# MeDe Innovation

EPSRC Centre for Innovative Manufacturing in Medical Devices

# ANNUAL REVIEW 2018

# CONTENTS



*Front cover image: Rayan Ibrahim Binduhayyim, University of Sheffield*

*Success in a rapidly moving medical devices sector requires game-changing innovation. That means more than producing good research, it's about addressing challenges at every step of the manufacturing value chain, from initial concept through to fully validated clinical product. This comprehensive engagement is what MeDe Innovation delivers.*

**PROFESSOR JOHN FISHER CBE**
**DIRECTOR, MEDE INNOVATION**

# EXECUTIVE SUMMARY

Over the past five years, the EPSRC Centre for Innovative Manufacturing for Medical Devices (MeDe Innovation) has made significant advances in developing a manufacturing research value chain for the 21st century.

From a core grant of £6M and six core university partners, we have leveraged an additional £69M of resources for research and innovation, focusing on four areas of the medical technology market:

- Musculoskeletal regenerative devices and therapies
- Orthopaedics, including total joint replacements
- Wound care and soft tissue reconstruction
- Dental and maxillofacial

Our portfolio includes nearly 100 research projects, involving a critical mass of university, industry and clinical partners.

**KEY ACHIEVEMENTS INCLUDE:**

- Further funding secured for **22 projects** to advance to next stage of technology development.
- Of these, **13 projects** are in commercial product development, clinical trial or full commercialisation
- Development of **5 IP packages**
- Creation of **6 new research tools** and **5 new research databases**
- **175 peer reviewed papers** in academic journals

We also play an active part in shaping the medical technologies landscape. By engaging effectively with our networks, we can be responsive and innovative within a fast-paced, highly regulated industry. This engagement has led not only to the development of new research partnerships, but also enabled us to play a part in developing policy to support growth both in the UK and globally.

Internationally, our partnerships span Asia, Australia, Europe and North America. They include 47 universities and 59 global companies, as well as healthcare institutions and policy makers. Through research exchanges and other collaborations, we have developed new research partnerships and contributed to global advancements in the sector.

These advancements include our work in developing international standards for device manufacture that enable companies to evaluate prostheses rigorously. These standards have already been adopted by a number of MeDe Innovation partners.

Our contribution to the sector goes beyond new technologies: we are developing a pipeline of skilled of researchers, too. By providing networks, training and exchange opportunities, we are creating an environment in which our next generation of researchers gain essential skills that will ensure the sector continues to flourish.

In the sections that follow we describe these achievements in more detail, and illustrate key accomplishments through a series of technology case studies.

# CREATING KNOWLEDGE AND ADVANCING TECHNOLOGY

**£6M**
Core Grant

**£69.7M**
Additional Funding

**98**
Research Projects

**111**
Researchers

**44**
Academic Staff

**26**
Events Held

**1595**
Attendances

**23**
Events Supported

MeDe Innovation creates new knowledge and advances technology across the whole of the manufacturing value chain. Our research begins at the product concept and clinical need stages, and progresses through design, manufacture, pre-clinical evaluation to patient delivery and market growth.

Over the past five years of operation, the MeDe Innovation programme has focused primarily on four areas of the medical technology market:

- Musculoskeletal regenerative devices and therapies
- Orthopaedics, including total joint replacements
- Wound care and soft tissue reconstruction
- Dental and maxillofacial

We are developing the manufacturing research and innovation supply chain for 21st century devices and interventions in these areas.

Through MeDe Innovation's multidisciplinary research, 21st century products can be delivered with greater precision, using earlier and less invasive interventions – and with more distributed manufacturing processes that are closer to the clinic and the patient. Importantly, we are also supporting a growing ageing population which expects an improved quality of life and to remain active for longer, with interventions and devices that last longer.

We have grown a critical mass of people and activities, working to develop sector-leading interventions, advance knowledge, contribute to economic growth, and set global standards for product testing.

## OUR FUNDING AND PARTNERS

Building on an EPSRC grant of £6M, awarded in 2013, MeDe Innovation has leveraged an additional £69.7M of resources for research and innovation. This includes £43.7M in new external research awards across the Universities of Leeds, Bradford, Newcastle, Sheffield, Nottingham and Cambridge, which form the core of the MeDe Innovation university partnership.

Our portfolio includes nearly 100 research projects, involving 44 academic staff and 111 researchers. Industry partners actively contributing to these projects have increased from 17 to 59 and we also collaborate closely with 25 clinical partners.



# SOLID FOUNDATIONS FOR A GROWING SECTOR

A core purpose of MeDe Innovation is to establish the UK as a global leader in medical device manufacture. To achieve that, we've taken an open-minded and responsive approach to innovation to ensure our research capabilities develop to meet the changing needs of a fast-paced, highly regulated industry.

From the outset, we defined a manufacturing chain that goes from product concept to patient delivery and created an extensive network of partners to co-develop projects that can progress effectively along that chain.

Over five years our UK network has grown to include 19 universities, and 35 industrial partners. We also work with 22 collaborative clinical partners including NHS Hospital Trusts, NHS Blood & Transplant, the Medicines and Healthcare Products Regulatory Agency, and Innovate UK's Health Knowledge Transfer Partnerships.

Through engagement with high profile conferences, participation in scientific meetings, and hosting workshop events, we've ensured that MeDe Innovation plays an active part in shaping this innovation landscape, including the development of a research portfolio of nearly 100 projects.

Alongside this activity, we have supported the development of a number of short projects at early Technology Readiness Levels through initiatives such as the Fresh Ideas Fund. These have enabled us to engage with new partners and enable early stage projects to prepare for larger funding bids.

## BUILDING EFFECTIVE COMMUNICATIONS

Communicating effectively with such a diverse network has been key to MeDe Innovation's success. Through website updates, e-newsletters and social media alongside our regular meetings and networking events, we have been able to keep our partners up to date and spread news of our activities to wider audiences.

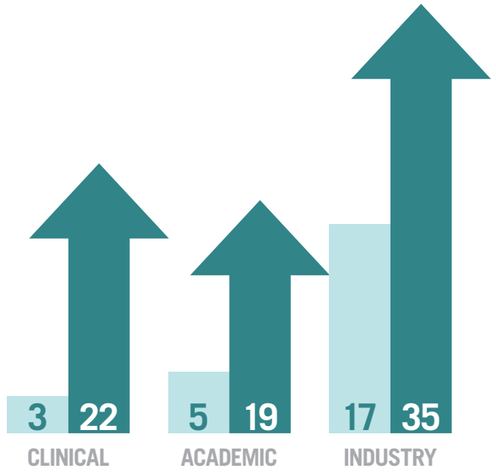
In addition, we have secured coverage in key industry media outlets including Business Quarter Magazine, UK Manufacturing Review, 3DMedNet and Orthopaedic Product News.

In 2017, MeDe Innovation was awarded an Academic Innovator Award by The Engineer, while in 2018, two of our investigators were nominated for the European Inventor of the Year Award, both of which led to further valuable PR opportunities.

## A STRATEGIC APPROACH

We've played our part at a wider policy level, too, leading a regional Science and Innovation Audit for the Government's Department of Business, Energy and Industrial Strategy and contributing to other regional and national industry strategies.

Through policy leadership, we are enabling our research environment and community to be strategically positioned to support continued innovation and growth across the medical device sector.




UK PARTNERSHIP GROWTH


GLOBAL PARTNERSHIP GROWTH

# DELIVERING INTERNATIONAL IMPACT

**35**
International visits

**34** of **175**
Publications written with an international collaborator

The research challenges addressed by MeDe Innovation are critical to the future development of the global healthcare market and industry system. We recognise that our response to those challenges must be similarly international in its scope and ambition.

Our international collaborations draw in research and healthcare institutions, commercial partners and policy makers. Our expertise has helped develop new international standards for device manufacture, while our work with both UK and global companies has supported economic growth and investment internationally.

After five years, the economic and social impact of our work is just starting and will continue in the future as more technologies supported by MeDe Innovation advance towards commercialisation. Equally, the international academic and industrial community that MeDe Innovation has helped shape and develop will continue to grow the global knowledge base in regenerative devices.

## OUR INTERNATIONAL COLLABORATIONS

We have forged partnerships with 28 international universities, including leading institutions in Asia and Australia, Europe and North America.


> *By introducing leading Chinese researchers to the MeDe Innovation brand, we've forged powerful research alliances and gained a valuable reputation among leading Chinese organisations.*
>
> **PROFESSOR PHIL COATES**

Our links with China, led by Professor Phil Coates and team at Bradford, build on the EPSRC-funded Science Bridges programme, which fosters collaborations between researchers, clinicians and business. Activities have included running annual international scientific meetings, and a workshop for early career researchers organised with the British Council, the Natural Science Foundation of China and the Newton Fund.

These have led to new projects receiving MeDe Innovation funding, and 20 research exchanges jointly funded by MeDe Innovation. Two of these, involving Dr Tom Paterson at the University of Sheffield, have led to collaborative research relationships with leading Chinese research groups at Sichuan University and the Beijing Institute of Nanoenergy and Nanosystems.

Our vibrant community of early career researchers has participated in other fellowship programmes, including the British Orthopaedic Research Society International Fellowship. Leeds research fellow, Dr Tony Herbert, was one of six UK researchers to take part in this networking trip to visit six prestigious US institutions.

Wider research collaborations include a partnership with India's Vellore Institute of Technology, funded by the British Council, which enabled the development of composite coatings through investigations in our joint simulation facility in Leeds.

And across Europe, our researchers have engaged in major EU consortia, including the £1.1M Research Council-funded SMARTSTEP programme in regenerative medicine (Cambridge); the €1.9M EMPIR Euromet award that brings together 19 European partners to investigate additive manufacturing within the medical sector (Nottingham); and an 11-partner, EC Framework award to investigate resorbable ceramic biocomposites in orthopaedics (Newcastle).

Our commitment to the global exchange of knowledge and expertise also led to the appointment of three international members to our advisory board to help guide MeDe Innovation's strategic direction.

## ADVANCING KNOWLEDGE AND TECHNOLOGY

MeDe Innovation researchers have led the development of the next generation international standard for pre-clinical testing of total hip joint replacements. The standard provides guidance to global medical device companies on how to evaluate prostheses in more relevant conditions. Equally important is the development of an international standard of friction measurement being devised by MeDe Innovation in partnership with the international standards organisation, ASTM.

> *Through the British Orthopaedic Research Society fellowship, I was able to present MeDe Innovation's manufacturing chain approach to prestigious US institutions and establish valuable contacts.*
>
> **DR TONY HERBERT**

MeDe Innovation academic, Dr Louise Jennings, and MeDe Innovation Leeds Senior Research Fellow, Dr Mazen Al-Hajjar, led the development of these standards at the University of Leeds' joint simulation facility. Dr Jennings chairs the ISO sub-committee for Bone and Joint Replacements.

## COLLABORATING WITH INDUSTRY

MeDe Innovation is working with Simulation Solutions to co-develop and validate new pre-clinical simulation equipment capable of implementing the new ISO standards, which have been sold across the world. Our global partners including DePuy Synthes and Mathys are also now using these standards.

We work with companies across the UK, enabling them to extend their reach into global markets by supporting the development of new products. These include a long-standing partnership with Tissue Regenix to develop its proprietary dCell™ technology, now available within the company's current international sales portfolio, and the establishment of new manufacturing facilities in Leeds. Work supporting new product development of an all-polymer knee with Invibio is focused on global markets with clinical and industry collaborations in Europe, USA and India.

We also work with 24 international companies to support new product development and to attract inward investment. Our long-standing collaboration with medical device company, DePuy Synthes, for example, has seen the company expand its research and development base in Leeds, securing around 500 jobs.

# DEVELOPING TRANSLATIONAL EXPERTISE

MeDe Innovation's distinctive approach to research translation leads us to engage with industry and clinical partners at the outset, ensuring our projects develop research with genuine commercial value.

People are a critical part of successful technology translation. MeDe Innovation has created a multidisciplinary and multi-professional research and innovation environment, enabling collaborations between different types of partners and stakeholders, strategically focused on challenges and research projects that are important to the future of UK industry and health and care services.

In this environment, researchers and early career academics not only generate high quality research outputs but also gain training in, and experience of, real world innovation and translation, with a focus on new product development and manufacturing. This new generation of commercially savvy researchers ensures a flow of highly skilled people into industry and the healthcare system. Thirty-one of our staff have moved into next career destinations over the lifetime of our programme.

*This new generation of commercially savvy researchers ensures a flow of highly skilled people into industry and the healthcare system.*

## OUR EARLY CAREER RESEARCH COMMUNITY

At heart of this activity is our lively Early Career Researchers (ECR) Forum, which organises industry visits, regular workshops and meetings. As well as engaging with MeDe Innovation programmes, these researchers have created opportunities to advance both their own careers and the MeDe Innovation brand.

Among the successful events co-ordinated by the Forum has been a three-day residential 'Dragons Den' sandpit event. Researchers collaborated to develop project proposals with colleagues from different universities, taking advantage of training on how to present and cost proposals. The event led to two successful project applications receiving £5k from MeDe Innovation's Fresh Ideas Fund.

A popular PhD secondment scheme has also been developed through the ECR Forum, with 15 postgraduate students receiving funding for industry, laboratory or policy placements. These were awarded in three funding rounds, with ECRs leading the selection process, as well as monitoring and evaluating placements.

MeDe Innovation is supported through two EPSRC Centres for Doctoral Training, one in regenerative devices and one in additive manufacturing.

## OPPORTUNITIES FOR WIDER ENGAGEMENT

Our ECR community plays an active part in wider MeDe Innovation events, with members invited to present their work at conferences and scientific meetings and take part in networking opportunities. This includes the opportunity for researchers to present their work in posters or one-minute business pitches.

Communication techniques are particularly important for successful industry engagement, and we have delivered training in this area, including help with creating video content. A competition for effective digital dissemination of research, for example, resulted in a YouTube playlist that attracted more than 7,000 views.

Internationally, MeDe Innovation ECRs have taken up opportunities for travel scholarships and exchange programmes. These include international training and workshops organised in collaboration with the University of Bradford and the Science Bridges programme, and eight new project collaborations established via an ECR workshop organised by the British Council/UK-China Research and Innovation Partnership Fund.

# MEDE INNOVATION CONSORTIUM

**70**
PhD students

**41**
PDRAs

**44**
Academic staff

**31**
MeDe Innovation staff have moved into new roles

**5**
Research students progressed to industry

**4**
Research students moved into new university roles

**13**
Postdoctoral researchers moved into new academic positions

**5**
Postdoctoral researchers progressed into private sector jobs

# CAREER PROGRESSION THROUGH MEDE INNOVATION

MeDe Innovation's multidisciplinary approach to research first attracted Bradford academic Dr Maria Katsikogianni to become involved in its Early Career Researchers Network. That initial step, taken while Dr Katsikogianni was a postdoctoral researcher at the University of Leeds, has led to a deeper engagement with the MeDe Innovation programme that has helped shape Dr Katsikogianni's career progression.

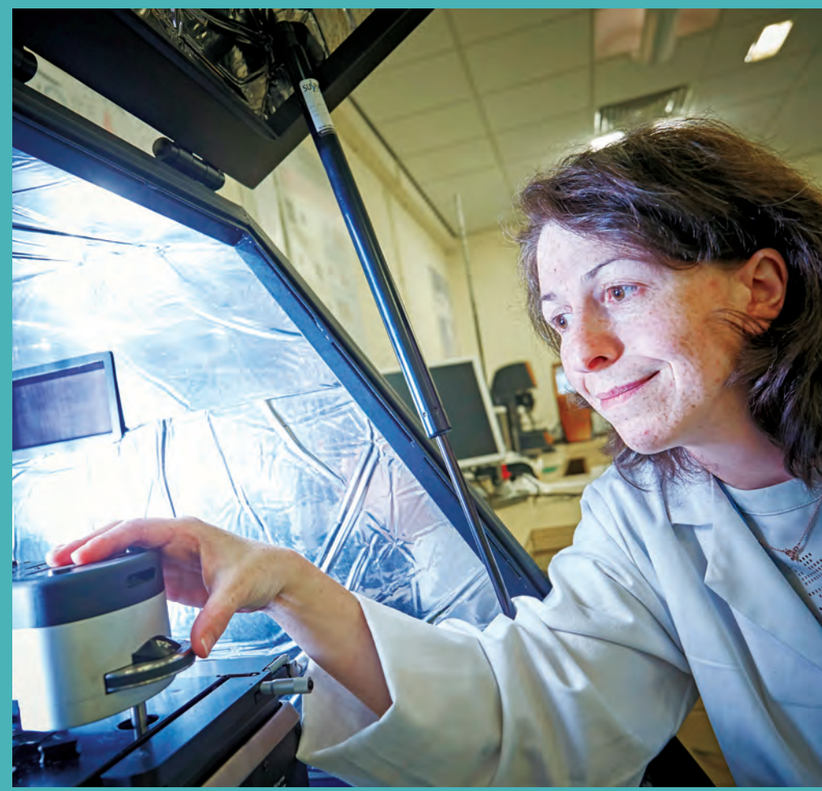
In 2016, newly appointed as a Lecturer in Chemistry at the University of Bradford, Dr Katsikogianni became a MeDe Ambassador for the University, organising ECR meetings and networking events. These enable researchers to present their work, learn about funding opportunities, and start shaping collaborative projects, as well as learning from other researchers and industry professionals.

Within a few months, Dr Katsikogianni had also applied successfully to MeDe Innovation's Fresh Ideas Fund, for a project with Professor David Williams at the University of Cardiff to develop antimicrobial technologies for medical devices.

Through MeDe Innovation's 'Dragon's Den' competition, Dr Katsikogianni was able to engage further with MeDe's network, developing two additional projects alongside partners at Bradford, Sheffield and Nottingham.

MeDe Innovation's reputation in the field of orthopaedic devices has also enabled Dr Katsikogianni to make a broader contribution to the field. She is currently leading the orthopaedic focus group of a COST EU Action looking at developing standardised testing for antimicrobial devices.

Now a Lecturer in Biomaterials Chemistry at the University of Bradford, Dr Katsikogianni is clear about how MeDe Innovation has influenced her approach and enabled her to develop a track record as a researcher.



*"Through MeDe's networks I've been able to maintain and broaden my research collaborations, which has enabled me to put together grant applications that are more ambitious and more robust. It's also helped me to see the importance of collaborating with industry and clinicians at a really early stage, so the route to commercialisation is built into the project design.*

**DR MARIA KATSIKOGIANNI**

# RESEARCH PROJECT PORTFOLIO

MeDe Innovation has supported 98 collaborative research projects, working with industry and clinicians across our four priority market areas.

Twenty-two projects have progressed to the next stage of support for technology development. Of these, 13 are now at the stage of commercial product development, clinical trial or full commercialisation.

The 98 projects have led to the publication of 175 peer reviewed papers in academic journals, the development of five IP packages and the creation of six new research tools and five new research databases.

## PROJECT NUMBERS

**52**
Musculoskeletal regenerative devices and therapies

**36**
Orthopaedics, including total joint replacement

**5**
Wound care and soft tissue reconstruction

**5**
Dental and maxillofacial

# MANUFACTURING AND TECHNOLOGY RESEARCH FACILITIES

MeDe Innovation has developed distinctive and specialised research facilities for use in design, manufacturing, simulation and evaluation, which have helped us to address research challenges across our priority market areas.

## MANUFACTURING PROCESSES

**Manufacturing fibrous nonwoven materials, including synthetic and biological materials**
- Wound care and soft tissue reconstruction
- Dental and maxillofacial

*University of Leeds*

**Manufacturing multiphase materials, composites, nanomaterials, multilayer structures and devices**
- Musculoskeletal regenerative devices and therapies
- Orthopaedics, including total joint replacement
- Dental and maxillofacial

*University of Nottingham*

**Ultra precision polymer processing and polymeric device manufacture**
- Musculoskeletal regenerative devices and therapies
- Wound care and soft tissue reconstruction

*University of Bradford*

**Dental biomaterials processing, including additive manufacture**
- Dental and maxillofacial

*University of Sheffield*

**Bioprocessing acellular tissue scaffolds**
- Musculoskeletal regenerative devices and therapies

*University of Leeds*

**Bioprinting and cell additive manufacturing**
- Musculoskeletal regenerative devices and therapies

*Newcastle University*

## DESIGN

**Advanced computational models for prediction of function to support design in stratified patient populations**
- Orthopaedics, including total joint replacement
- Musculoskeletal regenerative devices and therapies

*University of Leeds*

## PRE-CLINICAL SIMULATION AND EVALUATION

**Experimental simulation systems to evaluate the mechanics and tribology of total joint replacements**
- Orthopaedics, including total joint replacement

*University of Leeds*

**Experimental simulation systems to evaluate the mechanics and tribology of MSK tissue reconstruction**
- Musculoskeletal regenerative devices and therapies

*University of Leeds*

## CLINICAL EVALUATIONS

**Clinical evaluations of MSK interventions**
- Musculoskeletal regenerative devices and therapies

*University of Cambridge*

**Clinical evaluations of dental interventions**
- Dental and maxillofacial

*University of Sheffield*

# MUSCULOSKELETAL REGENERATIVE DEVICES AND THERAPIES

Our large research portfolio of 52 projects in musculoskeletal regeneration focuses on two areas:

- Stratified bioprocesses for the manufacture of acellular scaffolds, to provide an off-the-shelf solution that can be used without taking tissue from other parts of a patient's body and do not carry the same risk of immunological rejection of grafts from donated tissue. These have been successfully translated as new clinical products for wound repair, for heart valve replacement and for ligament repair by our industry partners and the NHS.
- Manufacturing at the point of need, to address defects in the musculoskeletal system as early as possible, through the development of more robust structural bioactive materials, such as bioactive glass-ceramics and biopolymers.

## INDUSTRY PARTNERS:

- **ALCYOMICS**
- **AZ DELTA**
- **CERAMISYS**
- **CERAPEDICS**
- **ROLLS-ROYCE**
- **TISSUE REGENIX GROUP**

# DEVELOPMENT OF MULTIFUNCTIONAL, MULTIPHASE SCAFFOLDS FOR REGENERATION OF OSTEOCHONDRAL DEFECTS

**Lead:** Professor David Grant, University of Nottingham
**Academics and researchers:** Professor Brigitte Scammel, Dr Virginie Sottile, Dr Colin Scotchford, Professor George Roberts, Dr Reda Felfel, Dr Jane McLaren, Dr Laura Macri Pellizzeri, Katherine Pitrolino

Damage to joints can commonly occur in people who play a lot of sport or in people as they get older. These osteochondral defects cause a lot of discomfort and pain. Current treatments, which involve transplanting a small plug of bone and cartilage from other locations in the joint, can lead to lengthy recovery times.

We have been investigating an alternative approach by providing biopolymer scaffolds that encourage the regeneration of the joint surface. The complex tissue structure in such defects makes this a particular challenge as it requires osteogenic regeneration on one side and chondrogenic regeneration on the other.

A common solution is to use two different materials that are bound together, but these can often delaminate at the point of weakness between the two materials. Our approach has instead focused on making complex scaffolds from a single material that will support the different cellular biology of bone and cartilage cells as they grow.

A novel method to make 'multiphase' chitosan scaffolds was developed using an innovative crosslinker and porogen. These use varying porosity and pore size to create layers that support different cell types, but without the mechanical weakness of an interface between them.

Our process allows us to distribute other materials through the chitosan scaffold, such as nanoparticles of hydroxyapatite, which can encourage bone growth and integration into the joint.

The structural, mechanical, physical and biological properties of these scaffolds have been carefully investigated both in vitro and in vivo. The scaffolds can also be compressed to less than 20% of their original size before recovering fully, allowing them to be delivered using arthroscopic devices.

Our work has also developed a process that allows us to use chitin from animal sources and also from fungus – giving the advantage of being able to produce chitosan osteochondral scaffolds that are free from animal products. This makes them more acceptable for use in a wider range of patients.

We are also investigating seeding these scaffolds with autologous cells from patients to help improve integration further.

The products are currently undergoing mechanical tests with a simulated knee model and we are working with industry partners to prepare for pre-clinical trials of the product.

> *Our new methods for making multiphase structures allow us to produce material that is cytocompatible and can be scaled up so it can be made in large quantities while keeping the cost down.*
>
> **PROFESSOR DAVID GRANT**



> *We are using a platform technology – phosphate-based glass – and applying it in totally new ways to enhance musculoskeletal regeneration and repair for the benefit of patients.*
>
> **PROFESSOR DAVID GRANT**

# MANUFACTURING FULLY RESORBABLE PHOSPHATE-BASED GLASSES TO ENHANCE BONE REPAIR

**Lead:** Dr Ifty Ahmed and Professor David Grant, University of Nottingham
**Academics and researchers:** Dr Joel Segal, Professor Ed Lester, Dr Emma Barney, Dr Virginie Sottile, Professor Brigitte Scammel, Dr Miquel Gimeno-Fabra, Dr Zakir Hossain, Dr Bryan Stuart, Dr Fernando Barrera Betanzos, Dr Uresha Patel

With an ageing population, the risk of fractures following a fall is likely to become a growing problem.

Our research has investigated a novel solution to this problem using fully resorbable calcium phosphate-based glass materials. Unlike other resorbable materials, phosphate-based glasses can be tailored to degrade gradually over time at controlled rates. By altering the internal cross-linking structure of this glass via the inclusion of modifier oxides, it is possible to tune the rates at which these materials degrade, from a few hours, to months or even several years.

Using proof of concept funding we developed a manufacturing method to produce highly porous phosphate-based glass microspheres. Further funding via the NIHR allowed us to show that stem cells migrated into microsphere pores. We also developed a method for injecting these microspheres directly into bone defects using fine needles. This treatment is aimed towards osteoporotic patients, who are considered to be at high risk of bone fracture, to help strengthen their bones to prevent fractures from occurring.

We have shown that these 'osteospheres' encourage good cell growth and have conducted a first stage safety efficacy pre-clinical trial. We have also established a patent on the porous microsphere manufacturing process.

The tuneable degradation of our phosphate-based glasses has also allowed us to produce fully resorbable composite materials that can match the mechanical properties of bone. By reinforcing polylactic acid with phosphate-glass fibres, we have shown that it is possible to even surpass the mechanical properties of cortical bone.

The aim is to manufacture prototype rods, which could be used as fully resorbable intramedullary nails. These are undergoing testing in vitro.

Another approach we have taken is to use phosphate-based glass as a coating that can enhance the surface properties of orthopaedic devices.

Using physical vapour deposition we can coat metallic or polymeric surfaces with a few nanometres or micrometres of phosphate-glass material that will then degrade over time to reduce microbial adhesion to the surface. This allows us to have an antimicrobial action without using antibiotics – something that is desirable in the face of increasing antibiotic resistance.

In vitro work has shown that these degradable coatings can prevent the growth of bacterial films whilst also helping to promote bone growth. We are now actively looking for industrial partners to help us take the technology forward as a commercial product.

# SOPHISTICATED NOISE REDUCTION AND IMAGE PROCESSING TECHNIQUES TO ENABLE ADDITIVE MANUFACTURING OF NOVEL MEDICAL DEVICES

**Lead:** Professor Donal McNally, Professor David Grant, University of Nottingham
**Academics and researchers:** Professor Ifty Ahmed, Professor Joel Segal, Professor Ed Lester, Dr Emma Barney, Professor Colin Scotchford, Dr Bronek Boszczyk, Dragos Axinte, Dr Alan Parish, Dr Cheeseng Aw, Dr Xiaobing Feng, Dr Gregory Kesteloot, Az Delta

Modern medical imaging is capable of providing detailed three-dimensional visualisations of a patient's joints. If combined with additive manufacturing techniques, these could offer enormous opportunities for manufacturing custom joint prostheses that fit individual patients or surgical tools, such as drill guides, that could enhance patient safety during surgery.

However, high resolution images are needed to produce the accurate computer modelling required for such innovations to be fully realised.

Our research has allowed us to develop sophisticated noise reduction and imaging processing techniques that can be used to help generate accurate three-dimensional models from medical images.

Working with industrial partners, including global medical manufacturers, we used these techniques to pilot three new medical device technologies related to spinal surgery. All three require precision shaping through additive manufacturing or multi-axis computer numerical controlled (CNC) milling.

Two of these devices are spinal implants, which have been evaluated by a combination of conventional pre-clinical testing and innovative computational modelling. This modelling assessed the impact that design and manufacturing parameters had on both the device and how the patient's tissues were loaded after implantation.

The third device is a guide that helps to improve accuracy in image guided and robotic surgery, whilst at the same time reducing operative times. We have assessed the geometric precision of the manufacturing process from the imaging to the finished product. We are now hoping to undertake pre-clinical evaluation of customised robotic surgery guides.

The virtual modelling developed for manufacturing of medical devices has also been adapted to help monitor the healing process in patients during the first six months after surgery. By applying advanced imaging processing and noise reduction techniques, it is possible to generate 3D models of the trabecular bone in the spine, which allows the remodelling of bone graft substitutes in spinal fusion to be studied in detail.

Our work has allowed us to develop strong links with industry partners including Cerapedics, Rolls-Royce and Az Delta.

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





# MANUFACTURING BIOPROCESSES FOR ACELLULAR PORCINE TENDON FOR ANTERIOR LIGAMENT REPLACEMENT

**Lead:** Professor Eileen Ingham, Dr Anthony Herbert and Professor John Fisher, University of Leeds
**Academics and researchers:** Dr Gemma Jones, Dr Hazel Fermor, Dr Jennifer Edwards

Treating injuries to the anterior cruciate ligament (ACL) currently requires transplants from healthy tendons elsewhere in the patient's body or the use of tissue from a deceased donor.

Taking tissue from the patient can cause donor site morbidity and the donated tissue is starved of oxygen during transplantation, leading to cell necrosis, while tissue from deceased donors contains dead cells. In both cases, the presence of cells delays the healing process and recovery time for the patient.

An alternative approach is to strip porcine tendon of its cells to leave a scaffold that can be implanted into the patient, which their own cells can then repopulate. The porcine superflexor tendon is an ideal candidate, with the right length and strength to be used as an ACL replacement.

A bioprocess for removing the living cells was developed and evaluated over a six-month period in sheep, where it showed good functional performance and evidence of regeneration.

Our goal was then to understand how variations in the manufacturing process affect the properties of the scaffold, with the aim of developing a product range that could be better matched to individual patient needs. This included investigating variables such as the method used to remove fat from the porcine superflexor tendon and the sterilisation process. Each had subtle effects on the performance of the final product.

Irradiation with different doses of gamma radiation was, surprisingly, found not to show a dose-dependent effect on the biomechanical properties of the acellular tendons. We established that 25 kGy irradiation, the recommended dose for the sterilisation of medical devices, is the ideal option for sterilising the product.

Decellularisation affected collagen crimp, tissue swelling and collagen fibre sliding in tendons, but the biomechanical properties are still sufficient for use in ACL reconstruction.

This know-how was transferred to Tissue Regenix Group to inform their manufacturing process of a decellularised porcine tendon implant, OrthoPure XT. The company has conducted a clinical trial of OrthoPure XT in Europe.

Recent work has examined how the thickness of the porcine superflexor tendon graft can affect the biomechanical properties. The cellular mechanisms of regeneration in grafts are also under investigation.

Looking to the future, there is scope to investigate how the surgical implantation methods of the acellular graft can further stratify the product.

> *It has given us a much deeper understanding of just how we can vary the manufacturing and sterilisation processes so that we can have a more stratified product range available.*
>
> **PROFESSOR EILEEN INGHAM**

# MANUFACTURING BIOPROCESSES FOR ACELLULAR HUMAN BONE-TENDON-BONE FOR ANTERIOR LIGAMENT REPLACEMENT

**Lead:** Professor Eileen Ingham, Professor John Fisher, University of Leeds.
**Academics and researchers:** Dr Jennifer Edwards, Dr Hazel Fermor, Dr Anthony Herbert

Around 70,000 anterior cruciate ligament (ACL) reconstructions are performed annually in the US, the majority of which either use hamstring tendon or bone-patella tendon-bone autografts.

While allograft tissues offer the opportunity for reduced operating time and no donor site morbidity, they can induce chronic immune responses that delay incorporation and ligamentisation at the recipient site. Our goal was to develop acellular allogenic bone-tendon-bone scaffolds that could be used off-the-shelf for ACL replacement, yet also be matched to patient needs.

The challenge, however, was to develop a process that could decellularise both tendon and bone without damaging either tissue. By pretreating the bone and using additional washing, it was possible to decellularise both the hard and soft tissue equally so they can be implanted.

Our work allowed us to develop standard operating procedures using approved reagents and establish microbial monitoring processes. Variations in the duration of decellularisation washes were also evaluated. Additional processes, such as the use of acetone to reduce lipid content or terminal sterilisation using 25 kGy of gamma irradiation, were shown to reduce the biomechanical properties of the acellular grafts, but still within the functional range of the human anterior cruciate ligament.

The results are being used to co-develop a Good Manufacturing Practice (GMP) process with NHS Blood and Transplant Tissue and Eye Services, which they will use to develop human bone-patella tendon-bone scaffolds for clinical trials. If successful it could provide a new treatment option for UK orthopaedic surgeons.

The functional performance of bone-patella tendon-bone scaffolds were tested in sheep over a six-month period and demonstrated excellent performance in comparison to the 'gold standard' ovine allograft. Evaluation of the cell infiltration during regeneration is ongoing.

A novel chemical sterilisation process, developed by NHS Blood and Transplant Tissue and Eye Services, has also been assessed to determine the concentrations and wash durations necessary to reliably obtain a sterilisation assurance level. Studies are now focused upon the effect of this sterilisation process, which uses copper chloride and hydrogen peroxide on the properties of the decellularised bone-tendon-bone grafts.

> *Sharing our knowledge with NHS Blood and Transplant Tissue and Eye Services will hopefully lead to a new product that can be supplied to surgeons within a couple of years.*
>
> **PROFESSOR EILEEN INGHAM**



# MANUFACTURING BIOPROCESSES FOR ACELLULAR OSTEOCHONDRAL SCAFFOLDS

**Lead:** Dr Hazel Fermor, Professor Eileen Ingham, Professor John Fisher, University of Leeds.
**Academics and researchers:** Dr Anthony Herbert, Fiona Walker, Philippa Bowland, Dr Louise Jennings, Andres Barco, James Warren

Osteoarthritis is one of the most common joint disorders in men and women aged above 60-years-old, causing severe pain and loss of movement. In the UK it is the second greatest cause of disability while in the US it is found in 10% of men and 13% of women, accounting for more than 27 million people.

Knee injuries that occur earlier in life, while patients are young and active, can often lead to the articular cartilage deteriorating over time, leading to the development of osteoarthritis. It is estimated that 10,000 people a year in the UK suffer such injuries, which can be treated with cartilage repair surgery. Globally 2.4 million of these procedures are performed annually.

Our goal was to develop off-the-shelf acellular scaffolds, matched to surgical and patient needs, which can repair cartilage by encouraging regeneration of tissue. We envisage these scaffolds being composite bone-cartilage plugs that can be surgically implanted into lesions in the knee. Using a composite scaffold in this way was determined to be the most effective way to get the grafts to integrate.

Early investigations examined the properties of cartilage from different species and led us to focus on tissue from young, healthy pigs as the most appropriate for implantation into the human knee.

While decellularised porcine bone showed excellent integration into the joints of sheep over a 12-week period, our research revealed that physically cutting cartilage out of a joint causes it to lose many of its biomechanical properties during the decellularisation process.

Repeated washing of the cartilage led to damage of the collagen fibres through the cut edge, and studies also revealed a loss of the glycosaminoglycans, which help to give cartilage its biphasic, shock absorbing properties.

To overcome this, a new bioprocess for removing the cells from cartilage from the whole pig knee joint condyle was developed to allow the integrity of the cartilage to be retained before grafts are shaped from the remaining scaffold. Self-assembling peptide-glycosaminoglycan mixtures were also used to restore biomechanical function to porcine knee cartilage that had been depleted of glycosaminoglycans.

A second pilot study in sheep is now due to take place to examine whether acellular osteochondral grafts produced in this way can be integrated without triggering inflammation.

Simple tribological studies of osteochondral grafts in the knee have also been completed but further work is still to be done on understanding how using cartilage of different thicknesses and congruency of its surface can help it integrate into different parts of the knee joint.

> *While it is tempting to view cartilage as a simple tissue, it is perhaps one of the most challenging of all the tissues we have worked with.*
>
> **PROFESSOR EILEEN INGHAM**

**Eileen Ingham and John Fisher were shortlisted for the European Inventor Award 2018 for their work in developing the decellularisation process.**

# CREATION OF MICROTISSUES FOR DRUG TESTING REQUIRES RELIABLE CELL PRINTING TECHNIQUES

**Lead:** Professor Kenny Dalgarno, Newcastle University
**Academics and researchers:** Dr Matt Benning, Dr Ana Ferreira-Duarte, Dr Richard Whalley, Dr Simon Partridge, Dr Huagui Zhang

Pre-clinical testing of candidate drugs for osteoarthritis currently involves using animal models, yet these are generally not very predictive of how effective a treatment might be in humans. This has led to a desire for more effective models of arthritis that can be used for drug testing and disease investigation.

Three-dimensional cell printing techniques, such as those we have been developing, offer a way of creating microtissues that can better replicate human tissue and disease. We have been working with academic and industry partners to produce a high throughput model printed from different human cell types to represent the human joint – so called osteoarthritis-on-a-chip.

These 'osteo-chips' will ultimately combine several human cell types – osteoblasts, osteoclasts, chondrocytes, synovial cells, immune cells and adipose cells – that can be drawn from a multichannel cell printer and deposited in different ratios to form the appropriate tissues found in a joint.

The printer is based on work originally undertaken as part of the MeDe Innovation programme, which focused on co-processing of cells and materials for use in micro-valve-based bioprinting techniques.

For the proof of concept studies, we developed an eight-channel cell printer, as no commercially available equipment could meet the required specification. This was achieved by fitting a new eight-channel print head to a commercial materials printer.

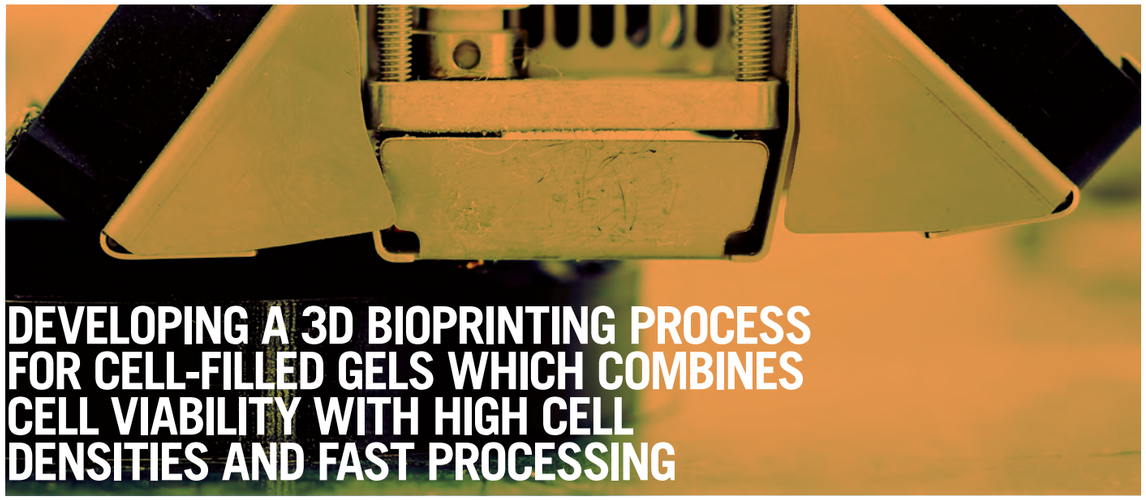
This was then used to create co-cultures of cells that maintained phenotype. It has led to a £1 million, three-year project, funded by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and led by Alcyomics Ltd, to develop the approach commercially, in collaboration with Newcastle University and the Universities of York, Leeds and Nottingham.

The aim is to be able to produce hundreds of microtissues, just a few millimetres in size, on well plates every hour. This would offer the opportunity to screen large numbers of drugs in different quantities and over varying timescales, a process that is important in the drug development process.

While work is ongoing to further enhance the reliability and reproducibility of the printing process, our collaborators are trying to optimise the biological composition of the model. Beyond this, work will be needed to validate the model.

We also hope to develop other printed models of cardiac and liver tissue for use in disease modelling and drug testing.

> *The advantage of our multichannel bioprinter is that we can take different cell types and fine tune their ratios to make microtissues that better mimic the mix of cells found in human joints.*
>
> **PROFESSOR KENNY DALGARNO**



# DEVELOPING A 3D BIOPRINTING PROCESS FOR CELL-FILLED GELS WHICH COMBINES CELL VIABILITY WITH HIGH CELL DENSITIES AND FAST PROCESSING

**Lead:** Professor Kenny Dalgarno, Newcastle University
**Academics and researchers:** Dr Matt Benning, Dr Ana Ferreira-Duarte, Ricardo Ribeiro, Aidan Bowes, Joe Dudman

In regenerative medicine, it is desirable to ensure that implanted cells will stay at the site where the surgeon wishes the repair to take place.

Cell-filled gels are an attractive solution to this problem as they can provide a hydrated, nutritious environment that will contain the cells while they start to develop into tissues. We have developed a new 3D bioprinting process to produce cell-filled gels called Reactive Jet Impingement.

This works by directing two jets of gel precursors at one another in mid-air, where they react and form a gel that drops onto a substrate. One of the precursor liquids – usually the crosslinking solution as this has the lowest viscosity – can be loaded with cells, so they become embedded throughout the resulting gels at a high density.

The advantage of this process is that the gel precursors are much easier to process than finished gels.

This process also allows us to print the cell-laden hydrogels in 3D structures or deposit them onto a biomaterial substrate, such as a bioceramic scaffold which would work as a bone analogue, to create composite structures where the gel would provide a cartilage analogue material.

Future work will allow a multiple jet head to be manufactured, capable of printing four different materials in one go. This will provide 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 in locations where it needs to be robust enough to survive handling during implantation, while in other locations the gel may be softer to help it bond to integrate into host tissue.

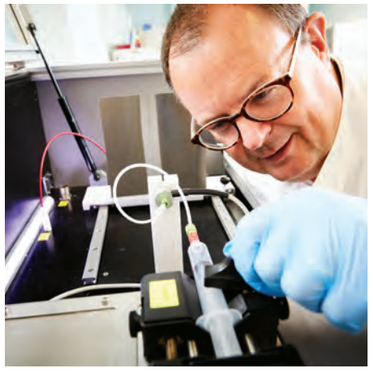
We have shown that cells including fibroblasts and mesenchymal stem cells embedded within hydrogels in this way can be processed rapidly while also maintaining viability. Microtissues formed in gels with a high density of cells also produce more mature tissue at a faster rate than when a low cell density is used.

We are continuing to develop the technology for osteochondral applications with support from the Arthritis Research UK Tissue Engineering Centre and we are seeking commercial partners to help exploit the techniques we have developed.

> *We are interested in printing our cell-filled gels onto harder components, such as a polymer or ceramic scaffold to create composite soft tissue-hard tissue implants.*
>
> **PROFESSOR KENNY DALGARNO**

# MANUFACTURE OF DEVICES TO COMBAT DEEP BONE INFECTION

**Lead:** Professor Paul Hatton, University of Sheffield
**Academics and researchers:** Dr Cheryl Miller, Dr Aileen Crawford, Dr Graham Stafford, Dr Caroline Wilcock, Dr Ilida Ortega, Dr Tom Paterson, Dr Robert Moorehead, Dr Joey Shepherd, Rayan Binduhayyim



Infections associated with deep bone and orthopaedic devices are a significant burden on healthcare services around the world, leading to patients enduring long and expensive stays in hospital. The only effective treatment is with powerful intravenous antibiotics.

Our team have been developing a range of new processes to manufacture innovative graft substitutes using surface active materials including bioactive glasses and modified calcium phosphates, biomaterials that are able to promote bone tissue regeneration while also combating infection.

One promising technology is based on a complex substituted calcium phosphate that contains ions that supress microbial growth.

Calcium phosphates are well known for their ability to promote bone regeneration in medical implants. Using a new 'rapid mix' process, we have been able to produce medical grade nanoscale calcium phosphate particles which can be formed into a paste for minimally invasive surgical implantation into a bone defect.

This process was then modified to dope the hydroxyapatite particles with an antibacterial element. Our initial proof of concept introduced silver ions to provide the antimicrobial action and demonstrated that they were able to inhibit the activity of common organisms that cause infections in patients after orthopaedic surgery.

We have since adopted an alternative inorganic modification to improve the antimicrobial activity further and are now working with our industry partner Ceramisys to scale up this manufacturing process with the aim of producing a commercial product.

MeDe Innovation sponsorship has also enabled a postdoctoral scientist to undertake a placement at Cardiff University to test a laboratory model for assessing the anti-infective properties and bone healing qualities of our materials.

A patent application for an innovative antimicrobial material has been submitted, and we have obtained funding to conduct initial in vivo studies in a project led by Dr Cheryl Miller.

Future work will also look at incorporating antimicrobial materials into additive manufacturing processes, and the potential for incorporating peptides at the surface of materials to deliver more specific antimicrobial activity compared to the broader spectrum activity provided by inorganic molecules. Using peptides offers the potential of adding additional functionality to implants.

> *Existing bioactive glass-based devices may have some incidental antimicrobial activity, but devices created using our materials and processes will be the first to have this behaviour designed into the product, delivering far more effective inhibition of pathogens.*
>
> **PROFESSOR PAUL HATTON**

# ORTHOPAEDICS, INCLUDING TOTAL JOINT REPLACEMENTS

MeDe Innovation's research portfolio in orthopaedics focuses on improving the reliability and lifetime of joint replacements. A much more sophisticated stratification of patient populations and activities is required to achieve this, and we have advanced methodologies for the simulation, design and pre-clinical testing of hip and knee prostheses. This has resulted in new international standards for pre-clinical testing, new commercial pre-clinical test equipment manufactured by Simulation Solutions and the use of the new methods and standards in new product development by our industry partners.

We are also exploring manufacture of fully bioresorbable multiphase fixation devices. These projects have 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.

## INDUSTRY PARTNERS:

- **BIOCOMPOSITES**
- **DEPUY SYNTHES**
- **INVIBIO**
- **MATHYS**
- **SIMULATION SOLUTIONS**

# SIMULATION, DESIGN AND PRE-CLINICAL TESTING OF HIP PROSTHESES

**Lead:** Professor John Fisher, Dr Louise Jennings, Dr Ruth Wilcox, University of Leeds
**Academics and researchers:** Professor David Barton, Professor Sophie Williams, Dr Mazen al Hajjar, Dr Alison Jones, Dr Murat Ali, Dr Oscar O'Dwyer Lancaster-Jones, Dr Susan Partridge, Dr Joanna Leng, Dr Xijin Hua, Dr Faezeh Jahani

Younger patients undergoing total hip replacement procedures often expect to be able to return to the same levels of activity they had earlier in life. The increased demand they can place on the prostheses can accelerate wear and lead to implant failure within the patient's lifetime. Around a third of hip replacements in this patient group need to be revised.

There is a clear need for hip joint prostheses that are able to deliver better performance and greater resistance to wear.

Using our advanced experimental and computational simulation methods, we can control variables in the design, pre-clinical testing and patient delivery stages to predict what influence they will have on the function and performance of an implant.

One important finding has been the effect that edge loading in a hip replacement has on its performance.

This work has led to a new ISO standard being adopted earlier this year on the wear testing of hip prostheses under variations in component positioning which results in direct edge loading. This will help to improve the prediction of hip implants' risk of failure in patients.

We have worked closely with Simulation Solutions to develop enhanced hip joint simulation equipment and experimental methods, which they have been able to manufacture and sell in the UK, Europe and Asia. Most recently we have been developing new six-axis hip joint simulators that will allow us to assess the result of offset in component positioning in the anterior/posterior direction as well as the medial/lateral direction.

Our industry partners, DePuy Synthes and Mathys, have also applied the advanced simulation methods we have developed to test both existing prostheses and new designs, giving them vital data for regulators and information to improve their products.

Combining experimental simulations with enhanced dynamic computational models has enabled us, for the first time in the world, to combine biomechanical, tribological and surgical factors to predict prosthesis function in pre-clinical simulations.

There is, however, still potential to further investigate how different variables in a hip joint design, patient type and surgical alignment combine together to affect the wear rate.

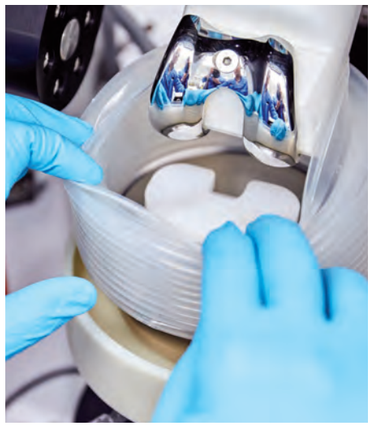
> *We have only just scratched the surface of how the different surgical, patient and design variables in a hip joint replacement can affect performance, and the next step is to look at how combinations of these variables can affect the wear of hip prostheses.*
>
> **DR LOUISE JENNINGS**





# SIMULATION, DESIGN AND PRE-CLINICAL TESTING OF KNEE PROSTHESES

**Lead:** Professor John Fisher, Dr Louise Jennings, University of Leeds
**Academics and researchers:** Dr Raelene Cowie, Dr Abdel Abdelgaied, Dr Raman Maiti, Dr Claire Brockett, Miss Ellie Johnston



> *Younger patients are placing more demands on joint replacements, which can lead to earlier failure due to abnormal mechanics and increased wear. Our research is trying to identify the factors that can increase wear in joint replacements so they can be made to last longer.*
>
> **DR LOUISE JENNINGS**

Most knee joint implants are assessed using a standard walking cycle in a joint replacement that has been perfectly aligned in an average patient. This fails to account for the wide variation in how a joint prostheses may be used in the real world.

Our goal was to develop enhanced simulation systems to evaluate how variations in patient anatomy, surgical alignment and implant design can influence the function, performance and lifetime of a knee joint replacement. These can be used to help make total knee replacements more robust so they can last patient lifetimes, particularly in younger patients.

We took a combined approach, using both experimental and computational methods. While we have a number of electromechanical knee simulators capable of replicating the movements from a wide range of day-to-day activities, such as climbing stairs, the computational approaches have provided additional information that cannot be obtained through physical simulation. For example, these virtual models have been able to calculate the contact stress and cross shear in a knee joint replacement, while also complementing the experimental information.

Our recent research has focused on the implications of four different surgical alignment positions on the mechanics and wear rate of existing total knee replacement devices. We have also been working with industry partners, including Invibio, Biocomposites and DePuy Synthes, so these methods can be used to help in the design, pre-clinical testing and patient delivery of new types of joint prostheses.

Invibio, for example, have adopted our methods to generate evidence for their product design process and to support regulatory approval of its new PEEK all-polymer knee before it is rolled out into global clinical trials. Our long-standing collaboration with Simulation Solutions has led to the manufacture and commercial sale of new electromechanical knee simulators based on our specifications in the UK, Europe and Asia.

Future work will look at how different variables in a total knee replacement can combine to influence the performance of implanted devices in patients.

# WOUND CARE AND SOFT TISSUE RECONSTRUCTION

Our portfolio of wound care and soft tissue reconstruction research projects focuses on the stratified design and manufacture of nonwoven collagen scaffolds.

Collagen can lack mechanical strength and stability and our research has sought to develop manufacturing processes that can overcome these limitations, while maintaining the other natural properties of collagen in a reliable way.

## INDUSTRY PARTNERS:

- COLLAGEN SOLUTIONS

# PHOTOACTIVE COLLAGEN-BASED MATERIALS FOR ADVANCED WOUND CARE

**Lead:** Professor Stephen Russell, University of Leeds
**Academics and researchers:** Dr Giuseppe Tronci, Professor David Wood, Dr He Liang


Chronic wounds are a major burden on healthcare systems around the world. In the UK alone, the annual cost of caring for patients with chronic wounds is expected to rise from £5.3 billion to £9.4 billion over the next five years.

Our aim has been to create new clinical products made from collagen, which are customised to improve healing time in wounds.

We have developed a new manufacturing platform capable of delivering atelocollagen, a low-immunogenic derivative of collagen, in a variety of product formats while still retaining the native triple helix structure that gives collagen its strength. This involves attaching a photosensitive organic compound to lysine groups on the atelocollagen backbone, which when exposed to UV or blue light, spontaneously cures the material by crosslinking.

This process means the collagen can be readily customised to enhance its strength, liquid absorption and degradation time according to clinical needs, either during the manufacturing process, or at the bedside. It is also possible to produce variants with unusual property combinations, such as very high liquid absorption combined with high wet strength.

Our patented platform can deliver the atelocollagen in a variety of forms – hydrogels, membranes, films, fibres, braids, surface coatings and nonwoven fabrics – that can be generated to precisely controlled dimensions while still being compliant with Good Manufacturing Practice.

By manufacturing atelocollagen fibres that can be assembled into nonwoven fabrics, it is possible to create clinically attractive low adherent dressings that can effectively manage wound exudate levels.

These dressings have been found to accelerate wound healing in pre-clinical evaluations and animal models, equivalent to market-leading products. They carry the additional capability of actively down-regulating the levels of matrix metalloproteinases, which can delay wound healing and cause inflammation.

Preparation is underway for a first-in-human pilot study of these dressings to treat digital ulcers in scleroderma patients, in collaboration with Chapel Allerton Hospital in Leeds. Meanwhile, work is ongoing to scale up the fibre and fabric manufacturing in a trial with a major European manufacturer of nonwoven biomaterial-based fabrics.

Among the other applications being developed with our clinical partners is a new membrane for guided bone regeneration in periodontal surgery. We are also working towards the production of ‘stem cell bandages’, where collagen-based fabrics are used to retain cells when wrapped around bone lesions to aid regeneration.

> *We are taking a natural biomaterial – one of the most important found in nature – and customising its format and physical properties to produce a new range of devices that can meet a variety of clinical challenges.*
>
> **PROFESSOR STEPHEN RUSSELL**

# DENTAL AND MAXILLOFACIAL

The aim of our dental and maxillofacial research project portfolio is to develop materials and surgical techniques for the production of novel complex implants in vitro, by developing bioactive cements and composites which can be processed in situ, to provide robust mechanical support to the musculoskeletal system. Core research has generated intellectual property now being applied to wider unmet clinical needs in dentistry.

## INDUSTRY PARTNERS:

- **DERMTREAT A/S**
- **CERAMISYS**

# ADHESIVE DRUG RELEASING ORAL PATCH

**Lead:** Professor Paul Hatton, University of Sheffield
**Academics and researchers:** Dr Martin Santocildes, Katherina Clitheroe, Dr Craig Murdoch, Dr Helen Colley, Professor Martin Thornhill, Professor Sarah Baker

Patients suffering with chronic mouth ulcers can experience severe impact on their quality of life, making eating and even speaking painful. These lesions are often difficult to treat as mouthwashes and creams only remain in the oral cavity for a limited period of time, making them poor methods for drug delivery. Equally, systemic medication needs to be taken in relatively large doses and can have undesirable side effects on the patient.

Techniques we have developed as part of our research on the manufacture of innovative medical devices for musculoskeletal tissue repair and regeneration offer a potential solution to this unmet clinical need in oral medicine.

We have created an electrospinning technique for manufacturing sheets of nonwoven polymer. Using this electrospinning technology, which was pioneered under MeDe Innovation, we have created adhesive patches that deliver drugs locally to mouth ulcers.

Working with an industry partner, Dermtreat A/S, we have optimised the composition of the patches to ensure a high surface area to volume ratio of fibres so they can rapidly deliver drugs that have been incorporated into the polymer fibre.

Adjusting the proportion of hydroscopic polymers in the patch also helped improve adhesion in the mouth – a particular challenge with high levels of moisture and movement in the oral cavity.

Our multidisciplinary team pioneered the use of live tissue engineered oral mucosa, which we used as a pre-clinical research tool to test the efficacy of the adhesive patches.

> *This is an unexpected outcome that has emerged from the electrospinning research conducted under MeDe Innovation, demonstrating how high quality research can potentially impact on a wide range of unmet clinical needs.*
>
> **PROFESSOR PAUL HATTON**

Work with our industry partner in Copenhagen has also shown in animal models that the drug is taken up directly at the site where pain is occurring.

A patent application for the techniques used to create these patches has been submitted, while Dermtreat has received a $17.7 million investment from Sofinnovo Ventures and Novo Seeds for the clinical evaluation of the technology, both as a direct result of our collaboration. Phase IIb multi-centre clinical trials are currently underway and the results are expected mid-2019.

There is also potential to use the technology to treat several other conditions in the mouth and other mucosal surfaces in the body. Working with an EPSRC sponsored CASE studentship, we are already making good progress in developing adhesive patches to combat infections caused by the yeast Candida albicans.

# ACKNOWLEDGEMENTS

## EXTERNAL ADVISORY BOARD

**Mr John Wilkinson (Chair)**
*MHRA*

**Mr Alan Ashby**
*DePuy Synthes*

**Ms Janette Benaddi**
*NAMSA Medvance*

**Dr Rob Bigsby**
*Biomet*

**Professor Gordon Blunn**
*UCL*

**Mr Phil Brown**
*ABHI*

**Dr Mark Claydon-Smith**
*EPSRC*

**Dr Simon Collins**
*Matortho*

**Mr Simon Denegri**
*NIHR*

**Mrs Sue Dunkerton**
*Knowledge Transfer Network*

**Mr Peter Ellingworth**
*ABHI*

**Professor Peter Gore**
*Newcastle University*

**Dr Suzanne Halliday**
*BSI Group*

**Professor Jane Jiang**
*University of Huddersfield*

**Dr Steve Kurtz**
*Exponent (USA)*

**Professor Nick Medcalf**
*Loughborough University*

**Professor Tony Miles**
*University of Bath*

**Dr Tim Morley**
*Smith & Nephew*

**Dr Claude Rieker**
*Zimmer Biomet (Switzerland)*

**Mr Christopher Rowe**
*Innovate UK*

**Dr Lim Ser Yong**
*SimTECH (Singapore)*

**Professor Alan Silman**
*Arthritis Research UK*

**Mr Richard Underwood**
*Exponent (USA)*

MeDe
Innovation

EPSRC Centre for
Innovative Manufacturing
in Medical Devices

MeDe Innovation
The EPSRC Centre for Innovative
Manufacturing in Medical Devices
c/o Institute of
Medical & Biological
Engineering,
University of Leeds,
LS2 9JT

+44 (0)113 343 0923
mede-innovation.ac.uk
info@mede-innovation.ac.uk
@MeDe_Innovation

EPSRC
Engineering and Physical Sciences
Research Council

UNIVERSITY OF LEEDS

UNIVERSITY of BRADFORD

Newcastle University

University of Nottingham
UK | CHINA | MALAYSIA

The University Of Sheffield.

UNIVERSITY OF CAMBRIDGE