MeDe Innovation

EPSRC Centre for Innovative Manufacturing in Medical Devices

Annual Review

CONTENTS

WELCOME

As one of the EPSRC's Centres for Innovative Manufacturing, our role is to maximise the impact of our innovative research. For MeDe Innovation, that means transforming the way replacement joints and other medical implants are designed, manufactured and tested.

The medical device industry is expected to grow by 10 per cent each year to meet the demands of a growing ageing population which expects to enjoy longer more active and healthy lives. If medical devices are to continue to work effectively to meet these expectations, they need to be more closely matched to patients' needs.

When we launched MeDe Innovation in 2013, we could already see huge opportunities for universities to work alongside industry colleagues to address these challenges.

We formed MeDe Innovation around a core partnership of universities and companies to ensure that our research projects directly addressed industrial and clinical needs. Around that we built – and are continuing to build – a collaborative community of researchers, clinicians and manufacturers working together to deliver solutions that can improve outcomes for patients.

The speed at which these partnerships have crystalised and the continuing interest in our approach from industry, academia and healthcare across the UK confirms the relevance of stratified medicine to the medical device sector. This is demonstrated by MeDe Innovation leveraging an additional £20m to support research in medical devices alongside the £6m grant from EPSRC in the last two years.

Two key approaches, based on the principles of 'stratified medicine', underpin everything we do. Firstly, we aim to deliver functionally stratified design and manufacture of devices, using appropriate criteria to group patients and developing computer models that will predict which device designs best meet the needs of different types of patients. The second approach requires new manufacturing techniques to enable devices to be produced at the point of need, tailored exactly to an individual patient.

In just two years we have already succeeded in addressing some key challenges faced by the sector. For example, we have been able to work with industrial colleagues, Simulation Solutions, to develop new hip and knee simulation machines and methods that are now being sold across the UK and Asia. New simulation techniques developed by our researchers are also being adopted by global orthopaedics companies such as DePuy Synthes, Invibio and Mathys. More fundamental work is advancing 3D printing methods for new materials and for cells, to potentially develop novel near patient manufacturing methods.

It's exciting to see our research work with industry and clinical partners bear fruit, as is beginning to be demonstrated in our case studies. We are also working to develop a robust innovation pipeline to progress new ideas through the different stages of technology readiness. Our Fresh Ideas Fund, launched in September 2014, supports projects at other universities across the UK developing innovations in musculoskeletal medical device manufacture.

The research and partnerships we are putting in place are all supporting the same goal: ensuring that the medical device sector can continue to innovate and keep us all fitter and more active for longer in our later years.

Professor John Fisher CBE
Director, MeDe Innovation

01. DELIVERING A NATIONAL CENTRE

MeDe Innovation brings together stakeholders from across the country to work together in different ways to find solutions to the sector's research challenges.

To find out more visit
mede-innovation.ac.uk/join-us
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A NATIONAL CENTRE

World-class collaborations at the heart of UK medical device innovation

£50m Collaborative investment

600+ Network members

215 From industry

349 Collective attendees of our events

152 Delegates at the Annual Conference

7 Fresh Ideas-funded projects

MeDe Innovation is leading a strong, integrated and inclusive international network of industrialists, academics, clinicians and regulatory body representatives. Together we are delivering world class research to support the musculoskeletal medical device manufacturing industry in the UK. The network is working together to translate the successful outcomes of our research into manufacturing practice in the highly regulated market of Class III medical devices, focusing on musculoskeletal interventions.

Through our network's outreach activities, we are bringing together the research infrastructure, tools and methods, expertise and personnel to support continued innovation and growth of the medical device manufacturing sector in the UK. The outreach programme has been steered and supported by our External Advisory Board, made up of independent industry representatives, clinicians, regulators and leading global and UK academics.

The Centre launched in partnership with 13 companies that included device manufacturers, simulation companies, material manufacturing specialists, software companies and design companies. These partners committed a total investment of £1.9m, and since then the Centre has levered a further £50m through collaborative investment into our related research projects. There are now over 600 members of the network, with over 215 from industry.

We have been working with our partners to deliver events that bring together our research community and sector members, ensuring the Centre's alignment within the current healthcare innovation landscape. Three successful workshops focussed on key scientific areas were delivered in 2014: biological and biomimetic materials; manufacturing at the point of need; and stratified design and manufacture. Collectively we had over 349 attendees. Following this, 152 delegates attended our annual conference 'Advancing Orthopaedic Medical Device Manufacturing' in January 2015.

Our early career researchers are blazing a trail for innovative medical device manufacture research, and we're continuing to support their personal growth and research career development through supporting events, initiatives and visits that our ambassadors lead.

> **PROMOTING INNOVATION AND NEW IDEAS IS A KEY OBJECTIVE FOR MEDE INNOVATION.**

In September 2014 we launched our second Fresh Ideas Fund call to provide small grants to develop projects that identify key challenges in medical device manufacturing. We are optimistic that the Fresh Ideas that were supported will lead to larger projects being funded by national and global funding sources. To date we have 7 Fresh Ideas-funded projects, approved by a panel of experts from our External Advisory Board. The Board explores and develops innovative ideas that will be developed with industry and clinicians to meet future needs of the medical device community.

In January 2014 we launched the MeDe Innovation National Capabilities Database - a dedicated and easy access mechanism for UK medical device manufacturing expertise and facilities. This accessible online tool has been developed to foster engagement and raise the profile and prominence of UK medical device manufacturing research and its unique capabilities.

The Centre has promoted its outreach activities at high profile national events to attract new members throughout 2014, including Manufacturing the Future (Glasgow), Arthritis Research UK Marketplace (Nottingham), MEIbioeng15 and Regener8 (Leeds), and the British Orthopaedic Association Annual Congress (Liverpool).

We also continue to engage our community through our dedicated website, regular newsletters, alerts, blogs and social media posts to stimulate dialogue and debate across the community. We look forward to our annual meeting in Newcastle on January 28th 2016.

To find out more visit
mede-innovation.ac.uk/events
MeDe_Innovation

OUR NATIONAL EVENTS

Annual Conference 01/15

MeDe Innovation's Annual Conference, held in January 2015, brought together more than 150 delegates to learn about the latest developments in orthopaedic device design and manufacture.

Fourteen presentations were made at this year's annual conference covering updates on key developments in the Centre's research, regulatory perspectives to access opportunities in both the UK and the USA, approaches and outcomes from other Centres for Innovative Manufacturing, along with a panel of representatives from industry, regulatory bodies, esteemed academics and clinicians.

Featured speakers included John Wilkinson from the MHRA who offered regulatory perspectives on personalised and combination approaches for medical devices. Finn Donaldson from the US Food and Drug Administration addressed changes to the pre-market approvals process to access opportunities in the USA, and Ben Gooding, consultant surgeon at Circle Nottingham, offered insights into the dislocation between finance and medical innovation that affects healthcare delivery in the UK.

Ten partner organisations hosted exhibition stands, engaging directly with delegates about current opportunities for MeDe Innovation members. Three quarters of our delegates made contacts at the event to follow up.

MeDe Innovation Outreach Workshops 2014/15

This year's outreach workshop series provided an opportunity to promote new approaches to device design and manufacture on an open stage, aimed at enabling national industry and academic delegates to become familiar with the research challenges and themes of MeDe Innovation.

Each workshop offered different perspectives on regulatory, clinical and intellectual property aspects of research translation with panels of experts working in these fields. Following each workshop, our research leaders took a fresh look at their challenge areas to assess progress and identify areas for future investigation.

Biological & biomimetic materials for medical devices & health technologies

09/14

In-clinic manufacture and minimally invasive implantation of materials

10/14

Functionally stratified design and manufacture of orthopaedic devices

11/14

The first outreach workshop, held in Sheffield, focused on **biological & biomimetic materials for medical devices & health technologies.** It looked at the distinctive properties of these materials that make them suitable for use in medical applications, and the challenges that manufacturers and regulators face in moving new materials forward into clinical use.

Delegates heard from national University researchers on recent scientific progress and emerging technologies, and from industry experts including Collagen Solutions and Ceramisys on product development and manufacturing, with the aim of contributing to a strategy to further exploit the opportunities offered by these materials.

In October, a second workshop was held at the Centre for Life, in Newcastle, which focused on **in-clinic manufacture and minimally invasive implantation of materials**. Delegates were invited to consider new approaches to materials processing and manufacturing that will lead to personalised treatments and minimised hospital stays through 14 presentations on clinical and regulatory perspectives, industry developments and challenges, and the MeDe Innovation research programme.

A third event, **functionally stratified design and manufacture of orthopaedic devices**, was held in November 2014 at the University of Leeds. It looked particularly at the definition of stratified design, the industrial and clinical need for a stratified approach to device manufacture, and the regulatory environment.

Delegates took part in debates about the challenges of implementing these new approaches across different sectors, establishing robust methods for pre-clinical testing and identifying tolerance levels of devices, the precision required for surgery, the effects on the price of implants, the potential impact on and new approaches to regulatory approval and the need for better opportunities to translate technologies from lab to clinic. The workshop helped to confirm the importance of the stratified approach and focused on the key issues being addressed in the challenge, from an industry, regulatory, clinical and economic perspective.

Annual Conference

Finn Donaldson (FDA) presents on changes to the pre-market approvals process

Outreach Workshops

Jennifer Durrant (BSI) spoke about the regulatory environment for biological and biomimetic materials

Outreach workshops provided discussion opportunities around key research challenges

> "The event was an excellent forum for exposure to new people, ideas and exciting new developments in the field."
>
> **Chris Holland,**
> University of Sheffield

Developing early career researchers

Creating the next generation of researchers in medical device manufacture in the UK is a key part of MeDe Innovation's mission. The Early Career Researcher Forum aims to help young academics interact with other early career researchers from the breadth of medical device manufacture to form new professional networks that may generate future innovative research ideas.

Our Early Career Researcher Forum Ambassadors – an enthusiastic researcher from each academic centre – take a lead in defining and developing workshops and events in MeDe Innovation's core research areas, influenced by ideas of the membership. Our ECR Workshop held in May, for example, was a great way to get first-hand information about MeDe Innovation projects, make connections with industry partners, and give researchers the opportunity to present about their expertise and the kinds of collaborations they would be interested in.

A Linked-In group keeps conversations going between meetings, enabling researchers to share information about conferences and prizes, and connecting researchers who want to collaborate on grant applications.

We're planning to expand and develop the forum and its membership, influencing the curation of MeDe Innovation events to feature speakers from non-academic fields, such as policy-makers, regulators and from government that will help early career researchers shape their projects and gain a better understanding of how their research might be translated into products.

Marlène Mengoni,
University of Leeds

"Our Early Career Researcher Forum not only has membership from academia but also those in their early careers in industry. The insight from discussion and networking opportunities in a safe environment with our peers is already leading to tangible benefits for our members."

To find out more visit
mede-innovation.ac.uk/innovation-challenges-and-research/fresh-ideas-fund
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MEDE INNOVATION'S FRESH IDEAS FUND

– growing a more diverse national research platform

Launched in September 2014, MeDe Innovation's Fresh Ideas Fund offers small grants of up to £50K to short-term or small projects that identify emergent challenges in musculoskeletal medical device manufacturing. We are confident that projects sponsored through this initiative will develop into larger projects being funded by national and global funding sources.

Using PEEK in cranioplasty surgery

Dr Hengan Ou, at the University of Nottingham, is using the Fresh Ideas Fund to investigate a cost-effective and more flexible method of manufacturing cranial plates for use in cranioplasty surgery. Using PEEK, a composite material increasingly used in this type of surgery, Dr Ou's team are employing a technique called incremental sheet forming (ISF) to produce the plates. The method enables the devices to be produced directly from computer-generated models, without the need to use dies or tooling. The aim is to develop the project and engage with industrial partners and potential end users to address research and development challenges.

Realising the potential of magnesium implants

A key challenge in developing resorbable medical devices is to be able to control the rate at which materials degrade in the body. Although materials made from magnesium and its alloys have great potential for orthopaedic implants, they degrade too quickly to be useful for most clinical applications. At Brunel University, Dr Yan Huang is investigating a new method of manufacturing medical implants that will allow the degradation rate to be controlled. The project will enable a number of different sample implant designs to be produced and sent to potential industrial partners.

A sandpit for fresh ideas

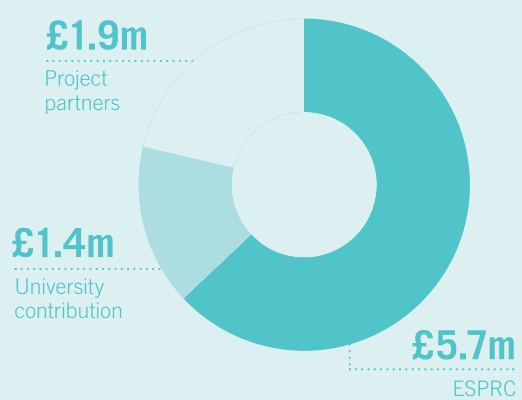
Academic teams who had submitted highly rated proposals to the Fresh Ideas Fund were invited to attend two sandpit events to identify complementary interests and scientific approaches that could form the basis for new collaborative projects. The first event, hosted by Professor Kenny Dalgano from Newcastle, considered the development of a project directed towards soft tissue fixation and repair. Key academics at the sandpit included Chaozong Lui, (University College London), Giuseppe Tronci, (University of Leeds), and Ana Ferreira-Duarte (Newcastle). The second sandpit focussed on new antimicrobial technologies for medical devices. This was facilitated by Professor Paul Hatton from the University of Sheffield with teams led by David Williams (Cardiff) and Maria Katsikogianni (Bradford). Both sandpit events successfully developed new Fresh Ideas projects that have been approved for funding by the MeDe Innovation Executive Board.

TOTAL FUNDS LEVERAGED

Centre sustainability

Successful leverage of research and translation funding through Research Councils, charities, industry and other partners, matched by our host universities, is essential to the sustainability of the Centre beyond year five. MeDe Innovation is already demonstrating strong support from other sources alongside the Centre funding:

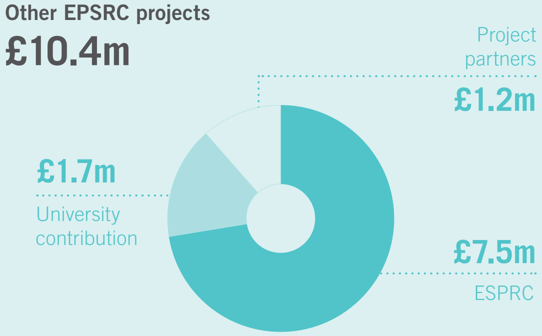
£9m
ESPRC Core Grant



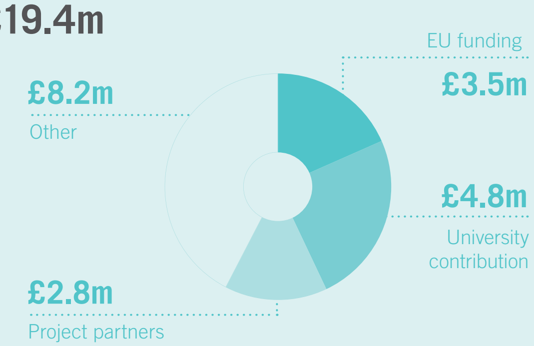
"As the Centre develops beyond year three, we will seek new external monies outside of the core funding stream for research challenges that become priorities, steered by our External Advisory Board, and embed robust approaches to secure a sustainable centre".

Prof John Fisher,
Centre Director

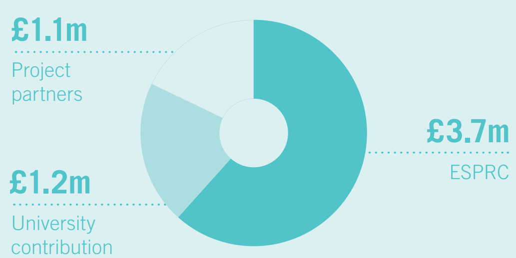
Other EPSRC projects
£10.4m



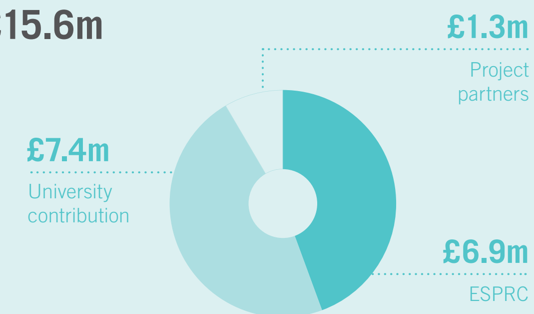
Other projects
£19.4m



EPSRC Centre for Doctoral Training
£6m



Capital grants
£15.6m



02. RESEARCH CHALLENGES

Current research challenges MeDe Innovation is working towards resolving

To find out more visit
mede-innovation.ac.uk/innovation-challenges-and-research/
MeDe_Innovation

RESEARCH CHALLENGE 1 – Stratified design & manufacture

CHALLENGE LEAD: Professor John Fisher, University of Leeds

THEME 1A:

Functionally stratified design and manufacture of hip and knee joints

It is estimated over 50 million patients worldwide have benefited from replacements joints, making them one of the most successful device interventions ever. Over two million joint replacements per year continue to meet the increasing needs of an active ageing population with long life expectancies. Design of replacement hip and knee joints needs to take into account substantial variations in the size, anatomy, activities and lifestyle of patients. The function and reliability of different implants can also be affected by variations in the surgical delivery and patient rehabilitation and age-related changes over the patient's lifetime.

Our research is aiming to identify which of these factors have the most impact on an implant's performance and reliability, and how replacement joints can be designed to match the needs of different patient groups. Through pre-clinical simulation and prediction of function, it will be possible to segment the product design solutions and match these to the stratified population with higher levels of precision. This approach will more cost-effectively generate improved outcomes across the population.

Our achievements

Hip prostheses

In partnership with the medical device company, DePuy Synthes, we've been able to develop new simulation methods that will allow the pre-clinical prediction of the effects of variations in surgical positioning on the function and performance of hip joint replacement surgery.

Our virtual computational simulation methods have the potential to be used as part of the design process (in functionally stratified design), while the experimental methods are used to validate the computer predictions of function as well as to pre-clinically evaluate prototypes in new product development and also test manufactured products for part of regulatory submissions.

Collaborative work to develop and validate ever-more sophisticated electromechanical simulators and enhanced methods is being carried out in partnership with Simulation Solutions and has resulted in a new hip simulator system, now in commercial production.

Knee prostheses

We have also been working with DePuy Synthes to produce similar testing methods for replacement knee joints. Over the past year, we have developed a suite of novel computational models to predict biomechanical function, contact stress and wear under different kinematic activities. These have been validated experimentally in laboratory simulators and can be used in design and prototype evaluation. They are also being used to define the application and use of the revised international standards on knee joint testing.

A new electromechanical knee simulator, developed in partnership with Simulation Solutions, is also now in production and our experimental methods are being adopted widely by customers. Data packages that have been generated and published are critical to support widespread adoption. Refining these simulators and creating new variations is ongoing and we will continue to work in this area.

> "We are collaborating with researchers around the world to reach a better understanding of the biomechanics of hip joints. All this data is used to develop better simulators."

Dr Mazen Al-Hajar
University of Leeds

Case studies on pages 21&22 explain how these developments have been adopted by industry.

Nick Eldred,
Simulation Solutions Ltd

> "We are working with MeDe Innovation to develop pre-clinical simulation equipment that takes into account patient, surgical and implant design variables that have greatest influence on function, performance and clinical outcome. If the research is successful, we can offer this novel simulation system as part of our portfolio to clients."

THEME 1B:

Stratified bioprocesses for the manufacture of acellular biological scaffolds

Damage to soft tissues in the knee caused by acute injury or by degenerative diseases such as osteoarthritis does not repair effectively. Most commonly, the damaged tissues such as ligaments, cartilage, or bone are replaced with healthy tissues harvested from other sites in the patient, but this has limitations of pain and morbidity at the donor tissue site and failure to restore full function.

Our researchers are developing acellular biological scaffolds from human cadaveric donor tissue and from pig tissue that can be implanted and regenerate in the patients' body without risk of rejection. Once the manufacturing methods are developed, these regenerative devices can be tailored to produce the best device for the right patient at the right time.

Our achievements

Acellular human bone-tendon-bone

We are working with the NHS Blood and Transplant Tissue Services on an acellular human bone-tendon-bone for the replacement of ruptured anterior cruciate ligaments (ACL). Rupture of the ACL is a very common sporting injury which, left untreated, will cause further damage to the knee joint and lead to osteoarthritis. At the University of Leeds we have developed a process for removing the living and dead cells from human-donated bone-tendon-bone, so it can be implanted into patients without rejection. The acellular human bone-tendon-bone is currently being tested in a large animal model to determine if the implant regenerates successfully in vivo.

Porcine superflexor tendon

Human-donated tendons for ACL replacement surgery may not be readily available, so it's important that we investigate alternatives. We have developed processes for producing and sterilising the acellular biological scaffolds from pig tendons, which can also be used to replace the ACL. These are currently being tested in a large animal model, with promising early results.

Bone and osteochondral graft

The success of recent work on acellular bone has enabled us to investigate whether our approach can be used to treat lesions in knee joint cartilage. We are developing an acellular cartilage on bone device using porcine tissue, which can be implanted into the knee joint to repair cartilage defects. Large animal trials of this regenerative device will start shortly.

Simulating and predicting success

The scaffolds we produce need to be tested in large animal models. However, it would be advantageous to be able to test the function of our devices prior to animal testing in order to minimise the use of animals. We are therefore developing computational and laboratory simulations to predict how the scaffolds will behave once implanted. We are working with our partners Simulation Solutions to develop natural knee laboratory simulators. See page 23 for a case study.

Professor Eileen Ingham,
University of Leeds

> "We're developing an understanding of how we can modify the processes used to produce acellular biological scaffolds so they are matched as closely as possible to different patient groups."

THEME 1C:

Stratified design and manufacture of nonwoven collagen scaffolds

Synthetic collagen, derived from biological tissues, is an important material for the repair of bone and soft tissue in areas such as maxillofacial surgery. This includes guided bone regeneration in dental surgery to direct growth of new bone and gingival tissue in locations where there is insufficient volume for proper function. Our researchers are developing synthesised collagen materials that are mechanically stable and engineered to degrade at predictable rates after implantation. They should not create an adverse reaction in the patient, and surgeons must be able to modify the materials during surgery to ensure their dimensions and physical properties are tailored to each patient.

Our achievements

Collagen kit for surgeons

Over the past 12 months the team has been implementing (patent-pending) technology in which commercially available medical grade collagen is converted into new clinically convenient forms including gels, fibres and nonwoven fabrics whilst retaining native collagen conformation with regard to triple helix and fibrillary architecture. Material format can now be adjusted based on different textile manufacturing routes developed in Leeds. The new platform is being used to construct grafts for clinical use in guided bone regeneration, where selective in vivo cell homing will be evaluated within the material to promote functional tissue repair.

Crucially, the new manufacturing approach enables customisation of key physical properties such as strength and modulus, whilst ensuring the collagen material remains mechanically stable in aqueous conditions. The resorption time within the body can also be adjusted, depending on clinical needs, which is particularly valuable in surgical procedures.

The team is assembling a collagen kit to provide surgeons with a selection of gels, fibres and fabrics so that materials can be chosen with the most appropriate form and physical properties for each patient. Over the next 12 months, the specifications of the kit and pre-clinical evaluation of the new materials will be accomplished in collaboration with our clinical partners.

Tuning properties using light

The manufacturing process also enables late-stage customisation of collagen properties using a light source operating within specific wavelengths. Surgeons will be able to customise at the point of implantation and then use a light source to rapidly stiffen the collagen material, aiding fixation and defining the correct size and shape of the graft for each patient.

Professor Stephen Russell,
University of Leeds

"We're making available customised design routes for collagen materials, in which the architecture and physical properties can be readily adjusted to meet precise surgical needs and improve clinical outcomes."

THEME 1D:

Manufacture of bioresorbable multiphase fixation devices to order

Multiphase bioresorbable materials have potential for medical fixation devices as their properties can be tailored precisely to their specific function in the body. The challenge is to optimise and fine tune their mechanical properties and the rates at which they degrade once implanted.

Our achievements

Encapsulating nanoparticles

The composite material is made up of two elements – a matrix, and a filler. Optimising the interface between these two elements in degradable composites is difficult because often the filler clumps into agglomerates which means the material will not have the desired characteristics. We have developed and demonstrated new methods to encapsulate nanoparticles that prevent filler material in composites from agglomerating. Instead, they disperse more evenly through the matrix, leading to better control of degradation and overall performance.

Phosphate degradable glass

A number of projects have developed from work on novel phosphate degradable glass. For example, we're developing phosphate-based, thin film coatings that can be applied in layers that are just nanometres thick. This means the coating is able to follow closely the morphology of the implant itself. The project is currently being tracked by industry partners JRI Orthopaedics and DePuy Synthes.

Our degradable glass porous microspheres technology is being developed to work with the body's own stem cells to promote bone repair in patients suffering from osteoporosis. The technology has been patented and an i4i grant has been awarded by the National Institute for Health Research to progress towards clinical trials with industrial partners.

Phosphate based glass fibres are also being used by MeDe Innovation researchers. For example, developing formulations for degradation rates in composite plates and investigating how this material can also be manufactured into rods, designed for use as intramedullary nails. A manufacturing route for this has been designed and we plan to start work with industrial partners to scale up the process.

Virtual modelling

Using existing scanning technology available in hospitals, modelling approaches have been developed to provide a full manufacturing pathway from initial device design, through validation to manufacture for degradable and non-degradable devices. For example, by utilising software products such as from Materialise who are a MeDe Innovation Industrial partner, the team at Nottingham have designed and manufactured a spinal device. A prototype is currently undergoing pre-clinical testing and a patent application has been filed. Commercial negotiations are underway with an industrial partner.

See case studies on pages 24-26 for more information about these projects.

Professor David Grant,
University of Nottingham

"These projects will make a significant impact to the next generation medical devices and working closely with our industrial colleagues means we are able to progress this research more quickly and efficiently."

RESEARCH CHALLENGE 2 – Manufacturing at the point of need

CHALLENGE LEAD: Professor Kenny Dalgarno, Newcastle University

THEME 2A:

Minimally invasive implantation of bioactive materials

The development of implantable devices that can boost tissue regeneration and restore function could have huge implications for repairing early stage joint damage. We're working on producing bioactive devices that are small and strong enough to be inserted into joints to carry out repairs using minimally invasive techniques.

Our achievements

Bioactive plugs for tissue repair

One of our approaches is to develop a bioactive material that can be implanted as a liquid and then converted to a solid within the body. Once the natural tissue has regrown, the plug will break down and be absorbed by the body, resulting in a natural repair. Over the past year, at Newcastle University, we've been able to develop the delivery process for this procedure. The liquids are introduced via a tube, and allowed to solidify. With repeated applications, the plug can grow to the required size. Our team has shown that the process can work within clinically relevant timescales and have good mechanical properties; the next stage is to refine the implant biomaterials before moving on to pre-clinical tests.

We have also developed solid plug designs made from bioceramics, which have been evaluated in vitro. We plan to carry out further pre-clinical tests during the next 12 months to understand more precisely what happens after the plugs are implanted.

Electrospun biomembranes

Work to create biomembranes using electrospinning technology is one of our early stage research projects, aimed at creating a long-term pipeline of technologies. Once implanted, these materials can interact with their environment to promote tissue regeneration.

Two different nanoscale techniques are involved: one uses covalent coupling to attach peptides to the membrane, which provide biofunctionality. The second design involves building up layers of material and implanting bioactive molecules between each layer. MeDe Innovation researchers are now focusing on developing the membranes to deliver biologically active molecules that can promote bone tissue regeneration.

Professor Paul Hatton,
University of Sheffield

"Through MeDe Innovation, we are able to engage with industry and industry regulators at a very high level and contribute to the debate about how these innovations are regulated."

THEME 2B:

Processes for in-clinic manufacture

Bone and cartilage implants that can be adapted for individual patients will deliver more successful and longer-lasting outcomes. Although technology to do this is available, the processes are time consuming and costly. MeDe Innovation researchers are working on different methods of combining cells and biocompatible materials that clinicians can use closer to the patient, saving time and money.

Our achievements

3D printing of cell scaffolds

One of the methods we're looking at is using 3D printing technologies to combine cells and biocompatible materials. We've developed a method of printing cells onto scaffolds to make a device that can be implanted into the patient to promote tissue regrowth. The aim would be to produce implants that could be adapted to fit precisely in each patient. This research is already at proof of concept stage: the next step is to pre-clinically test the methods to evaluate the effectiveness of the cell-laden scaffolds.

3D printing for larger defects

A further project looks at using 3D printing to create biomaterials that can be used to treat larger defects, such as structural repairs to knee joints. A number of different biopolymers and bioceramics are being tested via this method, which will enable clinicians to make implants to precise individual designs. The method involves producing a plastic cage, tailor-made to the patient, which can then be strengthened with ceramic materials. The patient's own cells can then grow into the structure to complete the repair.

A proof of principle study has shown that polymers with the right macroporosity can be printed successfully, and that the different parts of the replacement joint can be produced and joined together. The next step is to develop test devices and to identify the most promising clinical applications for this technology.

Shape memory polymers

Researchers at the University of Bradford are developing soft tissue fixation devices made from bioresorbable polymers. The University has developed a unique approach – using precision microinjection moulding and die drawing techniques – to achieve molecular orientation in these materials that allows their properties to be closely controlled. When inserted into bone using minimally invasive techniques, a 'trigger' can be applied, which will cause the material to expand and fix into the bone before being sutured into soft tissue.

Further development work includes improving the osteoconductivity of the polymers and designing shape memory materials for use in bone to bone repair, with a particular interest in hand repair.

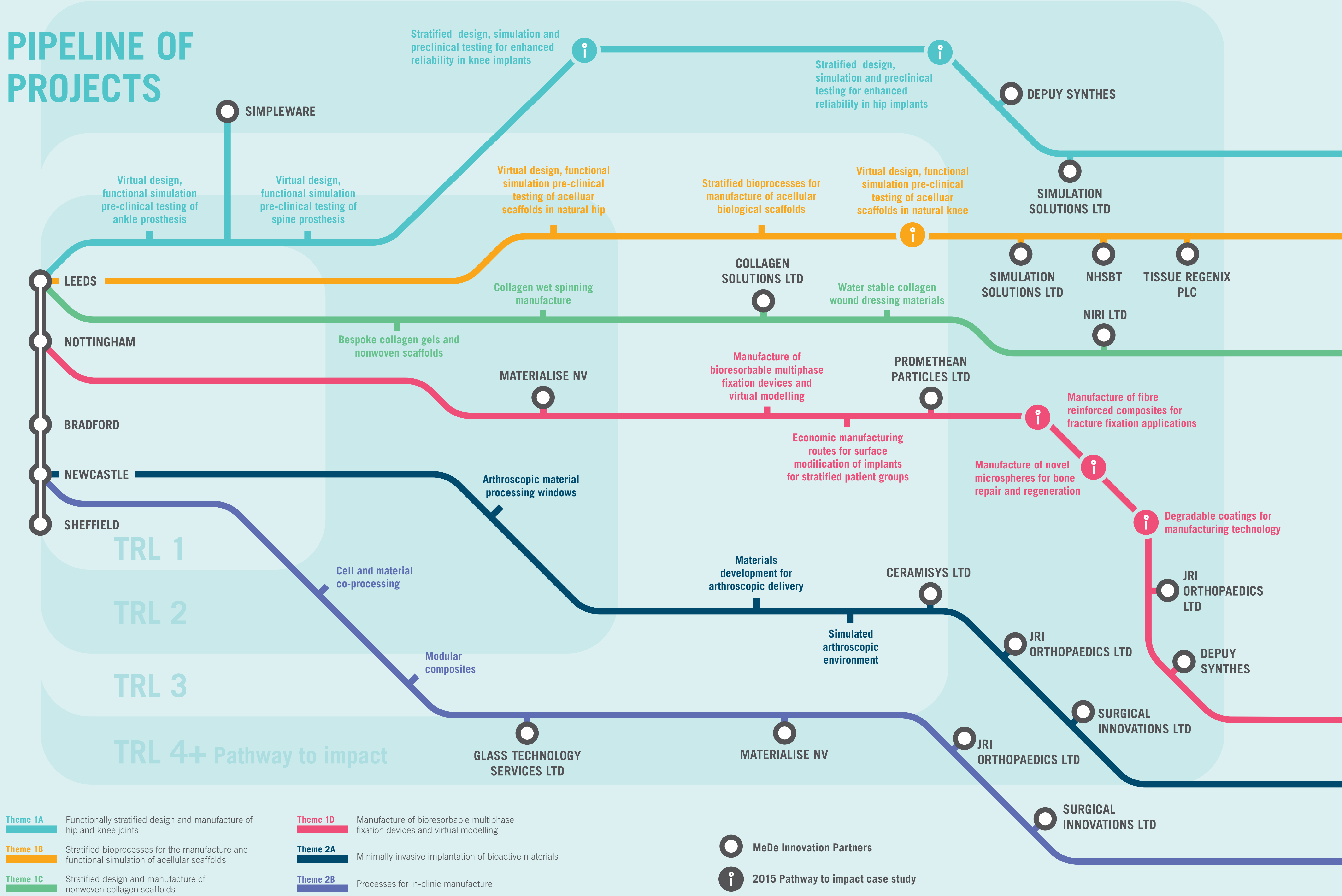
A patent in partnership with Smith & Nephew covers bioresorbable materials that can be triggered at body temperature.

Finally, linking with a Fresh Ideas Fund project (see page 9) MeDe Innovation researchers will investigate ways of controlling the nanotopology of fixation device surfaces to deliver antimicrobial properties.

Professor Phil Coates,
University of Bradford

"Our partnership with MeDe Innovation has opened doors to significant further funding as well as to highly relevant expertise amongst industry and colleagues at other universities."

PIPELINE OF PROJECTS



03. IMPACT CASE STUDIES

Research in application

A look at our research in application and case studies on how our research is being deployed in industry.

To find out more visit
mede-innovation.ac.uk/downloads
MeDe_Innovation

CASE STUDY 1

Advanced hip joint simulation system will improve implant design and reliability

Although hip joint replacement surgery is generally very successful, over the expected lifetime of several decades and in some patients the joint may start to fail. This may be due to the way the joint is positioned during surgery and it will happen more quickly in some patients than others.

To test the wear of the joint, device manufacturers use simulators – machines that predict the performance of the implant by simulating many millions of cycles of its use over time. This information can then be used by manufacturers to improve the design of implants for different groups of patients, and also inform the level of precision of implant placement during surgery.

MeDe Innovation has been working with medical device manufacturer, DePuy Synthes, and device simulator company, Simulation Solutions, to develop more advanced simulation techniques that can then be applied to test products made by DePuy Synthes and other companies.

MeDe Innovation researchers produced the design specifications for the new machines manufactured by Simulation Solutions.

They then evaluated the machines and developed detailed experimental methods and training packages for their use. Most recently new methods have been developed to predict more precisely how different surgical positioning will affect the replacement joint's performance over time. These are being used to define new draft international standards.

At the same time, MeDe Innovation has been working with the NIHR Leeds Musculoskeletal Biomedical Research Unit (LMBRU), at Leeds Teaching Hospital Trust, to develop computer models that can predict the function and outcome under a wider set of clinical conditions. These new virtual simulation methods are already being adopted by DePuy Synthes as design and simulation tools in their global product development programme.

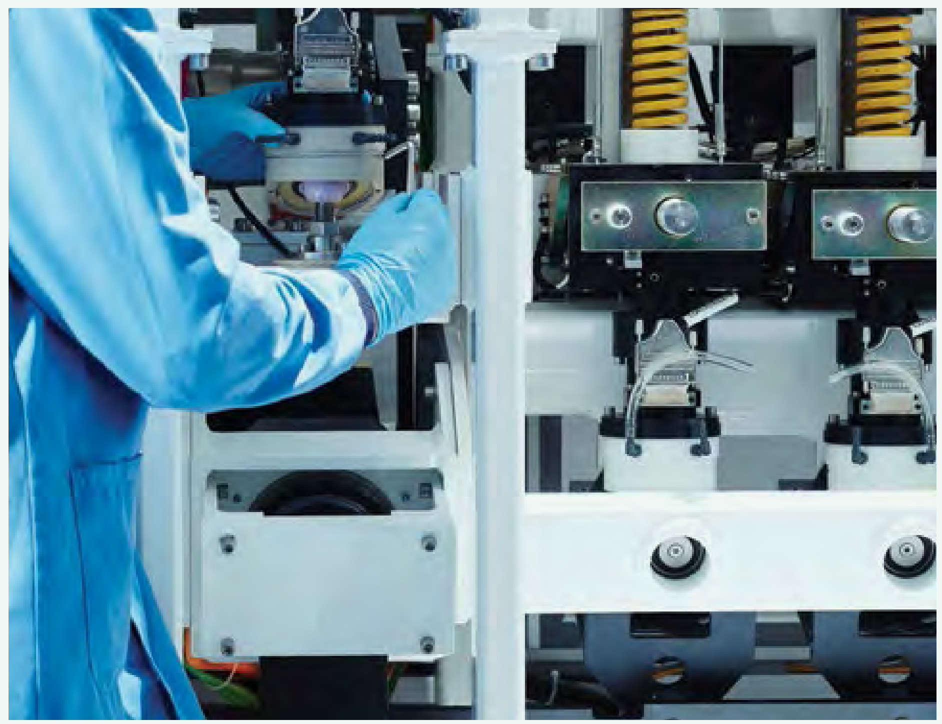
Professor Ruth Wilcox, of the University of Leeds, explains: **"Computer modelling means we can rapidly calculate the effects of many different positioning scenarios. From that, we're able to calculate a 'margin of error' for each implant, so the surgeon knows the parameters within which he or she must work to position the replacement joint and minimise wear post-surgery."**

MeDe Innovation's experimental methods are also being used to evaluate new ceramic biomaterials and devices manufactured by Mathys, for use in hip implants.

"We've been using our methods to see how resistant the material is to wear," says Dr Louise Jennings, of the University of Leeds. **"The results show the new ceramic composite is more resistant than the current industry standard material – so this new material could offer a real alternative."**

The new simulator designs and experimental methods developed collaboratively through MeDe Innovation are being sold by Simulation Solutions in the UK and Asia and MeDe Innovation researchers are also able to offer training and consultancy advice to support their use.

"Understanding better the different effects of surgical positioning on wear means better and longer-lasting outcomes for patients."



CS.1

Advanced hip joint simulation system will improve implant design and reliability

CASE STUDY 2

New knee joint simulators are being used in the development of novel knee implants and biomaterials

Replacement knee joints are difficult to design and implant because of a number of different factors. Variations in the size and shape of patients, as well as their differing lifestyles and activities – and the individual styles and techniques employed by surgeons – can all influence the success of the replacement joint.

Because the knee joint is not as constrained as the hip joint, it can also be very difficult to determine which of these variables contribute to wear and stress on the new implant.

Working with device simulator experts, Simulation Solutions, and device manufacturers, DePuy Synthes, MeDe Innovation researchers have developed advanced simulation techniques that can help address these challenges.

The research has included both experimental and computational methods - and a new electromechanical knee simulation system based on this research is now being sold by Simulation Solutions to clients in the UK and Asia.

MeDe Innovation researchers have also been working with biomaterials company, Invibio, which is developing all-polymer replacement knee joints made from a biocompatible material already cleared for clinical use. Called PEEK, the material could enable Invibio to offer the first metal-free knee replacement – a lighter-weight and cheaper alternative to current implants, which are made from cobalt chrome. A final product design is now being tested, with help from MeDe Innovation, before it goes forward into clinical trials.

"We've worked with Invibio on this project right from the first concept of using PEEK to replace metal alloys in knee implants through to developing a final design," says Dr Louise Jennings, at the University of Leeds. **"Invibio has adopted our experimental and computational methods to evaluate the product and the results so far are very promising."**

MeDe Innovation's work has also been adopted by Biocomposites, which manufactures materials for bone and soft tissue repair. The company is using MeDe Innovation's methods to help test bone void fillers, used for filling in gaps around the joint during joint replacement surgery.

"We've been able to work with Biocomposites to test whether bone joint filler could leak into joints and accelerate damage and wear," explains Dr Jennings. **"We developed a body damage simulation model that allowed us to trap the fillers in the knee and demonstrate that they had no effect on wear in the knee replacement joint."**

CS.2

New knee joint simulators are being used in the development of novel knee implants and biomaterials

CASE STUDY 3

Natural knee simulators for predicting the function of novel regenerative devices

Methods of repairing knee joint damage that use scaffolds and the patient's own cells to regrow bone and cartilage are an attractive alternative to joint replacement surgery.

For these less invasive methods to be successful, however, the biomechanical properties and function of the natural knee need to be restored, as well as restoring the interactions between the different surfaces of the joint – its tribological function. That means clinicians need to be able to achieve a good match between the scaffold and the patient.

MeDe Innovation researchers have developed computer modelling techniques to simulate the biomechanical and tribological function of the knee that can be used to predict the performance of scaffold implants during the design process. This will help implant design companies understand the different factors that affect performance and the parameters within which that performance will be acceptable.

Working with clinical and industrial partners from the outset, the aim is to have robust testing methods in place that can keep pace with the development of new implant technologies.

"If we can develop successful testing methods for these devices before they're introduced clinically, there's a real opportunity to optimise them," explains Professor Ruth Wilcox, of the University of Leeds. **"Because many of these new materials are still emerging from universities and medical research companies, there's a realisation that we need new and innovative testing methods in response, to enable us to pre-clincially evaluate new biomaterials."**

A big challenge with this research is that the host tissue surrounding the implant has a much bigger role to play in the repair. That means the scaffold's performance is much more complicated to simulate. A big step forward for the team has been developing the whole natural knee model that represents the multiphase properties of the natural knee.

Working with Simulation Solutions, the research team have developed, manufactured and validated the first ever six-axis natural knee simulator, which is now being used in a collaborative research and development project with NHS Blood and Transplant Tissue Services. The system is also ready for use by other manufacturers involved with the design and pre-clinical testing of new scaffolds and biomaterials.

The next step is to create a simulation that can represent how the different variables of the implant might vary from one patient to another so that, ultimately, it will be possible to create designs tailored to individual patient groups – **"stratified medical devices".**

CS.3

Natural knee simulators for predicting the function of novel regenerative devices

CASE STUDY 4

Fracture fixation devices that can be resorbed over time

Complex fractures in long bones such as the femur are commonly treated by fixing a metal rod into the cavity of the bone. These implants, called intramedullary nails, can disrupt the intramedullary blood supply, become painful over time and the patient may need to undergo additional surgery to remove the metallic rod.

At the University of Nottingham, our researchers have succeeded in developing specially designed dies which will be used to produce composite rods utilising calcium phosphate fibres to reinforce PLA polymer matrix. These calcium phosphate fibre composites can be implanted into the body and then resorbed over a controlled period of time.

Nottingham has developed expertise in manufacturing resorbable composite fracture plates, which are also used to fix bone fractures. The challenge was to find a manufacturing process capable of producing the calcium phosphate fibre reinforced composites in rod form with appropriate mechanical properties that could replace metallic intramedullary rods.

Existing composite manufacturing processes mainly use compression moulding techniques, which are labour intensive, with long lead times. In addition, the results from this process can be variable, meaning they may not pass the strict safety regulations for implants.

"Rods are more difficult to make than plates and require more complex manufacturing methods," explains University of Nottingham engineer, Dr Ifty Ahmed. **"We're investigating a method with variants of two techniques – pultrusion and extrusion – where the fibres will be pulled through a die containing the polymer and formed into a rod shape. Getting the process parameters right will be critical to maintaining the alignment and impregnation of the fibres to manufacture rods with the right mechanical properties."**

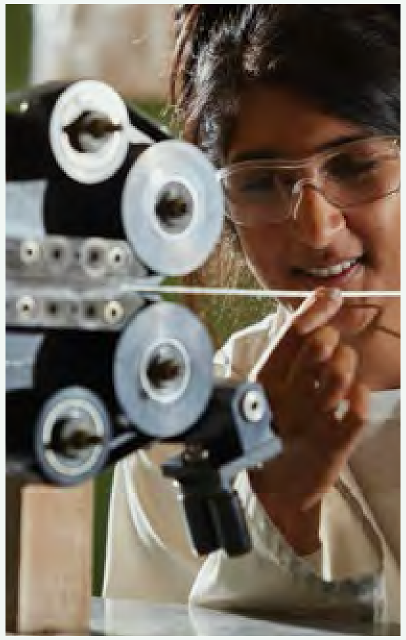
Over the past year, the team have been evaluating and testing alternative manufacturing processes for these materials. Researchers will now trial their method with calcium phosphate fibres and evaluate the properties of the material produced. The aim is to manufacture rods with mechanical properties matching cortical bone – the dense, compact outer layer of the bone structure.

The next steps will be manufacturing trials of composite rods and establishing the material's degradation profile. Natural bone takes around 8 - 12 weeks to heal, so the team is aiming to produce rods which can maintain their properties for that length of time before starting to degrade.

Through MeDe Innovation, the team is also working with partners at the University of Bradford and industry and clinical partners to test and evaluate alternative manufacturing processes, such as injection moulding, to determine which methods, ultimately, will be most effective for producing the rods.

CS.4

Fracture fixation devices that can be resorbed over time



CASE STUDY 5

Designing novel coatings for surgical implants in bone

Surgical implants in orthopaedics are often coated with materials to improve their biocompatibility and promote adhesion to bone. For example, current plasma spray technologies use a non-degradable hydroxyapatite coating that cannot be finely controlled, resulting in thick brittle coatings in which the final surface topography is different to the underlying device surface.

MeDe Innovation researchers at the University of Nottingham are developing new methods of application that will allow coatings to be applied in layers ranging from only a few nanometers thick. Therefore the coating follows the detailed surface structure of the device, which can be designed to optimise desired cellular response such as osteoconductivity. Using a technique called magnetron sputtering on commercial pilot scale equipment, the researchers have been able to deposit and build up layers of degradable ceramic or glass coatings. The layers deposited can be finely tuned to produce coatings of various compositions incorporating therapeutic ions and of different degradation rates.

This project is at an early technology readiness level and is a great example of the support that MeDe Innovation can offer industry to tackle manufacturing challenges. **"MeDe Innovation's partners, JRI and DePuy Synthes are tracking this project and helping us to evaluate the adhesiveness of the coatings,"** says Professor David Grant, of the University of Nottingham.

"Both companies have also been helpful with market advice for this technology so, through MeDe Innovation, we're able to work with industry to steer technological developments into areas where they may be applied."

The research team is currently conducting in vitro testing on the coatings. Over the next few months the team will be working to demonstrate the efficacy of the coatings and will investigate the adhesion of these coatings in comparison to existing technologies. They will also look at ways to reduce the costs involved in the manufacturing process to ensure the technology would be attractive to commercial companies.

"We now have a family of potential products for integration into medical devices and we're very optimistic that these have market potential – and potential to deliver bespoke coatings for specific patient groups," says Professor Grant.

CS.5

Designing novel coatings for surgical implants in bone

CASE STUDY 6

Using innovative microsphere technology to treat osteoporosis

Osteoporosis is a disease in which bones lose density and become brittle and fragile. It affects almost three million people in the UK, and places a significant burden on healthcare providers. It has also been termed as a 'silent epidemic' as there are usually no symptoms until a bone fractures.

Although drug treatments are available, they cannot replace the lost bone and around 300,000 patients are treated each year for fragility fractures caused by osteoporosis.

Researchers at the University of Nottingham are working on a minimally invasive technique to repair and regenerate osteoporotic bone that could reduce trauma, especially for those patients at high risk of fractures as well as significantly reducing healthcare costs.

The potential technique will allow for calcium phosphate microspheres loaded with the patient's own bone marrow cells to be injected into the injury site via a cannula or needle. Calcium phosphate, a naturally occurring material, is essential for bone repair. Once injected, the microspheres would resorb over time to facilitate bone repair and the patient's own stem cells would regenerate new bone tissue.

"The work we've done to design and test the microspheres could lead to a potential platform technology – a foundation for many future developments in the biomedical area," says Dr Ifty Ahmed, at the University of Nottingham.

"We have only just started to explore the potential of these microspheres and are discussing with potential industry partners how to develop our techniques."

Already, the team has succeeded in scale-up manufacture of the microsphere technology and have shown that stem cells can attach on and within these materials.

The team is working with clinical collaborators to establish a clinical processing route for the technology. In addition, a £1.2m NIHR i4i Challenge Award has been granted to progress this research further and advance the technology and its future exploitation, in partnership with Leeds, and Birmingham University Hospitals, Ceramisys, York Health Economics Consortium and Surgical Dynamics.

The next steps will be to model the delivery of the microspheres (in vivo) and to manufacture a minimally invasive delivery device.

Current research is focused on targeting osteoporosis, but other applications could also include delivery of drugs, proteins or other active agents.

CS.6

Using innovative microsphere technology to treat osteoporosis

Partners

Twelve companies are working alongside us to address our key research challenges. Each of these founding industrial collaborators has pledged time, expertise and funding and will work alongside our academic and clinical partners to shape research projects and 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
Annual Review

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

+44 113 343 0923
mede-innovation.ac.uk
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