# MeDe Innovation

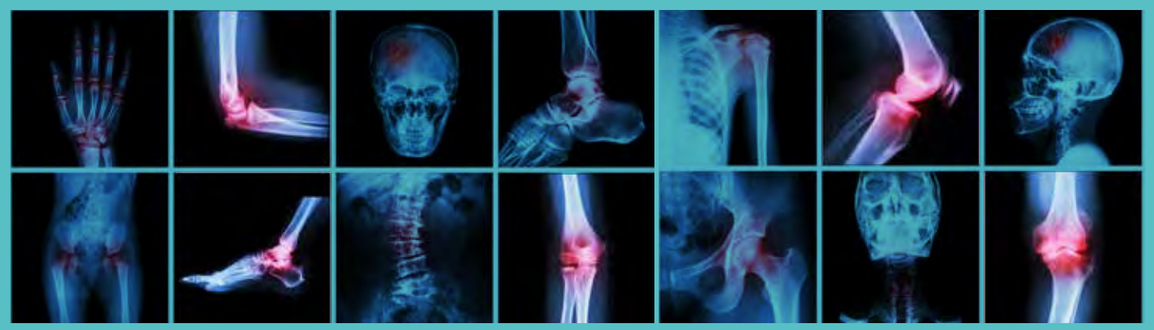
EPSRC Centre for Innovative Manufacturing in Medical Devices

# 2016 Annual review

# contents

Annual review









**This year marks an important milestone for MeDe Innovation as we reach the half-way point of our programme. Established with an Engineering & Physical Sciences Research Council (EPSRC) grant in 2013, we are taking the opportunity, in 2016, to assess what we have achieved in relation to the challenges we were set up to address. At the same time, of course, we are looking forward to the work we still need to do.**

As the EPSRC Centre for Innovative Manufacture in Medical Devices, MeDe Innovation's focus is the manufacture of implants, biomaterials and novel regenerative devices for the treatment of musculoskeletal disease and related disorders. This is a global market estimated to grow to $75 billion by 2020 which presents an opportunity of over £2 billion per year for UK manufacturing.

More than 50 million people have benefited from joint replacements worldwide since 1960, with 50 million more expected to do so by 2030. It's estimated another 50 million will benefit, over the next fifteen years, from emerging technologies such as regenerative devices and scaffolds. Enabling our ageing population to remain active improves overall health and quality of life and reduces the burden on our healthcare services. As such, our research addresses both a clear clinical need as well as a market opportunity.

The EPSRC Centres for Innovative Manufacturing were created to act as leaders in their field, driving forward innovative manufacturing research that addresses both long-term challenges and emergent opportunities.

One of the most important, long-term challenges for our sector is to improve the longevity and function of implants and devices, by increasing the precision of interventions. We are working with industry to support the future stratification of medical devices, developing the means to achieve more effectively targeted product ranges and working on personalised approaches to enable the right product to be designed and manufactured for each patient.

Our research is also supporting industry to respond to emerging opportunities offered by new technologies and materials, including scaffolds, regenerative devices, and 3D printed manufacture at the point of need.

Our achievements to date and the steps we plan to take over the next two years are laid out in the following pages. But we have not made this progress in isolation. Our collaborations – with industry and universities – have enabled us to generate £67 million of income working towards a strategically focused national effort.

We had 17 organisations on board in 2013. Today this number has grown to 39 and our research is feeding directly into our partners' design and manufacture processes. MeDe Innovation was set up as a collaboration between five universities – Leeds, Bradford, Newcastle, Nottingham and Sheffield. We now work with 15 UK universities and a further 27 international institutions – ensuring we are truly a national centre for innovation in medical device manufacturing. ■

**Professor John Fisher CBE**
Director, MeDe Innovation

# welcome

# A national centre

**MeDe Innovation was co-created with five founding universities – Leeds, Bradford, Newcastle, Nottingham and Sheffield – and 17 industry, clinical and regulatory partners. Three years on, our position as the national research centre for innovative manufacturing in medical devices has been consolidated, with 42 UK and global universities now on board, working with 39 organisations from outside academia.**

We've achieved this in a number of ways. We've invested in our people to create a critical mass of research and academic capacity within our core team that acts as a strong base for our activities: over the last three years, we've published 72 peer-reviewed journal papers and filed two patents.

Through our extensive development programme, 105 post-doctoral research associates and PhD students have received enhanced training opportunities, covering translation, innovation management and wider career development. Our early career researcher forum, spanning both academia and industry, provides networking and career development opportunities to help retain talent in the sector **(see pages 8-9).**

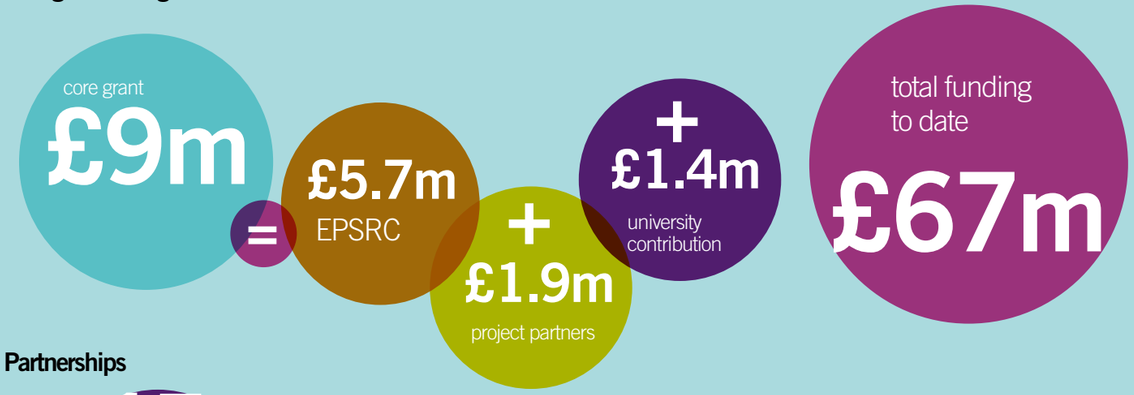
We've also reached out beyond our already extensive partnerships to create a national network of innovative medical device manufacturing expertise, with over 700 individual members.

This network is sustained through our successful events calendar, central to which is our annual conference, but that also includes workshops, seminars and lectures. These events help to both disseminate and inform our research, building and strengthening contacts across the sector **(see pages 6-7).**

Our patient involvement and public engagement work ensures our work is also reaching a lay audience.

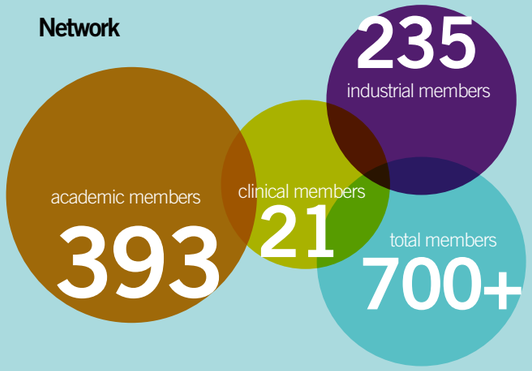
Finally, our Fresh Ideas Fund **(pages 10-11)**, has brought in new researchers and partners to the Centre, to work on innovative ideas that stand outside, but link into, our core research challenges. ■

## Leveraged funding

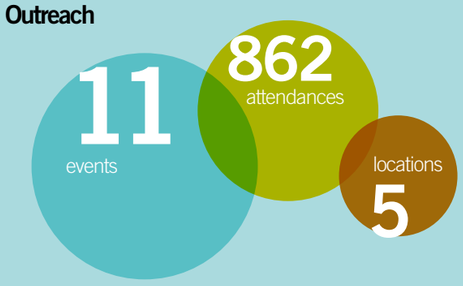



## Partnerships


## Network




## Outreach




## People


UNIVERSITY OF LEEDS · Newcastle University · The University Of Sheffield. · UNIVERSITY OF BRADFORD MAKING KNOWLEDGE WORK · The University of Nottingham UNITED KINGDOM · CHINA · MALAYSIA

# Our events

## Challenge Workshops

A series of half-day workshops addressing different challenges within the field of stratified device design and manufacture were held in Leeds during autumn 2015.

**Delegates heard presentations on current research in each area, before moving into discussion groups to consider the implications and potential impact of this research in industry and clinical practice. Stakeholders attending the workshops outlined the clinical and industrial need for novel devices and there was also the opportunity for delegates to discuss the potential impact and application of research findings, and the gaps and deficiencies that still need to be addressed.**

The first workshop focused on spinal applications. Presentations on current research outlined preclinical testing methodologies, as well as the development of a novel vertebroplasty cement, a nucleus augmentation gel, a bioresorbable fixation device and a lumbar fusion cage.

In the second workshop, delegates discussed applications for soft tissue, with presentations covering material assisted cell targeting, acellular biological scaffolds and nonwoven collagen scaffolds and wound dressings.

A knee and ankle workshop looked at preclinical knee and ankle simulation under a variety of kinematic conditions and using a combination of computational and experimental approaches.

In the final workshop, MeDe Innovation hip specialists considered a range of preclinical hip simulation approaches. Discussions on industrial perspectives were launched with a presentation from Cath Hardaker, WW Tribology Manager at DePuy Synthes and the ensuing debate focused closely on the international standards required for new simulation technologies to be adopted. ■



> A great event for both the high quality research presented and networking opportunities. I was particularly impressed with the content and standard of the short-format student presentations. Lots of new and informative content across many areas of orthopaedics/ bioengineering.
>
> **Dr Simon Collins, Research and Development Director, MatOrtho Ltd**

## Annual Conference 2016

Held in January, the event was MeDe Innovation's third annual conference.

**It was divided into three sessions, with the first, focusing on manufacture at the point of need, being led by Professors Kenny Dalgarno and Phil Coates. Professors Paul Hatton and David Grant led a second session focusing on manufacturing regenerative devices, biological and biomimetic scaffolds, while a third session, looking at stratified design and manufacture of orthopaedic implants, was chaired by Professors John Fisher and Ruth Wilcox.**

A number of MeDe Innovation researchers were also invited to deliver one-minute research 'pitches' about their projects. Topics ranged from the use of polyether ether ketone (PEEK) to manufacture orthopaedic trauma implants that resist microbial colonisation, to investigating the next generation of simulators for stratified pre-clinical wear simulation of total knee replacements.

The event also included a one-day meeting of MeDe Innovation Early Career Researchers. **See pages 8-9 for more details.** ■

> The conference provided a platform for me, as a researcher working in the field of medical devices development, to interact with colleagues from the medical device industry, and from healthcare providers and allowed me to understand developments in the medical devices field, especially on osteochondral scaffold development and their application.
>
> **Dr Chaozong Liu, Non-clinical Senior Lecturer in Orthopaedic Bioengineering, UCL**

**More than 150 delegates joined MeDe Innovation at the Centre for Life in Newcastle, to find out about the latest developments in the manufacture of medical devices.**

> The conference provided an excellent overview of the research being performed by MeDe Innovation partners and showcased the wealth of expertise available within the network. I found the event particularly useful for identifying academics or groups with mutual research interests and exploring potential collaborations.
>
> **Dr Becci Goodchild, Research Manager, Ceramisys Ltd**

# Developing our early career researchers

**MeDe Innovation's Early Career Researcher (ECR) network has created a vibrant forum for researchers to develop additional skills and, importantly, foster links with other academics and industry professionals in their field. Co-ordinated by Dr Marlène Mengoni at the University of Leeds, the network now has more than 60 participating researchers. Members have access to training and secondment opportunities, stay in touch via the ECR LinkedIn group and, of course, take part in MeDe Innovation events.**

## Presenting research

**MeDe Innovation's events calendar offers valuable opportunities for ECRs to gain experience in disseminating their work to a wider audience, as well as the chance to network with peers.**

Some ECRs presented their work as part of MeDe Innovation's guest lecture series, and the Annual Conference in January 2016, included a one-day ECR meeting, during which members contributed presentations about the expertise and experience they'd gained through being part of the ECR network.

Dr Danielle Miles, from the University of Leeds, spoke about her Wellcome Trust-funded secondment to JRI Orthopaedics Ltd, where she helped JRI's Technology Research Team develop an understanding of the regulatory framework for Advanced Therapy Medicinal Products (ATMPs), which covers many areas of regenerative medicine.

"It was interesting to see how the medicinal product regulatory standards differ from medical devices," says Danielle.

"Disseminating the knowledge I gained at JRI to the academic community was an important part of my secondment, and being able to do that through the MeDe Innovation ECR community was particularly valuable. It was also a really good way to practise what I had learned – not just about regulations, but about how industry, and in particular SMEs, operate.

"I am now putting that knowledge to use in my new role at Leeds as part of Translate: Realising medical technologies innovation in the Leeds City Region."

## ECR sandpit

**A new sandpit event, aimed at offering ECRs the opportunity to develop their expertise in larger, collaborative projects, takes place in York in autumn 2016.**

Organised by eight ECRs across the five MeDe Innovation academic centres, the event will be attended by academic coaches from the Leeds Medical Technologies Innovation and Knowledge Centre, who will help researchers enhance the key skills required to turn research ideas into grant-winning proposals.

Over two-and-a-half days, ECRs will share ideas, find links between their respective areas of expertise and pull together a research proposal, which they will then pitch to a panel of experts from academia and industry.

Dr Mazen Al-Hajjar, from the University of Leeds, is co-ordinating the event. "We're aiming to give ECRs the drive and focus to develop a robust proposal within a limited timeframe," he says. "They will improve their research writing skills as well as their presentation and communication skills. It's a big challenge to stand in front of a live audience and deliver your pitch!"

Two winning proposals will each receive £5,000 to spend on developing or delivering their projects.

## Postgraduate secondment programme

**Postgraduate secondment opportunities are also offered via the ECR network. The placement scheme, co-ordinated by Dr Natacha Rodrigues and Dr Ricardo Ribeiro at Newcastle University, aims to broaden researchers' experience while delivering impact in MeDe Innovation's research challenges.**

Successful applicants will each receive awards of up to £1,500 to spend a maximum of two months in local, national or international academic laboratories, companies, hospitals or government bodies.

The placements cover a variety of topics and aims: some researchers aim to enhance their own projects or get access to specialised facilities, while others look more broadly at developing new collaborations and gaining insight into clinical or industrial needs.

Secondees then report back to ECR meetings on how the funding has been spent and how it benefited the university and patients. ■

# Fresh Ideas Fund

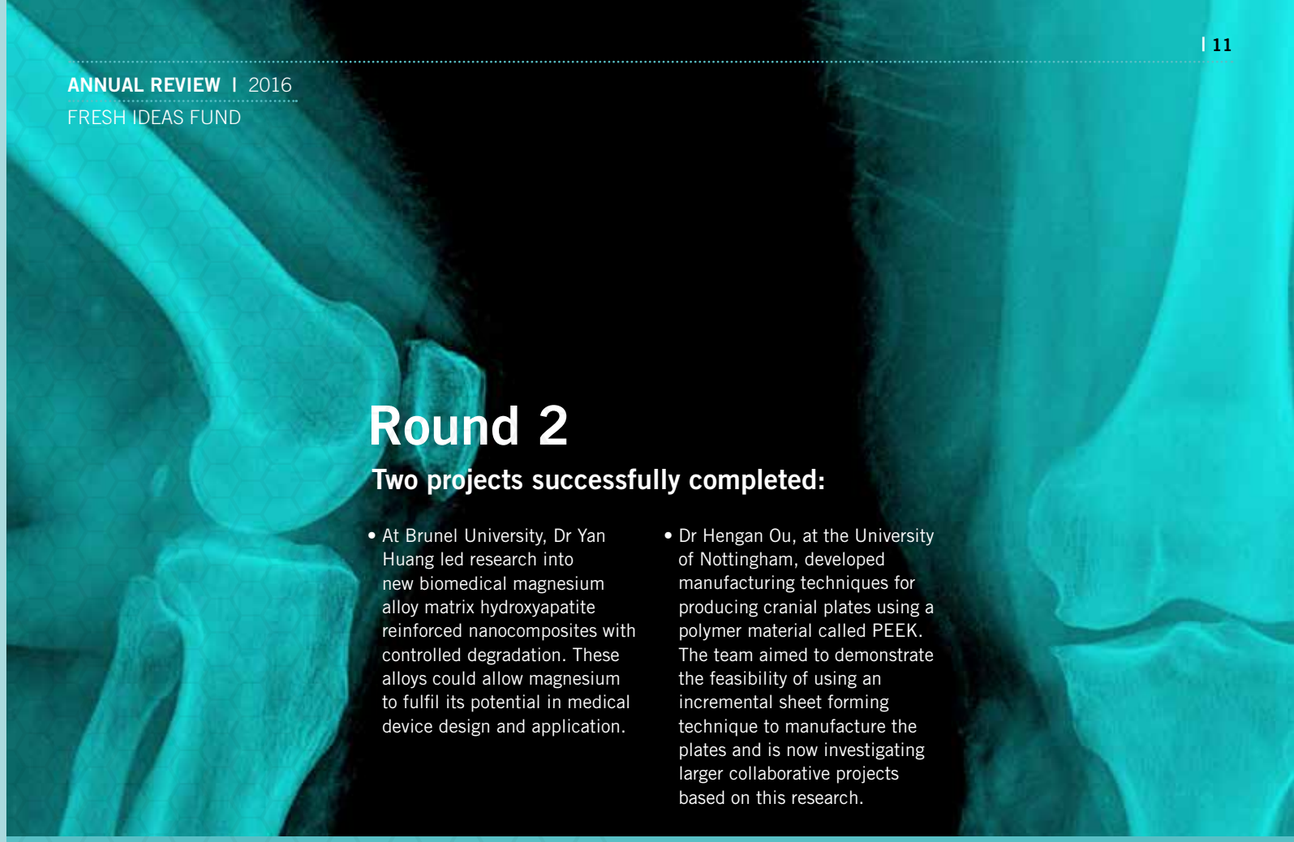
**MeDe Innovation's Fresh Ideas Fund was launched in 2014 to help researchers tackle small and short-term projects in musculoskeletal medical device manufacturing. The aim is to grow our portfolio of fresh ideas into big ideas by giving researchers up to £50k to develop projects to the point where they can be financed by larger funding streams.**

## Round 1

**Three projects successfully completed:**

- A team led by Professor Nicholas Dunne (pictured right) and Dr Helen McCarthy of Dublin City University and Queen's University Belfast directed a study into a thermosensitive gel that can form a biomimetic bone to ligament interface. The gel incorporates bioceramic and biological nanoparticles that are released to promote endochondral bone formation. The team successfully demonstrated the gel *in vitro* and *in vivo* and has established a number of national and international research collaborations through funding from the Medical Research Council, Science Foundation Ireland, National Science Foundation (USA), Invest Northern Ireland and the Department for Employment and Learning (Northern Ireland).
- A team at UCL has designed and fabricated an expandable scaffold for repairing large osteochondral defects (OCDs). Led by Dr Chaozong Liu, the team tested the scaffold's mechanical stability in sheep cadavers before filing a patent. A collaboration with Professor Noel Fitzpatrick, star of the Channel 4 TV series, *Supervet*, saw the scaffold used to treat a large OCD in a pet dog, with excellent results. The team is now testing the *in vivo* performance of the scaffold via proof of concept funding from Arthritis Research UK. If successful, the team will seek funding for a First in Man clinical trial starting in 2017.
- A way of producing patient-specific lumbar fusion cages using 3D printing from modified POSS-PCU material was investigated by a team led by Dr Deepak Kalaskar at UCL. The team has built partnerships with the Universities of Newcastle and Sheffield and internally with UCL's Medical Device Simulation Group. A collaboration with bioceramic implant manufacturer, Ceramisys Ltd, has secured £100k funding to investigate the optimum design and manufacturing process for the devices.





## Round 2

**Two projects successfully completed:**

- At Brunel University, Dr Yan Huang led research into new biomedical magnesium alloy matrix hydroxyapatite reinforced nanocomposites with controlled degradation. These alloys could allow magnesium to fulfil its potential in medical device design and application.
- Dr Hengan Ou, at the University of Nottingham, developed manufacturing techniques for producing cranial plates using a polymer material called PEEK. The team aimed to demonstrate the feasibility of using an incremental sheet forming technique to manufacture the plates and is now investigating larger collaborative projects based on this research.

## Fresh Ideas sandpits

MeDe Innovation's sandpit events enable researchers who submit highly-rated proposals to the Fresh Ideas Fund to come together to develop new collaborative projects.

### Butterfly wings inspire new implant surfaces

An interest in the design of implant surfaces that can resist microbial infection produced two separate research projects from a sandpit event directed by Professor Phil Coates and Professor Paul Hatton.

A joint project at the Universities of Bradford and Cardiff aims to create a surface for silicon-based prosthetic devices with self-cleaning properties similar to butterfly wings. Led by Dr Maria Katsikogianni and Professor David Williams, the researchers are combining physical and chemical engineering techniques to modify the surface of an implant to make it resistant to microbial adhesion.

A second project, based at Bradford, is investigating using micro-injection moulding techniques to produce implants using PEEK that have anti-microbial surface properties. Led by Dr Maria Katsikogianni and Dr Ben Whiteside, the team has produced a structured surface that prevents bacterial adhesion and biofilm formation.

### Prototype device for rotator cuff repairs

A sandpit event led by Professor Kenny Dalgarno at the University of Newcastle led to a joint project with the Universities of Leeds, Newcastle, and UCL to develop an advanced medical device prototype for rotator cuff tear repair, mimicking structure, function and mechanical properties of rotator cuff tissue components.

The team designed and manufactured a fibrous tendon tissue-like 'graft' to be joined to a porous titanium bone 'anchor' infiltrated with a protease-inhibiting, cell-homing collagen hydrogel. A proof of concept study will now be carried out, and next steps will focus on the biomechanical and biochemical evaluation of the device, as well as customisation of resulting prototypes. ■

# Research challenge 1

## Stratified design and manufacture

**Challenge Lead: Professor John Fisher CBE, University of Leeds**

The market in musculoskeletal implants and devices is growing globally, with the UK share expected to be £2 billion by 2020. Our ageing population, seeking to enjoy '50 active years after 50', is placing increasing demands and expectations on the orthopaedic medical device sector. Patients now want to continue to participate in a wider range of activities over their longer lifetimes, demanding increasing reliability and longevity from implants and devices, but at a lower cost.

**These demands raise significant challenges for the medical device sector, which our research is helping to address. The functional outcome and lifetime of medical implants is dependent on the degree of match between the design of the implant and the different variables among patients and surgical procedures.**

Reliability and longevity can be achieved through two approaches: customising a design to a specific individual, or by stratifying patients on the basis of relevant characteristics that enable the right design solution to be selected to fit each patient group. Designs also need to accommodate anatomical and surgical variation and provide the means for greater surgical precision.

Research challenge 1 incorporates four themes.

> "Because our research focuses on improving design and manufacture, the outcomes we achieve can be absorbed immediately into our partners' product development processes, helping these benefits reach the market and patients more quickly."
>
> **Professor John Fisher**

**Our first theme (1A)** focuses on functionally stratified design and manufacture of joint replacements – one of the most important surgical interventions worldwide. Over 50 million people have benefited from joint replacements since their introduction in the 1960s and it is estimated a further 50 million will benefit from improved, more reliable and longer-lasting joints by 2030. Through our sophisticated virtual and experimental simulations, we are helping manufacturers take a wider range of variables into account, including differences in surgical positioning and in patient anatomy and activity, to ensure designs function well across all these scenarios.

**Our second theme (1B)** is investigating stratified bioprocesses for the manufacture of acellular scaffolds – the next-generation treatment for osteochondral, cartilage and ligament repair. Traditionally, surgical repair has used synthetic biomaterials or tissue harvested from other sites in the patient. Neither provide an ideal match to restore or regenerate natural function. The bioprocesses we are developing to decellularise animal and human donor tissue will enable manufacturers to produce stratified acellular biological scaffolds tailored to the patient and specific tissue repair site, which can regenerate with the patient's own cells to deliver a more reliable and better outcome.

**Through our third theme (1C)** we are helping manufacturers develop a rapid and cost-effective process to functionally stratify all-collagen scaffolds to meet the needs of both patients and surgeons using novel nonwoven manufacturing technology. We are developing reliable methods of controlling the physical properties and reproducibility of collagen biomaterials, to enable performance to be customised to meet specific patient needs.

**Our fourth theme (1D)** is developing manufacturing processes for fully resorbable, hard tissue repair devices, with the ultimate aim of eliminating metallic implants. The manufacturing technologies we are developing will enable the production of next-generation multi-phase devices and new multi-phase materials for orthopaedic fixation and repair. Our research is also developing models to support both design and manufacture of implants and surgical interventions. ■

## Theme 1A

# Functionally stratified design & manufacture of joint replacements

### Outcomes

- New hip simulator now manufactured by Simulation Solutions
- Part 4 of international testing standard for hip replacement (ISO14242) out for consultation
- Revised international testing standard for knee replacement
- New simulation methods adopted and applied by DePuy Synthes, Invibio and Mathys.

### Key facts

Total funding: **£18.8m**
Clinical, industrial & academic partners: **22**
Researchers: **31**
Peer-review publications: **17**

### Leadership

Theme Leads: **Professor John Fisher, Dr Louise Jennings, Professor Ruth Wilcox – University of Leeds**

Academics: **Dr Alison Jones, Dr Sophie Williams, Professor Joanne Tipper, Professor Eileen Ingham – University of Leeds**

An increasingly active, ageing population is creating new demands and expectations for the lifetimes and function of joint replacements. For industry to effectively respond, deliver more reliable patient outcomes and remain competitive, manufacturers must design, develop and manufacture segmented product ranges targeted at stratified populations with high levels of precision.

This requires an in-depth understanding of the inherent variables in both the patient population – in terms of biomechanics and activity, and in the surgery – in terms of anatomy and positioning. Our research is creating virtual and experimental systems that can assess the impact of these variables on biomechanical and tribological function, for use in design, development, manufacture and regulatory approval. In collaboration with our industry partners, we are using these systems to develop new pre-clinical testing methodologies and standards for the hip, knee, spine and ankle, for our partners to apply in their product development processes.

## Our research

### PREDICTING THE IMPACT OF SURGICAL POSITIONING ON HIP PROSTHESES

We have developed both virtual simulation methods and pre-clinical experimental simulation that can assess the impact on function of combinations of differences in cup inclination angle and surgical positioning of the centres of cup and head along the medial-lateral plane.

Our virtual simulations can predict the combined impact of these surgical variations on the occurrence and severity of edge loading, the level of dynamic separation between the centres of the head and cup and the maximum force acting on the rim of the cup during edge loading. The virtual models, developed with DuPuy Synthes, are applicable to metal-on-polyethylene, and ceramic-on-ceramic bearings, and also simulate different levels of swing phase load and tissue tension. DuPuy Synthes is now using these models in the design phase of a new global product development programme.

We have experimentally determined the effect of surgical positioning in the medial-lateral plane on ceramic-on-ceramic bearings, and similar work is underway in metal-on-polyethylene bearings, using an enhanced simulator developed with our industrial partner, Simulation Solutions. This is currently being manufactured for commercial sale. On the basis of this research, we have drafted an addition to the new international standard for hip joint simulation testing (ISO14242), which is currently out for consultation. These advanced pre-clinical simulation methods are being applied and adopted by our industry partners DePuy Synthes and Mathys.


Our virtual simulations have advanced to combine the outputs of a dynamic model and a quasi-static, finite element, stress-and-strain model and we are now integrating these into a single model, to enable easier application in the design process.

Research is underway to determine variations in pelvic geometry and its relationship to both the spine and the biomechanical axis of loading in the body, in an anatomical co-ordinate system. This will help us develop virtual simulations to predict the impact of surgical positioning in both the medial-lateral and anterior-posterior planes. In parallel we are working with Simulation Solutions on commercial experimental simulation systems that can investigate the effect of variations in surgical positioning in all six degrees of freedom and aim to develop virtual simulations to support this.

We have also collaborated with engineers and clinicians from the University of Iowa, supported by the National Institutes of Health, to develop and validate new simulation methods of the effect of femoral head damage in metal-on-polyethylene hips.

### SIMULATION OF CONTACT MECHANICS AND WEAR IN KNEE AND ANKLE PROTHESES

Our novel virtual simulation system of contact mechanics, tribology and wear in the tibio-femoral bearing in knee joint replacements has been validated for different kinematic input conditions for both standard and crosslinked polyethylene.

This model, and the pre-clinical experimental methods we have developed in collaboration with

DuPuy Synthes and Simulation Solutions, have been used to predict wear for different simulator input conditions, kinematics and the positioning of the axis of rotation. We now plan to extend this work to include investigations of the effects of variations in surgical positioning of the femoral and tibial components.

Simulation Solutions has, with our support, developed a new electromechanical knee simulator, which has been validated against previous pneumatic simulation systems. We have also worked with DuPuy Synthes and Simulation Solutions to develop a new experimental simulation system for the patellar femoral joint and plan to extend this to incorporate different materials and designs.

These knee simulation systems have been used, in collaboration with Invibio, to study the tribological function of a new all-polymer knee replacement. We also aim to develop a hemi-arthoplasty model for when the patellar is not replaced.

By adapting a knee simulator to create an ankle joint simulator, in collaboration with Corin, we have investigated wear in ankle joint prostheses under different kinematic conditions and will extend this to include variations in surgical positioning.

As a result of our work, the kinematic input conditions for the international standard for testing knees have been revised. Our research is now using these new simulation systems to investigate the effect of different activities on knee prostheses, including high flexion, stair climbing and descent.

**SPINAL INTERVENTIONS**

Working with our industry partner, Simpleware, we have combined

shape and material property data from micro CT images to build finite element models that represent patient variance in the vertebrae. In a proof of principle project, we used these methods to determine the likelihood of subsidence following total disc replacement, based on the effect of disc sizing on vertebral bone stress. These patient-specific models have now been extended to represent the full functional spinal unit including disc and vertebral components. The models have been validated against experimental specimens and we are using them to assess the effect of patient variability on tissue sparing interventions such as nucleus repair and other surgical interventions such as vertebroplasty. ■

> “Matching the advances in existing designs and technology more closely to the patient population will provide substantial improvements and improve functional outcome and longevity. However, in other situations, the potential benefits of a new and radical design approaches can outweigh the additional cost and uncertainty. Our research, combining virtual and experimental simulation, enables industry to fully assess the relative value of these different approaches.”
>
> **Professor John Fisher**



## Theme 1B

# Stratified bioprocesses for the manufacture of acellular scaffolds

### Outcomes

- New natural knee joint simulator on the market
- NHS Blood & Transplant Tissue and Eye Services developing GMP process for human acellular scaffold
- Porcine acellular scaffolds in clinical trials for ligament and meniscus repair.

### Key facts

Total funding: **£17.5m**
Clinical, industrial & academic partners: **9**
Researchers: **39**
Peer-review publications: **10**

### Leadership

Theme Lead: **Professor Eileen Ingham, University of Leeds**

Academics: **Professor Ruth Wilcox, Professor John Fisher, Dr Louise Jennings – University of Leeds**

Acellular biological scaffolds – produced from animal or human donor tissue – can provide the next-generation treatment for soft tissue damage to the knee. Our research seeks to address some of the challenges that remain in developing acellular scaffolds for osteochondral, ligament or meniscus repair and replacement.

For manufacturers to produce a stratified product range with well-defined properties that can be matched to surgical and patient needs, they need to determine and control variations in the manufacturing process, from source materials, through process conditions to terminal sterilisation method, in order to deliver scaffold properties and function for patient and tissue specific repair. Effective pre-clinical testing and simulation methods are also required to ensure acellular scaffolds can be designed for, and their function and properties matched to, the individual patient.

# Stratified bioprocesses for the manufacture of acellular scaffolds

> The close involvement in this research on acellular biological scaffolds of both industrial and NHS partners demonstrates the important clinical need and market opportunity we are addressing. Our work spans both disruptive technologies and products that fit easily into existing surgical procedures, with the latter already moving quickly towards clinical use.
>
> **Professor Eileen Ingham**

## Our research

### OSTEOCHONDRAL REPAIR

Our initial research into the physical and biological properties of cartilage and bone from different animal species and different joints has led us to focus on two sources for osteochondral repair: porcine and bovine tissue.

We successfully developed a process to decellularise porcine bone. Twelve-week tests in sheep condyles demonstrated that the grafts showed excellent integration into the bone, a key step in achieving osteochondral repair.

Decellularisation of porcine and bovine osteochondral plugs can cause damage to the collagen fibres of the cartilage at the cut edge. Our solution was to develop a decellularisation process for a complete porcine condyle. Pilot studies of osteochondral grafts created through this process have been carried out in sheep condyles over a 12-week period.

A 52-week large animal study is planned for 2018 and we are developing an *in vitro* knee organ culture model to enable complementary pre-clinical evaluation of the osteochondral grafts. We are also continuing to look at the impact of surgical positioning, physical properties of the scaffold and relative defect size on the biomechanical and functional outcome of the repair.

### LIGAMENT REPAIR

We have developed bioprocesses to decellularise two scaffolds for anterior cruciate ligament (ACL) replacement – porcine super-flexor tendon and human donor bone-patellar tendon-bone (hBTB). This work also enabled us to understand how variables within the process impact on the scaffold's biomechanical properties. Large animal studies have been completed for ACL replacement in sheep, to study fixation and integration to bone and repair and regeneration in a full scale model. For the porcine super-flexor tendon, we have also looked at the impact of different terminal sterilisation processes on the scaffold's biological and biomechanical properties. Our research and IP has been translated to our industrial partner, Tissue Regenix Group, and clinical trials are now underway of a new product, OrthoPure™ XT dCELL® Tendon.

Following successful completion of large animal studies, our novel bioprocess for decellularisation of hBTB is feeding into a GMP manufacturing process, being developed by our clinical partner, NHS Blood & Transplant Tissue and Eye Services, which will enable a hBTB scaffold for ACL replacement to be available to UK orthopaedic surgeons. This includes work on a novel sterilisation process.

Future work will take forward our *in vitro* functional and preclinical testing of ligamentous repairs, including studies of fixation. We also plan to address whether differences in physiology and function between men and women will require ACL products to be stratified by gender.

### MENISCUS REPAIR

Our research is providing robust methods for the evaluation of the mechanical properties of decellularised porcine meniscus. We are also continuing to develop biomechanical models and carry out functional and biomechanical *in vitro* research to understand the effect of disease states and degeneration of the meniscus and its attachments on the mechanics of the knee. These include meniscus tears, meniscectomy and meniscus extrusion.
A decellularised porcine meniscus is already being commercialised for partial meniscus repair by our industrial partner, Tissue Regenix Group, with a clinical trial underway of OrthoPure™ XM (porcine meniscus), which, if successful, will enable a submission for a CE mark to be completed.

### NATURAL KNEE JOINT SIMULATION SYSTEMS

Our novel biphasic computational model of the natural knee has underpinned our work with industrial partner, Simulation Solutions, to create a natural knee joint simulator that will support the development and pre-clinical testing of acellular scaffolds for tissue repair in the knee. The system and methods have been validated and the natural knee joint simulator is now available commercially as well as enabling us to further our research within this theme.

The simulator will be further refined through studies of autopsy human knees and parametric studies to determine how individual soft tissue elements, including ligaments and the meniscus, impact on the knee's function. We will also be working with Simulation Solutions on a natural knee patellar femoral simulation model. ■

## Theme 1C

# Stratified design & manufacture of nonwoven collagen scaffolds

### Outcomes

- Patent application filed for new atelocollagen synthesis process
- New materials under evaluation for US medical device market
- First *in vivo* studies successfully completed.

### Key facts

Total funding: **£2.56m**
Clinical, industrial & academic partners: **8**
Researchers: **18**
Peer-review publications: **7**

### Leadership

Theme Lead: **Professor Stephen Russell, University of Leeds**

Academics: **Professor David Wood, Dr Giuseppe Tronci – University of Leeds**

A major barrier preventing more widespread use of all-collagen scaffolds in bone and tissue repair has been the lack of a rapid and cost-effective manufacturing process that will enable the final product to be functionally stratified to meet the needs of both patients and surgeons.

Our research is addressing this challenge, by developing reliable methods of controlling the physical properties and reproducibility of collagen biomaterials and incorporating these into a functionally stratified design and manufacturing process, to enable performance to be customised to meet specific patient needs.

From initial applications in maxillofacial surgery and wound care, our work is now investigating the use of atelocollagen hydrogels and nonwoven scaffolds for bone and tendon repair at other sites.

## Our research

**MANUFACTURING BIOPROCESSES FOR FUNCTIONALISED COLLAGEN**

We have developed a new bioprocess (patent pending) to manufacture functionalised atelocollagen biomaterials from commercially sourced GMP collagen.

In addition to creating 100 per cent collagen hydrogels through this process, we have also developed new manufacturing methods to create other clinically useful formats for functionalised collagen, including films, fibres and nonwoven fabrics.

A distinctive feature of the atelocollagen hydrogel produced using our technology is that it can be crosslinked by irradiation with commercially available UV light sources (similar to the curing of resin-based dental materials with blue light). This allows its physical properties to be both modified during manufacture to fit patient or surgical requirements and manipulated by surgeons in the clinic. Our atelocollagen hydrogels also retain over 70 per cent of the triple helical features of native collagen, while displaying high swelling ratios.

Potential applications for collagen hydrogel include a tooth pulp capping device, to prevent pain and/or infection due to pulp exposure as a result of decay, trauma or tooth cavity preparation.

We have also developed a new means of manufacturing wet-stable collagen fibres with superior tensile modulus and strength, using wet spinning and diacid-based crosslinking of collagen triple helices.

We can now determine how compositional and process factors will affect product properties and behaviour in physiological conditions, enabling us to customise fibre structure and properties by adjusting manufacturing parameters. By coating the crosslinked fibres with carbonated hydroxyapatite (CHA), we have been able to mimic the constituents of natural bone extra cellular matrix (ECM) to create an attractive biomaterial for guided bone regeneration (GBR).

An alternative to bone grafts or substitutes, GBR uses bio-absorbable membranes that form a conduit, guiding the migration and homing of endogenous stem cells towards the defect area.

We have worked with Collagen Solutions PLC to establish a GMP raw material supply that will enable the atelocollagen synthesis process to be scaled up to commercial levels. A small-scale manufacturing system for hydrogels and wet-spun fibres has been set up at the University of Leeds, which will enable us to evaluate material properties for commercial application.

Our future research will investigate the capability of the new atelocollagen materials to regulate molecular functions and control microbial activity to reduce the risk of infection – a key concern in periodontal surgery.

**We can now determine how compositional and process factors will affect product properties and behaviour in physiological conditions, enabling us to customise fibre structure and properties by adjusting manufacturing parameters.**

**WOUND HEALING AND ORAL SURGERY**
Our technology would enable the first fibre-based, nonwoven wound dressing to be made from 100 per cent collagen and we have already attracted interest in our new materials from a global fibre and nonwoven manufacturer, who is currently evaluating them for the US medical device market.

We have carried out an *in vivo* study using prototype atelocollagen materials manufactured by the new technology on hard-to-heal, full-thickness diabetic wounds in a mouse model. The materials promoted 99 per cent wound closure within 20 days, similar to two commercial gold standards used in chronic woundcare: Aquacel® and Mepilex®. Our materials showed faster wound healing in comparison to Mepilex®.

These findings are also relevant to oral surgery as the risk of developing oral soft tissue lesions from periodontal diseases is higher amongst diabetes patients than the general population.

Working with our clinical partners at Barts & The London School of Medicine and Dentistry, Queen Mary University of London and the University of Leeds School of Dentistry, we plan to run *in vivo* studies to assess the effectiveness of our membranes for use in GBR and wound healing in oral, periodontal and maxillofacial surgery.

**BONE AND TENDON REPAIR**
We are working with clinicians at the Leeds Teaching Hospitals Trust on two new applications for our materials for use in bone repair.

The first uses our atelocollagen membrane to contain a hybrid graft, made from a scaffold loaded with the patient's own bone marrow. The membrane is designed to act as a tissue-engineered periosteum, and the graft will be used to repair bone defects resulting from tumour resection or trauma, which are at a critical size that is difficult to treat.

The second application involves a membrane-based, tissue-engineered construct for complex fracture repair that would be implanted during surgery as a GBR device. The biomimetic membrane, combined with growth factors or minimally manipulated autologous stem cells, has the potential to greatly improve bone healing and repair.

We are also developing a new tendon-bone tissue connector for use in rotator cuff repair, using a cell-homing atelocollagen hydrogel reinforced with collagen fibres.

We are designing the device to have a biomimetic structure and graded mechanical properties, which should provide offer both mechanical repair and biological enhancement, to improve surgical outcomes. ■

Theme 1C

> A major advantage of our new manufacturing platform is that it enables the same basic material to be easily adapted to a surgeon's requirements and the needs of the patient. We believe this will enable the technology to be more readily adopted, particularly in the field of oral surgery.
>
> **Professor Eileen Ingham**



## Theme 1D

# Manufacture of bioresorbable multiphase fixation devices and virtual modelling

### Outcomes

- Two patents pending: for novel 'osteospheres' and a spinal surgery technique
- New manufacturing method developed for resorbable composite
- First ever visualisation of spine deformation under dynamic load.

### Key facts

Total funding: **£5.2m**
Clinical, industrial & academic partners: **29**
Researchers: **23**
Peer-review publications: **12**

### Leadership

Theme Leads: **Professor David Grant, Dr Ifty Ahmed, Dr Donal McNally – University of Nottingham**

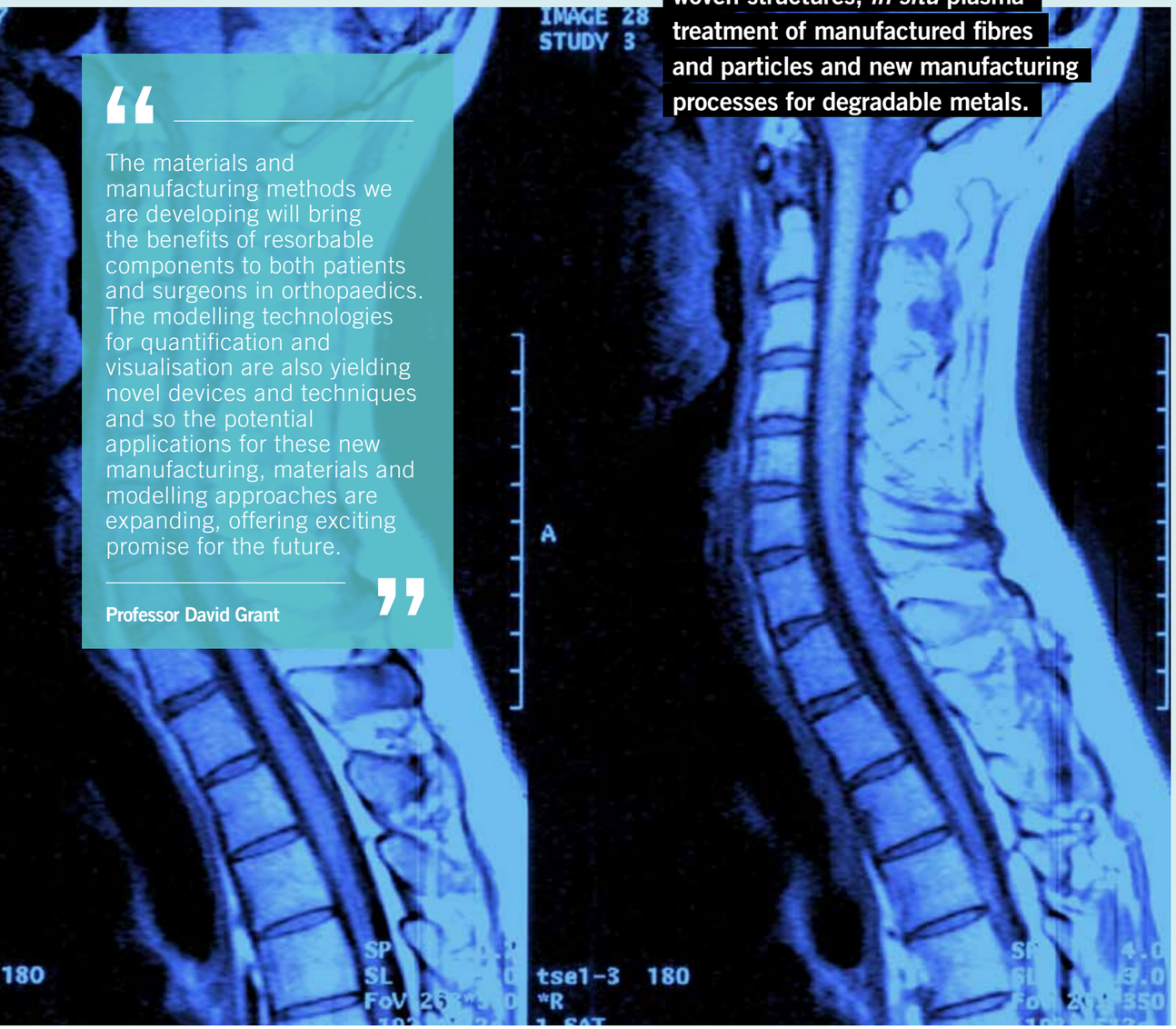
Academics: **Dr Davide De Focatiis, Dr Derek Irvine, Professor Edward Lester, Dr Joel Segal, Professor Nick Warrior, Dr Colin Scotchford, Dr Virginie Sottile – University of Nottingham**

Fully resorbable, hard tissue repair devices have the potential to greatly enhance quality of life for patients, by eliminating the need for metallic implants and the risks inherent in elective surgery to remove them, including additional trauma, anaesthesia and potential infection.

Our research is developing manufacturing technologies for next-generation multi-phase devices and new multi-phase materials, with initial applications in orthopaedic fixation and repair. We are also developing computational models, based on medical imaging, to enable the design and manufacture of patient-specific implants and to support surgical interventions.

# Manufacture of bioresorbable multiphase fixation devices and virtual modelling

**Future research is planned to investigate the modification of feed materials for manufacturing processes, incorporation of nanoparticles into woven structures, *in situ* plasma treatment of manufactured fibres and particles and new manufacturing processes for degradable metals.**




> The materials and manufacturing methods we are developing will bring the benefits of resorbable components to both patients and surgeons in orthopaedics. The modelling technologies for quantification and visualisation are also yielding novel devices and techniques and so the potential applications for these new manufacturing, materials and modelling approaches are expanding, offering exciting promise for the future.
>
> **Professor David Grant**

## Our research

### MANUFACTURING TECHNOLOGIES

Our research has designed a resorbable composite, composed of a matrix of polylactic acid reinforced with phosphate glass fibres. We have successfully developed a manufacturing method from which we have produced prototype plates and intramedullary nails.
Our compression moulding method ensures thorough melt impregnation with limited polymer degradation by pressure cycling during the consolidation stage. This enables our material to maintain 30 per cent higher flexural strength than that achieved using a conventional static pressure profile. We are now exploring scale-up methodologies and other manufacturing technologies, such as co-extrusion, wire-coating and *in situ* polymerisation, in collaboration with our industrial partners, GTS and NetComposites.

Phosphate-based glass (PBG) coatings of orthopaedic fixation devices, manufactured using physical vapour deposition (PVD), have the potential to promote osseointegration while undergoing controlled degradation, but their use has been restricted due to difficulties in targeting and in controlling the relative quantities of the different elements. Using radio frequency magnetron sputtering, we have overcome these challenges to develop a pilot-scale manufacturing technique which enables reproducible PBG thin films to be deposited on orthopaedic substrates. We are able to manipulate the process to affect the rate of degradation or bonding between materials, and are exploring methods to introduce other elements into the structure to enhance osseointegration or antimicrobial properties, the latter in collaboration with Zimmer-Biomet. We are now working to scale up the process and our research is being tracked by DePuy Synthes and JRI Orthopaedics.

In collaboration with Promethean Particles, we have developed an encapsulation technology to enable the co-precipitation of short chain oligomers onto osteoconductive nano-hydroxyapatite. Encapsulation can enhance dispersion compared to uncoated ceramic nanoparticles, to address agglomeration issues observed in nano-composite manufacture. We are now investigating a range of dispersants to understand the optimum length of the oligomer and end group required to deliver highly dispersed nano-composite structures and how these influence mechanical performance and different manufacturing processes. Evonik Industries AG and TESco Associates are in discussions with us regarding this area of research.

A patent is pending for our new manufacturing method to produce resorbable, porous calcium phosphate microspheres that can be loaded with autologous stem cells to support bone tissue regeneration. We are working with our industrial partners, Surgical Dynamics and Ceramisys, on a prototype device for minimally invasive delivery of these novel 'osteospheres' for potential prophylactic treatment of osteoporosis. We are working to further develop and scale up our manufacturing method for both porous and solid degradable microspheres.

With JRI Orthopaedics, we are also developing a resorbable, non-delaminating scaffold for oseochondral grafts made from chitosan, a fibre taken from crustacean shells, and are gathering *in vitro* data to support the commercialisation of this product.

Future research is planned to investigate the modification of feed materials for manufacturing processes, incorporation of nanoparticles into woven structures, *in situ* plasma treatment of manufactured fibres and particles and new manufacturing processes for degradable metals.

### VIRTUAL MODELLING

Our new technology for use in spinal surgery has undergone successful pre-clinical trials and a patent has been applied for. We are working on a commercial demonstrator of the technology, which also has applications in image guided and robotic surgery in other fields, including orthopaedic and maxillofacial surgery. In collaboration with a global spinal device manufacturer, we are planning a full clinical spinal surgery trial and will identify other partners to develop the technology in other areas.

We have developed intelligent noise reduction techniques to quantify the trabecular architecture of the spine from clinical cone beam computed tomography (CBCT) image data sets where the resolution is only just sufficient to identify trabeculae. This technique has enabled us to quantify the remodelling of bone graft substitute material (DBM with added peptide) into normal trabecular bone in anterior cervical fusions. By using different initial noise reduction and filtering, the technique should be applicable to high resolution CBCT and peripheral CT as well as conventional CT, though further validation will be required. It also has applications for other regions of the body.

Using an MRI-compatible spinal loading device, in combination with MRI imaging sequences and quantitative post processing, we have been able to quantify and visualise the deformation and motion of the spine under dynamic loading. We have successfully demonstrated the technique in one patient with a healed lumbar burst fracture.

The technique is the first to enable instantaneous elastic deformations to be studied, rather than 'creep' behaviour, while retaining good contrast between soft tissue and bone and reducing radiation exposure. This has opened up a new field of research for us to continue to explore. ■

# Research challenge 2

## Manufacturing at the point of need

**Challenge Lead: Professor Kenny Dalgarno, Newcastle University**

Our second research challenge is looking at innovative ways to treat musculoskeletal conditions at an early stage, by enabling the in clinic manufacture of individualised implants and creating robust implants that could be delivered arthroscopically. Our main focus for this challenge is on osteochondral repair and tissue fixation devices. Our aim is not that the surgeon or clinician would carry out every step of the manufacturing process, but that key elements of the final configuration can take place either in the clinic or *in vivo*.

**Many interventions for osteochondral repair currently require open surgery, because of the difficulty of creating osteochondral plugs that are strong enough to be load-bearing but small enough to be used in minimally invasive interventions, and we have developed and are testing new devices to achieve this.**

We are also researching implants that can be adapted to the patient *in vivo*, an important approach for enabling implants for both osteochondral repair and tissue fixation to be personalised to the patient. Artificial biomaterials already exist that are delivered *in vivo*, such as injectable bone cements used in vertebroplasty and kyphoplasty.

Our research seeks to extend the range of materials and structures which could be delivered in this way, while creating increased mechanical or biological functionality in the implant.

Our research is also adapting manufacturing techniques that could be used easily and cost-effectively by the surgeon or clinician to create a personalised implant for open procedures.

We are developing manufacturing processes which can enhance the functionality of implants by enabling them to be adapted to the patient in the clinic in a controlled and systematic manner, either by creating a geometry to match the patient or by incorporating some of the patient's own cells.



## Theme 2A

# Minimally invasive implantation of bioactive materials

### Outcomes

- Bioceramic scaffolds manufactured through 3D printing
- Successful *in vivo* studies of biphasic scaffolds
- Bioactive membranes created using new 'layer-by-layer' technique.

### Key facts

Total funding: **£10m**
Clinical, industrial & academic partners: **19**
Researchers: **19**
Peer-review publications: **6**

### Leadership

Theme Lead: **Professor Kenny Dalgarno, Newcastle University**

Academics: **Professor Paul Hatton, Dr Ílida Ortega Ascencio – University of Sheffield**

**Dr Piergiorgio Gentile, Dr Oana Bretcanu, Dr Ana Ferreira-Duarte – Newcastle University**

**Professor Phil Coates, Dr Pete Twigg – University of Bradford**

Minimally invasive interventions result in patients spending less time in hospital and recovering more quickly, thereby reducing overall treatment costs and enabling many more patients to be treated.

Our research aims to increase the scope and effectiveness of minimally invasive interventions by developing materials and processing techniques which will enable novel bioactive implants for osteochondral repair and tissue fixation to be arthroscopically delivered to the body or created *in vivo*.

# Minimally invasive implantation of bioactive materials

> Arthroscopic techniques are commonly used in orthopaedic surgery, including techniques to deposit biomaterials *in vivo*, such as injectable bone cements to treat spinal conditions. Our research is developing new materials to extend the options for arthroscopic techniques, so they can become common practice for osteochondral repair across the musculoskeletal system.
>
> **Professor Paul Hatton**

**We have now created a layer-by-layer functionalised membrane that incorporates peptides known to improve osteoblast adhesion and mineralisation. *In vitro* studies showed this membrane supported increased stem cell growth compared to untreated membrane and better bone tissue regeneration following *in vivo* studies.**

> Our research brings innovative materials and processing techniques to address an unmet clinical need – how to treat early stage osteochondral defects and tissue fixations without the need for open surgery. Collaboration with our industrial and clinical partners is enabling us to look at various approaches, including new bioactive materials, *in vivo* delivery and in-clinic manufacture.
>
> **Professor Kenny Dalgarno**

## Our research

### PREFORMED BIOACTIVE STRUCTURES

Using the 3D printing process of binder jetting followed by sintering, we have created bone replacement devices from apatite-wollastonite glass ceramic. We are able to control the evolution of material phases through the sintering process, creating mechanical properties within a porous scaffold that enables it to be load-bearing, with a modulus similar to cortical bone.

The 3D printing process allows us to create macroscopic channels within the scaffold, resulting in a geometry that can support new bone growth and vascularisation. *In vitro* tests have shown the bioceramic scaffolds support the growth of human bone marrow mesenchymal stromal cells (MSC), while *in vivo* studies in mice resulted in both osteoid and tissue growth on the implant. We have produced bone plugs and fixation devices using this method and are now progressing to bone anchors and larger, custom implants for bone repair.

To improve the scaffold's ability to support osteochondral repair, we have developed a technique to thermally bond macroporous polylactic acid (PLA) and polycaprolactone (PCL) structures onto the bioceramic surface. These macroporous polymer structures are manufactured through a combination of fused deposition modelling and laser cutting, which ensures that the porous structure is open across all external surfaces. *In vivo* studies in rats showed excellent osseointegration after 12 weeks, and these biphasic osteochondral plugs are now being tested in a large animal study, funded through Arthritis Research UK. We are also researching triphasic osteochondral implants by incorporating natural-synthetic collagen gels to promote cartilage regeneration.

In a different approach to developing osteochondral implants, we are working to develop materials that mimic the functional gradient in stiffness between bone and cartilage. As this differs by three orders of magnitude, an implant with a similar gradient should reduce interfacial shear stress and adhesive failure. We have successfully formulated one implant material using organic (polyvinyl alcohol) and inorganic (hydroxyapatite and tricalcium phosphate) phases and another comprised of self-reinforced PVA foam/PVA hydrogel composites. The dynamic mechanical properties of both these materials have been analysed and they have been tested *in vitro* to determine how they interact with chondrocytes, osteoblasts and stem cells. We now plan to move to *in vivo* studies and test their biotribological performance.

### MATERIALS FOR *IN VIVO* MANUFACTURE

We have developed a technique to manufacture osteochondral plugs *in vivo*, by building up the implant layer by layer through the sequential deposition and cure *in vivo* of a photocurable polymer. This technique is able to create implants of up to 8mm diameter and 7mm high within clinically useful timeframes (between 5-10 mins). Our initial research used HEMA, a commonly used photocurable dental biomaterial, as a model material but future work will focus on new materials for use in this technique.

Using our technique, the defect site could be isolated prior to the implant manufacture using a biofunctional membrane, which would also isolate surrounding tissues from the uncured material and contribute to the repair. We have created electrospun polylactide-co-glycolide (PLGA) polymer membranes made fibres with diameters ranging from several micrometres down to few nanometres. As PLGA membranes are not bioactive, we have

developed a layer-by-layer (LbL) technique which modifies their surface to improve their biological response.

The LbL technique is a solvent-free process, able to coat all the surface with a homogenous, ultrathin film incorporating biomolecules or drugs. The technique allows the film thickness and release of the biomolecules to be controlled. We initially used the technique to incorporate an antibiotic drug into the membrane to improve its anti-microbial properties.

We have now created a LbL functionalised membrane that incorporates peptides known to improve osteoblast adhesion and mineralisation. *In vitro* studies showed this membrane supported increased stem cell growth compared to untreated membrane and better bone tissue regeneration following *in vivo* studies. We are now looking to translate this work into the medical device manufacturing process.

We have also used the LbL technique to create a chondrogenic membrane, by incorporating transforming growth factor-ß (TGF-ß), to help maintain the native chondrocyte phenotype and enhance the biochemical composition and functional properties of the neotissue. *In vitro* studies using bovine articular cartilage cells have shown that the functionalised membrane is substantially better at supporting cell viability and proliferation than an untreated membrane.

We are looking at other options for membrane materials, including complex composite structures based on the combination of bioactive glasses or ceramics with biocompatible bioresorbable polymers. ■

## Theme 2B

# Processes for in-clinic manufacture

### Outcomes

- Two new techniques developed for cell deposition
- New osteochondral scaffold developed for large defect repair
- Fixation devices developed to adapt shape *in situ.*

### Leadership

Theme Lead: **Professor Kenny Dalgarno, Newcastle University**

Academics: **Professor Phil Coates, Dr Pete Twigg – University of Bradford**

**Dr Ana Ferreira-Duarte, Dr Piergiorgio Gentile, Dr Oana Bretcanu – Newcastle University**

### Key facts

Total funding: **£10m**
Clinical, industrial & academic partners: **13**
Researchers: **12**

An effective method of stratifying musculoskeletal implants is for them to undergo their final configuration in the clinic, potentially even during surgery, to adapt them to a specific patient.

Our research is developing methods for rapidly and reliably combining cells with structural biomaterials, to enable scaffolds to be impregnated with cells harvested from the patient as they are built in the clinic.

We are also developing manufacturing methods that will enable load bearing, bioactive, personalised osteochondral implants to be defined and configured in the clinic and researching bone and soft tissue fixation devices which can adapt *in vivo* in response to bone shape and fixation hole quality.

## Our research

**CO-PROCESSING CELLS AND BIOMATERIALS**

We have developed a cell encapsulation process that enables droplets of media containing single cells to be deposited using an ink-jet printing technique. Groups of encapsulated cells can also be deposited through the use of micro-valve cell deposition. The advantage of both approaches is that they enable cells to be reliably printed at rates of up to 1,000 cells per second using scalable bio-printing techniques.

Cells are encapsulated in poly-L-lysine (PLL), which creates a temporary, electrically charged shell. This prevents the bio-ink from agglomerating and clogging the print head.

The shell is resorbed within a few hours, restoring normal cell function.

A jet impingement process we have developed enables cells to be rapidly deposited within gels on biomaterial substrates. The process directs two jets of gel precursors at one another and these meet and react in mid-air, forming a gel which lands on the substrate. We have used the process to deposit a layer of fibrin gel, created by mixing thrombin and fibrinogen through two impinging jet flows.

Cells printed in fibrin gel using this process retain the same viability as those maintained in fibrin via conventional means. We are now looking at the processing conditions required for other gels, including natural-synthetic hybrid gels.

As we have successfully established reliable methods for cell deposition, we are now working on integrating our cell printing with scaffold production, and establishing the best processing route for different cell types.

> “Rather than try and enable an implant to be completely manufactured in the clinic, our research aims to enable the surgeon to be in control of the final stage of the process. The techniques and materials we’re developing will eventually allow surgeons to personalise an implant to a patient within the timeframe of a single operation.”
>
> **Professor Phil Coates**

# Theme 2B

### IN-CLINIC MANUFACTURE OF THREE PHASE STRUCTURES

We have successfully developed a biomaterial structure that could be used to repair larger osteochondral defects, combining cartilage, cortical bone and cancellous bone phases. We envisage this could be manufactured in the clinic using three different processes. A personalised cancellous bone analogue structure would be manufactured from an apatite-wollastonite and polylactic acid composite filament using the 3D printing technique of fused deposition modelling (FDM). A porous bioceramic-polymer composite would then be ultrasonically bonded to the structure, as an analogue for cortical bone. A gel phase, closely matched to native cartilage, would then be deposited using the jet impingement process described earlier.

We are now taking this forward by developing rules for the rapid design of the personalised cancellous bone analogue, and enhancing its 'logpile' structure through the addition of a ceramic filler in the polymer strands. We also plan to conduct *in vitro* studies of ultrasonic bond strength between porous ceramic and polymer structures.

### SHAPE MEMORY FIXATION DEVICES

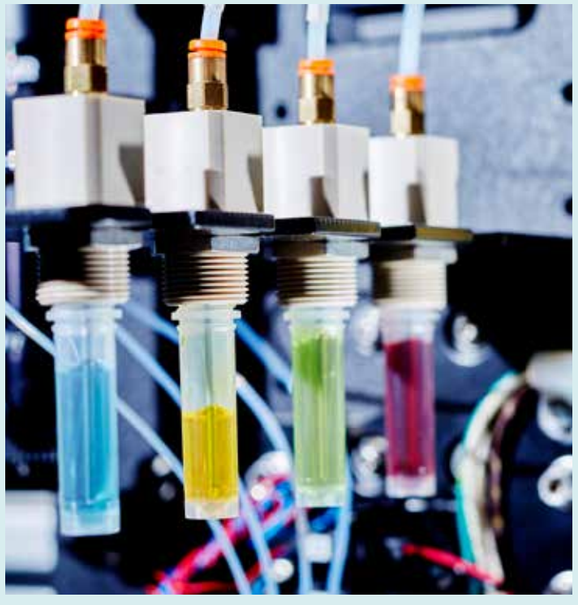
We are using die drawing techniques to create solid and cannulated fixation devices that can be programmed to change shape *in situ*, on exposure to temperature or body fluid, in order to adapt to the surrounding bone topology. The devices can also be programmed to degrade to expose salts or scaffolds that promote osteogenesis, although we are working on both resorbable and inert devices. The aim is to create devices that can be implanted through minimally invasive procedures for use in fixing soft tissue to bone or bone to bone.

We are looking initially at applications for shoulder repair, with future applications to include anterior cruciate ligament, knee joint and scaphoid repair. Our research is now looking at how to overmould features onto solid phase oriented cores and the use of 3D printing of two polymers with different functionalities for subsequent die drawing.

We are able to achieve the desired mechanical properties using die drawing processes because these enable control of polymer molecular orientation in the solid phase. We are also using micro-injection moulding to impart molecular orientation in specific regions, which allows us to confer shape memory properties to selected areas of the device. This might be used, for example, on a fixation device where only the main body, but not the ends, need to retain shape memory. We are continuing research to understand how to better control orientation and mould end-features for shape memory compression screws.

We are also investigating the implantation properties of these fixation devices and their recovery in the constrained geometry and under the forces and temperatures to which they will be subjected in the human body. Further study of reversion forces will help inform product design and control of surface features in the devices. We are also improving the materials involved by incorporating biocompatible plasticisers that can lower the glass transition phase of the polymer. ■

**We are also investigating the implantation properties of these fixation devices and their recovery in the constrained geometry and under the forces and temperatures to which they will be subjected in the human body.**





# Looking to the future

**Our core funding from the Engineering and Physical Sciences Research Council (EPSRC) runs for two more years, but we are already making plans beyond 2018.**

**With the £67 million total funding we've successfully achieved, we've established a substantial research programme in collaboration with our industrial partners. At least half of this funding supports research that will be undertaken between 2016 and 2018, with some programmes, projects and activities set to continue until 2022.**

Thirty-nine user and industry organisations are already involved in this long-term research programme and we aim to continue to work intensively with these partners, including jointly responding to funding opportunities and developing new collaborative research proposals. In addition, we plan to form a consortium to submit an expression of interest for a National Science and Innovation Audit in Medical Technology.

Outreach activities and events will continue to support our wider network of medical device expertise as we consolidate our position as a national centre for innovation in medical device manufacturing. Our network brings together clinicians, industry and academia, but our outreach activities will also continue to include patient involvement and public engagement, informing the wider public of advances in musculoskeletal medical devices and inspiring the next generation of medical engineers.

Through our Early Career Researcher support and our researcher training and development programme, we will continue to ensure a flow of skilled people between industry and academia and seek to address the future workforce needs for the sector.

During 2016 and 2017, we aim to work with a wide range of commercial, regulatory and clinical organisations, to take a long-term view of the research needs of medical device manufacturing in the UK and develop a plan and roadmap for MeDe's future direction over the next ten years.

**During 2016 and 2017, we aim to work with a wide range of commercial, regulatory and clinical organisations, to take a long-term view of the research needs of medical device manufacturing in the UK and develop a plan and roadmap for MeDe Innovation's future direction over the next ten years.**

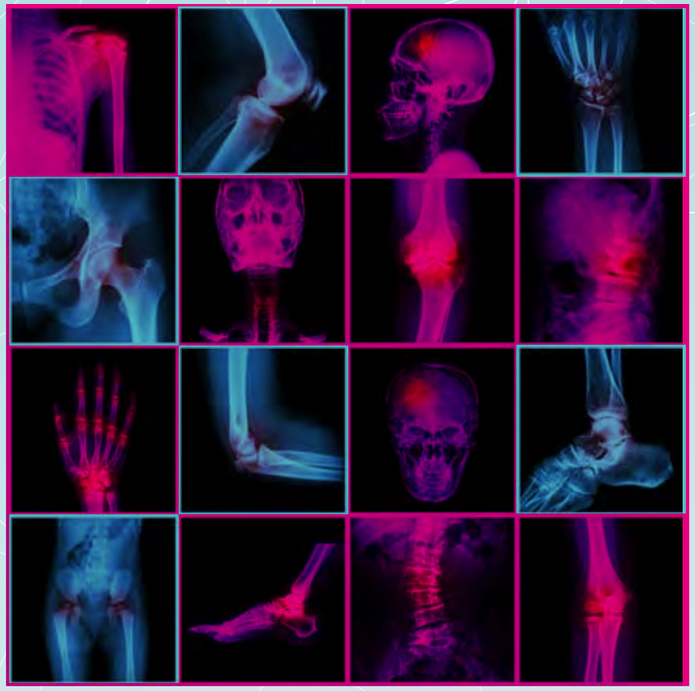
Our ten-year plan will draw on the information we have gathered during our extensive consultations with user and industry partners over the last three years. These consultations identified a need to address the future frontier technology needs of our current industry partners and to continue to increase reliability, improve patient outcomes and reduce manufacturing costs in current products and markets.

But they also suggested we consider broadening our scope of clinical need to consider a wider range of clinical applications, technology markets and new industrial partnerships.

Other issues raised during the consultations that will be addressed in our future plans include:

- The implications for the wider value chain of introducing increased precision, stratification and personalisation of devices, including regulation, trials and the need to create more evidence to predict or evaluate performance
- The development, manufacture and clinical introduction of combination technologies
- The convergence of different types of technologies, either into one product or into systems and companion technologies which support new product introduction and adoption
- The role of patients and the public as smart customers and in the generation of evidence and performance evaluation
- The need to adapt medical devices and technologies to meet the needs of low and middle income economies across the world. ■

With the potential to improve the lives of millions of people and make a significant economic impact, the medical devices sector faces an exciting future: a future in which **MeDe Innovation** is well placed to play a decisive and important role.




## ACKNOWLEDGEMENTS

**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 programmes.**

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Prof Alan Silman, Arthritis Research UK
John Wilkinson, MHRA

**We would also like to thank the companies that helped to found MeDe Innovation in 2013, pledging time, expertise and funding. They continue to work alongside our academic and clinical partners and a further 20 industry project partners to address our key research challenges, shape research projects and help us deliver value from our research.**

Ceramisys Ltd
Corinthian Surgical Ltd
DePuy Synthes Companies of Johnson & Johnson
Eminate Ltd
Fripp Design Ltd
Glass Technology Services Ltd
JRI Orthopaedics Ltd
Materialise NV
NetComposites Ltd
NIHR LMBRU
Promethean Particles Ltd
Simpleware Ltd
Simulation Solutions Ltd
Surgical Innovations Ltd


MeDe Innovation
EPSRC Centre for Innovative Manufacturing in Medical Devices

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