation partner university, with potential further collaboration with other institutions. The expectation is that high level joint publications will follow, and fuller collaborations develop.

Six further one-month research exchange opportunities will be offered following our most recent research workshop in July 2017.

ADVANCES BASED ON NEW RESEARCH IN THE ENGINEERING AND PHYSICAL SCIENCES WILL REVOLUTIONISE OUR ABILITY TO MANAGE OUR OWN HEALTH, HELP US TO MAINTAIN HEALTHIER BEHAVIOURS AND ENVIRONMENTS, AND TRANSFORM THE WAY CARE IS DELIVERED. NOVEL TECHNOLOGIES AND MATERIALS WILL CONTINUE TO IMPROVE OUR ABILITY TO PREDICT, DIAGNOSE AND TREAT DISEASE. RESEARCH WILL DELIVER BETTER QUALITY OF LIFE, HIGHER STANDARDS OF AFFORDABLE CARE AND WILL DRIVE UK GROWTH THROUGH NEW PRODUCTS AND SERVICES

EPSRC STRATEGY AND DELIVERY PLAN – PROSPERITY OUTCOMES: HEALTHY NATION

OUR RESEARCH: CASE STUDIES

THEME 1A

Stratified design and manufacture of joint replacements

Artificial hip and knee joints are among the most successful orthopaedic surgical interventions today, but they do not meet the needs of an increasingly active, ageing population. This has created a growing demand and expectation that joint replacements should last their lifetime, yet for patients in their 50s, the revision rate for hip replacement over their lifetime is 30% – and for knee replacements, this rises to 35%.

OUR RESEARCH

The future of truly stratified design and manufacture of joint replacements lies in marrying combinations of different technologies with a clearer understanding of the patient. We're already working towards that, and with better diagnostics, better characterising of disease states and patient need, we can differentiate and target interventions more specifically to improve outcomes.

PROFESSOR JOHN FISHER

Improving the reliability and lifetime of joint replacements involves not just the application of new and emerging technologies to existing devices and the design and manufacture of new products; crucially, it also needs to consider variations in surgical positioning and patient needs – and a much more sophisticated stratification of patient populations and activities.

These multiple variables present complex challenges to both researchers and to industry in addressing the growing demand for 50 active years after 50®.

To support the medical device industry's response to this global clinical and economic need, we are advancing methodologies for the simulation, design and preclinical testing of hip and knee prostheses. This is enabling us to increase the precision and reliability – and improve long-term outcomes – of hip and knee replacements and we're now taking similar approaches in developing methodologies for ankle joints and spinal interventions.

Our advanced simulation methodologies have been adopted by industry in the development of new prostheses and MeDe Innovation researchers have led and contributed to two new international standards for the pre-clinical testing of hip and knee replacements. Our collaboration with Simulation Solutions now sees our simulators being sold around the world.

Our experimental natural knee simulation system – the first of its kind – offers pre-clinical simulation of the biomechanical and tribological function of new tissue sparing devices we are developing, which will aid the design, manufacture and testing of new products.

Ultimately, we expect to see manufactured devices that are enhanced with digitally-enabled technologies that will aid their surgical positioning, performance and longevity. Our virtual simulation systems which are already being used to help design new products are one step towards that goal.

THEME 1A

CASE STUDY

Hip prostheses

Our goal is to advance methods for simulation, design and pre-clinical testing of hip prostheses to address variations in surgical positioning and patient anatomy.

These variations, alongside device design and patient activities, have a significant influence on the function, performance and lifetime of a hip joint replacement. With a revision rate of 30% in the younger, active population, there is a distinct clinical and economic need to deliver improvements.

Our experimental and computational simulation systems are the most advanced in the world. They can be used to control variables during the design, pre-clinical testing and patient delivery stages. They can also be used to predict the effect these variables will have on function and performance, enabling us to increase the precision and reliability of devices – and ultimately improving the long-term outcomes of hip joint replacements for different patient groups.

More specifically, our recent collaborative work with Simulation Solutions includes the development and validation of enhanced hip joint simulation equipment and experimental methods to investigate the effect of differential surgical positioning of components on friction, wear and fatigue of hip prostheses.

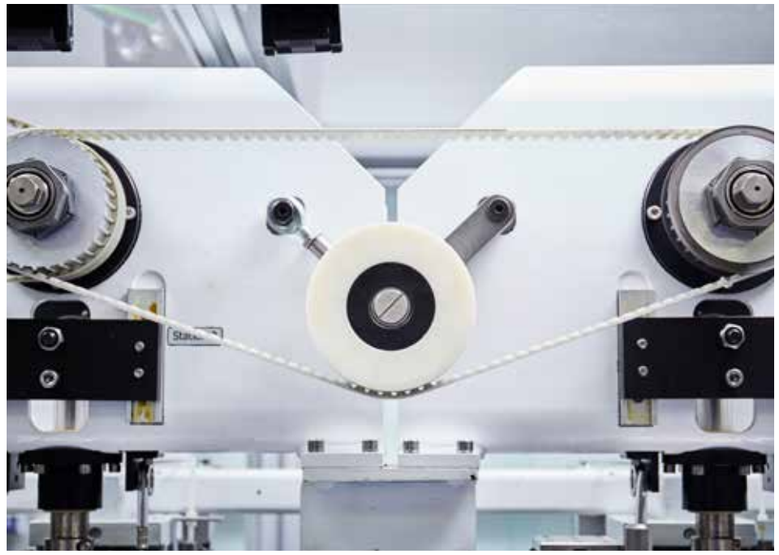
Alongside our industry partners, DePuy Synthes and Mathys, we're applying these advanced methods to both existing prostheses and new designs.

We've developed enhanced dynamic computational models that are able to predict the effect of surgical positioning on the contact mechanics and the material stresses and strains of hip prostheses. We have also delivered a world-first in combining biomechanical, tribological and surgical factors to predict function in pre-clinical simulations.

Our expertise continues to impact on the international community, with MeDe Innovation researchers leading and contributing to the drafting of new international standards for pre-clinical testing of hip prostheses. Our collaboration with Simulation Solutions is now seeing our co-developed simulators being sold around the world.

The next phase of our work see us move towards experimental simulations from a 3D perspective. To date we have used the input of motion and forces on five axes which do not include forces acting at the hip in the anterior/posterior direction. EPSRC's investment in four new 6-axis hip joint simulators will support this, and research is already underway in collaboration with DePuy Synthes and Simulation Solutions.

OUR EXPERTISE CONTINUES TO IMPACT ON THE INTERNATIONAL COMMUNITY, WITH MEDE INNOVATION RESEARCHERS LEADING AND CONTRIBUTING TO THE DRAFTING OF NEW INTERNATIONAL STANDARDS FOR PRE-CLINICAL TESTING OF HIP PROSTHESES



THEME 1A

CASE STUDY

Knee prostheses

THIS IS THE FIRST TIME THAT PREDICTIVE MODELS OF THE EFFECT OF KINEMATIC CONDITIONS ON CONTACT STRESS AND CROSS SHEAR ON WEAR HAVE BEEN POSSIBLE IN KNEE PROSTHESES, AND WE HAVE VALIDATED THESE PREDICTIONS WITH INDEPENDENT EXPERIMENTAL SIMULATIONS AND MEASUREMENTS

Despite the prevalence of joint replacements to treat osteoarthritis in the knee, functional outcomes do not meet the expectations of many patients and well over a third of prostheses need revision in the lifetime of younger, more active patients in their 50s.

These poorer outcomes in terms of function and performance are influenced by the design of the prostheses, but more importantly by the anatomy of the patient and the sheer range of physical activities they expect to be able to regain or maintain.

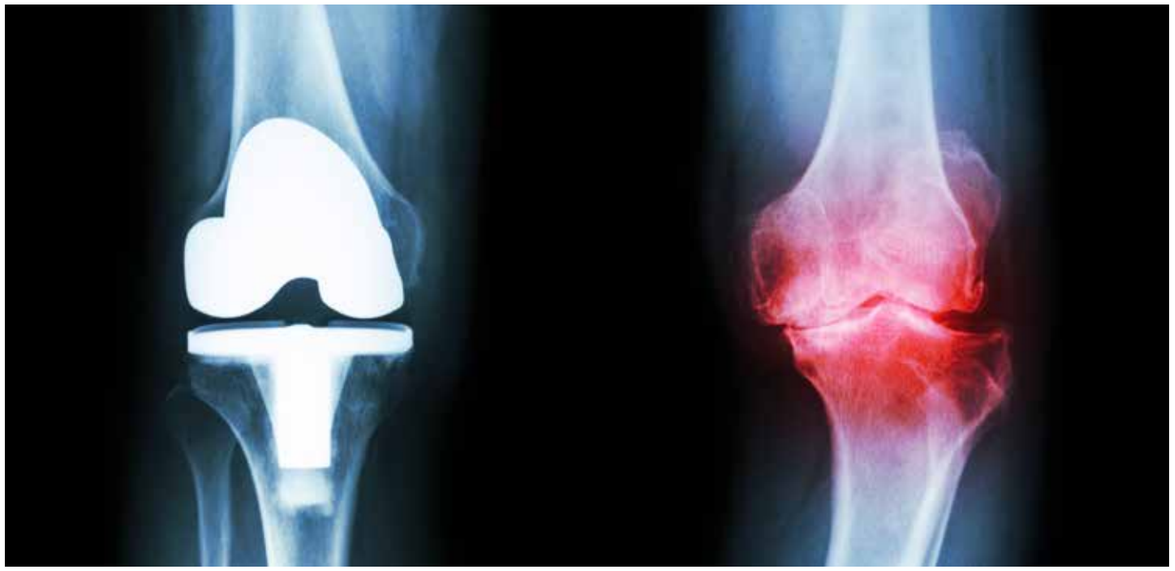
Current prosthesis designs have been primarily evaluated under a single set of kinematic conditions but, when used clinically, this is clearly at odds with diverse patient populations with a much greater range of kinematic demands and motions.

We are developing enhanced simulation equipment and experimental and computational methods to investigate the effect of different kinematics on the wear and performance of knee prostheses. Not only are we applying these methods to evaluate existing devices, we're working with industry partners to apply them during the design, pre-clinical testing and patient delivery of new prosthesis designs, enabling us to work towards knee joint replacements that meet patient expectations and last their lifetime.

We've produced enhanced dynamic computational simulations to predict the effect of different kinematics on contact mechanics, material stresses and strains and wear of knee prostheses, leading to the development of new computational wear models. This is the first time that predictive models of the effect of kinematic conditions on contact stress and cross shear on wear have been possible in knee prostheses, and we have validated these predictions with independent experimental simulations and measurements.

In industry, Biocomposites is using our simulation methods in studies to support new product development and Invibio has adopted our methods to generate evidence for its product design dossier and to support regulatory approvals of its new PEEK all-polymer knee which is to be rolled out into global clinical trials.

Our long-standing collaboration with Simulation Solutions has led to the manufacture and commercial sale of new electro-mechanical knee simulators to the UK, Europe and Asia.



THEME 1A

CASE STUDY

Tissue sparing orthopaedic devices

TO SUPPORT THIS IMPORTANT AREA OF RESEARCH, WE HAVE DEVELOPED AND VALIDATED THE WORLD'S FIRST EXPERIMENTAL NATURAL KNEE SIMULATION SYSTEM WHICH CAN USED TO PRE-CLINICALLY EVALUATE THE BIOMECHANICAL AND TRIBOLOGICAL FUNCTION OF THESE DEVICES IN THE NATURAL KNEE

MeDe Innovation researchers are developing next-generation tissue sparing interventions in the natural knee joint in the form of biological scaffolds and other regenerative therapies.

Intended for use as earlier interventions to treat osteoarthritis and traumatic injuries often caused by sports activity (see theme 1B), these show great promise in helping to avoid full knee replacement surgeries. However, to be fully effective, there's a clear need to match these interventions to the native properties and function of the individual patient's knee.

The advent and progress in the development of these tissue sparing interventions has presented new and significant challenges for testing in natural tissue, with pre-clinical simulation of biomechanical and tribological functions being critical to the success of their design, development, manufacture and implantation.

To support this important area of research, we have developed and validated the world's first experimental natural knee simulation system which can used to pre-clinically evaluate the biomechanical and tribological function of these devices in the natural knee. This is supported by the development of advanced biphasic computational models of the human knee.

This work has included the successful development and evaluation of experimental models for the simulation of ligament constraints and the development and evaluation of standard operating procedures for evaluating osteochondral grafts. We have validated the computational models and used these to complete initial studies of the function of allograft and synthetic osteochondral grafts.

Although it's too early to show patient benefits from this research, the methods we've developed have been translated for use by industry with simulators co-created with our partner Simulation Solutions that are being sold commercially. We are continuing to advance the simulation system to help realise the potential of innovations in tissue sparing interventions that are being developed by other research groups across the UK. ■

THEME 1B

Stratified bioprocesses for the manufacture of acellular scaffolds

Soft tissue damage to the knee is a common and debilitating problem, particularly for young and otherwise healthy adults who participate in sports. Our research seeks to produce a next-generation treatment for these types of injuries, which are currently repaired using autograft or allograft donations. Acellular biological scaffolds offer an off-the-shelf solution that can be used without taking tissue from other parts of a patient's body and so avoiding the additional damage this can cause. They also do not carry the same risk of immunological rejection of grafts from donated tissue.

OUR RESEARCH

> We have moved from creating scaffolds for relatively simple thin tissues to producing composite scaffolds that are showing excellent integration and healing.
>
> PROFESSOR EILEEN INGHAM

We are developing acellular scaffolds for osteochondral, ligament and meniscus repair and replacement. These include both single tissue scaffolds and composite scaffolds, comprising soft tissue and bone in a single graft, which helps to improve integration into the recipient site.

For such grafts to be used clinically, manufacturers need to be able to produce scaffolds with well-defined properties that can be matched to the patient's needs. Our work has focused on refining the processes needed to reliably source, process and sterilise scaffolds without adversely affecting the biomechanical properties or the capacity for recellularisation following implantation.

The knowledge and processes developed under this theme are being used by our partners in ongoing clinical trials and to develop Good Manufacturing Practice processes by NHS Blood and Transplant Tissue & Eye Services.

There is still further work to be done on refining grafts so they can be better matched to patient populations by varying the size, shape and mechanical properties of the harvested tissue.

Scaffolds can also be treated to increase or reduce the mechanical properties to more closely match the patient's tissue. This will be done with the aim of providing a wider range of off-the-shelf solutions that are suitable for the patient's sex, size and lifestyle.

THE KNOWLEDGE AND PROCESSES DEVELOPED UNDER THIS THEME ARE BEING USED BY OUR PARTNERS IN ONGOING CLINICAL TRIALS AND TO DEVELOP GOOD MANUFACTURING PRACTICE PROCESSES BY NHS BLOOD AND TRANSPLANT TISSUE & EYE SERVICES

THEME 1B

CASE STUDY

Ligament repair

Injuries to the anterior cruciate ligament (ACL) are a common sporting injury, resulting in loss of stability in the knee. They account for around 40% of all sports injuries and in the USA over 70,000 ACL reconstructions are performed annually. Most procedures use autograft transplants from a healthy tendon elsewhere in the patient's body while a smaller number use donor tissue from a deceased donor.

Allografts can reduce operating time and the need to damage another tissue site, but they bring problems with immune rejection and limited availability. Our goal is to develop acellular xenogeneic tendon scaffolds for ACL replacement, providing an off-the-shelf product to match surgical and patient needs.

The porcine superflexor tendon was identified as having the appropriate structure and properties for developing a decellularised class III medical device for use in ACL reconstruction. A bioprocess for removing the living cells from the porcine superflexor tendon was developed. This was evaluated over a six month period in sheep, where it showed good functional performance and there was evidence of regeneration.

The know-how from this research was transferred to Tissue Regenix Group Plc who began a clinical trial of OrthoPure XT, a decellularised porcine tendon implant, in 2015 and they remain on track to gain CE marking in Europe.

Our research has continued to examine the effects of variables in the decellularisation process on the biomechanical properties of the resulting scaffolds. This has included looking at the effects of different methods for reducing fat content and bioburden during the bioprocess. Sterilisation with gamma ray irradiation was also found to have some effect on the biomechanical properties of the acellular tendons, but they still retained sufficient strength and flexibility to be used as an ACL replacement. We are also continuing to analyse the cellular mechanisms of regeneration and integration after a graft has been implanted in a joint.

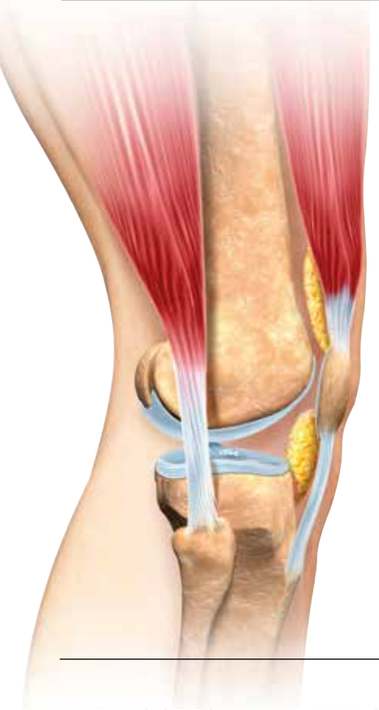
There is still research to be done to determine how we can better match grafts to patients. The ACL can vary greatly between a young female runner, for example, and a young male rugby player. We will explore how varying the age of the pigs the donor tissue is taken from and the bioprocess used to create the acellular implants can better tune ACL replacements to the patient's body.

OUR GOAL IS TO DEVELOP ACELLULAR XENOGENEIC TENDON SCAFFOLDS FOR ACL REPLACEMENT, PROVIDING AN OFF-THE-SHELF PRODUCT TO MATCH SURGICAL AND PATIENT NEEDS

THEME 1B

CASE STUDY

Ligament replacement



The majority of anterior cruciate ligament (ACL) reconstructions are carried out using either bone-patellar tendon-bone (BPTB) or hamstring tendon autograft. Our research has been aimed at developing off-the-shelf acellular allogenic bone-tendon-bone biological scaffolds for ACL replacement.

We have developed processes for the decellularisation of BPTB grafts from human cadaveric donors. By pre-treating the bone and using additional washing, it is possible to decellularise both the hard and soft tissue equally so they can be implanted. Our work allowed us to incorporate approved reagents into the processes, establish microbial monitoring procedures and gain an understanding of how variations in the duration of washes affect the robustness of the process.

These procedures have been transferred to our partners at NHS Blood and Transplant Tissue & Eye Services, who are now working with us to develop a manufacturing process that conforms to Good Manufacturing Practices. When complete, this will allow clinical trials of human BPTB scaffolds for ACL replacement to go ahead and it could provide a new treatment for UK orthopaedic surgeons.

Meanwhile, our work has shown that while additional processing of grafts – such as using acetone to reduce the lipid content and sterilising with gamma irradiation – can reduce the biomechanical properties of the resulting acellular graft, these are still within range of human ACL.

Trials of acellular BPTB scaffolds in sheep have shown excellent functional performance over a six month period along with demonstrating their regenerative capacity. Evaluation of the cell infiltrate during regeneration is now ongoing.

Further work is underway to evaluate different surgical fixation methods. This will include evaluation in a natural knee joint simulator and virtual models to predict function. Work has also started with NHS Blood and Transplant Tissue & Eye Services to develop a novel chemical sterilisation process for the scaffolds.

TRIALS OF ACELLULAR BPTB SCAFFOLDS IN SHEEP HAVE SHOWN EXCELLENT FUNCTIONAL PERFORMANCE OVER A SIX MONTH PERIOD ALONG WITH DEMONSTRATING THEIR REGENERATIVE CAPACITY. EVALUATION OF THE CELL INFILTRATE DURING REGENERATION IS NOW ONGOING

THEME 1B

CASE STUDY

Osteochondral scaffolds

Osteoarthritis is the progressive deterioration of articular cartilage, which can lead to severe pain and loss of mobility in sufferers. It is one of the most common joint disorders and is the second cause of disability in the UK. In the USA it is found in 10% of men and 13% of women over the age of 60, accounting for more than 27 million people.

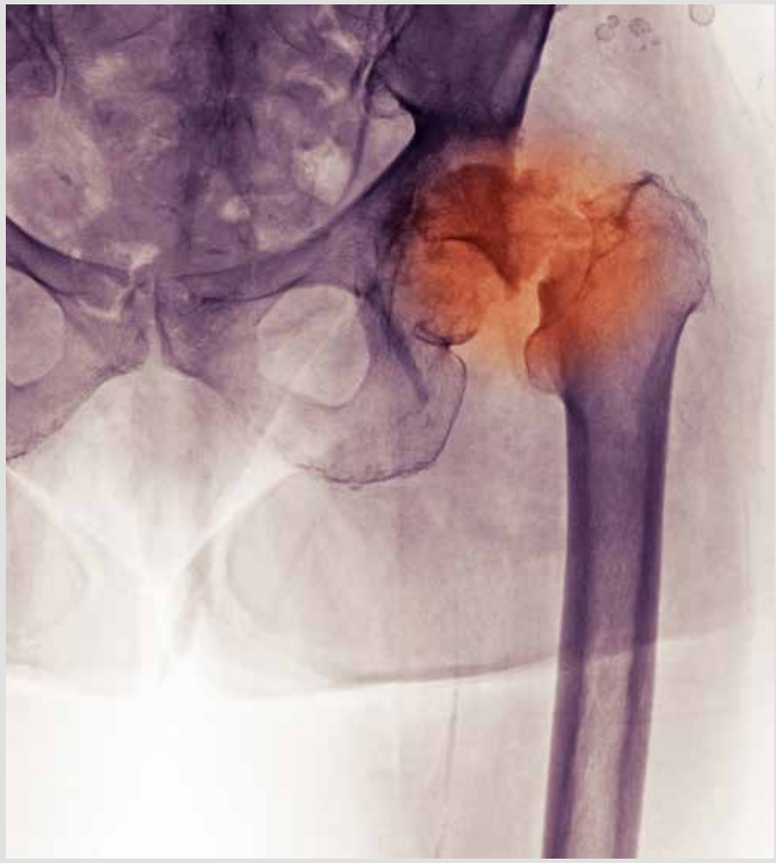
One of the leading causes of early onset osteoarthritis is injury, particularly among younger people who are engaged in sports. Damage to the cartilage, which occurs most often in the knee, is unable to heal and leads to a progressive deterioration. An estimated 10,000 people in the UK suffer knee injuries each year that require cartilage repair surgery. Globally there are more than 2.4 million procedures to repair cartilage lesions carried out annually. Cartilage allografts are currently rarely performed as the high water content of the tissue means it cannot be easily cryopreserved or frozen, making storage difficult.

To overcome this, our research aims to develop off-the-shelf acellular osteochondral scaffolds that can be implanted to restore cartilage function and encourage regeneration over time that will, in the long term, either delay or even prevent the onset of osteoarthritis.

Our research has investigated the properties of cartilage from different animal species and joints to find those that are most appropriate for implantation in the human knee. This identified two potential sources and led us to focus on tissue from young healthy pigs.

In order to get good cartilage replacement, however, our work determined that both bone and cartilage would need to be harvested to produce composite scaffolds. This can help to ensure the graft will fix sufficiently to allow it to integrate.

While acellular porcine bone shows excellent integration into sheep condyles over a 12-week period, the bioprocesses needed to decellularise osteochondral plugs caused the cartilage to be damaged. To overcome this, a new bioprocess was developed to decellularise whole pig knee joint condyles while allowing the integrity of the cartilage to be retained. This involved additional washing steps and treatment of the bone component prior to the standard washing process.



Acellular osteochondral grafts produced in this way will be implanted into sheep for 12 months to allow evaluation of these implants. Sterilisation methods will also be evaluated in future work, as will the confluency of grafts in joints. We also have funding to support the translation of the methods and knowledge to human donor tissue for use by the NHS. ■

OUR RESEARCH HAS INVESTIGATED THE PROPERTIES OF CARTILAGE FROM DIFFERENT ANIMAL SPECIES AND JOINTS TO FIND THOSE THAT ARE MOST APPROPRIATE FOR IMPLANTATION IN THE HUMAN KNEE. THIS IDENTIFIED TWO POTENTIAL SOURCES AND LED US TO FOCUS ON TISSUE FROM YOUNG HEALTHY PIGS

THEME 1C

Stratified design and manufacture of nonwoven collagen scaffolds

As the main structural protein in most hard and soft tissues in the human body, collagen has great potential for use as scaffolds in regenerative medicine. It has low immunogenicity, a fibrillary structure, good biocompatibility and will biodegrade, avoiding the need for surgical procedures to remove it at a later stage. Industrially processed collagen scaffolds can, however, lack mechanical strength and stability when hydrated, which limits their usability. Our research has sought to develop manufacturing and synthetic processes that can overcome these limitations, while maintaining the other natural properties of collagen in a reliable way.

OUR RESEARCH

Our multiscale manufacturing platform has allowed us to use the same chemistry to make prototype devices with different properties that are designed to meet the demands for each clinical application.

PROFESSOR STEPHEN RUSSELL

The multiscale manufacturing platform we have produced allows precise control of the physical properties and chemical architecture of this important biomaterial so that performance can be customised to meet specific clinical requirements. This allows collagen systems to be produced in a wide range of formats, from the molecular up to the macroscopic scale, and with physical properties that can be tuned to meet different clinical demands.

This can be done either at the manufacturing stage or at the point of delivery in order to meet the needs of patients. Importantly, the collagen system can be realised in nonwoven formats that are already familiar to clinicians and patients, meaning there is no need to learn new techniques for manipulating these products.

The flexibility of our manufacturing platform has allowed us to work with clinicians on a number of different applications. Initially, we have developed solutions for guided bone repair in maxillofacial surgery and hydrogel films for use in wound care. We are now working towards studies that will aid the translation of these into the clinic. There is also work underway to investigate the use of collagen-based nonwoven fabrics for bone repair at other sites.

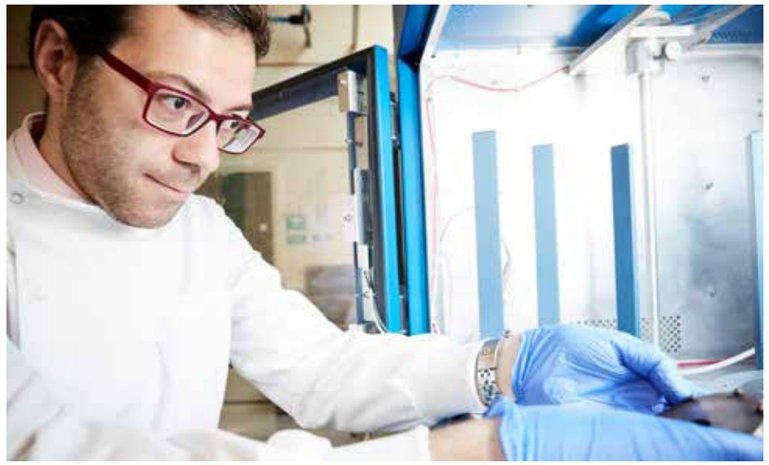
Our future work includes exploring the properties of the new photoactive atelocollagen materials produced by our platform, including their ability to control microbial activity. Alongside this, we are continuing development of a wet-spinning manufacturing platform to ensure fibres can be produced consistently. We are also planning to address the scalability of our manufacturing process as well as ensuring it meets Good Manufacturing Practice.

INITIALLY, WE HAVE DEVELOPED SOLUTIONS FOR GUIDED BONE REPAIR IN MAXILLOFACIAL SURGERY AND HYDROGEL FILMS FOR USE IN WOUND CARE

THEME 1C

CASE STUDY

Multiscale manufacturing platform for photoactive collagen-based scaffolds



Collagen scaffolds are used extensively for tissue regeneration both as a way of maintaining structure and delivering cells for repair. For some uses, however, collagen can degrade too rapidly after implantation to allow adequate repair to take place. Our goal was to develop a novel, multiscale manufacturing platform that would enable the formation of collagen systems with its native triple helix structure still intact, but would allow the stability of the scaffold product to be tuned as desired.

WE ARE IN THE EARLY STAGES OF PRODUCING 'STEM CELL BANDAGES', WHERE COLLAGEN-BASED FABRICS CAN BE LOADED WITH STEM CELLS AND WRAPPED AROUND BONE LESIONS. THIS CAN DELIVER STEM CELLS TO THE SITE OF A DEFECT TO AID REGENERATION WHILE ALSO PROVIDING A PHYSICAL BARRIER TO KEEP SOFT TISSUE FROM INTRUDING

Our process introduces photosensitive organic compounds to the lysine groups on the backbone of atelocollagen in a way that does not denature the collagen structure. Exposure to ultraviolet or blue light then causes covalent cross-linking between the collagen triple helices, resulting in an increase in the stability of biomaterial. This can be achieved using commercially available ultraviolet lights and is similar to the curing of resin-based dental materials using blue light. This means that the physical stability of the collagen structure can be modified during manufacture and also by surgeons in the clinic.

Our process also allows us to produce a number of clinically useful forms of functionalised atelocollagen, including fibres, filaments, yarns, nonwoven fabrics, films and hydrogels. These can be produced with unusual property combinations not found in natural collagen, including a high degree of swelling without a significant loss of stability. We have been able to produce collagen hydrogels that can swell as much as commercially available hydrogels but have three times the compressive strength, meaning the material is easier to handle. This is an important factor in the clinic.

Among the applications we are developing with our clinical partners is a biomaterial for guided bone regeneration in periodontal surgery. Dental surgeons require bone to secure implants and so need to encourage regeneration in cavities where bone has been lost. Our approach uses collagen to create a membrane that can be placed over the bone cavity to prevent soft tissue from growing into the space, hampering bone regeneration.

Our manufacturing process produces membranes that can last over four weeks, in contrast to commercially-available dental membranes, which vary greatly in when they fail. We are currently conducting pre-clinical in vivo studies that will pave the way for the first human clinical studies in collaboration with the Institute of Dentistry at Queen Mary University of London.

Our platform also allows us to produce larger scaffolds that are more suited to wound healing. By creating atelocollagen fibres that can be assembled into nonwoven fabrics, these can be applied as a wound dressing, helping to manage the moisture levels and so aid healing. These nonwoven fabric assemblies not only combine the stable swelling capacity of our atelocollagen, but the fabric itself is also porous, giving the material a high absorbent capacity while remaining strong enough to be used as a dressing. These dressings have shown accelerated wound healing in vivo in comparison to commercial benchmark products. There are plans for a first-in-human pilot study of this material on digital ulcers in scleroderma patients, in collaboration with Chapel Allerton Hospital in Leeds.

We are in the early stages of producing 'stem cell bandages', where collagen-based fabrics can be loaded with stem cells and wrapped around bone lesions. This can deliver stem cells to the site of a defect to aid regeneration while also providing a physical barrier to keep soft tissue from intruding. We will also continue research to explore the ability of atelocollagen materials to control microbial activity and regulate matrix metalloproteinases, which play a key role in wound healing. Further work will also be done in the future on ensuring the long term reliability and consistency of wet spinning of atelocollagen fibres. ■

THEME 1D

Manufacture of fully bioresorbable multiphase fixation devices to order

Repairs to hard tissue often require metallic pins, screws and plates to be surgically implanted to allow healing. These fixation devices can then require further surgery at a later stage to remove them. This carries inherent risks to the patient, so it is attractive to instead use fully resorbable devices that will be replaced over time by cells. One of the main hurdles to achieving this is the different degradation rates that can occur with resorbable devices, which can often lead to premature loss of mechanical properties, preventing proper integration and tissue remodelling.

OUR RESEARCH

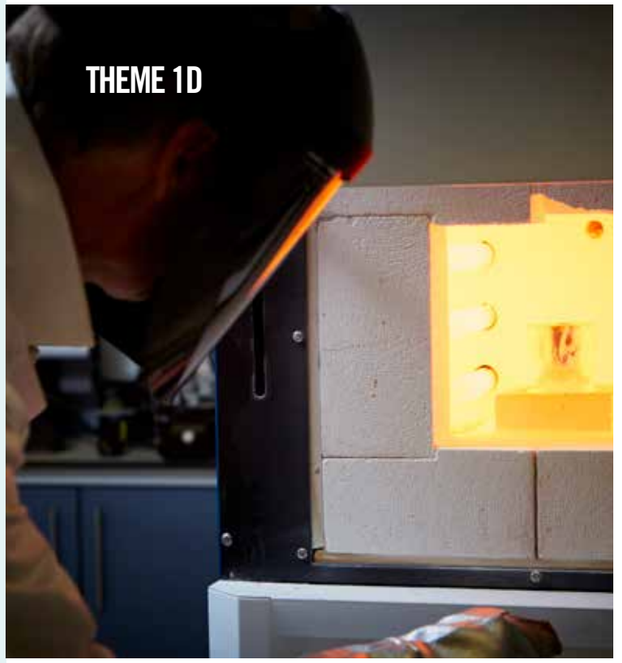
Our research is developing manufacturing technologies for glasses where the resorption rate can be controlled to avoid this loss of mechanical properties too early. This has allowed us to create next-generation multiphase materials and devices that can progressively be resorbed, allowing a gradual replacement of the composite fibres with cells.

The initial applications are in orthopaedic fixation and repair, but we are also exploring other applications for these resorbable glasses. We have developed processes that can apply the glasses as coatings for medical implants and this work is now developing into new areas, such as creating sacrificial layers or layers with antimicrobial activity. Another innovative manufacturing process we have developed also produces glass microspheres for use in repairing damaged bone tissue.

We are also developing computational models to produce three dimensional images from a range of different medical imaging technologies. These detailed 3D models can then be used to enable the design and manufacture of patient-specific implants or surgical tools. The imaging can also be used post-surgery to assess the performance of an implant. We have been working with partners in business to develop medical devices using this technology and have applied for a patent.

We have also developed new cost effective manufacturing processes to produce multiphase biopolymer scaffolds which do not delaminate and have controllable pore sizes along their length with sufficient elasticity to be delivered through a cannula, either wet or dry. The first application we are targeting is an osteochondral plug, which has received further funding to undergo the first stage of pre-clinical trials in vivo.

Other manufacturing initiatives include coating nanoparticles in polymers during processing thereby improving nanoparticle distribution, with collaborations with Promethean Particles. Other collaborations include TESco Associates, Evonik Industry and Thermo Electron, investigating enhancing the manufacture and mechanical properties of these nanocomposite structures.



CASE STUDY

Phosphate-based glass manufacturing technologies

> **Often degradable composites have a rapid drop in mechanical properties due to interfacial problems, but we have now partially solved this by controlling the degradation rate through a combination of advanced manufacturing methods combined with new materials development.**
>
> **PROFESSOR DAVID GRANT**

One major challenge facing the use of resorbable materials in medical implants is the sudden loss of mechanical properties while the degraded product is still present, preventing tissue ingrowth. Instead, it is desirable to have controlled degradation so cells can gradually repopulate an area as the device is resorbed.

Our research has generated phosphate-based glasses where we can tailor the degradation rate by altering their chemical composition. We have produced phosphate-based glass fibres that have varying resorption rates, which can be bundled together, coextruded with degradable polymers and then these bundles manufactured into products. This reduces the rapid degradation of the interface between the fibres and the polymer matrix, producing a composite that has mechanical properties that match human bone. Other manufacturing methods include oscillating compression moulding to prevent porosity and improve interfacial strength between the fibres and the matrix. These methods are being used to manufacture prototype resorbable intramedullary nails, which are currently undergoing testing in vitro.

We have also developed a method for enhancing the surfaces of orthopaedic devices by coating them in phosphate-based glass of differing compositions.

Using plasma-assisted sputtering, we can produce highly reproducible phosphate-based glass layers with thicknesses of a fraction of a nanometre up to several micrometres. This allows coatings to be applied while preserving the fine topography of an implant. We are currently exploring how to use this technique to introduce coating layers with different properties. Sacrificial layers, for example, can be added to protect the implant during handling before degrading to reveal an osteoconducting layer underneath. Similarly, a thin antibacterial layer can be created to help stop microorganisms forming on the surface of implants, reducing the risk of infection. We are now examining the antimicrobial effect of different glasses and how rapid degradation of a surface layer can prevent bacteria from attaching. Our research is being tracked by DePuy Synthes, JRI Orthopaedics and Zimmer Biomet.

We have also used an innovative manufacturing process to produce unique porous glass microspheres from phosphate, borate and silicate glasses. These have potential use in multiple applications, including as a bone filler in regenerative medicine. Patients with low bone density could receive an injection of these microspheres together with their own stem cells to encourage the bone to densify. Animal trials are currently underway and work is ongoing with our industry partners, Surgical Dynamics and Ceramisys, to translate this technology further.

THE VIRTUAL MODELLING DEVELOPED FOR MANUFACTURING MEDICAL DEVICES CAN ALSO BE USED TO HELP ASSESS THE HEALING PROCESS FOLLOWING SURGERY. APPLYING THE ADVANCED PROCESSING AND NOISE REDUCTION TECHNIQUES TO MEDICAL IMAGES HAS MADE IT POSSIBLE TO GENERATE 3D MODELS OF THE TRABECULAR OF THE SPINE, EVEN IF THE MEDICAL IMAGES ARE ONLY JUST SUFFICIENT TO IDENTIFY THESE. THIS CAN ALLOW DETAILED MONITORING OF THE REMODELLING OF BONE GRAFT SUBSTITUTES USED IN SPINAL FUSION

THEME 1D

CASE STUDY

Virtual modelling of the spine

Modern hospitals use a variety of different medical imaging technologies and the combination of these with additive manufacturing techniques offers enormous opportunities for the production of highly patient-specific medical devices and surgical tools. The images needed to create such products, however, need to have a high degree of resolution. We have developed intelligent noise reduction and imaging processing techniques to help generate accurate three dimensional models from medical images. We have also developed analysis and design protocols to ensure that custom medical devices and tools are manufactured with sufficient accuracy to ensure patient safety.

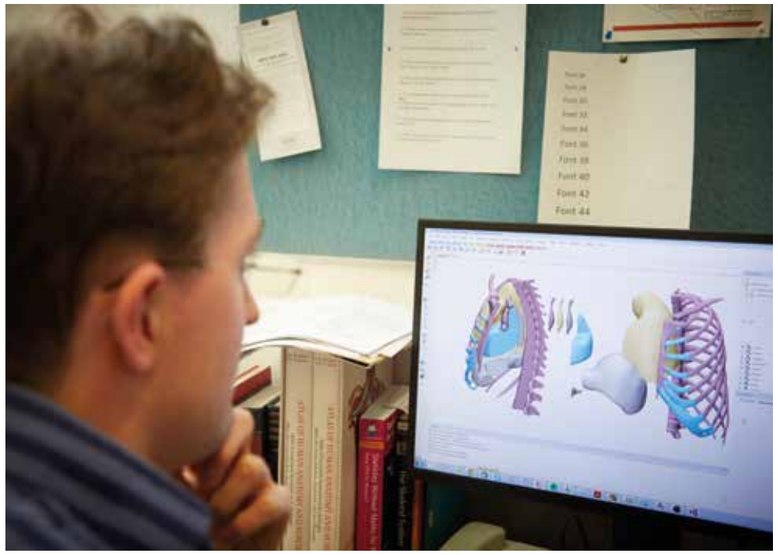
We have used these technologies to pilot new medical device technologies related to spinal surgery, in collaboration with industry partners. Two of these devices are spinal implants created using additive manufacturing or multi-axis CNC milling. These have been evaluated using a combination of pre-clinical testing and computational modelling to assess the impact the design will have on the device and the loading of the patient's tissues. Pre-clinical work is to be conducted with the aim of taking these forward to clinical trials.

We have also demonstrated that the technology can be used to produce devices such as drill guides to enhance accuracy in image-guided and robotic surgery. This offers the potential to enhance patient safety and reduce the time needed to conduct surgery.

The virtual modelling developed for manufacturing medical devices can also be used to help assess the healing process following surgery. Applying the advanced processing and noise reduction techniques to medical images has made it possible to generate 3D models of the trabecular of the spine, even if the medical images are only just sufficient to identify these. This can allow detailed monitoring of the remodelling of bone graft substitutes used in spinal fusion.

Using an MRI-compatible spinal loading device, in combination with MRI imaging sequences and post processing techniques, we have also been able to visualise and quantify the motion of the spine under dynamic loading and assess its deformation.

We also now exploring how the lessons learned from this work in orthopaedics can now be applied to cardiac devices.



THEME 2A

Minimally invasive implantation of bioactive materials

Repairing osteochondral damage can often require open surgery, which carries greater risks of infection and longer recovery times for patients. Creating suitable devices that are strong enough to be load bearing yet small enough to be delivered through minimally invasive procedures is challenging. Our work has focused on developing manufacturing methods to produce new devices that might overcome these difficulties.

OUR RESEARCH

> **Our collaboration with colleagues at the Chinese Academy of Sciences has allowed innovative materials developed in China to be used to create unique products here in the UK.**
>
> PROFESSOR PHIL COATES

> **We have been able to tackle some key manufacturing challenges to produce nanoscale calcium phosphates cheaply so they can be used as an injectable paste for bone regeneration.**
>
> PROFESSOR PAUL HATTON

This has included the manufacture of membranes with enhanced biofunctionality for use in osteochondral repair. By using innovative assembly techniques, we have been able to deliver new properties to these membranes, such as enhancing bone tissue regeneration and drug delivery. This work has led to an unexpected commercial translation as an innovative device for tissue regeneration in oral medicine.

Another approach has been to develop new economic methods for producing nanoscale bioactive materials that can be used as injectable bone graft substitutes. We are now exploring ways of adding new biofunctionality to these commercially important products.

Infections associated with implanted devices can be a serious risk to patients and are a significant burden on health service resources. In an attempt to address this, we have collaborated with partners in Europe on research to design new generations of bioactive glasses with antimicrobial properties. We are now working with commercial partners to develop these further.

We have also developed 3D printing techniques to create bone replacement devices in a range of bioceramic materials that have load bearing capacity while still supporting bone growth. This work has been performed in collaboration with international partners and our work in the future with industry will focus on developing the ability to produce specific devices at a large scale.

WE HAVE ALSO DEVELOPED 3D PRINTING TECHNIQUES TO CREATE BONE REPLACEMENT DEVICES IN A RANGE OF BIOCERAMIC MATERIALS THAT HAVE LOAD BEARING CAPACITY WHILE STILL SUPPORTING BONE GROWTH

THEME 2A

CASE STUDY

Materials development for arthroscopic delivery

WE ARE NOW ALSO EXPLORING WAYS TO INTRODUCE NEW BIOFUNCTIONALITY TO THESE INJECTABLE NANOSCALE CALCIUM PHOSPHATES. THIS RESEARCH, CONDUCTED IN PARTNERSHIP WITH CERAMISYS, IS ATTEMPTING TO ENHANCE THE MATERIAL'S BIOACTIVITY TO FURTHER IMPROVE BONE REGENERATION AND ALSO TO INTRODUCE ANTIMICROBIAL ACTIVITY

Calcium phosphates are well known for their ability to promote bone regeneration in medical implants. Producing them as nanoscale particles is an attractive approach, as this means they can be mixed into a putty or paste that can be injected into a bone defect, allowing repairs to be conducted in a minimally invasive way.

Manufacturing nanoscale calcium phosphates, however, has required complex procedures and is consequently expensive, making this approach prohibitively costly for use in general healthcare settings.

Our research has produced a rapid mix process that can produce medical grade nanoscale hydroxyapatite. Work is now ongoing with our industry partner Ceramisys to scale up this manufacturing process with the aim of producing a commercial product.

We are now also exploring ways to introduce new biofunctionality to these injectable nanoscale calcium phosphates. This research, also conducted in partnership with Ceramisys, is attempting to enhance the material's bioactivity to further improve bone regeneration and also to introduce antimicrobial activity.

The risk of bacterial infection in bone following surgery represents a major clinical threat, especially in elderly patients and in immunocompromised patients. While antibiotics can offer some solution, excessive use of these drugs is undesirable as it can drive antibiotic resistance.

By adding elements to nanoscale calcium phosphates that can suppress pathogens, these innovative materials offer a potential alternative to reducing infection. We have received funding to develop these materials into a new generation of bone graft substitutes for orthopaedic and dental surgery.

THE POROUS SCAFFOLDS PRODUCED IN THIS WAY HAVE BEEN SHOWN TO HAVE MECHANICAL PROPERTIES SIMILAR TO CORTICAL BONE. THE 3D PRINTING PROCESS ALLOWS US TO CREATE MACROSCOPIC CHANNELS WITHIN THE SCAFFOLD, WHICH CAN HELP TO SUPPORT NEW BONE GROWTH AND VASCULARISATION. TESTS IN VITRO HAVE SHOWN THE 3D PRINTED SCAFFOLDS SUPPORT THE GROWTH OF MESENCHYMAL STEM CELLS, WHILE IN VIVO STUDIES IN MICE HAVE SHOWN OSTEOID GROWTH WITHIN POROUS SCAFFOLDS

THEME 2A

CASE STUDY

3D printing of load bearing bioceramic structures

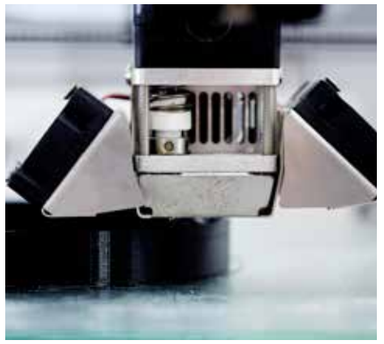
The development of 3D printing has offered the ability to produce highly specific and customised structures on demand. For osteochondral surgery, this presents the possibility of creating implants where both the macro and micro porosity can be controlled, allowing them to be tailored to the needs of the patient in the clinic. Using bioactive materials for 3D printing, however, has meant it has been difficult to produce structures with sufficient load bearing capacity.

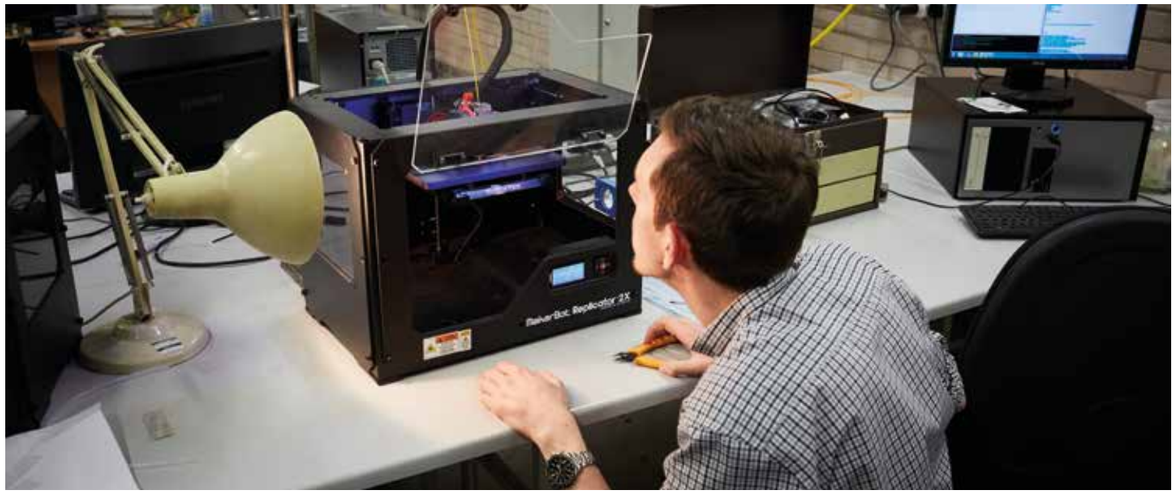
We have used the binder jetting 3D printing process, which uses powdered raw material bonded with a polymer, to create novel bioceramic structures that have load bearing capacity. The composite printed structures are heated in a furnace to burn off the polymer binder and sinter the powder, creating a part that is porous. We have shown that a range of bioceramic materials can be processed, including apatite-wollastonite and silicate glasses.

In a collaboration with the Chinese Academy of Sciences (CAS), we have shown it is possible to process a novel sol-gel synthesised phytic acid-derived bioglass, developed at the CAS Institute of Chemistry in Beijing, into scaffolds. This work involved a highly productive exchange of early career researchers between Newcastle University and the research group in China.

The porous scaffolds produced in this way have been shown to have mechanical properties similar to cortical bone. The 3D printing process allows us to create macroscopic channels within the scaffold, which can help to support new bone growth and vascularisation. Tests in vitro have shown the 3D printed scaffolds support the growth of mesenchymal stem cells, while in vivo studies in mice have shown osteoid growth within porous scaffolds.

The next stages of this work will focus on developing devices for specific applications on a large scale with industry partners.





THEME 2B

Processes for in-clinic manufacture

There is currently no treatment for patients with small defects in hip or knee joints, often meaning these deteriorate over a number of years, leading to osteoarthritis. To repair such defects and prevent deterioration requires implants that can be delivered with minimally invasive surgery.

OUR RESEARCH

Bioprinting in a clinical sense is still an emerging technology. It needs to become much more reliable to the point where it can be put into the hands of people who are not engineers, and made to work all day, every day.

PROFESSOR KENNY DALGARNO

Our research is developing methods for rapidly and reliably combining cells with structural biomaterials so it is possible to create musculoskeletal implants that can be delivered without the need for major surgery. The aim is for implants to be produced, incorporating cells harvested from the patient, as they are being built in the clinic, potentially even during surgery.

To do this, however, requires synthetic and biological materials to be processed alongside each other, reliably and at speed. We are developing cell printing techniques that will enable load bearing, bioactive, personalised osteochondral implants to be produced to meet these demands in the clinic. Part of this has involved developing novel bio-inks that can be co-processed with materials to create implants. This work has also led to a new strand of work developing possible replacements for animal models of osteoarthritis.

Our research has also included developing a new way to 3D print cell-laden hydrogels that can be used to create gel based structures with high precision. Looking forward, we aim to develop bioprinters to the point where they can be used as genuine plug and play systems for use in the clinic.

This will require collaborations with clinicians and colleagues in the biosciences to validate and trial the technology. We have also been researching techniques to create solid and cannulated fixation devices that can be programmed to change shape in situ on exposure to body temperature or body fluid. The aim is to create devices that can used to fix soft tissue to bone, or bone to bone.

THEME 2B

CASE STUDY

Fast, reliable cell printing

While 3D printing technology offers a potentially powerful way of creating customised implants in the clinic, combining these with cells to allow tissue regeneration is challenging. Printing a single cell is understood, but producing cultures of multiple cells brings problems of agglomeration, where the natural tendency of the cells to adhere to surfaces can cause blockages. To overcome this, we have developed a cell encapsulation process that allows droplets of media containing single cells to be deposited using an ink-jet printing technique.

Cells are encapsulated in poly-L-lysine (PLL), which creates a temporary electrically charged shell, preventing the bio-ink from coagulating. The shell breaks down and is resorbed within a few hours, restoring normal function to the cells in the printed structure. This approach has allowed us to reliably print cells at rates of up to 1,000 per second.

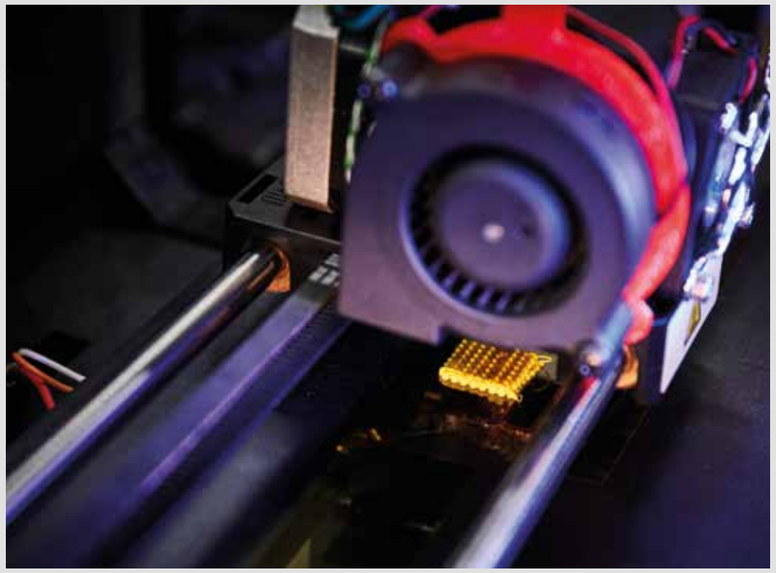
In addition, we have shown that groups of cells can also be deposited through a microvalve printing technique. This research has led us to develop new printhead assemblies, which allow multiple cell types to be dispensed in parallel, allowing the creation of co-cultures. This could eventually lead to the manufacture of entire implants made from multiple cell types in the clinic.

Our research on printing multiple cell types has also opened up new lines of research, where co-cultures can be printed for drug testing or disease modelling. We have just received an award, as part of a collaboration led by Alcyomics, from the National Centre for the Replacement, Refinement and Reduction of Animals in Research to print osteoarthritis-on-a-chip for in vitro testing. The "Osteo-chip" will combine several cell types - osteoblasts, osteoclasts, chondrocytes, synovial cells, immune cells and adipose cells - to mimic the human knee and potentially replace the need for animal models. Osteoarthritis models in animals have limitations and there is a need for more consistent, predictive ways of modelling the disease and testing treatments. This work promises to lead to new collaborations with industry partners.

In the future, we will aim to develop other printed models of cardiac and liver tissue for use in disease modelling and drug testing. We will also continue to develop our printing techniques to produce multicellular microtissues for regenerative medicine.

CELLS ARE ENCAPSULATED IN POLY-L-LYSINE (PLL), WHICH CREATES A TEMPORARY ELECTRICALLY CHARGED SHELL, PREVENTING THE BIO-INK FROM COAGULATING. THE SHELL BREAKS DOWN AND IS RESORBED WITHIN A FEW HOURS, RESTORING NORMAL FUNCTION TO THE CELLS IN THE PRINTED STRUCTURE. THIS APPROACH HAS ALLOWED US TO RELIABLY PRINT CELLS AT RATES OF UP TO 1,000 PER SECOND

THEME 2B



CASE STUDY

Reactive Jet Impingement

Producing hydrogels laden with cells offers an attractive way of creating composite structures that have both soft and hard elements. Depositing a gel onto a bone analogue, such as a bioceramic scaffold, provides a cartilage facing modality that can be embedded with cells.

The most common way of bioprinting a hydrogel structure is to use a syringe based system, but these can suffer from slow rates of deposition and, in some cases, poor cell viability after printing. We have developed a jet impingement process that attempts to overcome these issues and enables cells to be rapidly deposited within hydrogels on other biomaterial substrates.

The process directs two jets of gel precursors at one another in mid-air, where they react and form a gel that lands on the substrate. The advantage of this process is that the gel precursors are much easier to process than finished gels. By having the gel-forming reaction at a late stage, it allows printing to be faster and more reliable. We have printed cells in fibrin gels by mixing thrombin and fibrinogen through two impinging jet flows. It has also been possible to print cells in alginate gels by impinging droplet streams of alginic acid sodium salt solution and calcium chloride solution. We have been able to show that cell-filled gels printed in this way have high viability.

Our work has also led to the manufacture of a multiple jet head that is capable of printing four different materials at once. This provides new levels of control over the kinds of hydrogel structures that can be produced. By varying the gel formation from point to point, for example, it becomes possible to vary the stiffness of the gel. This could prove useful in a clinical setting where it might be desirable to have a stiffer gel on the outside that is robust enough to survive handling during implantation, while inside the gel may be more liquid to help it bond to the harder bone analogue material.

A patent application has now been filed around the Reactive Jet Impingement technology and the methods for controlling the process. This is the first stage towards commercialisation of this new 3D printing process.

Future work will continue to showcase the full capabilities of the process and its ability to create complex, 3D cell-laden cell structures. We are also working on integrating our cell printing technique with hard scaffolds for load bearing applications.

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MeDe Innovation: Future perspectives

Our goal is to enable 50 active years after 50® for an ageing population that expects to remain active for longer. In addressing these societal challenges, we are also supporting the UK's medical device industry in realising the substantial economic opportunities that this presents.

Towards the EPSRC's strategic aims, MeDe Innovation is already providing researchers with an environment in which ideas and innovations can flourish. This is underpinning the expansion of our networks and collaborations and attracting additional funding and investment. Furthermore, we're already seeing how this environment is creating new jobs, new products and services and supporting the UK industry to grow within the global market.

Delivering 21st century medical devices – including biologically enhanced and digitally enabled combination devices, interventions and therapies – will require increased levels of precision and predictability to deliver improved outcomes to more stratified and differentiated patient populations.

Major progress in this regard is expected in the next 5-10 years. The Science and Innovation Audit for the Leeds City Region, which we completed on behalf of BEIS, provides evidence for increased use of devices that combine advanced materials and biological function and the expansion of digital enablement of products and devices – and indeed the whole value chain. This will enable earlier diagnostics, greater precision in surgery and the more detailed collection and analysis of device performance data than ever before, all of which will support a transformation in the sector.

This is exciting because technologies that we're already working on at MeDe Innovation will form part of that transformation: for example, our digital technologies are already enabling advanced modelling and pre-clinical simulations in the design of new products. The technology used to evaluate new products and devices is as important as the technology used to develop them, and we will progress our work in this area so that we can generate the evidence required to support the commercial proposition and use of future products and interventions.

The UK has particular strengths in the development and manufacture of devices to treat patients in orthopaedics, dentistry and wound care. More research is needed to develop and evaluate new processes, methods, tools, systems and equipment to support the overall manufacturing value chain in these areas, which represent 20% of the global Med Tech market by value – and in markets that are set to grow by 50% by 2025. (BEIS Med Tech SIA report 2017).

Through our research into 'Manufacturing Future Medical Devices', MeDe Innovation will continue to bring together many different disciplines and converge existing and emergent technologies to address the medical device industry research needs to underpin all stages of the manufacturing value chain, from diagnosis and clinical need, through system and product design, manufacturing process, pre-clinical evaluation, clinical delivery and clinical evaluation.

Professor John Fisher CBE
Director, MeDe Innovation

Our work would not be possible without our External Advisory Board, comprising global leaders in medical device innovation. The EAB provides us with academic, industrial, clinical and regulatory perspectives, and their insights shape and steer the strategic direction of our programme.

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