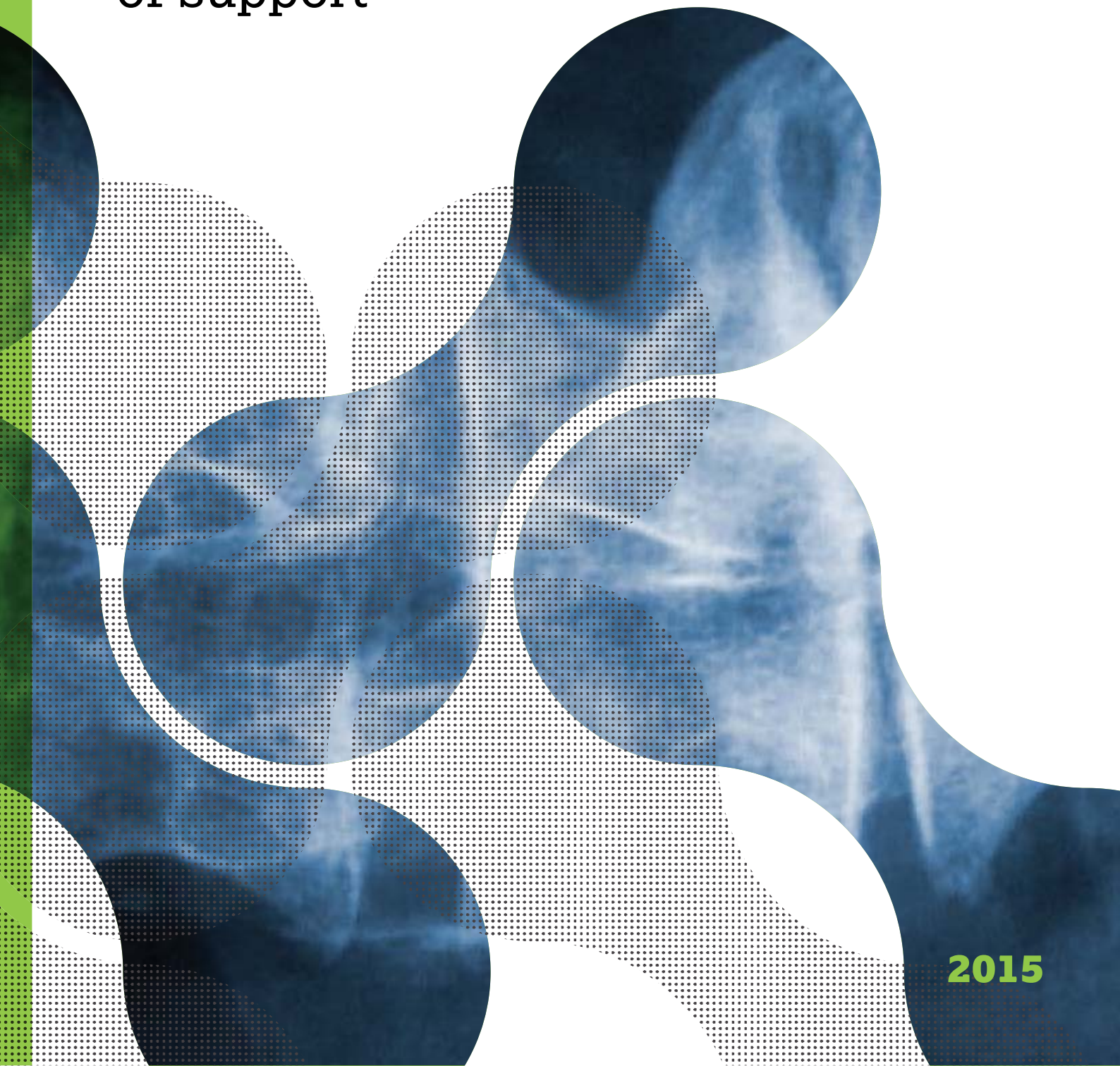
bringing movement to life

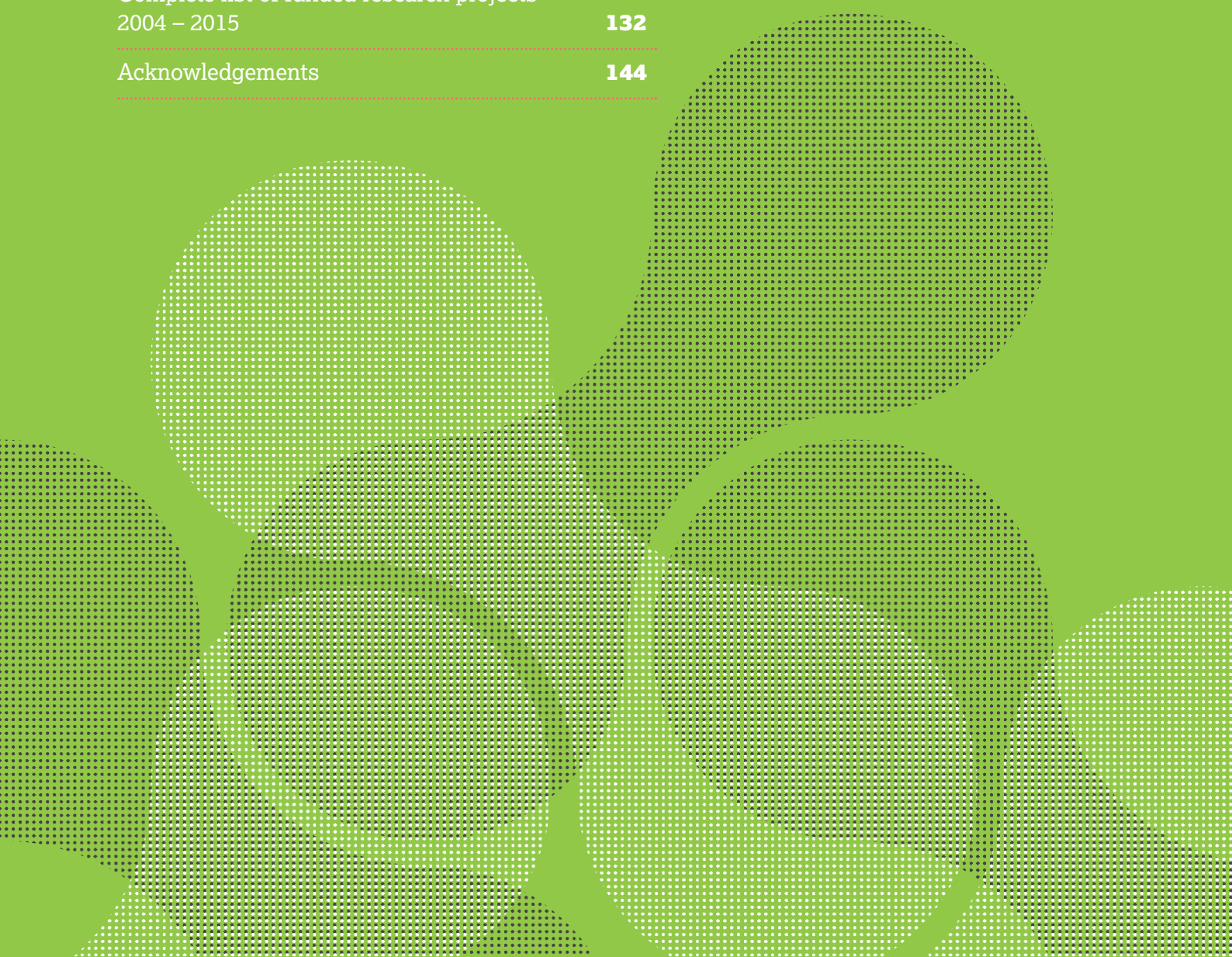
orthopaedic research UK

Research Impact Report: a decade of support



2015

Contents



A note from the Chairman of the Board of Trustees

Orthopaedic Research UK (ORUK) has come a long way over the last ten years and looks forward to the next decade with confidence. It is a good opportunity both to reflect on what has been achieved and to peer into the future.

Ronald Furlong founded the Furlong Research Foundation (FRF) in 1989. It was a small private charity through which he channelled all his ground breaking research in orthopaedics and most notably, the development of the hydroxyapatite coating for prostheses in total hip replacement (THR). His world famous HAC coating has proved to be one of the most reliable and long lasting for THR and remains so to this day.

Mr Furlong was ably supported in the creation and development of Joint Replacement Instrumentation (JRI) by his wife, Eileen and at the date of his death in 2002 - was employing over 100 people and making substantial profits.

Both Mr and Mrs Furlong had made similar wills. They left everything to each other and on death of the survivor left their joint estate to FRF.

Mrs Furlong died in 2003 and immediately a small private charity trust became a substantial grant making charity, its principal asset being the 100% ownership of JRI.

FRF became the Furlong Research Charitable Foundation (FRCF), a company limited by guarantee and the Directors, formerly Trustees, embarked on the development of the FRCF into one of the leading grant making charities in orthopaedic research.

Ten years down the line the Directors have:

• Formed one of the most highly regarded scientific advisory committees in the sector, to review and advise the Board on all grant applications.

• Built a state of the art factory in Sheffield, which has been let to JRI. This was in part to diversify the Foundation's assets where too many eggs were deemed to be in the JRI basket.

• Purchased the freehold of Furlong House as further diversification of its investment portfolio.

• Changed the name of the charity to Orthopaedic Research UK so as to give the charity a rebranding.

The Directors would have been unable to have achieved this without the dedication of their staff under the direction of Brian Jones, the Chief Executive. Brian had assisted Mr Furlong in his lifetime and had intimate knowledge of both FRCF and JRI.

The time has now come for Brian to retire and the Directors have unanimously decided to offer the Chief Executive position to Dr Arash Angadji, whose task will be to take ORUK forward to the next stage of its development.

Arash will have the full backing of a very committed Board of Directors, who share his vision of growing ORUK into the charity to whom everyone will look as the major donor in orthopaedic research.

Robert Vallings

Chairman of ORUK

Notes from the Executive Team

As the average age of the UK population increases and we remain active for much longer, more people suffer from musculo-skeletal ailments and infirmities. More than ever before we now need to understand the aetiology of these conditions and improve patient treatments more quickly and effectively.

ORUK is proud to fund research in all areas of orthopaedics, as it may alleviate suffering in patients of all age groups, from juvenile arthritis through lower back pain to fragility fractures in osteoporotic bones.

By funding research of the highest quality we can establish new areas of basic research for others to build upon as well as translate previously conducted research to direct patient benefit.

Some of the projects contained in this report are breaking new ground in orthopaedic research and some are incrementally adding to our knowledge of how to improve current treatments. The impact of this total programme of research is to generate greater resources for clinicians to eliminate pain and restore mobility to all patients who may be affected by musculo-skeletal infirmities.

After more than 25 years working in Furlong Research Foundation (ORUK) I am proud and pleased to have contributed to the work and ethos of this charity. Its unique organisational structure allows funds that are derived from supplying orthopaedic devices to hospitals around the world to be directed back into research to improve practices and to advance technologies in the field of orthopaedics. I now leave it to others to carry forward and expand the good work and I thank all those who have helped along the way.

Brian Jones

Despite being a small charity that aims to improve the quality of patients' lives, in the vast field of orthopaedic disorders, ORUK has gained an incredible amount of attention from the research community over the last decade; acknowledging that we fill a significant gap in funding studies, that are otherwise not normally supported by larger charities such as the EPSRC, BBSRC or ARUK.

To date, ORUK has successfully processed over 750 grant applications since 2004. This has led to awarding of over 120 grants – totalling around £8.2m – to 37 Universities, NHS Trusts and research centres in the UK. It wouldn't have been possible without the support of our reviewers who continue to devote their time and expertise – free of charge – to ensure that our unique charitable purpose is fulfilled.

In my new capacity as the Chief Executive of ORUK, I aim to continue with the existing momentum with our research strategy, and further encourage researchers to focus more on innovative and translational solutions that are much closer to patients.

We will continue to expand and enhance our engagement with our stakeholders, as well as increase the number of our educational events for clinicians, scientists and engineers. It is our intention to build stronger and long-lasting partnerships with academia, charities and other professional bodies, whom we share similar interests, in order to provide outcomes that possess outstanding quality.

I would like to thank my predecessor, Brian Jones for all his support and guidance over the years and wish him a long, happy and healthy retirement.

Dr Arash Angadji

Meet our Trustees

Robert Vallings
Chairman

Kate Allen

John Edge

Patrick Latham

David Martin

Brian Jones

We depend upon our Board of Trustees to oversee our activities and ensure the organisation meets its objectives as a charity.

Our objectives are the advancement of medical education and research, particularly orthopaedic knowledge, by funding research and training and by encouraging co-operation between surgeons, scientists and engineers working in the field of orthopaedics. This should benefit the general public, so the results of all funded research should be published.

Scientific Advisory Committee (SAC) members

Professor Julia Shelton

Professor Matteo Santin

Mr Vikas Khanduja

Dr Ralf Kettner

Mr Ben Ollivere

Mr John Edge

Professor Lucy Di Silvio

Professor Neil Rushton

Professor Victor Duance

Professor Gordon Blunn

Professor Damian Griffin

Dr John Egan

Our Scientific Advisory Committee (SAC) meets twice a year to consider research proposals we have received and to make recommendations to our Board of Trustees for funding. The committee comprises eminent members of the orthopaedic research community.

Professor Jeremy Fairbank

Member of

amrc
ASSOCIATION OF MEDICAL RESEARCH CHARITIES

Institute of Fundraising
ORGANISATIONAL MEMBER

NHS
National Institute for Health Research

Collaborations and Partnerships

RCS
ADVANCING SURGICAL STANDARDS

The Royal Society of Medicine

ASiT The Association of Surgeons in Training

National Osteoporosis Society

Arcana ossium quis explorat
B.O.R.S.

BSMB British Society for Matrix Biology

British Orthopaedic Association
Caring for Patients; Supporting Surgeons

MILLER Orthopaedic Review Course United Kingdom
REVIEW OF ORTHOPAEDICS

BOTA
British Orthopaedic Trainees Association

THE GREAT DEBATE

Bespoke

UKITE
The United Kingdom and Ireland In-Training Examination

The Bespoke Study: a successful partnership story

Jamila Kassam

Jason Pott

Mr Manoj Ramachandran

Professor Tim Harris

Bespoke

The Bespoke study is a collaboration between the Orthopaedic and Emergency Department Research Teams of Barts Health NHS Trust, partnered with Orthopaedic Research UK, to explore bicycle related injuries in London. The Royal London Hospital (RLH), a major trauma centre in central London, receives a high volume of cyclists involved in collisions every year; a high proportion of these patients have sustained orthopaedic injuries. The primary objective of the study is to explore the epidemiology of cycling crashes through an observational prospective cohort study. Secondary objectives include mapping crash locations to identify hotspots, and to better understand the circumstances leading to cycling collisions. Furthermore, the study aims to explore return to activities of daily living, quality of life and return to cycling following cycling trauma.

Why?

Cycling is becoming an increasingly popular mode of transport, with the benefits of physical activity well-documented. There is much discussion and debate around the safety of cycling, and what can be done to reduce the number of deaths and injuries. Although the recording of deaths is rigorous though a national data set called Stats19, there are notable gaps in the recording of near misses and collisions where the emergency services are not called. There are further limitations with the data set due to the injury classifications used in reporting. Bespoke will help identify the impact of cycling collisions on the individual. Results will be available to transport authorities to enable measures to be put in place to reduce cycle-related trauma.

How?

All patients who attend the Emergency Department at RLH following injury sustained whilst cycling will be invited to participate in the Bespoke study. Data will be collected at three time points; baseline, death, discharge or 28 days, and at six weeks. A patient and public involvement (PPI) group was pivotal in selecting key outcomes that were considered important by cyclists.

To capture data on collisions not presenting at the RLH, an online self-reporting application called Collideoscope has been developed, where cyclists can submit information on their collisions and 'near misses'. Reports from Collideoscope will be sent to local transport authorities, and cyclists will be sent a follow-up questionnaire at six weeks post-collision. Research findings will be published in peer reviewed journals, as well as producing reports accessible to the public, Transport for London and policy makers.

"The innovative Bespoke data project lead by researchers in London's biggest Emergency Department is key to unlocking data which is currently lacking from the debate about cycle safety in London. I urge all London cyclists to get involved!"

Jon Snow, presenter, journalist and cycling champion

Surgical Speciality Lead (SSL) in orthopaedic surgery

Royal College of Surgeons of England

Over the last three years Orthopaedic Research UK has been collaborating with the RCS to fund two outstanding leads in orthopaedic surgery. We are delighted to announce that this successful partnership has been extended for another 3 years.

Professor Amar Rangan

Professor Matt Costa

Professor Rangan, with support of Orthopaedic Research UK has been busy setting up new trials, as well as exceeding recruitment figures for his current trials. Professor Rangan has been instrumental in carrying out changes to the T&O Training & Curriculum, by pushing for the inclusion of GCP training to become mandatory for CCT in T&O. In addition to this, he hopes for trainees to demonstrate that they have screened and recruited 5 patients into approved clinical studies to complete their training. In 2014 Professor Rangan aims to open up New Trials and continue to push for incorporation of clinical trials training into the T&O curriculum.

Professor Costa, with the support of Orthopaedic Research UK has been active in promoting his role as an SSL through the British Orthopaedic Association, the NIHR CRN and Orthopaedic Trauma Society meeting as the 'go to' Orthopaedic Surgeon for guidance on Trauma Orthopaedic trials. Professor Costa has opened 11 new clinical trial sites since January 2013 and will submit 5 new trial applications in the first quarter of 2014 alone. He has developed 10 new Principle Investigators in 2013 from Plymouth to Middlesbrough and aims to train another 10 in 2014, as well as train 2 new Chief Investigators. Professor Costa hopes to introduce complete coverage of Major Trauma Centres in recruiting for trials in musculoskeletal trauma in 2014.

Supporting the UKITE exam

UKITE

The United Kingdom and Ireland In-Training Examination

The United Kingdom and Ireland In-Training Examination (UKITE) is a national, online examination providing immediate results to trainees and allows practice for the 'real' FRCS Orth (Tr&O) examination with similar formatted questions based on the UK T&O curriculum. Orthopaedic Research has been a proud partner in this successful national initiative since 2014.

Mr Ajay Malviya (left) and Mr Mike Reed (right) from the UKITE team

Funding data

Status & Values

Live	29	£1,112,144.49
Completed	91	£7,095,900.65
Total	**120**	**£8,208,045.14**

£ by Study Stream

PD	£3,262,166.91	39%
PhD	£2,508,804.86	31%
CF	£1,879,911.14	23%
MD	£463,906.23	6%
Mphil	£93,256.00	1%
Total	**£8,208,045.14**	**100%**

Distribution of Study Streams

PD	41	39%
PhD	38	32%
CF	32	22%
MD	8	6%
Mphil	1	1%
Total	**120**	**100%**

PD: Postdoctoral Fellowship

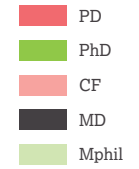
PhD: Doctor of Philosophy

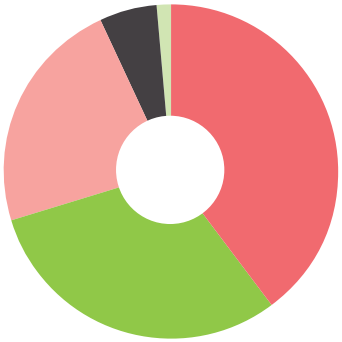
CF: Clinical Fellowship

MD: Doctor of Medicine

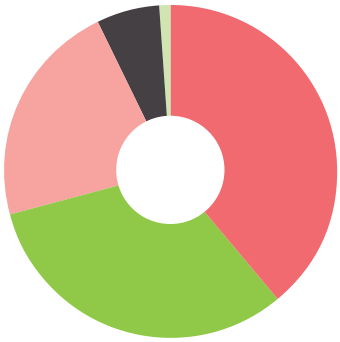
MPhil: Master of Philosophy

All data valid until February 2016

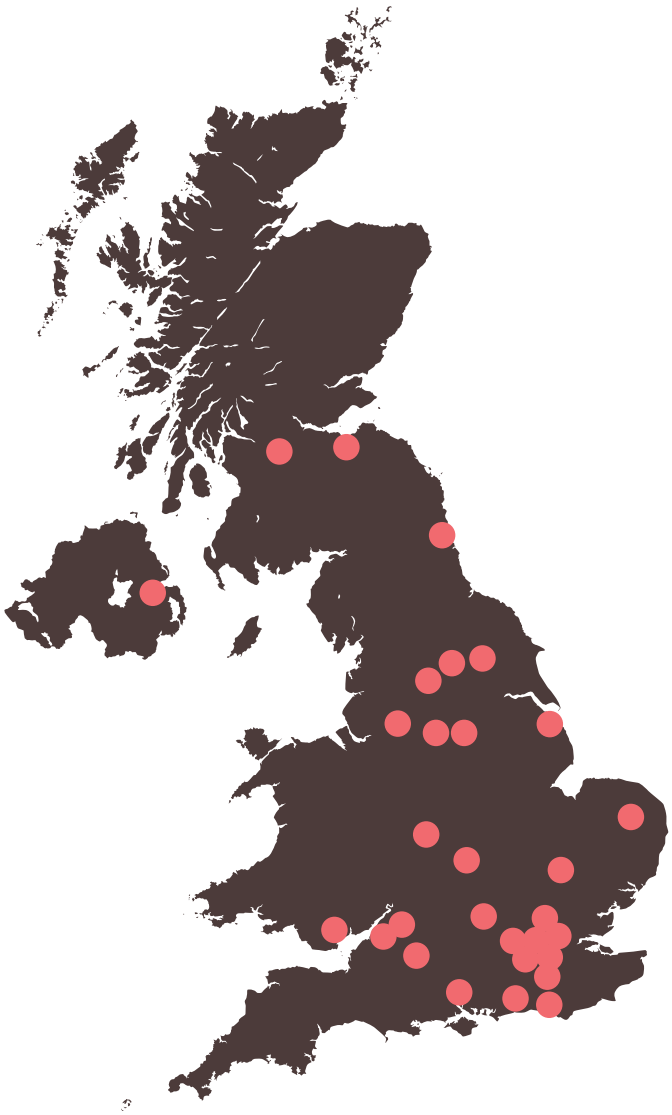




£ by Study Stream



Distribution of Study Streams



Research institutions

Institution	Total amount	%	No. of grants
University of Oxford	£1,588,512.27	19.35%	23
University College London	£1,047,521.62	12.76%	15
Imperial College London	£836,676.50	10.19%	14
University of Cambridge	£625,498.70	7.62%	8
University of Leeds	£372,480.91	4.54%	2
Western Sussex Hospitals NHS Trust	£363,125.00	4.42%	5
King's College London	£297,436.82	3.62%	4
University of East Anglia	£295,306.33	3.60%	4
Newcastle University	£262,411.11	3.20%	3
Queen Mary, University of London	£247,713.00	3.02%	4
Royal Veterinary College	£215,755.00	2.63%	4
University of Manchester	£156,527.63	1.91%	2
University of Birmingham	£152,774.96	1.86%	3
University of Sheffield	£152,454.00	1.86%	2
University of Edinburgh	£139,998.00	1.71%	2
Aarhus University (Denmark)	£122,788.67	1.50%	1
St George's University of London	£120,000.00	1.46%	2
Radboud University (Holland)	£101,809.04	1.24%	1
University of York	£94,000.00	1.15%	1
University of Warwick	£93,930.00	1.14%	1
University of Strathclyde	£89,000.00	1.08%	1
University of Brighton	£88,999.98	1.08%	1
The Rizolli Institute	£83,242.70	1.01%	2
University of Bath	£81,266.99	0.99%	1
Queen's University Belfast	£79,592.00	0.97%	1
Sheffield Children's NHS Foundation Trust	£73,042.00	0.89%	1
Swansea University	£68,549.00	0.84%	1
University of Southampton	£65,766.09	0.80%	1
Cardiff University	£63,416.00	0.77%	2
University of Bristol	£60,000.00	0.73%	1
North Bristol NHS Trust	£47,657.00	0.58%	1
Royal College of Surgeons of England	£45,000.00	0.55%	1
Northumbria Healthcare NHS FT	£29,875.00	0.36%	1
National Osteoporosis Society	£24,203.82	0.29%	1
Dewsbury & District Hospital	£12,015.00	0.15%	1
London School of Hygiene & Tropical Medicine	£7,500.00	0.09%	1
Grimsby - N. Lincs & Goole Hospitals	£2,200.00	0.03%	1
Total	**£8,208,045.14**	**100%**	**120**

Quality impact in healthcare by supporting more translational research

The main activity of Orthopaedic Research UK (ORUK) is to provide funding to centres of excellence to conduct research in the field of orthopaedics and musculoskeletal pathology, in order to benefit patients suffering from such disorders. However, the majority of the research grants awarded to universities will not make it to the market as a products, surgical techniques or novel rehabilitation approaches, etc. Therefore, in general, grants are made with no expectation of a financial return and very often with little patient benefit.

There is a huge need to translate the fundamental knowledge gained from basic science discoveries into a benefit for patients. We want to focus on the importance of translational research and promote the innovation process to ensure that the money invested in research is given the best opportunity to translate into meaningful outcomes and improve IP identification, so that the discoveries will be given the best chance of becoming a novel treatment, product or service.

Designing a translatable idea is a complex process and involves many players. This should be carried out through collaboration between all the stakeholders, which is key in determining a successful outcome. All parties must align their agendas and goals to deliver benefits for patients.

The Association of Medical Research Charities (AMRC) has placed emphasis into actively encouraging collaboration between charities and industry to maximise impact in healthcare. This is because they correctly recognise the fact that industry is at the forefront of 'innovation' – a key element in order to survive in a competitive business environment.

Translational proposals generally possess the following qualities:

- have a commercial partner, providing a solid support and input based on robust preliminary research
- address a clear clinical need/defined patient group
- support the development of treatments that are likely to be safe and acceptable to patients and clinicians
- have a clear and sensible commercialisation plan
- have a clear route through clinical trials to market associated with strong IP

We want to actively encourage collaboration between ORUK and industry to maximise the chances of generating an impact on healthcare. For more information about how to apply for this type of funding, please visit our website.

Research impact reports

Impact report

In vitro model of distraction osteogenesis

Researcher Dr Cynthia Chang

Supervisor Associate Professor Philippa Hulley

Stream PhD

Duration 72 months

Cost £20,000

Other funders National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, USA

Focus Bone biology, fracture healing

Dr Cynthia Chang

Cynthia currently works as a biomedical engineer at the U.S. Food and Drug Administration. Primarily, she serves as a medical device reviewer for plastic and reconstructive surgery devices, to ensure that safe and effective medical devices are developed and approved. Recently, she has also served on temporary assignments for the Center for Drug Evaluation and Research at the FDA as a liaison for antimicrobial products and counterterrorism project and as an acting branch chief in the Division of Surgical Devices.

What is the basic problem that you are trying to address?

Distraction osteogenesis (DO) is a unique process of bone formation used for clinical correction of skeletal deformities. In DO, bone is osteotomised and the cut ends are slowly pulled apart by mechanical means to induce new bone to form. Despite the extensive current and historical use of DO, the mechanisms involved are not well understood. A novel mouse model of DO featuring a custom-developed external fixator was validated and characterised by using radiography, immunohistochemistry, and microarray techniques. Concurrently, a novel three-dimensional in vitro model of DO was developed to assess the mechanobiological effects of distraction.

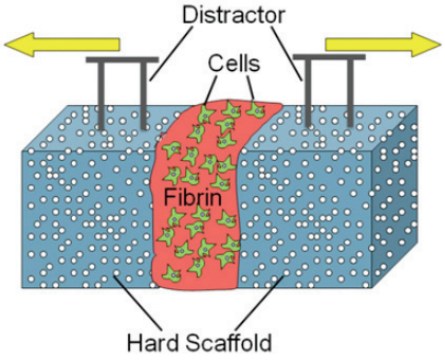
What is the estimated incidence of this particular problem in the general population?

Distraction osteogenesis is widely used for limb lengthening procedures due to its unparalleled ability to build new bone. It is also used to correct craniofacial or other skeletal deformities caused by injury, disease or surgery.

What are the aims and objectives of this research study?

Our first aim was to use an in vivo model of DO to discover pathways controlling the DO process in a whole-transcriptome time course micro array. Genes relevant to osteogenesis, angiogenesis, mechanotransduction, cytoskeletal signalling and the Wnt pathway were highly expressed. Time course statistical methods applied to the micro array data enabled profiling of global gene expression throughout DO and identification of genes and functions that showed significant differential expression over time. Secondly we aimed to develop a novel three-dimensional in vitro model of DO to assess the mechanobiological effects of distraction. The system consists of two pieces of hard mineral scaffold held in a rigid distractor which allowed live cell imaging. A cell-seeded fibrin clot bridges the scaffold

ends to simulate the in vivo distraction gap. Using this in vitro model, the effects of a single application of tensile strain on the model were assessed.



Is this research going to solve the problem?

In this project, a new mouse model and a novel in vitro model were shown to be useful tools for understanding the process of clinical DO. Additionally, time course statistical analyses and in situ 3D staining techniques provide new tools for understanding and improving surgical bone lengthening.

What are the long-term benefits to patients with this problem?

At present bone anabolic drugs are able to increase bone mass and bone connectivity on a micro scale throughout the skeleton. This does not work when inches of bone are needed to lengthen a limb or replace part of a missing jaw. Our work and that of others over decades shows the considerable regenerative potential of the distraction osteogenesis process and more work is needed in this area to understand and harness the process better.

"A new mouse model and a novel in vitro model were shown to be useful tools for understanding the process of clinical Distraction Osteogenesis"

Impact statement

- Several regulatory pathways involved in distraction osteogenesis induced bone formation have been identified
- A novel miniature system has been developed and used to study how bone cells respond to mechanical loading of the soft tissue-bone interface in a healing fracture
- This work has resulted in further grants to study the unique process of bone formation during distraction osteogenesis

Publications

1. Patents: ISIS GB1009939.8 and US 61/354,625, In vitro multiple sample model of bone callusdistraction and In vitro model for distraction osteogenesis

2. Thesis: In vivo and in vitro models of distraction osteogenesis; Chang, Cynthia J; Oxford University; Date of Award:2011 http://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.558214

Impact report

The role of specific metalloproteinases in Dupuytren's disease

Supervisor Professor Ian Clark, Dr Graham Riley and Mr Adrian Chojnowski

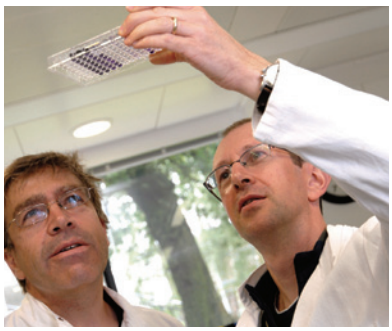
Stream Postdoctoral Fellowship

Duration 24 months

Cost £76,726

Other funders Gwendoline Fish Trust

Focus Dupuytren's disease



Dr Riley (left) and Professor Clark (right) in the laboratory

Ian Clark and Graham Riley are molecular cell biologists with interests in diseases of extracellular matrix. These include Dupuytren's disease, tendinopathy and osteoarthritis. Adrian Chojnowski is a consultant orthopaedic surgeon with interests in the upper limb. We work across the clinical scientific border to move from discovery to clinical application.

What is the basic problem that you are trying to address?

Dupuytren's disease (DD) results from a thickening of tissues in the hand which contract and shorten, leading to deformity and disability. It affects over 2 million people in the UK. At present, the only treatment for DD is surgery to remove the thickened tissue. Inevitably DD returns over time with further surgery less likely to be successful. There is no medicine which can slow or prevent DD and no way to predict those patients in whom the disease will return rapidly after surgery. This research aimed to address this problem.

What is the estimated incidence of this particular problem in the general population?

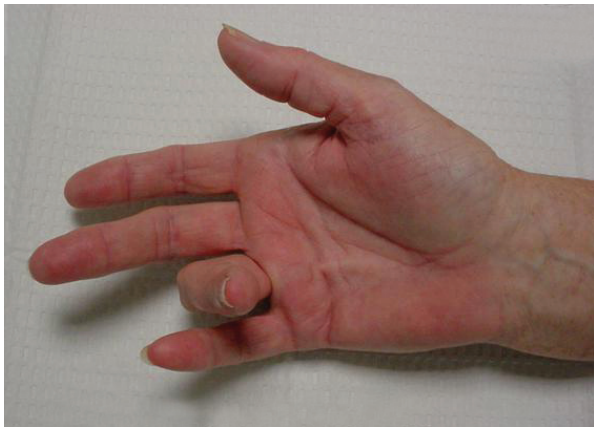
DD affects over 2 million people in the UK. It is usually progressive and irreversible, causing significant disability. The most common surgery, fasciectomy, is associated with a 41% recurrence rate after 5 years.

What are the aims and objectives of this research study?

MMPs (matrix metalloproteinases) are a family of 23 enzymes which break down tissues in the body. They can be viewed as biological scissors which chop up the components making up these tissues, particularly one called collagen. We recently discovered which of the MMPs are present in DD tissue. We also discovered that the level of some of these MMPs in the DD tissue is associated with how rapidly the disease will return after surgery. This research aimed to uncover the role of specific MMPs in the disease process.

Is this research going to solve the problem?

Understanding in detail how DD occurs and progresses will enable the development of a drug which can slow or prevent the disease. Such a drug may also be used alongside surgery to stop the recurrence of the disease after surgery.



What are the long-term benefits to patients with this problem?

The long term benefits are in developing treatments outside of the current surgical or mechanical options in DD and in finding ways to optimise them. It may also be applicable to other forms of tissue fibrosis (e.g. liver or lung fibrosis) and lead to new therapies.

"Our results may lead to the development of a drug which can slow or prevent contractions of the fingers or stop the recurrence of the disease after surgery"

Impact statement

- The roles of MMP-1, MMP-2, MMP-3, MMP-13 and MMP-14 in the contraction of an extracellular matrix by cells from Dupuytren's tissue has been uncovered.
- This work is an initial step in targeting a specific MMP for therapy

Publications

1. Wilkinson JM, Davidson RK, Swingler TE, Jones ER, Corps AN, Johnston P, Riley GP, Chojnowski AJ, Clark IM (2012) Biochim Biophys Acta Mol Basis Dis 1822 897-905
MMP-14 and MMP-2 are key metalloproteases in Dupuytren's disease fibroblast-mediated contraction

2. Wilkinson JM, Jones ER, Riley GP, Chojnowski AJ and Clark IM (2012) In: Dupuytren's Disease and Related Hyperproliferative Disorders, pp143-149. Eds C.Eaton et al.
The expression of collagen-degrading proteases involved in Dupuytren's disease fibroblast-mediated contraction

Impact report

Functional smart deposition of nano-sized calcium phosphate for medical applications

Researcher Dr Gillian Munir

Supervisor Dr Jie Huang

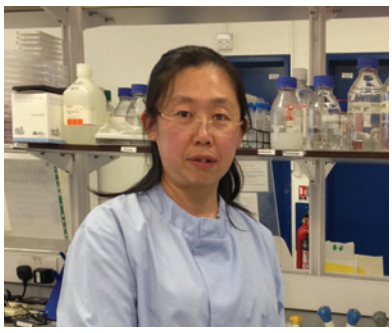
Stream PhD

Duration 18 months

Cost £30,000

Other funders No

Focus Surface modification, medical implant, nanobiomaterials, cell-material interaction



Dr Jie Huang

Dr Jie Huang heads the Biomedical Materials group at the Department of Mechanical Engineering, University College London. Her PhD study was focused on the development of second generation biomaterials with enhanced bioactivity and biocompatibility at the IRC in Biomedical Materials Queen Mary, University of London.

She has been interested in the synthesis of nanobioceramics for biomedical applications since working at the Cambridge Centre for Medical Materials, the Department of Materials Science and Metallurgy, University of Cambridge. She has published over 70 papers in leading journals and has been invited to contribute to three books on biomaterials and medical devices. Currently she has research projects on developing nano- and bio-materials for medical implants, tissue engineering scaffolds and drug delivery carriers.

Dr Gillian Munir obtained her BSc in Genetics and Microbiology at the University of Leeds, and MSc in Biomaterials and Tissue Engineering at University College London, where she then completed her PhD on surface modifications of medical implants by creating patterned topography with tailored materials chemistry. She is a part-time lecturer on the MSc module: 'Introduction to Biomedical Imaging'.

What is the basic problem that you are trying to address?

With the ageing global population, the number of patients that require artificial joints, medical implants and devices is increasing rapidly. The success of orthopaedic implants, for example, depends on the bone-implant osseointergration. Metallic implants have been widely used in major load bearing applications, owing to their excellent mechanical properties, but metallic materials have low osteoconductivity, resulting in slow bond formation with bone. Hydroxyapatite (HA) ceramics, which closely resemble bone minerals, are well known for their high bioactivity and osteoconductivity. Thousands of patients have benefited from HA coated implants, which has increasingly become the choice for joint replacement prostheses as the general population lives longer. In particular, silicate-substitute hydroxyapatite (SiHA) has been shown to promote bone formation and is therefore a highly attractive alternative to conventional HA for bone replacements. The application of these advances in material chemistry and nanotechnology into implant manufacture will be addressed in the project.

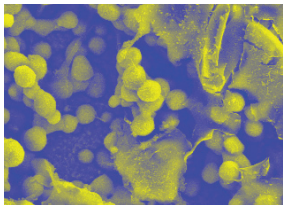


Figure 1:
SEM micrograph of the attachment of osteoblast cells on nano-silicate substituted hydroxyapatite (nSiHA) deposited surface.

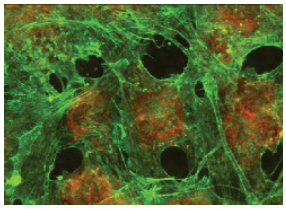


Figure 2:
Confocal microscopy of the alignment of cell actin cytoskeleton (green) on nSiHA patterned surface.

What is the estimated incidence of this particular problem in the general population?

Hip replacements are one of the most common and effective major surgical procedures performed in the NHS. There are over 77,000 total hip and 82,000 total knee replacements carried out annually in the UK, which leads to regained mobility and relief from pain.

What are the aims and objectives of this research study?

Silicon is essential for bone development - the addition of Si to HA alters its chemistry and grain size, whilst the dissolution at grain boundaries also promotes bone apposition. The aim of the research is to develop a new way to deposit nano-scaled SiHA on titanium surfaces to improve the bioactivity and biocompatibility of metallic implants. The first step to achieve this goal is to optimize the processing parameters for the deposition and find the best condition in which to obtain the nanoSiHA with well-defined surface structure. The second step is to evaluate and understand the biological responses of osteoblast (bone forming) cells to these nanostructured surfaces for the implant design.

Is this research going to solve the problem?

We hope so! There are many factors as to why an implant fails. However, if we eliminate the problems caused by a lack of integration between the bone and implant by promoting and accelerating the healing process after surgery, we are closer to a solution. Bone defects can be more effectively repaired by understanding of interactions of surface structure with cells and tissues. This study is the vital first step on the path to achieve our goal.

What are the long-term benefits to patients with this problem?

Increasing the bonding between implant and bone will prevent loosening of the implant, therefore extending the life-time of the implant. This in turn should prevent further surgery to be required. The development of a highly bioactive new coating will pave the way for a new generation of implants, prostheses to promote tissue repair and regeneration. Furthermore it will be socially, psychologically and economically beneficial to patients in the long term.

"Our results will lead to a better understanding of the interaction of surface micro and nanostructure with cells to promote osteo-integration of medical implants"

Impact statement

- Nano-scaled silicate substituted hydroxyapatite has been deposited on glass and metallic alloys using a novel low temperature deposition technology
- Surface patterning of micro- and nanostructured silicate substituted hydroxyapatite on titanium has been able to guide and direct the growth of osteoblast cells
- This work has resulted in a better understanding of the design for a new generation of implants with enhanced cellular interactions

Publications

1. G. Munir, M.J. Edirisinghe, G. Koller, L. Di Silvio, W.Bonfield and J. Huang (2011), The Pathway to Intelligent Implants: Osteoblast Response to nano Silicon-doped Hydroxyapatite Patterning, J. Royal Soc. Interface, 8 (58), 678-688.

2. G. Munir , M. Edirisinghe, L. Di Silvio, W. Bonfield and J. Huang (2010), A novel surface topographical concept for bone implant, Proceeding of the MRS Fall Meeting Symposium, 916992.

3. G. Munir , M. Edirisinghe, L. Di Silvio, W. Bonfield and J. Huang (2012), Surface patterning of nanoSiHA: in vitro response from osteoblasts, Proceeding of the 9th World Biomaterials Congress

Impact report

The use of antimicrobial nanomaterials as coatings for the next generation of prostheses

Researcher Dr Kaveh Memarzadeh

Supervisors Professor Robert P. Allaker and Dr Jie Huang

Stream PhD

Duration 3 years

Focus Nanoparticles, Microbiology, Biomaterials and Cell biology

Professor Robert Allaker (left) and Dr Kaveh Memarzadeh (right)

After graduating from my MSc at UCL, I became fascinated by how various biomaterials could be utilised to enhance our daily lives. In the year 2010, a project which entailed the use of nanoparticles as coatings for bone related prosthesis was offered to me by Prof. Allaker (QMUL) and Dr. Huang (UCL). This was a great opportunity to start a journey into the field of nanomaterials and I have enjoyed the challenges ever since.

What is the basic problem that you are trying to address?

There are an increasing number of patients requiring medical devices, such as artificial joints to enable everyday activity and movement. An improvement of current implants, i.e. infection-resistant prostheses, will offer tremendous benefits to countless patients. External fixation is also widely used in orthopaedics and is prone to pin tract infection that could potentially result in osteomyelitis, a condition that is often difficult to treat. There is therefore an urgent need for technologies to effectively improve the fixation of implants/devices in bone without infection occurring.

What is the estimated incidence of this particular problem in the general population?

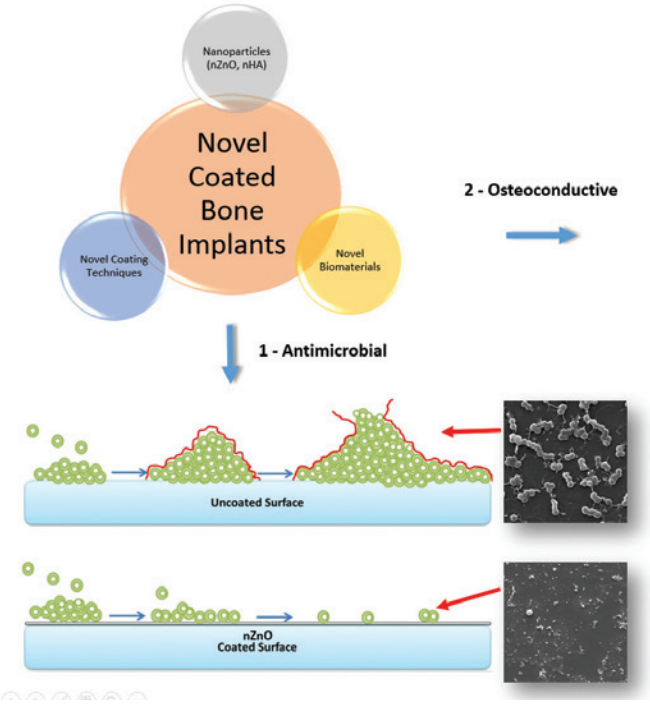
An ageing population is key. The UK has around 10 million people over the age of 60 and this will increase in the coming years. Although the incidents of contamination have decreased in orthopaedic related procedures between years 2008/09 and 2013/14, the challenge of total prevention still remains. Official reports suggest that patients who leave the hospitals and readmitted are at a greater risk of infection. The predominant species in orthopaedic related operations (hip, knee, repair of neck of femur and spinal related surgery) was Staphylococcus aureus, causing ≥ 40 % of all infections. Because of this the issue of orthopaedic related infections in nosocomial environments is still a major concern. Some medical devices incorporate antibiotics to help resist infection, however due to certain limitations for example, decreased release at the later stages of implantation, resistance continues to rise. Antibiotics have been used to combat these infections for many years but as a result of over-use and over-prescription, bacteria have evolved mechanisms to avoid their effects with microbial resistance rising significantly. Therefore development of innovative methods which deliver an alternative approach to antimicrobial function is therefore much in demand. In particular, the potential of antimicrobial nanoparticles as future agents has received much attention.

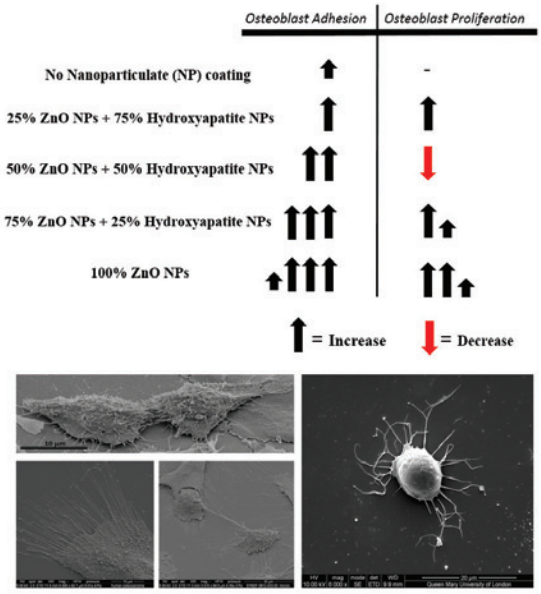
What are the aims and objectives of this research study?

- To understand, compare and analyse the antimicrobial capability of a number of novel nanomaterials for potential future medical use.
- To provide mechanistic evidence as to how nano-ZnO is able to instigate its antimicrobial effect.
- To optimise a novel nano-based coating system in order to create a thin but functional surface that is both biocompatible and potentially osteoconductive.
- To compare and contrast novel coatings with conventional orthopaedic coatings.
- To innovate and bring new ideas as to how manipulation of coating surfaces can maximise implant stability and performance.

Is this research going to solve the problem?

Partly – I believe no research is ever complete. As a researcher you tend to always ask and solve as many relevant problems as possible. We are committed to find the right combination of the bactericidal as well as osteoconductive properties of the materials we are working with. A collective knowledge of a specific topic in research allows solving complicated problems and this is precisely how charities such as ORUK enable and empower scientists to tackle complicated problems and eventually be a step closer to the answer.





"We are committed to finding the osteoconductive properties of the materials we are working with"

What are the long-term benefits to patients with this problem?

The potential product could increase the lifespan of most prostheses by preventing bacterial attachment to the surface of implants. As with all antimicrobial agents there is the need to determine the right balance between biocompatibility and antimicrobial activity, which often involves complex investigation. Also as well as being antimicrobial, the surface of these future products can provide a suitable environment for osteoblasts (bone forming cells) to proliferate and promote bone growth surrounding the structure of the implant, therefore providing long term benefits for patients.

Impact statement

- The antimicrobial and selective activity of nanoparticles against bone-related pathogens.
- The right balance between biocompatibility and antimicrobial activity of nanoparticles, which often involves complex pathways.
- This research has provided novel evidence for the suitability of nano-ZnO coated surfaces in addition to highlighting the superiority of these coatings as compared to conventional bone implants.

Publications

1. Memarzadeh, K., Sharili, A. S., Huang, J., Rawlinson, S. C., Allaker, R. P. 2015. Nanoparticulate zinc oxide as a coating material for orthopedic and dental implants J Biomed Mater Res A, 103, 981-989

2. Allaker, R. P., Memarzadeh, K. 2014. Nanoparticles and the control of oral infections Int J Antimicrob Agents, 43, 95-104

3. Vargas-Reus, M. A., Memarzadeh, K., Huang, J., Ren, G. G., Allaker, R. P. 2012. Antimicrobial activity of nanoparticulate metal oxides against peri-implantitis pathogens Int J Antimicrob Agents, 40, 135-139

4. Memarzadeh, K., Vargas, M., Huang, J., Fan, J. 2012. Nano metallic-oxides as antimicrobials for implant coatings Key Engineering Materials, 493-494, 489-494

Impact report

Porous metal implants for enhanced bone ingrowth and stability

Researcher Dr William van Grunsven

Supervisor Dr Gwendolen Reilly and Dr Russell Goodall

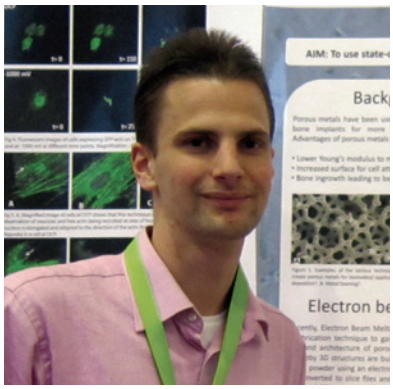
Stream PhD

Duration 36 months

Cost £60,000

Other funders No

Focus Bone, implants, bioengineering



Dr William van Grunsven

William was born in the Netherlands and graduated in 2010 with an MSc in Biomedical Engineering from the University of Twente. Later that year he started his PhD degree, funded by Orthopaedic Research UK, at the Department of Materials Science and Engineering of the University of Sheffield. In 2014 William submitted his thesis and started a job as a researcher in the Department of Human Health and Development of the University of Southampton. The project is a part of the UK regenerative medicine platform and looks at angiogenesis in tissue engineering and the implications for research into bone regeneration.

William was supervised by Dr Gwendolen Reilly, Senior Lecturer in Bioengineering and President of the European Society of Biomechanics who has been undertaking research into orthopaedic biomaterials at the University of Sheffield since 2004. He was co-supervised by Dr Russell Goodall, Senior Lecturer in Metallurgy, expert in the science of porous metals.

What is the basic problem that you are trying to address?

Orthopaedic implants improve mobility and quality of life but implants can fail due to loosening between the metallic surface of the implant and the bone into which it embedded. A key cause of this loosening is poor bone growth into the implant and a mechanical mis-match between the bone and the implant surface. Although there are different coatings and roughening techniques available to improve bone ingrowth these usually only affect a thin surface layer and can easily detach from the implant creating particles which further exacerbate loosening. This project takes advantage of advances in porous metal manufacturing techniques to create a porous structure from a titanium alloy material commonly used in medical implants. The novelty of our approach was to create a graded structure from a single material to combine the best mechanical properties with favourable bone ingrowth.

What is the estimated incidence of this particular problem in the general population?

Over 150,000 people receive a total joint replacement in the UK each year. About 10% of these are revisions caused by implant loosening.

What are the aims and objectives of this research study?

The first aim of this study is to compare different manufacturing methods to create a graded porous structure.

“Our results may lead to a novel orthopaedic implant design that improves bone-implant integration reducing the incidence of loosening and revision surgery”

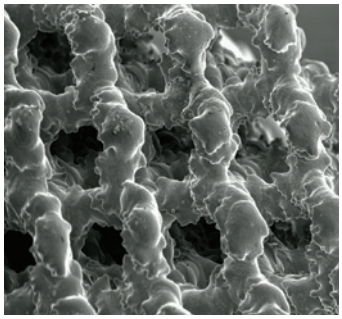


Figure 1:
A porous titanium alloy structure created by the additive manufacturing method – electron beam melting which can accurately and reproducibly create the graded porosity implant design.

The second aim is to investigate the mechanical properties of implants created by the various methods and to compare single sized pores with graded porosity for their effects on the compressive strength of the implant. The third aim is to investigate how well bone cells attach to the structure, grow on it over time and deposit the components of bone matrix (the protein collagen and the mineral hydroxyapatite).

Impact statement

- This project has explored the potential of Electron Beam Melting (EBM) as a fabrication technique for orthopaedic implants and has investigated structure-property relationships of porous structures produced by EBM.
- We have investigated cell and tissue ingrowth into these porous structures and used static and dynamic culture models to predict their clinical potential.
- The project resulted in a reproducible graded porous structure that can be used by orthopaedic and dental implant companies to improve bone ingrowth reduce expensive and traumatic revision surgeries.

Is this research going to solve the problem?

This study promises to advance our understanding of how modern advanced manufacturing techniques can be used to create tailored implant designs to optimise both mechanical and biological properties. Using the design technique and manufacturing method created here we can explore the development of related graded porous structures for the stem and cup of hip replacements and the stems of knee replacements.

What are the long-term benefits to patients with this problem?

The results of our study are also likely to be transferable to other clinical situations where porous materials are used as bone replacements and bone ingrowth is critically important; for example in spinal fusion surgery, dental and oral and maxillofacial surgery and non-healing fractures. Our results may lead to a delivery vehicle for stem cells when a patient’s own bone cells don’t have the capacity to grow into the implant.

Publications

1. van Grunsven, W (2014) Porous metal implants for enhanced bone ingrowth and stability PhD thesis, University of Sheffield. http://etheses.whiterose.ac.uk/id/eprint/8612.

2. van Grunsven, W.; Hernandez-Nava, E.; Reilly, G.C.; Goodall, R. Fabrication and Mechanical Characterisation of Titanium Lattices with Graded Porosity Metals 2014, 4, 401-409. doi:10.3390/met4030401.

Impact report

Bio-engineering hips for the future: smart patterning by Template-assisted electrohydrodynamic atomisation (TAEA)

Researcher Anouska Nithyanandan

Supervisor Professor Mohan Edirisinghe

Stream PhD

Duration 24 months

Cost £262,700

Other funders EPSRC

Focus Orthopaedics, Joint replacements

Anouska Nithyanandan

Anouska Nithyanandan was awarded her MEng Masters degree in Mechanical and Manufacturing Engineering from the University of Warwick, UK, and is a completing PhD student at the Department of Engineering at University College London, under the academic supervision of Prof. Mohan Edirisinghe and Dr. Jie Huang. She has already been appointed to an EPSRC-sponsored research assistantship and her post-doctoral work is a collaborative project between the EPSRC, UCL and JRI Orthopaedics Ltd. It is centred on developing template-assisted electrohydrodynamic atomisation (TAEA) spraying into a generic patterning process for bioactive materials and substrates for clinical use in orthopaedic implant technology.

What is the basic problem that you are trying to address?

Human joints are susceptible to trauma and degenerative and inflammatory diseases, all of which can cause pain, reduced mobility and diminished quality of life. The most common degenerative diseases are osteoarthritis and osteoporosis, which have been found to affect 80% people over the age of 40. Globally increasing ageing populations require more orthopaedic procedures such as hip replacements (>70,000 each year in the UK). The bioengineering task of effectively and efficiently coating the surface of metallic joint prostheses with bioactive materials can enhance direct biological fixation of implants in the body, resulting in shorter recovery times and fewer revision surgeries for patients.

What is the estimated incidence of this particular problem in the general population?

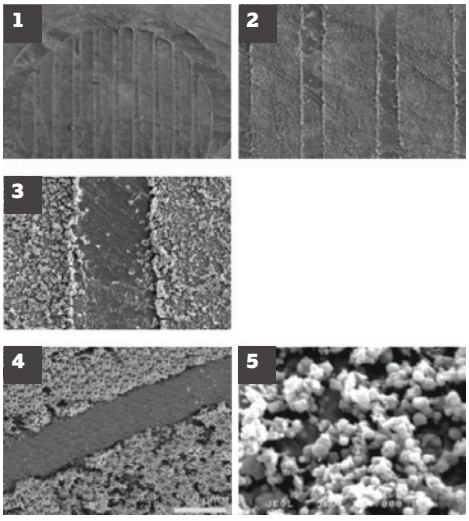
At least 70,000 total hip replacement operations are carried out in the UK each year, with only 85% lasting for 20 years before needing revision surgery. The main reason for a total hip replacement surgery is due to loosening. In addition one in eight women and one in twenty men will have a hip fracture over their lifetime. The main correlation to the likelihood of a fracture is age: the incidence rate doubles with every decade over 50 years of age. Approximately 90% of fractures occur in individuals over the age of 50: 55% in those over 80 and 33% in those over 85. All of these people need hospitalisation and treatment.

What are the aims and objectives of this research study?

The research is concerned with investigating the use of TAEA bioactive patterning on curved surfaces in order that the process is ideal for the preparation of clinical inserts and implants, especially for the orthopaedics sector which is the business of the industrial project partner. This will ensure that the process can be implemented in many real implants that have both flat and curved surfaces. The innovative work is the focus of a patent application (European Patent 0976455814 granted 20th March 2013) and this is the very first patent application of Orthopaedic Research UK. The project work endeavours to systematically investigate TAEA spraying of bioactive nanostructured hydroxyapatite onto curved biometallic substrates, such as orthopaedic titanium alloys, starting from well-characterised suspensions and solutions - the viscosity, surface tension and electrical conductivity of which affect stable jetting. Convex and concave titanium alloy substrates of different diameters will be prepared, together with a variety of fitting curved copper mesh-templates which allow different patterns to be deposited - lined, hexagonal and square. One key difference between flat and curved surface TAEA will be the varying working distance encountered as spraying takes place. This can result in uneven coating thicknesses and inhomogeneities. In order to counteract this, an automated conveyer system which will enable the substrate to be held and moved in and out and/or rotated will be put in place, and the design, construction and implementation of this strategy will be a key part of the project. The microstructures of the curved surface TAEA coatings produced will be studied mainly by electron microscopy. Adhesion and mechanical properties of the coatings will be fully assessed using scratch- and nano-indentation techniques; evaluating adhesion, hardness/scratch hardness and the generation of load-displacement data from which the elastic modulus and the yield strength will be estimated. An attempt will also be made to calculate fracture toughness and residual stresses using any indentation cracks which might be present on the coatings. The coatings will also be subjected to cell culture tests in order to ascertain bioactivity. Two other aspects will also be investigated: Firstly, using an improved and simpler on-line heat treatment to consolidate the titania buffer layer on the substrate will be tried out. Secondly, we shall attempt to do co-axial (co-flow) TAEA which will pave the way for composite polymer-ceramic bioactive deposits or bioactive deposits doped with other ingredients like antibiotics and growth factors.

Is this research going to solve the problem?

Template-assisted electrohydrodynamic atomisation (TAEA) spray-patterning is a novel, recently patented, method which allows the production of interlocked bioactive coatings on flat metallic substrates. The pattern geometry can be varied by simply changing the template geometry and dimensions. The process is based on stable jetting of a flowing liquid/suspension subjected to an electric field and is carried out at the ambient temperature and pressure. It is easy to control this rapid process using the applied voltage, the flow rate and the working (collection) distance between the flow nozzle and the substrate. Because of the interlocking of the bioactive coating with a patterned buffer layer coating, previously deposited via TAEA, this method of bioactive patterning also allows better adhesion of the



Figures 1, 2, 3:
Optical micrographs of interlocked HA on TiO2 pattern on curved Ti substrate (concave diameter 25.4mm) using parallel copper template with strut width of 50 µm and inter-strut spacing of 100 µm.

Figures 4, 5:
Electron micrographs of interlocked patterns on flat substrates. All images depict spraying of suspension 4 wt% TiO2 and 6wt% HA with flow rate, applied voltage and collection time 20 µl/min, 10 kV and 300 s, respectively.

coating. Also, the biological response to TAEA patterned bioactive deposits by cellular entities has proven to be more favourable. These factors compare very favourably when considering the fact that conventional plasma spraying, which is usually used to just plainly cover-coat bioactive materials on metallic substrates, is carried out at extremely high temperatures (about three orders of magnitude higher) and is difficult to control especially when it comes to the preparation of thin coatings. According to industry sources, economic loss due to malfunction and shutdown time involved with plasma spraying is very significant and the industry is looking to uncover and implement alternatives. The TAEA process is highly controllable and compatible on a range of substrate geometries, including flat, concave and convex substrates. Due to the versatile nature of the process, TAEA can provide increased capabilities for the coating of biomedical implants.

What are the long-term benefits to patients with this problem?

Load bearing joint prostheses require bulk mechanical properties such as high tensile strength and high yield strength of titanium alloys to withstand the physical demands exerted on the joint. The surface of the implant also plays a critical role in its integration with the surrounding bone i.e. osseointegration. Modifying the surface composition can also increase osteoconductivity. This enables direct biological fixation through enhanced cell adhesion and accelerated cell movement, which can minimize fixation times, extend functional service life, and reduce the risk of aseptic loosening. The ability to create patterns of bioactive materials on metallic orthopaedic implant surfaces is a crucial feature in influencing cell response, adhesion, orientation and growth. Initial cellular response has been shown to have considerable influence on tissue regeneration, and the orientation of the cells attaching onto the implant significantly affect the structure of resultant tissue.

“Due to the versatile nature of the process, TAEA can provide increased capabilities for the coating of biomedical implants”

Impact statement

- Adapt the TAEA process for application on a range of substrate materials and geometries.
- Evaluate the mechanical adhesion and biological interactions of patterns and coatings produced via TAEA.
- Bring TAEA patterning closer towards commercialisation, increasing the functional service life of orthopaedic implants such as joint replacements.

Publications

1. Nithyanandan, A.; Mahalingam, S.; Huang, J., Rehman, S., Draper, E., and Edirisinghe, M. Bioinspired electrohydrodynamic ceramic patterning of curved metallic substrates Bioinspired, Biomimetic and Nanobiomaterials 2014, Vol 4, Issue 1, 59-67.

2. Nithyanandan, A.; Mahalingam, S.; Huang, J., Rehman, S., Draper, E., and Edirisinghe, M. Template-assisted electrohydrodynamic atomization of polycaprolactone for orthopedic patterning applications Materials Science and Engineering: C 2013, 33, 4608-4615.

3. Li, X.; Koller, G.; Huang, J., Di Silvio, L., Renton, T., Esat, M., Bonfield, W., and Edirisinghe, M. A novel jet-based nano- hydroxyapatite patterning technique for osteoblast guidance Journal of the Royal Society Interface 2010, 7 (42), 189–197.

Impact report

Complex mechanical loading of cell-seeded constructs can lead to functional repair of cartilage defects

Queen Mary University of London

orthopaedic research UK

PhD

Researcher Dr Erica Di Federico

Supervisor Professor Julia C. Shelton

Stream PhD

Duration 36 months

Cost £60,000

Other funders No

Focus Cartilage, Mechanotransduction, Collagen, Proteoglycans, Bioreactor

Figure 1:
Setting up of the specially designed bioreactor, which enables the delivery of complex biaxial loading regimens to chondrocytes seeded in 3D constructs, by Dr Erica Di Federico.

Dr Erica Di Federico attained her Engineering degree at the University of Rome 'Tor Vergata', followed by a MEng in Medical Engineering with specialisation in Biomaterials. In 2015, Dr Di Federico completed her PhD studies in Biomedical Engineering at Queen Mary (QMUL) on mechano-regulation of chondrocytes biosynthetic activity. Dr Di Federico is a researcher with a keen interest in biomechanical conditioning of cell seeded constructs for tissue engineering, the development of bioreactors and tissue engineering strategies for soft tissue repair.

What is the basic problem that you are trying to address?

The mechanical competence of articular cartilage is critical in supporting normal physiological activities of synovial joints over many decades. However, when cartilage is damaged its avascular nature limits its regeneration potential. Articular cartilage injuries are complex and difficult to treat. Untreated cartilage defects lead to early osteoarthritis, one of the most common causes of pain and disability in the UK. Chondral and osteochondral injuries are increasingly presented in younger adults in clinical practice. Current orthopaedic strategies involving total joint replacement (TJR) for end-state degenerative disease are clearly not appropriate for young individuals with cartilage defects who demand an active lifestyle and require alternatives to a series of TJRs. This has stimulated considerable activity in developing cell therapies and tissue engineering strategies to develop long term functional solutions, which will function in the internal biological and mechanical environment over the lifetime of the individual. The existing treatment methods of cartilage regeneration have shown encouraging short and mid-term results but, unfortunately, none have proved to be the ultimate solution. Indeed, no single method guarantees a long term solution of pain-free functional activity.

The aim of our project was to find an optimised way to develop functional cartilage for the effective repair of local defects in joint cartilage.

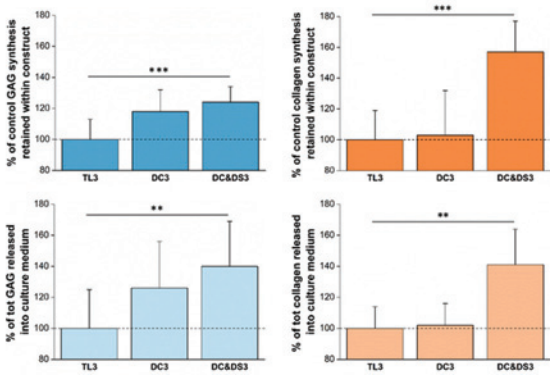


Figure 2:
Percentage of control (TL :tare load) of GAG and collagen synthesis either retained within the construct or released in culture medium by chondrocytes seeded in constructs pre-cultured for 16 hours and subjected to 48 h of continuous dynamic compression (DC) and dynamic compression superimposed on dynamic compression (DC&DS), (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

What is the estimated incidence of this particular problem in the general population?

The overall impact of osteoarthritis varies depending on the joints involved, the level of pain, and extent of loss of function. In severe cases, osteoarthritis is a substantial barrier to people's mobility and independence, and significantly compromises their wellbeing and quality of life.

Around 8.75 million people aged 45 years and over in the UK, have sought treatment for osteoarthritis. Between 1990 and 2010, disability due to osteoarthritis in the UK increased by 16%. This trend is expected to continue, as osteoarthritis is more common in older people and in people who are obese; the proportion of the population within these groups is set to rise. Future projections based on both growth and ageing of the UK population alone estimate an increase incidence of osteoarthritis that may reach 36% by 2035.

What are the aims and objectives of this research study?

This study was designed to support the development of neo-cartilage with structural competency and long term functionality. This was approached by identifying protocols for mechanical conditioning of chondrocytes seeded in an appropriate 3D construct which develop organized extracellular matrix (ECM) with a ratio of collagen to proteoglycan matching that of native tissue. This was undertaken by completing the following objectives:

- Design and implementation of loading systems, which accommodate a range of modalities, including compression and shear, for use with 3D cell-seeded constructs.
- Development robust method(s) to estimate collagen content and organisation within 3D cell-seeded constructs.
- Development of finite element models to predict the degree of deformation of chondrocytes within agarose constructs as a result of different loading modalities and to determine the diffusivity of solutes with different molecular weights within the construct.

"Our results may enable the implementation of a scaffold, characterised by adequate composition and mechanical properties, to consistently reduce the postoperative rehabilitation time following surgical repair"

Is this research going to solve the problem?

This research will provide an improvement of the current cell-based therapy available to treat defects which affect the partial or full thickness of cartilage. The success of this approach will also depend on early detection of localised cartilage damage. This may require screening of susceptible individuals e.g. those following rupture of the anterior cruciate ligaments.

What are the long-term benefits to patients with this problem?

This study developed knowledge of the mechanisms by which cell deformation imposed by external mechanical stimuli is related to the resulting chondrocyte activity.

This research holds the potential for a more effective preconditioning of cell-seeded constructs intended for use to resolve defects in joint cartilage. The systematic investigation of the response of chondrocytes to a complex physiologically relevant deformation profile may enable the implementation of a scaffold, characterised by adequate composition and mechanical properties, to consistently reduce the postoperative rehabilitation time following surgical repair.

In achieving the stated goals, this approach allied to early detection methods, will lead to successful orthopaedic management of chondral/osteochondral defects, particularly associated with young active adults. It could be used as a template for future strategies, possibly involving genetically modified chondrocytes, to address the more challenging problems associated with osteoarthritis. As a by-product of the project, the developed in vitro systems will be able to be used for drug discovery and pre-clinical testing. Through the computational approach it will be possible to calibrate the magnitude of compressive and shear loads to obtain deformation modalities of chondrocytes seeded in appropriate scaffolds comparable with the cells deformation observed in vivo during physiological loading of the cartilage tissue.

Impact statement

- This work has shown that dynamic shear loads are important in cell mediated up-regulation of collagen
- Findings from this study suggest that Proteoglycan and collagen synthesis by chondrocytes seeded in constructs may be regulated by uncoupled cell responses
- This study will enable the development of tuned conditioning protocols to stimulate the mechanisms which underpin the up-regulation of extracellular matrix

Publications

1. Di Federico E, Bader DL, Shelton JC. 2014. Design and validation of an in vitro loading system for the combined application of cyclic compression and shear to 3D chondrocytes-seeded agarose constructs Medical Engineering & Physics 36: 534-540.

Impact report

Effect of mesenchymal stem cell ageing on the efficacy of musculoskeletal tissue engineering/ regeneration strategies

Researcher Dr Kimberley Swinton

Supervisor Dr Stephen Richardson

Stream PhD

Duration 36 months

Cost £58,650

Other funders No

Focus Adult (mesenchymal) stem cell biology, musculoskeletal tissue engineering, ageing

Dr Stephen M. Richardson

I am currently a Lecturer in Cell and Tissue Engineering at The University of Manchester (since 2013), having previously worked as a researcher in the UK Centre for Tissue Engineering and then the UK Centre for Tissue Regeneration, before obtaining a Research Councils UK academic fellowship in 2008. Throughout my career I have focused on the development of adult (mesenchymal) stem cell therapies for age-related musculoskeletal disorders. This includes cartilage regeneration to treat osteoarthritis, intervertebral disc regeneration to treat back pain, and bone regeneration in applications such as revision hip surgery. In 2006 I was named 'Northwest Young Biotechnologist of the Year' and in 2009 received the UK Tissue and Cell Engineering Society 'Early Stage Investigator Award' for my work in the field.

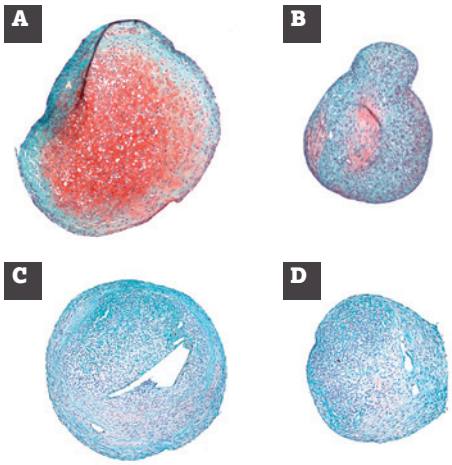
What is the basic problem that you are trying to address?

Age-related diseases, such as osteoarthritis, osteoporosis and low back pain, affect musculoskeletal tissues (cartilage, bone and intervertebral disc respectively) causing pain and limited mobility and represent a significant clinical, social and economic burden.

Adult stem cells are special cells found in bone marrow and fat tissue, that have the ability to turn into (differentiate into) cells from musculoskeletal tissues and it is hoped that they can be used to repair or regenerate such tissues following injury or age-related disease. However, at present we do not know whether disease or stem cell ageing affects the ability of bone marrow or fat derived stem cells to differentiate and regenerate musculoskeletal tissues. This study aims to investigate the potential of adult stem cells from bone marrow and fat for musculoskeletal regeneration and determine whether the age of the donor, or culture in the laboratory affects this potential.

What is the estimated incidence of this particular problem in the general population?

The prevalence of age-related musculoskeletal diseases is increasing as the population ages and they now represent a major socio-economic burden for countries around the world. For example, low back pain is the second most common cause of pain behind the headache and affects around 80% of adults at some point of their lives, with about 10% of these suffers being chronically affected. Cost of back pain to the UK economy is estimated at between 1 and 2% of GDP, or £14-28 billion per year. Novel cell-based therapies have the potential to offer a long-term treatment, reducing the socio-economic burden of age-related musculoskeletal conditions in the UK and internationally.



Figures A to D:
Adult stem cells producing cartilage (red staining). Stem cells from bone marrow (A and B) are better able to produce cartilage than stem cells from fat (C and D). Growing stem cells in the laboratory reduces their ability to form cartilage (A and C show cells which have only been grown for a short period of time vs B and D which are cells from the same donor which have been grown for a long time).

"Our results will be vital in the decision-making of researchers and clinicians developing cell-based therapies and will aid the development of treatments with an enhanced efficacy"

What are the aims and objectives of this research study?

The aims of this study are to investigate (1) whether stem cells from bone marrow or fat tissue have more potential for regenerating diseased musculoskeletal tissues; (2) whether patient age and/or diseases such as osteoarthritis affect the ability of adult stem cells to differentiate; and (3) whether growing stem cells in the laboratory (which is usually required for regenerative medicine applications) affects their ability to differentiate and produce new tissue.

Is this research going to solve the problem?

The findings from this study will advance our understanding of how donor age and cell expansion will affect the function of adult stem cells. The study will also identify whether stem cells from bone marrow or fat tissue are more appropriate for regenerative therapies aimed at treatment of age-related musculoskeletal disorders. This information will be vital in the decision-making of researchers and clinicians developing cell-based therapies and will aid the development of treatments with an enhanced efficacy.

What are the long-term benefits to patients with this problem?

The increase in prevalence of age-related musculoskeletal disorders and the associated costs to the economy means new therapies are required. Cell-based, particularly adult stem cell-based therapies offer the potential to regenerate tissue and hence restore long-term function and reduce pain associated with diseases such as osteoarthritis and back pain. Through an improved understanding of how aging (both cell donor age and ageing caused by cell expansion in the laboratory) impacts of the function of adult stem cells, the potential long-term benefits for patients is the development of regenerative strategies which offer the greatest chance of clinical success. These findings will have implications across a wide range of musculoskeletal conditions, as well as other age-related conditions for which adult stem cell-based therapies are proposed.

Impact statement

- The role ageing plays on function of adult stem cells and their potential for application in musculoskeletal tissue engineering and regenerative medicine therapies has become better understood as a result of this work
- The findings from this study have implications for the development of novel stem cell based regenerative therapies for age-related musculoskeletal disorders such as osteoarthritis and back pain.

Impact report

Optimising fixation in osteoporotic bone fractures

Researcher Dr Alisdair MacLeod

Supervisors Dr Pankaj Pankaj

Stream PhD

Duration 36 months

Cost £60,000

Other funders No

Focus Fracture fixation using locked plating

Dr Alisdair MacLeod

Alisdair is a recently graduated PhD student and Dr Pankaj is a Reader in the Institute for Bioengineering at The University of Edinburgh.

We use computer simulation to investigate the performance of different types of implants employed to treat bone fractures and joint replacements. Simulation allows us to examine the effect of different bone properties, fracture patterns and device configurations without any risk to patients..

What is the basic problem that you are trying to address?

When you have a fracture, a surgeon must decide what the best method of treatment is. Often a simple cast will suffice, however, in more challenging or severe fractures, surgeons may choose to use metal implants with screws to help the fracture heal. A newer type of implant, called locking plate, functions differently to older styles and the manner of use of these implants varies considerably between surgeons, even for similar fracture patterns. While most of these implants perform well and will never cause any problems, in some cases the fractures will not heal, and in others the implant can break or come loose. There are some situations where the failure rate is considerably higher such as in the elderly or where the patient has previously had a joint replacement operation. We are trying to identify why these problems occur, and provide surgical guidance to ensure the risk to patients are minimised.

What is the estimated incidence of this particular problem in the general population?

With increasing ageing population, which results in deteriorated bone quality, the number of fracture incidents is increasing at an alarming rate. Amongst those whose fractures are treated with locking plates the incidence of failure is around 14%. Reasons for failure include: fracture does not heal; the plate breaks; re-fracture occurs; or screw loosens and the device is no longer effective. The failure rate in high-risk situations has been reported to be as high as 26%.

What are the aims and objectives of this research study?

The aim of this research is to improve the performance of fracture fixation implants. Using the computer models developed over the course of this project, the influence of different implant types and the manner in which they need to be configured to prevent failure and optimize healing was investigated. The influence of patient-specific variables such as bone quality, body-weight

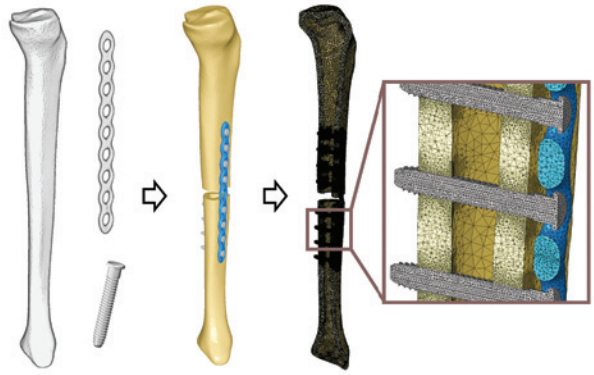


Figure:
Development of a 3D computer model of a bone with a metal implant and screws. Once the model is made, structural analyses can be conducted.

and fracture pattern were also evaluated. We aim to inform surgeons and the wider academic community by publishing our results.

Is this research going to solve the problem?

Current research suggests that the majority of failures are caused by incorrect choice of implant or an inappropriate configuration of screws. This means that most of the failures are avoidable. With improved understanding of the mechanics we will be able to more accurately and consistently choose the optimal implant for the patient.

What are the long-term benefits to patients with this problem?

This will reduce patient suffering caused by device failure directly, but also reduce the financial burden of costly revision surgery – where the implant has to be removed and a 'plan B' operation conducted. Working with surgeons and using simulation we can learn the best way to use healing devices in a variety of situations to ensure patients' fractures heal quickly and without complications.

Impact statement

- This work has improved our understanding of how fracture healing implants function in the body.
- We have developed guidance to help surgeons select the correct implant & screw configuration for the patient.
- The surgical guidance uses information about the patient such as their bodyweight, fracture pattern, and bone quality.

"Computer simulations provide a very cost effective approach to examine how fracture fixation devices work in a variety of situations to ensure patients' fractures heal quickly and without complications"

Publications

1. MacLeod AR, Pankaj P, Simpson AHRW. Does screw-bone interface modelling matter in finite element analyses? Journal of Biomechanics 2012; 45(9): 1712–1716.

2. MacLeod AR, Simpson AHRW, Pankaj P. Reasons why dynamic compression plates are inferior to locking plates in osteoporotic bone: a finite element explanation Computer Methods in Biomechanics and Biomedical Engineering. 2015; 18(16): 1818–1825.

3. MacLeod A, Pankaj P. Computer Simulation of Fracture Fixation Using Extramedullary Devices: An Appraisal In: Doyle B, Miller K, Wittek A, Nielsen P, editors. Computational Biomechanics for Medicine. Springer: 2014. p. 87–99.

Impact report

Optimising shoulder replacement by selecting ideal bone for fixation

Researcher Dr Mittal Shah

Supervisor Professor Andrew Pitsillides, Professor Roger Emery and Dr Claire Clarkin

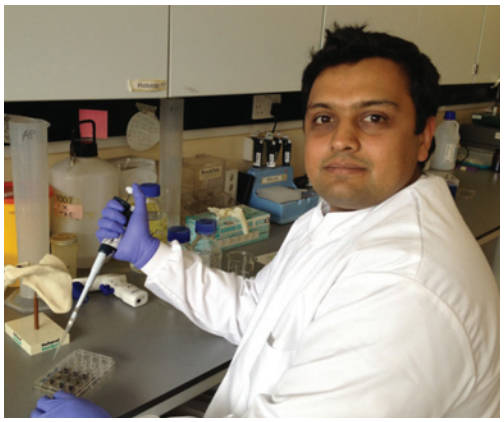
Stream Postdoctoral Fellowship

Duration 22 months

Cost £80,000

Other funders No

Focus Shoulder, osteoblasts, osseointegration



Dr Mittal Shah

I attained my BSc from University of Wales, Cardiff and subsequently undertook a research based MSc at King's College London. I then graduated with a PhD from the Royal Veterinary College, London. I was privileged to continue at the Royal Veterinary College as a post-doctoral research associate undertaking this ORUK funded study.

What is the basic problem that you are trying to address?

Safeguarding long-term fixation is a major challenge in shoulder replacement surgery, particularly in cementless fixation in the joints of osteoporotic and arthritic patients. Improving the success of fixation will alleviate this clinical problem. It is established, however, that uncemented surface replacements, which in contrast rest on the subchondral bone (underneath cartilage) of the humeral head, achieve surprisingly robust fixation. This highlights the likelihood that, whilst fixation uses their mechanical properties, little or no allowance is made for any distinction in the biological bone-forming behaviour of cortical (compact bone) and trabecular (spongy bone) bone sites.

What is the estimated incidence of this particular problem in the general population?

There is growing clinical need for total shoulder replacements. The substantial (>$650 million spent globally, expected to rise to > $1.3 billion) market for shoulder implants illustrates that many problems are far from resolved in shoulder pathology.

What are the aims and objectives of this research study?

The first aim of this study was to determine whether osteoblasts derived from cortical, trabecular and subchondral bone within the human shoulder exhibit distinct basal growth capacities as measured by their growth dynamics and whether these differences are disease specific in osteoarthritic and osteoporotic patient derived cells.

The second aim of this study was to investigate whether cortical trabecular and subchondral bone type osteoblasts isolated from osteoarthritic and osteoporotic patients exhibit different potentials for bone forming capabilities and abilities to influence the vasculature (pro-angiogenesis) which is important for bone regeneration and healing.

“Our findings may lead to targeted control of bone forming cells in selective bone regions, to enhance implant integration and thus reveal a new potential for securing long-term fixation”

Is this research going to solve the problem?

Our study illustrated the divergent bone forming and vasculature influencing potentials of osteoblasts from different bone types, which could influence the design and selection of future orthopaedic implants in the human shoulder. Perhaps more broadly, such that they reveal a new potential for securing long-term fixation and thus limit complications, such as implant loosening, and fractures.

What are the long-term benefits to patients with this problem?

Our findings have shown that it may be possible to target control of osteoblasts in selective sites, to enhance bone integration with implants. A beneficial outcome is the likely generation of new implant designs that do not solely exploit the mechanical properties, but now also harness biological activity to enhance bone-forming behaviour of a particular bone site. This re-designing of implants will efficiently target bone with optimum long-term fixation and allow for new rationales to manipulate local cells to aid the efficiency of these biological ‘repair’ mechanisms.

Impact statement

- Bone cells from different bone types derived from within a single anatomical location have the potential to have distinctive growth, bone forming activities and relationships to the vasculature and that these are diminished in osteoporotic patient cells compared to osteoarthritic counterparts.
- This study may influence the design, and selection of future orthopaedic implants in the human shoulder, harnessing the biological activity to enhance bone-forming behaviour of a particular bone site.

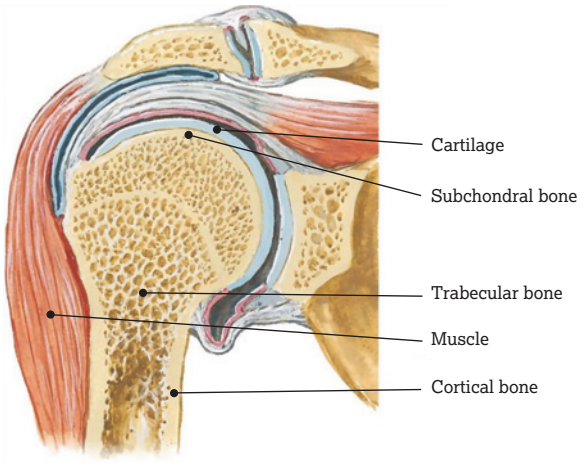


Figure 1 (top):
Anatomical bone regions of interest where bone-forming cells (osteoblasts) were isolated from are reflective of areas where various types of implants would rest.

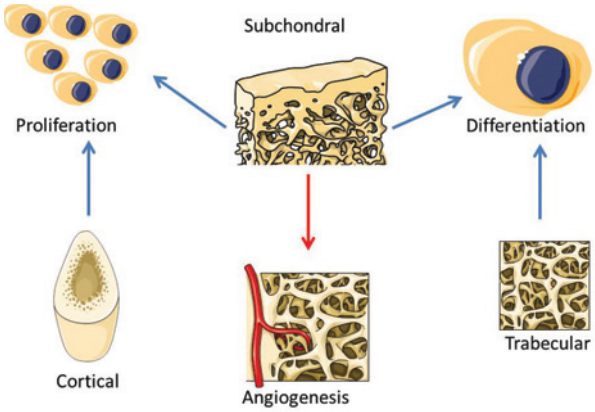


Figure 2 (bottom):
Cortical bone osteoblasts appear to possess greatest growth capacities and trabecular bone osteoblasts appear to exhibit greatest potential for bone formation. Subchondral bone osteoblasts appear to possess ample growth and differentiation capacities, inlcuding pro-angiogenic signalling, compared to trabecular and cortical bone type osteoblasts. Not all bone type osteoblasts exhibit similar osteogenic and pro-angiogenic behaviour.

Publications

1. Shah M, Gburcik V, Reilly P, Sankey RA, Clarkin CE, Emery RJ, Pitsillides AA. Local origins impart conserved bone type-related differences in human osteoblast behaviour EurCellsMat. 2015 Mar; 29:155-179 http://www.ncbi.nlm.nih.gov/pubmed/25738584

2. Taylor S, Shah M & Orriss I. Generation of Human and rodent osteoblast cell cultures BoneKey, Nature Publishing Group. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25396049

Impact report

Development of a 'bioconnecting' nanoscomposite scaffold for hard and soft tissue repair and regeneration

Supervisors Professor Lucy Di Silvio and Dr Jie Huang

Stream Postdoctoral Fellowship

Duration 24 months

Cost £80,000

Other funders No

Focus Osteochondral, soft & hard tissue biology

Professor Lucy Di Silvio

Lucy Di Silvio is Head of the Tissue Engineering & Biophotonics Division, based in the Dental Institute, King's College London, Guy's Hospital. Her group's research is focused on the regeneration of tissues using stem cell technology and its translation for specific clinical problems. Currently her research projects include development of cell seeded grafts for reconstruction of maxillo-facial tissues and also strategies for musculo-skeletal conditions relating to bone and articular cartilage damage, in particular osteochondral defects using cell-seeded scaffolds to direct differentiation of stem cells for in vivo bone and cartilage regeneration and in addition, vascularization of grafts ex-vivo and their integration with host tissue.

Dr Jie Huang heads the Biomedical Materials group at the department of Mechanical Engineering, University College London. Her research interest focusses on the development of novel bioactive materials for biomedical applications. Currently her research projects include surface modification of titanium implants, synthesis of mesoporous nanocalcium phosphates for drug delivery, smart nanocomposite scaffolds for skeletal tissue repair and regeneration and antimicrobial coatings for orthopaedic implants.

What is the basic problem that you are trying to address?

With increased sports injuries in young people and the global ageing population, the demand to replace, repair and regenerate tissues is increasing. Included in this, are a large number of musculoskeletal disorders causing damage to cartilage and bone. Osteochondral lesions can be painful and disabling because they have insufficient intrinsic repair potential, and constitute one of the major extrinsic risk factors for osteoarthritis. Often, these are accompanied by significant pain, restricted mobility and high socioeconomic costs.

Damaged tissues are currently replaced by synthetic biomedical implants, which often fail as a result of not fully integrating with the host tissue. Current approaches to repair cartilage and bone give unpredictable results, and are usually aimed at treating the medical conditions, rather than curing them. Where synthetic materials are used, complete integration or regeneration can only be achieved if the implant mimics the natural tissue being replaced. Biological tissues exhibit different gradients across a spatial volume, with each tissue having specific properties and roles, and the ability to work in a synchronised biofunctional manner is necessary if tissue regeneration is to take place. Previous work has focused on repairing the individual damaged tissue, without considering the interface structure between cartilage and bone. By understanding the interactions between articular cartilage

and subchondral bone, treatment options could in the future be directed to the osteochondral unit, rather than focusing on the articular surface only.

What is the estimated incidence of this particular problem in the general population?

Osteochondral lesions of various types are found in approximately 61% of patients manifesting with joint pain and are most prevalent indicators for surgical repair. The incidence of severe grade III lesions and full chondral grade IV lesions in knee joints are 40% and 19% respectively (according to International Cartilage Repair Society)

What are the aims and objectives of this research study?

The main aim of the project is to develop a 'smart' integrated design scaffold to make functional reconstruction possible, by mimicking the unique structure of the osteochondral tissue. A biomimetic, bioactive calcium phosphate reinforced hydrogel nanocomposite scaffold will be developed with the aim of assembling a porous interconnected scaffold, cultured with both osteoblasts and chondrocytes. The main objectives include (1) Development of a 3D nanocomposite with functional gradient mineral content, (2) Selection of candidate 3D construct to specifically support differentiated stem cells (chondrocytes, osteoblasts) and (3) Development of a continuum 3D model for regenerating cartilage and bone.

The novelty factor of this project is based on 'learning from nature' and mimicking the structural properties of bone and cartilage and using nanotechnology for designing a nano- composite gradient scaffold for the osteochondral continuum interface. This has several structural advantages including conferring substantial pore interconnectivity to provide optimal conditions for cell migration, nutrients and cell viability. Furthermore, incorporation of stem cells with appropriate signalling molecules provides an integrated system, to control the challenging simultaneous regeneration of both tissue types, bone which is vascular and cartilage which is avascular.

Is this research going to solve the problem?

This project aims to advance our knowledge in the development of materials to repair osteochondral defects. We aim to do this by understanding the ultrastructure of natural tissues so that we can mimic this in the design of scaffolds that will be used to repair damaged tissues which will integrate better with host tissue for clinical application.

What are the long-term benefits to patients with this problem?

The great long-term benefits to patients are the development of new materials for treating patients with cartilage damage. Current treatments are limited as they address either cartilage or bone damage rather than the interface between the two. Developing a biomimetic material that has the potential to "bioconnect bone and cartilage would ideally repair and replace the damage tissue/lesion, preventing the need for major procedures such as joint replacement, which is expensive and which requires revision every 10-15 years. Such a scaffold might also be made available to patients who are currently unable to undergo a major elective operation such as joint replacement, where longer periods of anaesthesia are required. In addition, using non-invasive imaging techniques to characterize tissues may in the future contribute towards earlier detection of lesions, resulting in earlier treatment and repair, and improving long-term quality of life and reducing health care costs.

"Our results may lead to a better understanding of the ultrastructure of musculoskeletal tissues and their interface in order to develop more successful biomaterials for tissue repair"

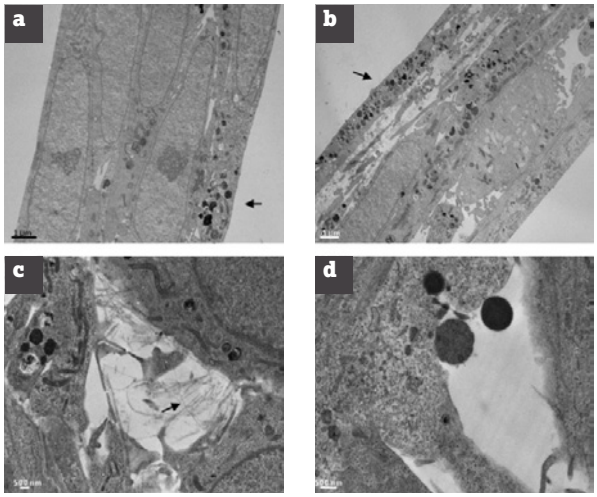


Figure:
Transmission electron microscopy showing transverse view of bone cell layers 7 days in culture in the developed material (a) control-no nanoparticles, (b) with Hydroxyapaptite nanoparticles, showing higher levels of matrix vesicles towards the top of the culture, compared to controls (arrow); (c,d) extracellular matrix being laid down (c=arrow). Scale bars in (a) and (b) 1 µm; in (c,d) 500 nm.

Impact statement

- This work has resulted in a better understanding of the ultrastructure of osteochondral tissues, which is vital in order to develop more effective treatments for bone and cartilage repair
- This work has improved our understanding of material design and fabrication to create scaffolds that mimic the natural tissues
- This work has improved our understanding of the biological responses to nanostructured materials

Publications

1. Kalia, P, Vizcay-Barrena, G, Fan, JP, Warley, A, Di-Silvio, L & Huang, J 2014, Nanohydroxyapatite shape and its potential role in bone formation: an analytical study Journal Of The Royal Society Interface, vol 11, no. 93, 20140004, pp. N/A., 10.1098/rsif.2014.0004

2. Fan, JP, Kalia, P, Di-Silvio, L & Huang, J 2014, In vitro response of human osteoblasts to multi-step sol-gel derived bioactive glass nanoparticles for bone tissue engineering Materials Science and Engineering C: Materials for Biological Applications, vol 36, pp. 206-214., 10.1016/j.msec.2013.12.009

3. Parisi, C, Gervaso, F, Scalera, F, Kunjalukkal Padmanabhan, S, Nobile, C, Cozzoli, D, Di-Silvio, L & Sannino, A 2014, Influence of the precipitation temperature on properties of nanohydroxyapatite powder for the fabrication of highly porous bone scaffolds KEY ENGINEERING MATERIALS, vol 587, pp. 27-32., 10.4028/www.scientific.net/KEM.587.27

4. Kalia P, Vizcay-Barrena G, Fan JP, Warley A, Di Silvio L, and Huang J, Changes to ultrastructural response, intracellular ion levels, and ECM assembly of human osteoblasts in the presence of differently-shaped HA nanoparticles Proceeding of the 25th European Conference on Biomaterials, 2013

Impact report

Why is post-traumatic arthritis more common than primary arthritis in the ankle?

Researcher Dr Emma Blain

Supervisor Professor Victor Duance

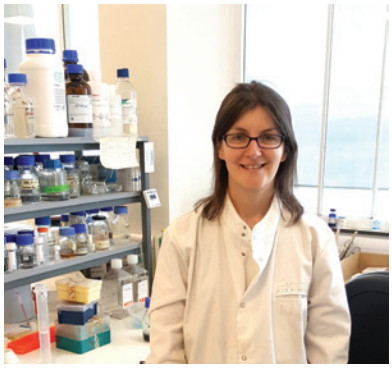
Stream Postdoctoral Fellowship

Duration 36 months

Cost £24,000

Other funders No

Focus Ankle



Dr Emma Blain

I became a lecturer in the School of Biosciences at Cardiff University in 2014, having completed a 5 year academic fellowship within the Arthritis Research UK Biomechanics and Bioengineering Centre of Excellence. My research interests encompass the cellular and molecular events that are involved in maintaining articular cartilage tissue homeostasis, and the mechanism(s) that promote degeneration of the tissue as observed in the pathology of osteoarthritis. Osteoarthritis is a multi-factorial disease and one of the major risk factors is abnormal mechanical load i.e. through sports injury, obesity, etc. My research group is interested in understanding how mechanical load regulates cartilage tissue homeostasis, and more specifically the underlying mechanisms of cartilage destruction propagated by abnormal mechanical load, such that we can identify candidate targets for drug development/ intervention to alleviate symptoms associated with this debilitating disease.

What is the basic problem that you are trying to address?

It is well known that primary osteoarthritis of the knee arises due to one or more risk factors including age, obesity and mal-aligned joints. Interestingly, the incidence of ankle osteoarthritis is low and known to develop predominantly only after trauma to the joint. The question is why is there such a difference in the incidence of osteoarthritis between these two joints? Is there something uniquely different in the composition of the tissues or how they respond to signals, for example mechanical load (brought about by everyday activities)? This research area is still poorly understood. Comparing the composition of ankle and knee cartilage and how they respond to mechanical load will give us a better understanding of which mechanisms are critical for maintaining tissue integrity, thereby largely protecting the ankle cartilage from damage. This may go some way to explaining differences in the incidence of osteoarthritis between the knee and ankle. Therefore, this project will enable us to characterize the differences between cells in these different joints and will hopefully, in the long term, facilitate development of therapeutic strategies for early detection and prevention of osteoarthritis.

"The ankle provides an invaluable tool for studying protective response mechanisms that are absent or diminished in the knee. Our results may increase our knowledge of how post-traumatic and primary osteoarthritic cartilages differ to identify early stages of tissue damage that may precede osteoarthritis, allowing us to develop tools to halt/reverse disease progression"

What is the estimated incidence of this particular problem in the general population?

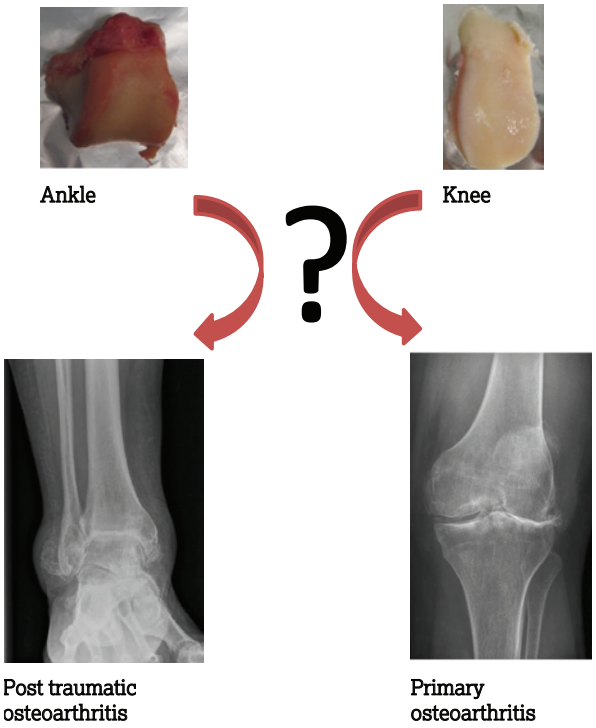
The incidence of osteoarthritis varies significantly from joint to joint, with approximately only 4% of osteoarthritis diagnoses in the ankle compared to over 40% in the knee. However, although ankle osteoarthritis only represents a small proportion of arthritic joints, the physical, emotional, functional pain and limitation of end-stage ankle osteoarthritis is equal to those with primary osteoarthritis of the knee or hip. Patients with ankle osteoarthritis are usually younger than those diagnosed with primary osteoarthritis; our projected longer life span, combined with the substantial decrease in health-related quality of life underscores the profound impact that ankle osteoarthritis has on the patient's disability.

What are the aims and objectives of this research study?

Primary osteoarthritis is multi-factorial with major risk factors including ageing, obesity, joint misalignment and genetic predisposition; in comparison, it is thought that trauma is the most common cause of ankle osteoarthritis i.e. due to a sports injury or vehicle accident. However, it is still unclear how or why the ankle only develops osteoarthritis in response to a previous trauma, whereas primary osteoarthritis has many associated risk factors. This study has begun to investigate why the ankle, unlike other joints e.g. the knee, is largely protected from primary osteoarthritis and only develops as a result of previous mechanical trauma. The first aim of this study is to investigate the composition of the articular cartilage found in human ankle and compare it to the composition of knee articular cartilage, i.e. which molecules are present, to determine whether there are differences that may explain why the ankle is largely protected against primary osteoarthritis. In conjunction with this, the mechanical properties of the two tissues will also be compared to determine whether the ankle cartilage can withstand greater loads applied to it, which could explain why obesity for example, is not a risk factor for ankle osteoarthritis. This aim will be achieved by taking ankle and knee cartilage removed during joint replacement surgery and analysing the amounts of key molecules in the tissues and recording how the tissues respond to mechanical load. The second aim of this study is to investigate how the cartilage cells in the ankle respond to mechanical load by investigating the pathways activated by mechanical stimulation. These pathways will then be compared to those that are activated in knee cartilage cells to determine whether they respond differently to the same stimulus, thereby giving us an insight into why the ankle might be different. We believe that the ankle provides an invaluable tool for studying protective response mechanisms that are absent or diminished in the knee, and thus the study has the potential to allow us to develop tools to halt/reverse disease progression.

Is this research going to solve the problem?

This study promises to help advance our understanding of why the ankle, unlike other joints, e.g. the knee, is largely protected from primary osteoarthritis and only develops as a result of previous mechanical trauma. Understanding the unique physiological and biomechanical properties of ankle cartilage that influence its function and metabolism is imperative for the subsequent capacity to treat ankle osteoarthritis, as well as treat patients with primary osteoarthritis.



What are the long-term benefits to patients with this problem?

Regardless of which joint(s) are affected by osteoarthritis, the continuing clinical challenges to this disease remain the reduction of pain and restoration of joint function. Understanding the unique physiological and biomechanical properties of ankle cartilage that influence its function and metabolism is imperative for the subsequent capacity to treat ankle osteoarthritis. Increasing our knowledge of how cartilages differ will enable us to identify early stages of tissue damage that may precede osteoarthritis, allowing us to develop tools to halt/reverse disease progression. The great long-term benefit to patients, from our knowledge of differences between cartilage cells from different joints, is that it will facilitate development of therapeutic strategies for early detection and prevention of osteoarthritis, not only in the ankle but in the sites of primary osteoarthritis too.

Impact statement

- Why the ankle is largely protected from primary osteoarthritis, unlike the knee or hip, will become better understood as a result of this work
- Current findings suggest that there are differences in the composition of the cartilage from ankle versus knee

Impact report

The Relationship between Alignment, Function and Loading in Total Knee Replacement: In-Vivo Analysis of a Unique Patient Population

Researcher Dr June Madete

Supervisors Professor Cathy Holt, Mr Andy Metcalfe, Dr Gemma Whatling

Stream Postdoctoral Fellowship

Duration 12 months

Cost £40,000

Other funders Arthritis Research UK, Biomechanics and Bioengineering Centre

Focus Knee replacement, Biomechanics

Dr June Madete

I was born and raised in Kenya and came to Cardiff with a scholarship to study engineering. I stayed on to complete a PhD in biomedical engineering, with a special interest in motion capture. This ORUK grant was my first post-doctorate appointment and allowed me to interact much more closely with surgeons, and develop my ability to do clinical research with patients whilst also using the engineering skills and techniques that I had learned in my PhD. After working on this project, I returned to Kenya to become a Lecturer at Egerton University, and I am now working as a Senior Lecturer in Biomedical Engineering at Kenyatta University. I continue to be heavily involved in research and also have teaching, mentoring and leadership roles as I continue to work to develop biomechanics in Kenya.

The data which was collected during this project continues to provide a wealth of information, and further research work has been done with additional investment from Cardiff University, particularly by David Williams and Ishaak Saleem. They have worked towards further improvements in the software and processing methods that we use to perform the image matching, to improve the quality of the outputs and provide further and clearer answers to the key questions in this study.

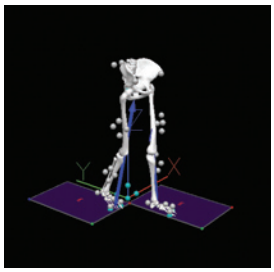
"The aim of this study is to examine the link between how a joint is positioned and how it functions in people having knee replacements"

What is the basic problem that you are trying to address?

Total knee replacement is a very common operation, and surgeons take great care is making sure the joint implant components are correctly sized and aligned to the bones around the knee. However, we do not have a good understanding of the margins for error, or even what the perfect position for a knee replacement might be.

What is the estimated incidence of this particular problem in the general population?

Approximately 80,000 knee replacements are performed in England and Wales every year according to the UK's National Joint Registry. Most give good pain relief but a proportion of patients (up to 20%) may be dissatisfied with the outcome.



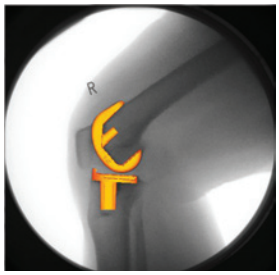


Figure:
Gait analysis and image matching – two of the techniques used in this study

What are the aims and objectives of this research study?

The aim of this study is to examine the link between how a joint is positioned and how it functions in people having knee replacements. To do this, we recruited patients from a unique group in our region, who had all had the same implant design used by the same hospital, but had differences in the position in which the joint had been aligned surgically. We measured the position of the joint using scans and x-rays of the whole leg, and then patients attended our laboratory twice – once to have the way they walk measured and once to have the function of the knee replacement measured whilst the patient took a step. We did this using a very precise method that had been developed in Florida, using low dose video x-ray to 'watch' the joint move, and then matching it to a computer model of the knee replacement to show how it moves in 3 dimensions.

The overall aim is to guide surgeons about the ideal positioning of the implant for a knee replacement, what the margins for error are, and whether there are any particular positions that they need to be careful to aim for or avoid when they insert a knee replacement. By doing this, surgeons will be better informed leading to more consistent and successful knee replacements.

Is this research going to solve the problem?

This study has already identified certain positions that appear to be linked to worse gait function (ie walking abnormally), and may steer surgeons to take care in avoiding those abnormal positions. The data is being analysed further and in the process of doing this we have advanced the technology and software that is currently used to make these assessments. We have also made new discoveries about the way in which knee replacement function differs from normal knee function, and will have developed new ways of assessing joint function that will be of great value in future research. This study will represent one of the largest collections of real-life biomechanical data in knee replacement patients and is expected to provide surgeons with a wealth of data for the future.

What are the long-term benefits to patients with this problem?

The long-term benefits to patients are that this study will help surgeons to improve the way in which they insert and align a knee replacement, potentially reducing the number of dissatisfied patients by making the joints function more like a normal knee.

In performing the analysis for this study, we have furthered the technology used to study joints in this way and have refined a technique that will allow larger numbers of patients to be studied in a reproducible way. This piece of research has also allowed the development of larger studies which will be able to provide further and more detailed answer to this important question.

Presentations & Posters

1. International Society of Biomechanics, Glasgow, July 2015
2. Orthopaedic Research Society, Las Vegas, March 2015 (Poster)
3. World Congress of Biomechanics, Boston, July 2014 (Poster)
4. The British Association for Surgery of the Knee Annual Meeting, Norwich, April 2014

Impact report

Modelling mechanical signalling at the bone-tendon interface

Researcher Dr Andrew Jones and Dr Maria Kuzma-Kuzniarska

Supervisors Associate Professor Philippa Hulley

Stream Postdoctoral Fellowship

Duration 24 months

Cost £80,000

Other funders No

Focus Soft tissue biology

Dr Andrew Jones

Dr Maria Kuzma-Kuzniarska

Dr Andy Jones is currently Senior Lecturer in Molecular Biology and Genomics. Department of Biological and Medical Sciences - Faculty of Health and Life Sciences, Oxford Brookes University, Oxford.

"My laboratory is interested in gene diversity and the resulting functional/pharmacological properties of ligand-gated ion channels, using genome sequence analysis, molecular biology and electrophysiology. In particular, I am focusing on cys-loop ligand-gated ion channels of insects. The cys-loop ligand-gated ion channel superfamily includes nicotinic acetylcholine receptors, GABA receptors and glutamate-gated chloride channels, which play key roles in signalling and are also of interest as they are targets of pesticides."

Dr Maria Kuzma-Kuzniarska is currently a freelance Scientific Illustrator and Artist, working from Paris. She says "My work is an exploration of the human form, its inherent beauty and dynamics. Using a variety of digital and conventional media, I study the complexity and beauty of the human body. I am particularly fascinated by the constant changes it undergoes throughout life. Through my work, I examine how our bodies are shaped, not only by genes, but also by the cultural and economic conditions in which we live."

What is the basic problem that you are trying to address?

Tendon problems often start at the junction between tendon and bone. This is a specialist tissue described as enthesis and displays a graded change in properties between flexible tendon, through stiffer fibrocartilage and into the rigid lattice of bone. This serves like the sleeve on an electric plug which limits movement of the electric flex as it enters the plug and stops it wearing down. Tendon cells live in this region and experience different loads during daily activities depending on which tissue zone they occupy. We set out to study tendon cell communication and response in these different materials and also in whole tissues.

What is the estimated incidence of this particular problem in the general population?

The rotator cuff is a typical, but not only, site of enthesopathy, causing painful shoulders and torn tendons. 54% of patients aged ≥ 60 years have partial or complete tears of the rotator cuff on an MRI scan.

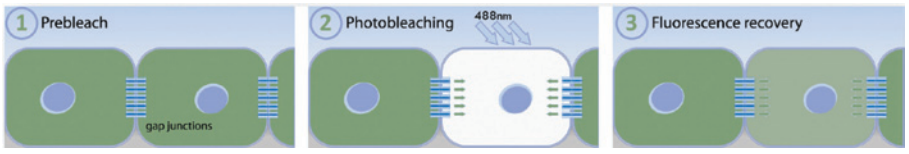


Figure:
Schematic representation of a FRAP experiment

What are the aims and objectives of this research study?

This study aimed to fill in a number of gaps in our knowledge of how tendon cells detect and respond to mechanical loading. We first screened human tendon cells for all possible mechanosensitive ion channels. We selected the channels linked to primary cilia, hair like projections on the surface which sense movement in the surrounding tissue matrix, and channels that form gap junctions or communication portals between adjacent cells, for further study.

Is this research going to solve the problem?

This research has opened new ground in our ability to study tendon and enthesis tissue. We initially developed methods to express primary cilia on tendon cells and compared loading response in those with and those without cilia to begin to understand how the presence and absence of these structures, which disappear during periods of rapid growth or repair, affect response to loading. We also developed a novel confocal microscopy method to follow inter-cellular communication through gap junctions, live and in real time. These gap junctions proved druggable so we focused on their behavior with loading and in monolayer or in 3D gels. We rapidly developed a more advanced technique to measure the function of gap junctions in whole tendons from mouse tails and also used this in the enthesis tissue and in both mouse and human whole cartilage slices. This new technique makes it possible for confocal microscopists to study intercellular communication networks in whole soft tissues without electrophysiology expertise or equipment.

"This new technique makes it possible for confocal microscopists to study intercellular communication networks in whole soft tissues"

What are the long-term benefits to patients with this problem?

The cellular network in tendon forms a fragile, interconnected web that senses and co-ordinates response of the whole tissue to changes in mechanical loading. Our work graphically demonstrates that loss of connectivity in these cells prevents transfer of information. This highlights the critical need to diagnose and treat tendon problems early in order to retain full regenerative capacity. Drugging some of these channels may be a way to protect tendon cells and enhance tendon repair and will also help us to understand the purpose, limits and extent of the cellular network in whole tissue.

Impact statement

- Novel research tools have been developed to study the function of tendon cell communication networks
- We have a better foundational knowledge of the mechanosensory repertoire of tenocytes
- This work has uncovered specific areas of fragility in tendon biology and suggests possible drug targets for tendon rehabilitation

Publications

1. Illustrations for Orthopaedic Basic and Clinical Science for the Postgraduate Examination: Viva Practice and Diagrams. http://www.oruk.org/news-and-events/news-stories/s5dcc9q5l3.html

2. Kuzma-Kuzniarska M, Cornell HR, Moneke MC, Carr AJ, Hulley PA. Lovastatin-Mediated Changes in Human Tendon Cells J Cell Physiol. 2015 Oct;230(10):2543-51. doi: 10.1002/jcp.25010. PubMed PMID: 25846724.

3. Kuzma-Kuzniarska M, Yapp C, Pearson-Jones TW, Jones AK, Hulley PA. Functional assessment of gap junctions in monolayer and three-dimensional cultures of human tendon cells using fluorescence recovery after photobleaching J Biomed Opt. 2014 Jan;19(1):15001. doi: 10.1117/1.JBO.19.1.015001. PubMed PMID: 24390370; PubMed Central PMCID: PMC4019415.

Impact report

Investigation into synovial fluid markers of disease activity in knee osteoarthritis

Researcher Mr Chethan Jayadev

Supervisors Associate Professor Philippa Hulley, and Professor Andrew Price

Stream Clinical fellowship

Duration 12 months

Cost £40,000

Other funders NIHR Musculoskeletal BRU

Focus Soft tissue biology, osteoarthritis

Mr Chethan Jayadev

I am an orthopaedic surgeon who took time out of my training to complete a DPhil in Oxford. Having returned to my surgical training rotation in London, I have recently obtained my Fellowship of the Royal College of Surgeons examinations. At present, I am a final year Specialty Registrar in Trauma and Orthopaedics at the Royal London Hospital. I intend to be actively involved in research in to knee osteoarthritis during my career.

What is the basic problem that you are trying to address?

Current methods of detecting osteoarthritis progression are limited and insensitive. In this project we used biological markers from knee joint fluid in a pattern recognition approach to derive sensitive and specific fingerprints for early joint injury, end-stage osteoarthritis and inflammatory arthritis. Our hypothesis is that cartilage and other joint cells start to respond to stress long before gross wear and tear becomes visible, and will therefore provide the earliest detectable stress markers. Equally, they will be the first to show an improvement, whether through weight loss, a corrective operation or drug therapy. They will respond in days and weeks, rather then the months and years needed to see changes with imaging, and provide essential insight into disease mechanisms, progression and the success or failure of interventions.

What is the estimated incidence of this particular problem in the general population?

According to the NHS, more than 70,000 knee replacements are carried out in the UK each year and over 60,000 hip replacements in England and Wales. Many of these could be prevented or delayed if we were able to develop effective alternative treatments and to detect the problem early enough.

What are the aims and objectives of this research study?

The aims of this study were to (1) Optimise & validate methods for multi-marker joint fluid analysis.
(2) Determine if the anatomical site of sampling effects joint fluid measurements. (3) Establish whether joint fluid measurements are stable over short intervals. (4) Assess whether structurally progressive types of end-stage knee osteoarthritis demonstrate differences in their joint fluid biology. (5) Define a 'biological fingerprint' for end-stage knee osteoarthritis from a diverse range of relevant joint fluid biomarkers.

> **"This unique biomarker tool allows us for the first time to accurately diagnose the type of knee joint problem using a few drops of synovial fluid"**

Is this research going to solve the problem?

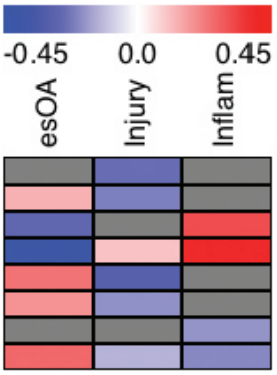
This study produced robustly distinct biological fingerprints for 3 major knee conditions, injury, end-stage OA and inflammatory arthritis. This unique biomarker tool allows us for the first time to accurately diagnose the type of knee joint problem using a few drops of synovial fluid. Not only does this provide us with a possible early diagnostic tool for irreversible joint damage, but gives us a method that works better than any previous approach and that will improve in its accuracy and usefulness as we add more markers and more patient groups.

What are the long-term benefits to patients with this problem?

This discovery has the potential to diagnose osteoarthritis much earlier than any other test, allowing earlier and more effective intervention and potentially avoiding years of pain before eventual diagnosis and joint replacement. It also provides a tool for sensitively monitoring response to treatments other than total joint replacement so that we can judge their efficacy more quickly and accurately. Scientifically, being able to accurately separate patient groups into different types and stages of disease will help enormously to understand the different causes of osteoarthritis.

Impact statement

- Development of sensitive and accurate biomarker fingerprints of common knee conditions
- Major advance in understanding how to combine markers to separate different disease groups on the basis of knee joint fluid
- This work has provided a technical tool for us to use in understanding, monitoring and effectively treating knee problems



Publications

1. Thesis: Chethan Jayadev, (2014). A synovial fluid fingerprint for end-stage knee osteoarthritis DPhil. University of Oxford. Citable link to this page: http://ora.ox.ac.uk/objects/uuid:b3f41800-5ede-437d-a2fc-df7cbb54c081

2. Jayadev C, Rout R, Price A, Hulley P, Mahoney D. Hyaluronidase Treatment of synovial fluid to improve assay precision for biomarker research using multiplex immunoassay platforms J Immunol Methods. 2012 Dec 14;386(1-2):22-30. doi: 10.1016/j.jim.2012.08.012. Epub 2012 Aug 28. PubMed PMID: 22955210.

3. Rout R, McDonnell S, Hulley P, Jayadev C, Khan T, Carr A, Murray D, Gill H, Price A. The pattern of cartilage damage in antero-medial osteoarthritis of the knee and its relationship to the anterior cruciate ligament J Orthop Res. 2013 Jun;31(6):908-13. doi: 10.1002/jor.22253. Epub 2013 Feb 19. PubMed PMID: 23423802.

4. Jayadev C, Khan T, Coulter A, Beard DJ, Price AJ. Patient decision aids in knee replacement surgery Knee. 2012 Dec; 19(6):746-50. doi: 10.1016/j.knee.2012.02.001. Epub 2012 Mar 2. Review. PubMed PMID: 22386538. 5. UK Patent Application No. 1404518.1 OA Markers for Isis Innovation Limited and a follow up, GB Application No: 1404634.

Impact report

Is HLA-B27 expression abnormal in Ankylosing Spondylitis joints?

Researcher Ms Kirsty McHugh

Supervisors Professor Paul Bowness

Stream Postdoctoral Fellowship

Duration 12 months

Cost £40,000

Other funders No

Focus Arthritis

Professor Paul Bowness

Paul Bowness is a consultant rheumatologist at the Nuffield Orthopaedic Centre, Oxford Universities NHS trust, and professor of Experimental Rheumatology at NDORMS, University of Oxford.

What is the basic problem that you are trying to address?

Ankylosing Spondylitis (AS) is a common rheumatic disease causing severe pain in the back and other joints, that can lead to bony fusion. There is a strong genetic component, with the HLA-B27 gene the most important genetic factor. We are trying to understand how this gene leads to AS.

What is the estimated incidence of this particular problem in the general population?

In adults in the UK the prevalence of AS is about 0.4%.

What are the aims and objectives of this research study?

We wished to determine if abnormal HLA-B27 proteins are expressed on AS patient cells and especially in the joints, using monoclonal antibodies (mAbs). One monoclonal antibody, made in collaboration with Christoph Renner, Zurich, HD6 detects homodimer expression in patients with Ankylosing Spondylitis,

Is this research going to solve the problem?

This study promises to help advance our understanding of why AS patients develop inflamed joints. This understanding will help us try and improve treatment.

What are the long-term benefits to patients with this problem?

The long-term benefits to patients are the development of new treatments for patients with AS and other inflammatory joint diseases.

"Our results may lead to a better understanding of what causes inflammation in arthritis and help develop new drugs that may be used in these conditions"

Impact statement

- Abnormal HLA-B27 expression in joints is now recognized as a possible cause of inflammation in AS.
- This work has improved our understanding of the human immune system and what causes joint inflammation.
- This work has resulted in a better understanding of AS disease pathogenesis, which is vital in order to develop more effective future treatments for patients with AS and related diseases.

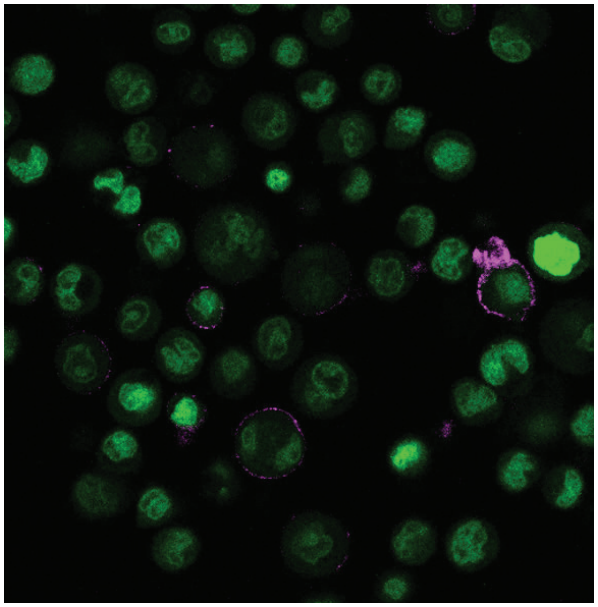


Figure:
Abnormal HLA-B27 molecules on white blood cells (in green) demonstrated in purple using a monoclonal antibody

Publications

1. Cauli, A., Shaw, J., Giles ,J., Hatano, H., Rysnik, O., Payeli, S., McHugh, K., Dessole, G., Porru, G., Desogus, E., Fiedler, S., Hölper, S., Carette, A., Blanco-Gelaz, M.A., Vacca, A., Piga, M., Ibba, V., Garau ,P., La Nasa, G., López-Larrea, C., Mathieu ,A., Renner, C., Bowness, P., Kollnberger, S. The arthritis-associated HLA-B*27:05 allele forms more cell surface B27 dimer and free heavy chain ligands for KIR3DL2 than HLA-B*27:09 Rheumatology 2013 52. 11 1952-62.

2. McHugh and Bowness The link between HLA-B27 and SpA—new ideas on an old problem Rheumatology 2012 Sep;51(9):1529-39.

Impact report

Identification of optimal clonal subpopulations within bone marrow derived mesenchymal stem cells for bone and cartilage repair

Researcher Mr Wasim Khan

Supervisor Dr Jayesh Dudhia

Stream MD

Duration 24 months

Cost £36,700

Other funders No

Focus Stem cells, cartilage and bone

Dr Jayesh Dudhia

My research interest is in the extracellular matrix of cartilage and tendon and the degenerative diseases that affect these tissues. There are many similarities between these tissues both in their molecular composition as well as having a high prevalence of disease with increasing age and exercise. I have a special interest in stem cells as they have a great potential for the repair and regeneration of injured tissues. My recent research has involved the application of stem cells for the clinical treatment of tendon injuries in athletic horses, which can serve as an excellent clinical translation model for human orthopaedic conditions.

What is the basic problem that you are trying to address?

The erosion of the cartilage that occurs in osteoarthritis is a particular challenge to treat as the tissue heals poorly and there are no treatments to arrest or reverse the disease. As the disease advances it results in significant pain of the joint and often morbidity over many years. Options for repair are limited to surgery involving joint replacement, which, although successful in sedentary patients, has a limited lifetime in more active, younger patients. Similarly, some bone fractures heal poorly and become chronic and painful for many years and surgical interventions have limited benefits. There are therefore numerous ongoing efforts to develop new treatment strategies for both osteoarthritis and non-healing bone defects. In recent years bone marrow derived stem cells have shown promise for repairing diseased tissues.

These cells have the ability to become specialised cells such as cartilage or bone producing cells but evidence suggests there is heterogeneity in their phenotype or makeup when isolated from the bone marrow.

This research address the important question of whether a particular cell phenotype exists that is better at making cartilage or bone and if this population may be superior in healing cartilage or bone defects compared to the mixed population.

What is the estimated incidence of this particular problem in the general population?

Osteoarthritis affects nearly 9 million people within the UK of which about 4.7 and 2.4 million involve the knee and hip, respectively. The incidence of radiographic osteoarthritis is estimated to be about 2% in women and about 1.4% in men. Its prevalence is particularly increased in the older age group with 33% of people aged 45 years seeking treatment and increasing (49% women, 42% men) in those over 75 years. The incidence of bone fractures is estimated at about 3.6%, which rises considerably in middle age men and women over 75 years of age.

What are the aims and objectives of this research study?

The first aim of this study was to identify the heterogeneity of the stem cell population isolated from the bone marrow using specific markers and then to select individual cells and compare their phenotype with the mixed population. The second aim of this study was to correlate the ability of clonal (single cell) populations to become cartilage or bone cell-types with the cell markers.

Is this research going to solve the problem?

This work was aimed at understanding the fundamental biology of bone marrow mesenchymal stem cells. The study helps to advance our knowledge of the markers that identify the heterogeneity of the cells and the spontaneous capacity of sub-populations of cells to become cartilage and bone type cells. The ability to select stem cell populations that are more driven to produce cartilage or bone is essential to develop effective stem cells therapies for these tissues.

What are the long-term benefits to patients with this problem?

The ability to prepare stem cell populations that are optimal at making cartilage or bone is an important step towards repairing or regenerating cartilage and bone defects. Improving the clinical efficacy of the stem cells will have long-term benefits to patients because it would reduce the need for repeat surgical intervention, significantly impact the chronic phase of the disease and therefore positively improve pain and morbidity.

“Our results show that clonal stem cell populations can form bone (unipotent) or both bone and cartilage (bipotent) but not cartilage only, which advances our understanding of these cells for treating bone and cartilage defects”

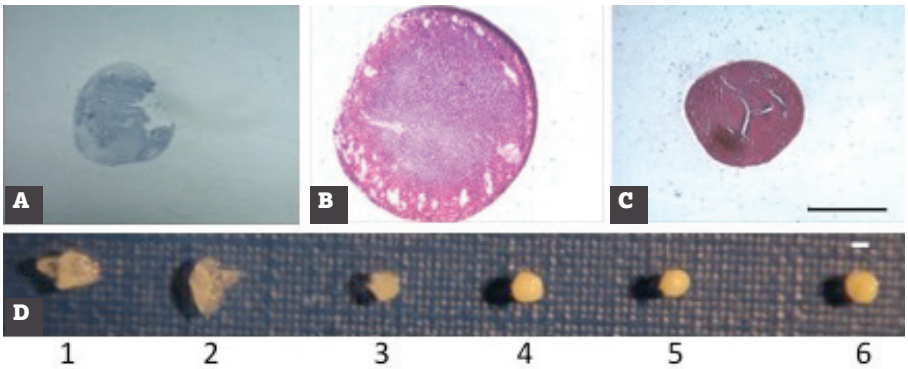


Figure:
Propensity of clonal stem cell lines to form cartilage nodules. Cell lines 1- 3 (and A & C showing histology section through a nodule) exhibited poor capacity with small, poorly defined nodules compared to 4 – 6 (and B) with bigger and better defined nodules.

Impact statement

- This work has improved our understanding of the wide heterogeneity in the phenotype of human bone marrow derived mesenchymal stem cells.
- This work has improved our understanding of markers that might identify a stem cell that can only form bone or cartilage
- This work has improved our understanding of the relationship between the heterogeneous property of stem cells and their capacity to become specialised cells, which may help with identifying a cell population that may be better at bone or cartilage repair.

Publications

1. A Chandrashekran, R Alam, D Marsh, W Khan and J Dudhia. Clonal heterogeneity in trilineage potential of human bone marrow derived mesenchymal stem cells International Journal of Experimental Pathology (2014);

Impact report

The effects of obesity on bone structure and strength

Researcher Amy Evans

Supervisor Dr Jennifer Walsh

Stream PhD

Duration 24 months

Cost £25,000

Other funders National Osteoporosis Society

Focus Osteoporosis, fracture

Dr Jennifer Walsh

I am a Senior Clinical Lecturer in Bone Metabolism. I am interested in the microarchitecture of bones, and how this affected by age, body weight and different disease.

What is the basic problem that you are trying to address?

Obese people generally have fewer fractures than normal weight people, but have more foot, ankle and humerus fractures. We wanted to know if this is due to weaker bones at those sites. We used a state-of-the-art scanning technique – high resolution peripheral quantitative computed tomography (HR-pQCT) – to assess bone structure and build computerized models of the bones for strength testing.

What is the estimated incidence of this particular problem in the general population?

One in two women and one in five men over the age of fifty will have a fracture due to osteoporosis.

What are the aims and objectives of this research study?

To understand how body weight and fat affect bone structure and strength. This helps us to predict how health care needs will change as our population gets older and more obese. It also helps to understand the fundamental biology of how different systems in the body (fat and bone) interact, and how we might use this to improve osteoporosis treatment and prevent fractures.

Is this research going to solve the problem?

We didn't find out why obese people have more fractures at these sites- so we are going onto to study other possibilities such as muscle weakness and load to strength ratios. However, we have learnt how obesity makes bones denser and stronger.

"Understand the fundamental biology of how different systems in the body (fat and bone) interact could improve osteoporosis treatment and prevent fractures"

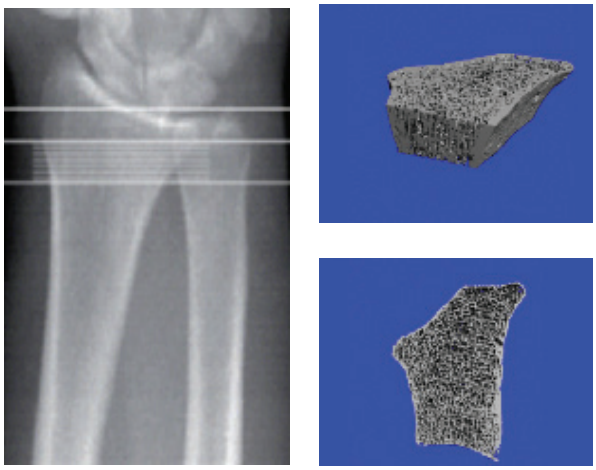
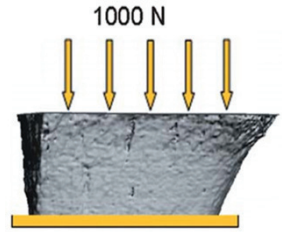


Figure 1:
HR-pQCT of the radius



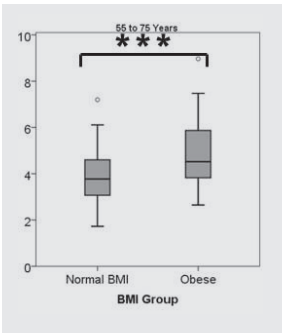


Figure 2:
Radius estimated failure load (kN)

Impact statement

- As the population gets older, and obesity is becoming more common it is important to understand how obesity might affect osteoporosis and fractures
- We now know that the excess foot, ankle and humerus fractures in obese people is not due to weaker bones – these bones are more dense and stronger than in normal weight people
- We have identified some hormones which are affected by obesity, and have effects on bone strength. This is useful information for the understanding of osteoporosis in all patients

What are the long-term benefits to patients with this problem?

Identifying the mechanisms through which fat tissue influences bones to become more dense opens up new possibilities for developing osteoporosis treatments in the long term.

Publications

Evans AL, Paggiosi MA, Eastell R, Walsh JS. Bone density, microstructure and strength in obese and normal weight men and women in younger and older adulthood Journal of Bone and Mineral Research 2015; 30: 920-928

Impact report

Dietary-derived diallyl disulphide as a chondroprotective agent in osteoarthritis

University of East Anglia

orthopaedic research UK
Postdoctoral Fellowship

Supervisors Professor Ian Clark and Professor Simon Donell

Stream Postdoctoral Fellowship

Duration 24 months

Cost £79,319

Other funders No

Focus Osteoarthritis

Professor Ian Clark

Ian Clark is a molecular cell biologists with interests in diseases of extracellular matrix. These include osteoarthritis and Dupuytren's disease. Simon Donell is a consultant orthopaedic surgeon with interests in the knee, particularly patellar instability and patellar syndromes. We work across the clinical scientific border to optimize outcome and translation.

What is the basic problem that you are trying to address?

Osteoarthritis is a major health and economic burden for which there are no medicines which can slow or prevent the disease. Current treatments attempt to address symptoms e.g. pain, but are frequently inadequate. Surgical treatments (e.g. joint replacement) are available in late-stage osteoarthritis, but increasing numbers of patients (see below) make this unsustainable. We aim to gain evidence for the ideal diet to maintain healthy joints and prevent the development or progression of osteoarthritis. This will likely need to be implemented as early as possible for the best outcome. This research investigates the impact of components of the diet on cell and tissue models of osteoarthritis. Clearly, an approach to treatment which relies on dietary modification is attractive, with low risk and implementable at a population level.

What is the estimated incidence of this particular problem in the general population?

A 2012 survey estimated that 8.5 million people in the UK have moderate or severe osteoarthritis, of which 71% of patients are in constant pain. Since the two major risk factors for the disease are increasing age and increasing obesity, the numbers are predicted to double by 2030.

What are the aims and objectives of this research study?

The aims of this study were to test allyl sulfides, found in garlic or garlic-derived products and supplements, on laboratory models of osteoarthritis. Particularly, to test the ability of these compounds to prevent the production of cartilage-degrading enzymes by cartilage cells. MMPs (matrix metalloproteinases) are a family of 23 enzymes which break down tissues in the body. They can be viewed as biological scissors which chop up the components making up these tissues including cartilage. A number of these MMPs are involved in osteoarthritis and we can measure their production by cartilage cells.

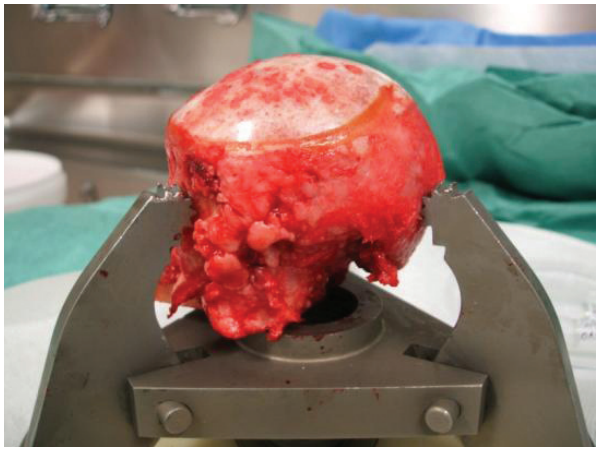


Figure:
Laboratory experiments at UEA

Is this research going to solve the problem?

This research contributes to our knowledge of compounds derived from the diet on joint health and osteoarthritis. We are gaining the evidence which will enable us to give osteoarthritis patients dietary advice which will slow or prevent their disease. It may also be possible to make supplements or functional foods which will be beneficial for joint health.

What are the long-term benefits to patients with this problem?

The long-term benefits are clear in enabling patients to modify their diet in order to help their osteoarthritis. This requires evidence from research such as ours.

"Our results may allow the development of dietary supplements or functional foods to prevent the onset or delay the progression of osteoarthritis"

Impact statement

- We discovered that allyl polysulfides found in garlic oil were able to decrease the production of cartilage-degrading enzymes made by cartilage cells
- Increasing the number of sulfur molecules in diallyl polysulfides increased this activity
- This may allow the development of dietary supplements or functional foods to prevent the onset or delay the progression of osteoarthritis

Impact report

Electrical stimulation optimisation for bone healing

Researchers Dr Nigel Cassidy and Dr Richard Balint

Supervisor Professor Sarah Cartmell

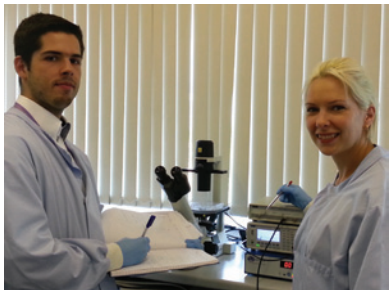
Stream PhD

Duration 28 months

Cost £50,000

Other funders EPSRC

Focus Orthopaedic Tissue Engineering



Dr Richaed Balint (left) and Professor Sarah Cartmell (right)

Through the kind support of the ORUK foundation, Dr Richard Balint has successfully completed his research project obtaining a PhD degree in Biomedical Materials from the University of Manchester. Following his PhD work he has successfully been awarded a prestigious two year EPSRC Doctoral Prize fellowship, and is now pursuing his own research in creating electrically conductive smart biomaterials for tissue engineering purposes.

Professor Cartmell continues her orthopaedic bioengineering research at The University of Manchester. She has recently been awarded a BBSRC Follow on Fund translational grant which will further the electrical stimulation research performed on the ORUK grant and translate this work to 3D perfused in vitro tissue samples.

Dr Nigel Cassidy continues his research developing Electrical and Electromagnetic systems, devices and software for medical, geophysical and engineering applications at Keele University and both Dr Cassidy and Dr Balint are co-investigators on the Professor Cartmell's BBSRC funded FoF grant.

What is the basic problem that you are trying to address?

Our main aim is to address the potential of utilizing electrical stimulating regimes in vitro for bone Tissue Engineering (TE) purposes in order to progress the potential of using this technique for clinical applications. We are addressing two problems: Bone non-unions (fractures that do not heal) and large size defect (defects in bone too large to treat in conventional ways). Tissue Engineering could solve both these problems. Unfortunately this novel therapeutic method cannot yet be applied effectively in the clinical setting. Our Electrical Stimulation based approach could potentially overcome this.

What is the estimated incidence of this particular problem in the general population?

Bone non-union and large size defects are clinical problems that affect millions of patients worldwide. Every year out of 100, 2.4 people suffer from a fracture. Non-unions result in approximately 10% of all fractures, when the bone tissue fails, for a variety of reasons, to regenerate itself. Large defects in bone due to trauma or disease can also occur and due to their size have limited ability for repair. Severe pain, loss of function, reduced work capability and an overall reduced life quality together with a high socio-economical cost are associated with both of these situations. The current clinical treatment for these

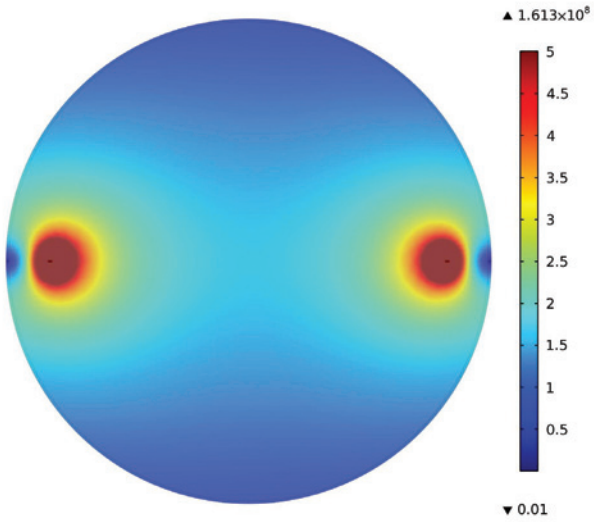


Figure:
Simulation results of the current density in the culture medium (XY plane). Colour bar represents the connection between colour and current density levels (A/m2), with red being highest and blue the lowest values.

cases is bone graft transplantation. However, the use of autologous grafts is hampered by donor site morbidity, the limited availability of tissue and lengthened operation time, while allografts are difficult to process and carry an additional risk of infection.

One of the emerging therapies promising to overcome these problems is TE. Despite the promising animal and clinical trials, the desired quality of the tissue engineered constructs has not been achieved yet. Problems associated with controlling the behaviour of the cells, nutrient delivery/waste removal, the achievable construct size, the time necessary to generate these and their in vivo integration, together with the issues with the structure and functionality of the end-product, have limited the use of TE products and are still to be overcome. Electrical Stimulation (ES), as a novel tool in musculoskeletal TE, has the potential to be a significant step towards augmenting the TE process and bringing these novel bone implants closer to widespread clinical application.

What are the aims and objectives of this research study?

Our main aim is to address the potential of utilising electrical stimulating regimes in vitro for bone Tissue Engineering (TE) purposes in order to progress the potential of using this technique for clinical applications.

Objectives:

1) Develop an electrical stimulating regime that can promote human Mesenchymal Stem Cell (hMSC) proliferation (and thus address cell number scale up issues due to cell biopsy limitations that exist in TE).

2) Develop an electrical stimulating regime that has the capability to promote hMSC differentiation and ECM production (thus produce a construct with increased mechanical integrity and shortened in vitro culture time).

3) Identify the intracellular mechanism of these electrical effects on the hMSCs.

4) Translate the data that we obtain in 2D to a more clinically relevant 3D environment.

“We have made significant advances in the development of in vitro based electrical stimulation systems and the understanding of how various regimes affects mesenchymal stem cell activity”

Is this research going to solve the problem?

The main outcome of this study is that it will establish electrical stimulation as a reliable and useful tool for Tissue Engineering, with a diverse range of potential applications. How will this benefit patients? Those patients that suffer from non-unions or large size defects currently have to go through difficult treatments (e.g. multiple surgeries) that can turned out to be ineffective. Tissue Engineering has great promise, but it cannot yet and thus has not been used widespread, due to a number of still unresolved issues that hinder its effective application. Electrical Stimulation could very well be the tool that will help us to overcome these issues and allow the reliable, fast and also importantly economical generation of TE implants and their use in medicine.

With these new TE implants patients could be treated fast and effectively, making non-unions and large size defects, together with the associated disability, pain and socio-economical cost a thing of the past. This study holds the potential to improve the lives of tens of thousands of patients all around the world.

What are the long-term benefits to patients with this problem?

Tissue Engineered implants have only been used in very few instances thus far, because of the aforementioned hindering issues. On the other hand the results of these clinical trials are very promising and there is a high probability that the patients will recover completely, their disability and pain will disappear and will enjoy after the treatment a quality of life that is equal to that they had before the onset of these ailments.We must also note that even so our research explores the bioelectricity and the mechanisms behind its positive effects with bone Tissue Engineering in the focus the knowledge we will obtain will also benefit those working in the engineering of other musculoskeletal tissue, those that are developing and applying Electrical Stimulation as a bone healing tool in the clinical setting and, in the end, the whole of the orthopaedic community.

Impact statement

- This project has yielded important practical knowledge on the delivery of electrical stimulation to cells and tissue constructs
- This understanding can later benefit patients if transferred to electrical stimulation devices used in to the clinical setting
- Our subsequent currently funded BBSRC follow on fund is translating this work further into 3D and for a variety of other tissue types

Publications

1. Balint R, Richardson SM, Cartmell SH. Low-density Subculture: A Technical Note on the Importance of Avoiding Cell–Cell Contact During Mesenchymal Stromal Cell Expansion J Tissue Eng Regen Med. (In Press.), 2015 (IF: 4.428)

2. Balint R, Cassidy NJ, Cartmell SH. Conductive Polymers: Towards a Smart Biomaterial for Tissue Engineering Acta Biomaterialia, 10, 2341, 2014 (IF: 5.684)

3. Balint R, Cassidy NJ, Hidalgo-Bastida LA, Cartmell S. Electrical Stimulation Enhanced Mesenchymal Stem Cell Gene Expression for Orthopaedic Tissue Repair J. Biomater. Tissue Eng., 3, 212, 2013 (No IF available)

4. Balint R, Cassidy NJ, Cartmell SH. Electrical Stimulation: A Novel Tool for Tissue Engineering Tissue Engineering: Part B, 19, 48, 2013 (IF: 4.254)

Impact report

Role of metal ions in metal-on-metal total hip replacement

Researcher Mr Darren Ebreo

Supervisor Professor Simon Donell
Professor Ian Clark and Mr John Nolan

Stream MD

Duration 24 months

Cost £60,000

Other funders No

Focus Bearing Surfaces, Arthroplasty, Hip

Mr Darren Ebreo

Having completed a research fellowship at UEA and the Norfolk & Norwich University Hospital, I am now an ST4 trainee in Trauma & Orthopaedic Surgery in Wales.

What is the basic problem that you are trying to address?

Metal-on-metal (MoM) total hip replacement (THR) offered theoretical advantages of decreased wear and better functional outcomes for patients. These implants have been associated with sterile inflammatory masses and significant soft tissue destruction with poorer outcomes following revision surgery.

The natural history of these adverse reactions to metal debris (ARMD) is unknown, but may represent contributions from wear at the bearing surfaces and corrosion of metal particles. Immunological and genetic factors may influence individual susceptibility to development of ARMD.

Management of these patients has evolved beyond regular follow up in the clinic with plain x-rays and now includes sophisticated surveillance monitoring of trends in levels of blood and staging of disease using specialist MRI scans. How to optimize the use of these methods to reliably identify patients who might benefit from revision surgery has been the subject of much debate and our work aims to clarify this.

What is the estimated incidence of this particular problem in the general population?

An estimated 1 million MoM hip bearings have been implanted worldwide since 1996 with approximately 35% of all hip implants in the USA involving a MoM bearing. In the UK 31,171 stemmed MoM prostheses were implanted between 2003 and 2011 which represents 8% of THRs performed in that time. According to the National Joint Registry report in 2012, ARMD was the second most common cause for revision surgery (13%).

What are the aims and objectives of this research study?

The first aim of this study was to investigate differences in gene expression between patients undergoing revision surgery for ARMD arising from MoM THRs, patients undergoing surgery for loosening of a metal-on-polyethylene (MoP) THR, and those patients with primary osteoarthritis of the hip. This would enable us to compare and contrast the cellular processes occurring in each of these conditions and to identify any biological pathways that might contribute to a more reliable way of identifying patients that may benefit from revision surgery.

Impact statement

- This research has enabled a better understanding of the biology of adverse reactions to metal debris in patients with metal-on-metal (MoM) hips
- We have helped to refine surveillance strategies for patients with a MoM THR in order to detect and stage ARMD

The second aim of this study was to investigate the natural history of ARMD in 28mm MoM THR using metal artifact reduction (MAR) MRI scans. There exists no recommendation as to the optimal intervals for MAR MRI scans in order to detect a change which may influence the decision for revision surgery prior to development of severe ARMD.

There is evidence that exercise by fit patients with a MoM bearing results in measurable increases in levels of cobalt and chromium detectable in the blood. It is not known if metal levels in the blood and urine fluctuate during the course of normal daily activity in a fashion similar to blood glucose. Our final aim was to establish of such a variation exists and if there was any correlation to patient symptoms, MAR MRI scan, or functional scores.

Is this research going to solve the problem?

This study promises to help advance our understanding of cellular processes occurring in ARMD. We have built a repository of gene expression data which can be used in the future to identify individual genes and biological pathways which may contribute to the development of ARMD and periprosthetic osteolysis which lead to implant failure.

This study will also help us to develop more robust surveillance strategies for patients who have a metal-on-metal hip implant and enable us to offer them revision surgery prior to extensive soft tissue destruction.

What are the long-term benefits to patients with this problem?

The gene expression data we have collected will help future research into the cellular mechanisms of failure both in metal-on-metal THRs and more conventional metal-on-polyethylene hip replacements. This would aid in the development of more sensitive and specific methods of detection of implant failure using biological markers that might be readily detectable in bodily fluids. In the future this might enable surgeons to identify patients at risk of premature implant failure and to optimally time revision surgery.

The results of our studies have demonstrated that blood metal ion levels do not tend to fluctuate during the course of normal daily activity and so have added to confidence in blood metal levels being used as an appropriate method of surveillance. We have also demonstrated most patients with a MoM THR who do not undergo early revision have normal MRI scans. Late progression from normal to abnormal or from mild to more severe MoM disease is uncommon and occurs over several years. These results have helped to refine and optimise surveillance strategies for patients with MoM implants.

“Our results may lead to a better understanding of the biology and natural history of adverse to metal debris in patients with metal-on-metal hip replacements”

Publications & Presentations

1. Ebreo D, Booth B, Clark A, McDowell I, Ingham CJ, Nolan JF, Donell ST. Diurnal Variation of Plasma Cobalt and Chromium in Metal-on-Metal Total Hip Arthroplasty: A Feasibility Study in a Cohort of 28mm MoM THRs British Hip Society, London 2015

2. Ebreo D, Bell PJ, Arshad H, Donell ST, Toms A, Nolan JF. Serial magnetic resonance imaging of metal-on-metal total hip replacements: Follow-up of a cohort of 28mm Ultima TPS THRs Bone Joint J 2013;95-B(8):1035-9 PMID: 23908416

3. Ebreo D, Court P, Donell ST, Ivory K, Carding S. Immune system involvement in patients with failed metal on metal total hip replacement EFORT, Instanbul, 2013

4. Ebreo D, Bell P, Arshad H, Toms A, Nolan J. Metal ion levels are not associated with abnormal MARS MRI in 28mm head metal-on-metal THR British Hip Society, Manchester 2012

Impact report

The role of high frequency loading in the treatment of tendinopathy

Researcher Chineye Princess Udeze

Supervisors Dr Hazel Screen, Dr Dylan Morrissey and Dr Graham Riley

Stream PhD

Duration 36 months

Cost £72,913

Other funders No

Focus Tendons, tendinopathy, mechanics, tendon cells, mechanotransduction

Chineye Princess Udeze

I have a MEng in Medical Engineering during which I undertook a two month summer placement working on tendon mechanics, at QMUL. I am currently in the third year of my PhD. My project is to study and explore the effects of vibrational loads on injured tendon. We have a hypothesis that vibration at a certain frequency promotes tendon repair and want to see if it is true. My research interests in general are focused around understanding how cells and tissues respond to mechanical loading, a topic called 'mechanotransduction'. I hope to continue in research after my PhD, focusing more on understanding tendon injury and how it is influenced by the tendon cells. In my spare time I enjoy swimming, travelling and going out with family and friends.

What is the basic problem that you are trying to address?

Tendon injuries, commonly referred to as tendinopathies, are increasingly common in our more active society, and are the second most common musculoskeletal injury seen by GPs and physiotherapists. Tendinopathies are thought to occur when the tendon gets damaged from too much load and then fails to heal properly. They result in swelling and substantial pain for patients, which can be highly debilitating and hugely affect a patient's way of life. However, while there have been numerous studies examining tendinopathy, the details of how the condition develops remain largely unknown, making treatment very difficult.

Tendinopathies are usually treated by GP's or physiotherapists using a range of treatments such as physiotherapy, corticosteroid injections or shock wave therapy. However, while some people get better with one or more of these treatments, others do not, and we do not understand why. To try and understand why, this project is investigating the most consistently effective treatment method for tendinopathy over the last sixteen years, called "Eccentric Exercise" to try and establish the underlying ways in which it acts to treat tendinopathy. Eccentric exercise is a physiotherapy exercise, where the patient carries out exercises on the injured leg to load the tendon, as shown in figure 1 for the Achilles tendon. In a previous project at QMUL looking at the forces in the tendon during eccentric exercises, we discovered that the tendon vibrates during eccentric exercise in a way it does not with other less effective types of rehabilitation exercises. We are now trying to look directly at that vibration to see if it is responsible for assisting tendon repair. If so, we may be able to find other ways to apply the vibrations to make them even more effective for a larger number of injured individuals.

"Our goal is to better understand how eccentric exercise effectively treats tendinopathy, so we can optimize its use to best treat patients and improve recovery"

What is the estimated incidence of this particular problem in the general population?

Achilles tendinopathy is frequently seen by GPs with an incidence of 18 cases per 1,000 registered persons. However, the actual incidence is likely to be higher as people often directly visit physiotherapists or try and self-manage the pain, so would not be included in these numbers. Tendinopathy is particularly common among those participating in any sort of sport or exercise, even at a recreational level. It accounts for about 30-50% of all sport injuries. The cardiovascular and general health benefits of fitness and exercise are becoming more universally realised. Whilst this is excellent for population health, it means the incidence of tendinopathy is rising, and it is increasingly important we find ways to treat these conditions to ensure individuals can maintain an active lifestyle.

What are the aims and objectives of this research study?

The primary aim of this research is to investigate how the vibrational loads seen during eccentric loading directly affect tendon cells, to see if this encourages the cells to stimulate tendon repair. We aim to establish the tendon loading regimes which provide the most beneficial effects on cells.

The Objectives are:

1. Find an appropriate way to apply the required loads and vibrations directly to the cells.

2. Investigate how long the loading should be applied for, and which types of loading best produce a healing response from the cells.

3. Compare the response of healthy and tendinopathy human tendon cells to the load, to determine if the cells in injured tendon behave differently. This will help us optimize how we load the cells for different stages of tendon repair.

We can then provide information concerning the best loading regimes for tendon healing to other researchers and clinicians, who can consider the best ways to translate this information into methods of loading a patient's tendon in a clinic.

Figure 1:
A patient performing eccentric exercises for an injured Achilles tendon, to try and stimulate a healing response. The patient starts with the heel raised, and then drops the heel to the floor (or lower if on a step), loading the injured Achilles tendon.

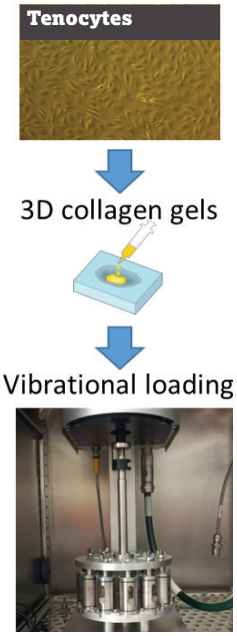
Is this research going to solve the problem?

This study takes a major step towards investigating how and why certain tendinopathy treatments might work. Once we have that level of understanding established, we have the critical knowledge we need to design truly effective and targeted treatments for tendinopathy.

We can begin developing new ways of delivering the important cell loading parameters clinically, and begin working with patients to determine their efficacy.

What are the long-term benefits to patients with this problem?

The reason we currently have so many tendinopathy treatments is because we do not really know the mechanisms involved in tendon healing, so have simply tried a wide range of approaches to see which will improve the condition. Whilst some of these are very effective for some patients, it is unclear why and why other patients do not respond at all. Once we have established the underlying mechanisms that enable tendon repair, then we can easily develop other treatments that deliver that repair mechanism in a really effective way, and ensure we develop appropriate and targeted treatments for tendinopathy. These will help a wider range individuals suffering with tendinopathy more rapidly and effectively. Eventually, we hope this approach can penetrate into other branch of orthopaedics too, and the same ideas be used to stimulate repair in other tissues.



Impact statement

- This work will help us understand how different types of loading can be used to encourage tendon repair.
- Improving understanding of what happens during eccentric exercise at the cellular level, will help physiotherapists see how best to adapt eccentric loading protocols to provide the most beneficial cell level mechanical stimuli.
- This work may provide ideas for new ways in which we can stimulate tendon repair and treat tendinopathy.

Impact report

Protecting tendon from lifestyle-induced epigenetic and metabolic alterations

Researcher Zuzana Kalivodova

Supervisors Associate Professor Philippa Hulley and Dr Mark Thompson

Stream PhD

Duration 36 months

Cost £75,000

Other funders No

Focus Soft tissue biology

Zuzana Kalivodova

I studied as an undergraduate at the University of St Andrews in Scotland and am currently in my third year of DPhil studies at the Botnar Research Centre, University of Oxford.

What is the basic problem that you are trying to address?

Diabetics have a considerably increased risk of tendon problems, including tendinopathy, frozen shoulder, Dupuytren's contractures and ruptures. Tendons of the foot are affected by diabetes, causing altered gait and much greater risk of injury, ulcers and amputation. Tendon tissue is highly specialized to cope with mechanical loading and has a rope like collagen matrix. I am studying tendon cells and the matrix they produce when subjected to chronic high levels of glucose. Our group has identified the handling of oxidative stress as a problem in diabetic tendon cells so I am testing possible therapies in my experimental model and studying their mechanism of action. This will inform the development of new clinical treatments as well as providing necessary fundamental insight into diabetic tendon problems.

What is the estimated incidence of this particular problem in the general population?

There are currently 3.2 million people in the UK with diabetes and this is predicted to rise to 5 million by 2025. 90% of these are Type 2 diabetics and most of them will end up with foot problems as a result of their disease. There are 6,000 leg, toe or foot amputations each year in England or 100 amputations per week for diabetics specifically.

What are the aims and objectives of this research study?

To study the effects of chronic high glucose on tendon cell function using human cells in a type 2 diabetic culture model and whole tendons from type 1 diabetic rats. To test the ability of several drugs to correct alterations in tendon cell function that have been induced by chronic high glucose exposure.

Is this research going to solve the problem?

Tendons have been neglected as a site of diabetic tissue damage but are markedly glucose sensitive. Our results confirm that oxidative stress may be an important target in protecting soft tissues from type 2 diabetic complications. In understanding how they respond to diabetes we can begin to design and test effective protective strategies.

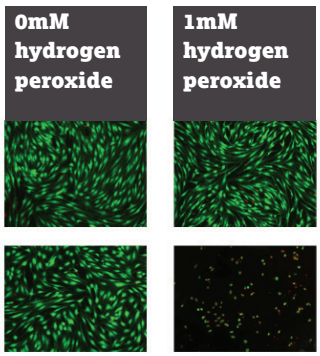


Figure:
Human tenocytes die in response to 1mM peroxide in hyper- but not normo-glycaemic conditions

What are the long-term benefits to patients with this problem?

Chronic diseases need chronic treatments and patients with type 2 diabetes typically struggle with blood sugar control for decades. Simple and safe tendon protective treatments need to be found that can be taken for decades and will limit accumulating tendon damage, allowing patients to exercise comfortably and remain injury free.

Impact statement

- Describing for the first time the effect of chronic high glucose load on tendon cells
- Identifying changes in diabetic tendon tissue
- This work will result in a better understanding of disease pathogenesis, which is vital in order to develop more effective future treatments for patients with diabetic tendinopathy

"Our results confirm that oxidative stress may be an important target in protecting soft tissues from type 2 diabetic complications"

Publications

Z Kalivodova, P Hulley. Effects of chronic high glucose on primary human tenocytes Br J Sports Med 2014;48: Suppl 2 A30-A31. (doi:10.1136/bjsports-2014-094114.47)

Kalivodova Z, Ingram N, Tucker RP, Thompson MS, Hulley PA. Effect of nutrition and mechanical loading on human tenocyte metabolism International Journal of Experimental Pathology, 2014, 95, A18

Impact report

A target for therapy of tendinopathy?

University of East Anglia

orthopaedic research UK
Postdoctoral Fellowship

Researcher Dr Graham Riley

Stream Postdoctoral Fellowship

Duration 18 months

Cost £79,337

Other funders No

Focus Tendon, Soft tissue biology & pathology

Dr Graham Riley

I am a biochemist and cell biologist, with an interest in the molecular pathology of chronic tendon problems.

What is the basic problem that you are trying to address?

Tendons are often injured, in many cases leading to a chronic painful condition known as tendinopathy. My research is aimed at addressing some of the major unanswered questions in tendinopathy. Our aim is to understand why tendons weaken and rupture, how they become painful, why they fail to repair, and to address the role of inflammation (or lack of it) in the progression of the disease.

What is the estimated incidence of this particular problem in the general population?

It is difficult to be precise, because a variety of sites can be affected, in a wide range of different patients. The annual incidence of tendinopathy has been estimated to be between 1 and 3%, and more common in individuals over 30. Half of all sports injuries are thought to be due to 'overuse' and the bulk of these affect the muscle-tendon unit. Affected individuals do not have to be athletic and millions are affected worldwide, many with unknown causes. There are over 100 million musculoskeletal injuries annually worldwide, of which 30-50% affect either tendon or ligament.

What are the aims and objectives of this research study?

We want to find out if the substance known as interleukin 6 (IL6) is a cause of chronic painful tendons. We aim to find out if IL6 is more abundant in painful tendons from patients. In addition, we shall identify which cells are producing IL6 in the tendon and whether there is any evidence of its activity in the tissue. We shall also investigate what effect IL6 has on tendon cells and tissues and how this effect occurs. If IL-6 is confirmed to have a central role in the development of chronic tendinopathy, therapeutic approaches to modulate this activity may have utility for the treatment of tendon lesions.

Is this research going to solve the problem?

No, not yet. Our studies have shown that cyclic loading of tendon at levels that induce fatigue damage to the tissue result in the up-regulation of inflammatory and degradative pathways by the affected tenocytes.

We think that the cellular changes in tendon are initiated by changes in the local cell strain environment, perhaps

as a result of a local loss of strain. We have shown that certain inflammatory mediators produced by the tenocytes (and not by infiltrating inflammatory cells) play a role in the initial response to the tendon microdamage, although whether this is part of the normal repair or adaptive response (and therefore required for resolution of the tendon injury) has not yet been established.

What are the long-term benefits to patients with this problem?

We are still a long way away from new treatments, but we have discovered more about the way that tendon is damaged and how the cells respond to injury and mechanical strain. These studies have paved the way for future research, which should identify potential new approaches to therapy.

Impact statement

- The role of the inflammatory mediator IL6 in tendinopathy has become better understood as a result of this work
- This work has improved our understanding of what drives tendon degeneration, and the inflammatory systems involved
- This work has resulted in a better understanding of disease pathogenesis, which is vital in order to develop more effective future treatments for patients with tendon pain

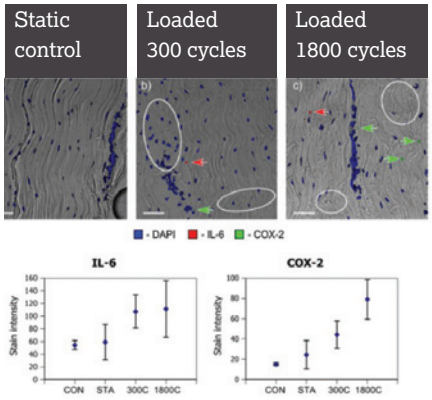


Figure: Stimulation of inflammatory mediators in tendon by cyclic loading

"A full understanding of the tendon response to overuse and microdamage will enable a better understanding of the cause of tendinopathy, and should help the development of new and effective forms of treatment"

Publications

1. Thorpe CT, Chaudhry S, Lei II, Varone A, Riley GP, Birch HL, Clegg PD, Screen HRC. Tendon overload results in alterations in cell shape and increased markers of inflammation and matrix degradation Scandinavian Journal of Medicine and Science in Sports 2014 Dec 30. doi: 10.1111/sms.12333. [Epub ahead of print]

2. Spiesz EM, Thorpe CT, Chaudhry S, Riley GP, Birch HL, Clegg PD, Screen HR. Tendon extracellular matrix damage, degradation and inflammation in response to in vitro overload exercise J Orthop Res. 2015 Jun;33(6):889-97

3. Legerlotz K, Jones GC, Screen HR, Riley GP. Cyclic loading of tendon fascicles using a novel fatigue loading system increases interleukin-6 expression by tenocytes Scandinavian Journal of Medicine and Science in Sports 2013;23(1):p31-7

4. Legerlotz K, Jones ER, Screen HR, Riley GP. Increased expression of IL6 family members in tendon pathology Rheumatology (Oxford). 2012 Jul;51(7):1161-5

Impact report

TAEA deposition of multifunctional nanoCalcium Phosphate with controlled release of drugs for skeletal tissue repair

Researchers Dr Gillian Munir

Supervisors Dr Jie Huang and Dr Junang Tang

Stream Postdoctoral Fellowship

Duration 12 months

Cost £40,000

Other funders No

Focus Nanomaterials; calcium phosphates, surface topography; TAEA processing; controlled drug release

Dr Gillian Munir

Dr Jie Huang heads the Biomedical Materials group at the department of Mechanical Engineering, University College London. Her research interests focus on the development of novel nano- and biomaterials for biomedical applications. Currently, her research projects include surface modification of titanium implants; synthesis of mesoporous glass and nanocalcium phosphates for imaging and drug delivery; smart nanocomposite scaffolds for skeletal tissue repair and regeneration, and antimicrobial coatings for orthopaedic implants.

Dr Gillian Munir obtained her BSc in Genetics and Microbiology at the University of Leeds, and MSc in Biomaterials and Tissue Engineering at University College London, where she then completed her PhD on surface modifications of medical implants by creating patterned topography with tailored materials chemistry. 3D printing technology has also been applied in her postdoc research for further advancing surface pattering of implant with nanomaterials. Currently, she is a part-time lecturer on the MSc module: 'Introduction to Biomedical Imaging'

What is the basic problem that you are trying to address?

Bacterial infection is a serious problem in fracture fixation, and is also a factor that contributes to implant failure. With the increasing worry of the antibiotic resistant 'super bug', and the high hospital infection rates in the UK (European Antimicrobial Resistance Surveillance System data 2002), an improvement to current implants, e.g. infection-resistant prostheses, will offer tremendous benefits to elderly patients.

Bone is a complex tissue with hierarchical organization from the macro- (centimeter) scale down to nano-scaled collagen and bone minerals. Calcium phosphate ceramics, which closely resemble bone minerals, are well known for their bioactivity and osteoconductivity. Their applications range from bone grafts to bioactive coatings for implants. However, the current coating technology has some limitations, such as the high cost and high temperature involved. We are aiming to develop a more cost-effective, ambient temperature processing technique, namely a template-assisted electrohydrodynamic atomization (TAEA) deposition, to create well-defined surface topography with nanocalcium phosphate for bone repair and regeneration.

What is the estimated incidence of this particular problem in the general population?

With increasing numbers of accidents, occurrences of obesity and an ageing population, orthopeadic solutions

for treating joint and bone repair remain in great demand. For example, according to the American Academy of Orthopaedic Surgeons, over 750,000 Americans undergo surgery for hip, knee and shoulder replacements each year. The number of procedures for younger, more active individuals are projected to increase steadily.

What are the aims and objectives of this research study?

Inspired by the native bone architecture, the use of nanostructured biomaterials in bone regeneration has recently become an attractive approach, due to its unique functionalities, which result from the highly specific interactions with small-scale biological structures, such as proteins, etc. The aim of this study is to develop new coating technology to enhance tissue repair and regeneration by the incorporation and controlled release of drugs or growth factors. The first step is to design the templates for scaling up the TAEA processing; the second step is to design the drug loaded surface deposition method; the third step is to evaluate and understand the protein release profiles with the surface topography created by TAEA processing.

Is this research going to solve the problem?

The bone repair can be enhanced by the control of surface chemistry and topography. We aim to produce multifunctional medical devices/ implants to stimulate bone formation and also inhibit bacterial (including 'super bug') infection, thus providing an ideal combination for a rapid healing as well as tissue repair and regeneration. We believe this will offer an effective solution.

What are the long-term benefits to patients with this problem?

By fast healing and reducing the possibility of infection, the new implant will bring enormous benefits for the patient to improve mobility and reduce pain. More patients will have better treatment if the revision due to infection can be reduced. The results of our study will pave the way for industrial partners to apply this new technology.

"Our results may lead to an advanced technique of surface deposition of nanobiomaterials for joint prostheses, medical implants and devices"

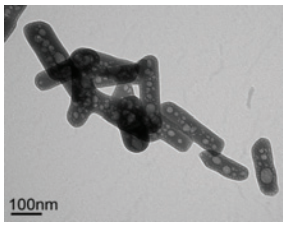


Figure 1:
Transmission electron microscopy of mesoporous calcium phosphate nanoparticles

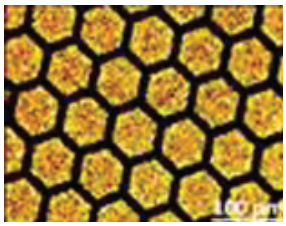


Figure 2:
optical microscopy of hexagonal shaped surface topography created by TAEA processing

Impact statement

- Mesoporous calcium phosphate (mCaP) ceramic nanoparticles have been synthesized for the delivery of model drugs (proteins)
- A layer-by-layer assembly has been used for drug loadings on mCaP deposition
- TAEA templates have been designed and produced by 3D printing, which is vital for scaling up the process for biomedical applications
- This work will provide a novel deposition method for advanced medical implants and devices.

Publications

1. G. Munir, J. Huang, R. Nangrejo, M. Edirisinghe and W. Bonfield (2013), Electrohydrodynamic Processing of Calcium Phosphates for Coating and Patterning on Medical Implants Nano LIFE, 2 (1), 1-17

2. G. Munir, M.J. Edirisinghe, P. Kalia, L. Di Silvio, W. Bonfield and J. Huang (2013), Surface Patterning of nanoSilicon Substituted Hydroxyapatite for Medical Implants Proceeding of Combined Orthopaedic Research Societies (CORS) meeting

3. G. Munir, M. Edirisinghe, L. Di Silvio, W. Bonfield, M. Rafailovich and J. Huang (2014), Guiding bone cells with surface patterned nano-calcium phosphate Proceeding of the Royal Society Cell adhesion Conference

Impact report

Understanding the biology of bone healing: The role of immunoregulatory and regenerative cells

UNIVERSITY OF LEEDS

orthopaedic research UK
Clinical Fellowship

Researcher Mr Hiang Boon Tan

Supervisors Dr Frederique Ponchel, Dr Elena Jones and Professor Peter Giannoudis

Stream Clinical Fellowship

Duration 30 months

Cost £80,000

Other funders No

Focus Bone biology, fracture healing, trauma

Professor Peter V Giannoudis

I work as the Professor (School of Medicine) and Honorary Consultant at Leeds General Infirmary (LGI), a major teaching hospital serving a population in the region of 3.5 million. It is a major trauma unit, accepting complex trauma patients from other hospitals of the region. I have completed an AO trauma fellowship in Hannover Germany and a Trauma fellowship at Louisville Kentucky, USA.

My research interest is focused on the immune-inflammatory response following accidental and surgical trauma, biology of mesenchymal stem cells and their role in bone regeneration, bioengineering, and clinical outcomes following fracture fixation.

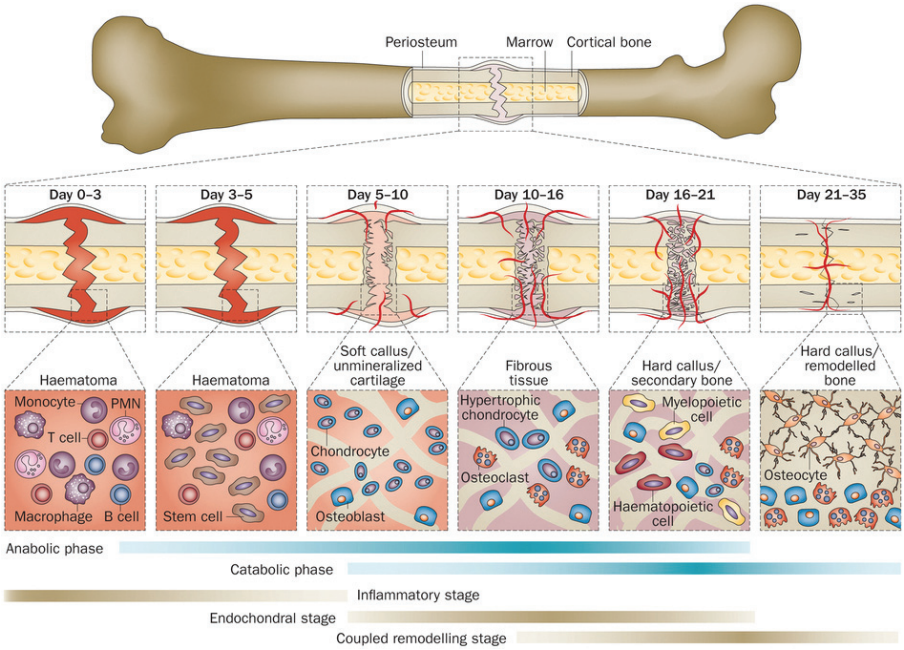
This project has been supervised by Dr Frederique Ponchel (Senior Lecturer, Head of Translational Research in Immune-mediated Inflammatory Diseases group) and also guided by Dr Elena Jones (Associate Professor in Stem Cell Biology) who is an expert in mesenchymal stem cells.

What is the basic problem that you are trying to address?

Bone fracture healing is a normal physiological process that leads to repair and restoration of bone function. However in approximately 10% of patients fractures fail to heal. Fracture non-union represents a serious healthcare burden for the NHS but its risk factors remain obscure. The aim of this research was to discover novel biomarkers, indicative of patient's predisposition to non-union, based on a better understanding of the dynamics between immune and repair cells at the fracture site early after trauma. These biomarkers would inform the management of patients suffering from fractures, ultimately reducing the incidence of non-unions.

Impact statement

- The role of local immune cells and their mediators soon after fracture is better understood as a result of this work
- This work has improved our understanding of cellular and molecular dynamics after fracture in humans
- This work has resulted in identifying novel molecules, which could be considered in the future as predictors of developing fracture non-union



What is the estimated incidence of this particular problem in the general population?

Delayed bone healing and non-union occur in approximately 10% of long bone fractures. Atrophic non-union is a condition where bone fails to heal due to an insufficient biological response at the fracture site. It has a different etiology to hypertrophic non-union which results from insufficient stabilisation of the fracture.

What are the aims and objectives of this research study?

The first aim of this study was to investigate in detail which immune and repair cell populations are present at the fracture site at different time points after fracture. This was studied using multi-parameter flow cytometry following an enzymatic cell release from bone. Large-scale gene expression analysis was performed in parallel to establish a list of transcript candidates that were:

1. abundant locally;

2. specific for fractures that healed well;

3. encode for soluble proteins that could be measured in patient's blood.

The second aim of this study is to analyse whether these candidates are also detectable in serum of patients who suffered non-union and verify if serum levels, particularly early after fracture, could be used to predict patient's risk of developing non-union.

"Our results may lead to the discovery of biomarkers of patient at risk of developing fracture non-union based on a better understanding of the cellular and molecular dynamics early after fracture"

Is this research going to solve the problem?

This study promises to help advance our understanding of the biology of fracture healing and the roles of various immune and non-immune cell types and soluble factors during fracture repair. This understanding is likely to contribute to the development of novel early biomarkers of patients at risk of developing non-union.

What are the long-term benefits to patients with this problem?

Although the primary aim of this study was to discover novel biomarkers of the risk of non-union, it also provided unique knowledge related to the cellular and molecular dynamics of fracture repair in humans that could be further developed towards new treatment strategies for acute fractures as well as fracture non-unions.

Work emanated from this funding has not been submitted for publication yet.

Impact report

Developing a dual-action titanium surface to deter bacteria and enhance osteoblastogenesis

North Bristol NHS Trust

orthopaedic research UK
Postdoctoral Fellowship

Researchers Dr Jason Peter Mansell and Professor Ashley Blom

Stream Postdoctoral Fellowship

Duration 12 months

Cost £47,657

Other funders No

Focus Titanium, bone cells, implantology, microbiology

Dr Jason Peter Mansell

I am a Senior Lecturer in Bone Biology at the University of the West of England, Bristol. I have studied bone composition and metabolism in health and disease for over two decades. In more recent times my research has extended to finding new ways of enhancing the surface properties of bone implant materials so that they are more likely to integrate into our own tissues during bone repair. Such materials include entire joint replacements made from titanium or mineral-based bone substitutes for aiding bone regeneration. One especially challenging area in bone biomaterials design is finding a solution that benefits our own tissues but is capable of deterring or killing bacteria that could lead to infections. These "dual-action" materials are currently being developed in collaboration with a team of highly skilled researchers and clinicians at the Universities of Bristol, Brighton, Cardiff and the Serum Statens Institute, Copenhagen.

What is the basic problem that you are trying to address?

Approximately 10% of all total joint prostheses for replacing osteoarthritic hips and knees fail through a process of prosthesis loosening. An additional 1% will fail because of infection. In both cases these are distressing outcomes to patients and these failed devices need replacing through a process known as revision arthroplasty. These revisions are more problematic than the original procedures and they often have poorer outcomes. The financial impact of revision surgery for loosening alone costs an estimated £3oom each year in England and Wales. Clearly there is an incentive to reduce the incidence of revision arthroplasty. Specifically we are working to address this by attaching suitable small agents to the surfaces of prosthetic materials so that the integration of replacements joints into our own tissues is more superior and robust.

What is the estimated incidence of this particular problem in the general population?

Currently around 10% of men and 18% of women over the age of 60 will present with osteoarthritis. As it stands the incidence of osteoarthritis necessitates approximately 160 thousand total joint replacements each year in England and Wales alone. However the extent of the problem is predicted to rise given the prediction of a more elderly demographic. In addition the impact of lifestyle leading to obesity is likely to mean increases in total joint replacements for this group as well. It is generally agreed that the burden of degenerative joint disease on our healthcare providers is set to increase.

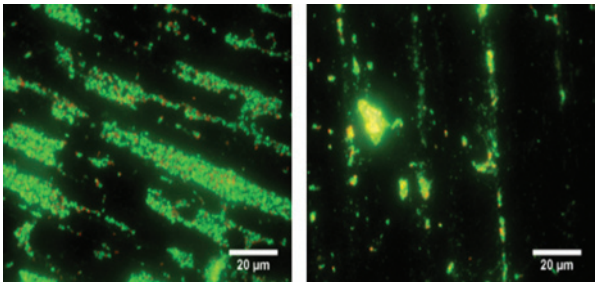


Figure:
Depicted control titanium (left) and FHBP-functionalised titanium (right) exposed to MRSA. Note the presence of fewer bacteria on the functionalised surface compared to control titanium.

What are the aims and objectives of this research study?

The overall aim is to develop fit-for purpose bioactive titanium-coated devices for future orthopaedic applications. The bioactive component for surface conjugation is a phosphatase resistant analogue of lysophosphatidic acid (LPA), (3S) 1-fluoro-3-hydroxy-4-(oleoyloxy)butyl-1-phosphonate (FHBP).

There are two important properties of FHBP that make this a desirable agent for bone biomaterial modifications. First, we discovered that FHBP synergistically co-operates with active vitamin D3 (VD3) to enhance human osteoblast maturation. Since mature osteoblasts are responsible for the provision of a mechanically sound, mineralised bone matrix, coating devices with an agent (FHBP) that acts in concert with VD3 is a logical step in the fabrication of new bone biomaterials. Second, we have new evidence that FHBP, when coated to titanium, deters the attachment of Staphylococcus aureus, a bacterium often implicated in implant failures through infection.

Collectively we have identified a novel, dual-action surface finish for future orthopaedic applications. Realising the development of our devices necessitates a number of key objectives which collectively pertain to optimizing the surface coating and ascertaining to stability and robustness to cleaning, sterilisation and storage under ambient conditions.

“Our novel bone biomaterial coatings have put us in a unique clinical advantage because they support desirable host cell responses yet deter the attachment of bacteria”

Is this research going to solve the problem?

Finding suitable agents as coatings for artificial knee and hip joints is especially challenging; besides developing a coating strategy, which can often be rather complex, costly and time consuming, the selected agents need to withstand the rigors of surgery and remain functional after prolonged storage and sterilisation. At the same time any surface modifications made must not appeal to microorganisms. Our initial findings are very encouraging and we anticipate that we are drawing closer to the facile development of bio-functionalised bone biomaterials in solving the problem of orthopaedic prosthesis failures.

Impact statement

- Osteoarthritis is a leading cause of pain and disability resulting in approximately 160 thousand total joint replacements (TJRs) each year in England and Wales alone
- 10% of TJRs fail within the lifetime of the patient necessitating revision arthroplasty to the tune of £300m per year. Reducing failure rates by developing novel material coatings offers a much needed solution
- Our research has led to coatings that could enhance initial implant bonding so that failure rates through loosening and infections can be reduced

What are the long-term benefits to patients with this problem?

Enhancing the process of early osseointegration of prosthetic materials provides a solution to the ongoing problem of implant failures through loosening. The agent we have selected for titanium functionalisation co-operates with VD3 to promote osteoblast formation from bone marrow-derived stem cells. The agent also stimulates osteoblast maturation from committed, immature osteoblasts. Since these mature bone forming osteoblasts are responsible for bone formation, bolstering this event at the material surface will facilitate superior integration of that material into host tissue. Ultimately the aim is to reduce the huge financial and social burden of surgical revisions by improving the longevity of implantable devices. Another appealing property of our coating is the ability of the modified surface to deter the attachment of bacteria which could also help realise a reduction in implant failures through infection.

Publications

1. Mansell JP, Barbour M, Moore C, Nowghani M, Pabbruwe M, Sjostrom T, Blom AW. The synergistic effects of lysophosphatidic acid receptor agonists and calcitriol on MG63 maturation at titanium and hydroxyapatite surfaces Biomaterials. 2010. 31: 199-206.

2. Mansell JP, Brown J, Knapp JG, Faul CFJ, Blom AW. Lysophosphatidic acid-functionalised titanium as a superior surface for supporting human osteoblast (MG63) maturation. European Cells & Materials. 2012. 23: 348-361.

3. Mansell JP, Blackburn J. Lysophosphatidic acid, human osteoblast formation, maturation and the role of 1,25-Dihydroxyvitamin D3 (calcitriol) Invited review. BBA (Mol. Cell Biol. Lipids). 2013. 1:105-108.

Impact report

Designing a robust process for clinical translation of tissue engineered bone to bone ligament replacements

UNIVERSITY OF BIRMINGHAM

orthopaedic research UK
Postdoctoral Fellowship

Researcher Dr Richard L Williams

Supervisor Professor Liam Grover

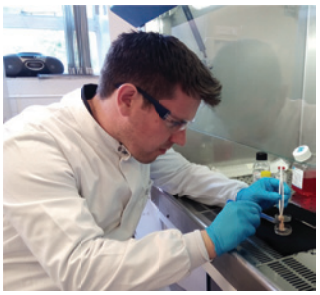
Stream Postdoctoral Fellowship

Duration 24 months

Cost £80,000

Other funders No

Focus Biomaterials, Knee, Tissue Engineering



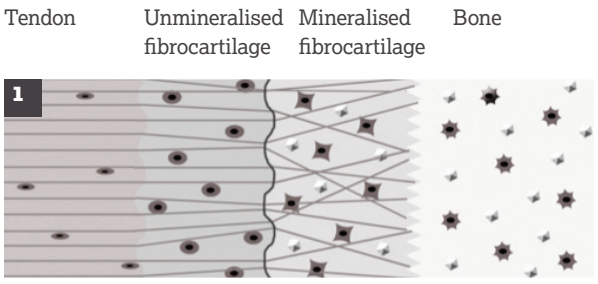
Dr Richard L. Williams

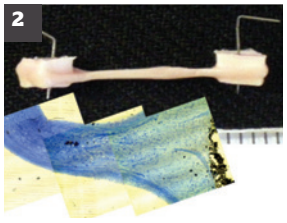
My work within the Tissue Regeneration and Interface Lab (TRAIL) at the University of Birmingham involves developing implantable materials and devices to regenerate diseased and damaged bones, ligaments and tendons in the human body. My background is in Physics and Biomedical Imaging, which have strong influences on my research work in regenerative medicine today. The general approach is to exploit and/or direct the body's mechanisms of tissue healing and maintenance towards rebuilding the affected tissue. This could involve anything from designing injectable materials that suppresses inflammation while stimulating healing, to devising methods of non-invasively tracking materials around the body to enable accurate placement of implants and monitoring their integration into the body over time. Identifying the fundamental physical and chemical processes behind the progression of disease and healing acts as starting point for designing the next generation of treatments. A good example of this approach is outlined in this report on tissue engineered ligament replacements, which both myself and Dr. Jennifer Paxton (now a Lecturer at University of Edinburgh) have been working on.

What is the basic problem that you are trying to address?

Every year many individuals damage ligaments usually while undertaking a sporting activity, resulting in loss in knee joint stability. Ligament rupture typically requires that the patient undergo invasive surgical reconstruction involving replacement of the damaged ligament with either a synthetic structure or a piece tissue grafted from, for example, knee or hamstring tendons. Neither approach is ideal as the act of removing donor tissue for use in the reconstruction often leads to pain and instability, while synthetic materials are linked to unacceptably high incidence of osteoarthritis. Even when successful, surgical regeneration using these methods rarely results in a perfect repair and many athletes and sports people at the top of their game rarely fully recover their athletic ability after reconstruction (e.g. Michael Owen and Alan Shearer).

The underlying weakness of the current approaches is that they fail to recreate the strong mechanical bond between the hard bone and soft ligament (the "hard-soft tissue interface") that naturally existed prior to the injury and is essential to maintaining the stability of the knee joint. The technology developed in this project aimed to resolve this issue by exploiting the biology of tissue formation to grow replacement ligaments which incorporates this crucial hard-soft tissue interface.





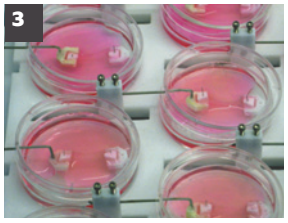


Figure 1:
The gradient structure of a human ligament – from bone to soft tissue.

Figure 2:
One of our ligaments grown in the lab, replicating this gradient-like change in structure.

Figure 3:
Towards scaled up production of ligaments in the lab.

What is the estimated incidence of this particular problem in the general population?

The incidence of ligament damage in the developed world is high. Considering only the anterior cruciate ligament, there are 100,000 ruptures in the US per year (0.05% of the population). Since this technology could be applied to a range of other ligament and tendon ruptures (reattachment of the achilles tendon, rotator cuff repair), it is reasonable to assume that this technology could be of benefit to a significantly higher proportion of the population.

What are the aims and objectives of this research study?

We have developed a method to grow ligaments in culture dishes in our laboratory. Although we have had some extremely encouraging results, we have found that how quickly we can grow the ligaments, and how strong they are depends strongly on the cell types and materials that we use. Clearly, to be of benefit in humans, it is important that we can grow human tissues using human cells in a predictable way. In the proposed work, we have two main objectives. The first is to develop a method to grow human tissue using human cells, using the work that we have already undertaken with animal cells to guide us. Second, we will develop a bioreactor system that will allow us to grow human tissues in a precisely defined mechanical environment. By the end of the study, we will have structures that can be used for pre-clinical trials in humans.

“Our approach to regenerating damaged musculoskeletal tissues could have huge impact on patients from all walks of life. Whether it’s regaining pain-free daily motion or returning as a high performance athlete, patients could return to their active lifestyles in a shorter period of time”

Is this research going to solve the problem?

This approach to reconstructing damaged ligaments aims to produce the entire mechanical linkage between bone and the soft ligament tissue ready for implantation into the patient without the drawbacks of harvesting tissue from other parts of the body. By using materials derived from the patient and exploiting the biology of healing in the lab, we are able to replicate this intricate structure to a degree very close to that found naturally in the body and hence maximise the chance of successful treatment. By producing a ligament from cells and materials derived from the patient, we minimise the risk of rejection and maximise the chance of the structure integrating with the surrounding native tissue. This research will provide an essential step for translating this highly promising technology to the clinic.

What are the long-term benefits to patients with this problem?

The long-term benefits of this technology to patients and the NHS would be substantial. It should provide an improvement on the efficacy of currently available ligament regeneration technologies that cause significant pain as a result of the harvesting procedure and the high long-term chances of developing osteoarthritis following reconstruction. If this technology is able to reduce the number of complications associated with reconstruction, it should also provide a cost benefit to the NHS by reducing the need for revision surgeries or further medical treatments.

Impact statement

- This research has enabled a deeper understanding of how the biological composition and structure of ligaments relate to their mechanical function
- The result is the development of a process for manufacturing replacement ligaments for implantation into patients
- The technology is currently being explored as a means of treating a range of other musculoskeletal injuries (such as rotor cuff tears) and as musculoskeletal disease/injury model, thus acting as a catalyst for further research in the field.

Publications

1. Enhancing Engineered Ligament Strength Using a Multi-Stranded Approach Jennifer Z. Paxton and Liam M. Grover. The Journal of the Federation of American Societies for Experimental Biology, 29:1, 346.1, 2015.

2. Exploiting cell-mediated contraction and adhesion to structure tissues in vitro Uchena N. G. Wudebwe, Alistair Bannerman, Pola Goldberg-Oppenheimer, Jennifer Z. Paxton, Richard L. Williams and Liam M. Grover. Phil. Trans. R. Soc. B 370: 1661, 2015.

3. Imaging the hard/soft tissue interface Alistair Bannerman, Jennifer Z. Paxton, Liam M. Grover. Biotechnol. Lett. 36:403–415, 2014.

Impact report

Stem cell based bone engineered vascular grafts

Researcher Dr Priya Kalia

Supervisor Professor Lucy Di Silvio

Stream Postdoctoral Fellowship

Duration 27 months

Cost £80,000

Other funders No

Focus Bone grafts, bone biology & vascularization

Professor Lucy Di Silvio

The major focus of Lucy Di Silvio's research is based on Tissue Engineering and translational research for clinical applications. Research in tissue engineering within her group focuses on stem cell technology, development of two and three dimensional cell models, cell-material interaction, and application of tissue engineering solutions largely for musculo-skeletal tissues for orthopaedic and maxillo-facial applications. Of particular interest to the group, is vascularization of grafts and their integration with host tissue in critical size defects and 3D printing for prosthetic rehabilitation and biological implants for clinical application.

What is the basic problem that you are trying to address?

Trauma, disease, and cancer therapy, often involve a significant loss of tissue, requiring surgical reconstruction. The scant availability of autologus bone (taking bone from one area of the body to reconstruct another), donor site morbidity and quality vascularized flaps limit their use. Many materials have been developed as bone grafts with osteoconductive (allow bone to grow on the surface) properties but they lack in osteoinductivity (the potential to regenerate new bone). Lack of osteoinductive potential can be partly overcome by adding mesenchymal stem cells in combination with growth factor stimulating factors to the scaffold prior to implantation. However, a major problem still remains; insufficient vascularization of the central part of larger scaffolds. Tissue engineering holds tremendous potential for a wide range of medical conditions. It basically focuses on regeneration of new tissues from stem cells with the support of a scaffold and growth factors. The development of engineered vascularized grafts provide an alternative for improving vascularization throughout the scaffold in larger defects.

What is the estimated incidence of this particular problem in the general population?

Bone grafting is the second biggest transplant after blood. An estimated 1.6 million bone grafts are performed annually to regenerate bone as a result of trauma or disease of which 6% are cranio-maxillofacial in nature. In the USA, bone graft sales generate over $2.5 billion a year and of more than 3 million musculoskeletal procedures performed annually approximately half involve bone grafting with either an autograft or an allograft. Worldwide, autografts or allografts are used in approximately 2.2 million orthopaedic procedures annually.

“Our results will lead to a better understanding of bone grafts and how they can be designed to provide faster and better vascularization in highly compromised patients suffering from trauma or disease”

What are the aims and objectives of this research study?

This project is applying the concept where reconstruction of a defect is based on mimicking the natural environmental niche. It aims to do this by developing a viable bone graft using stem cells to initiate vascularization of the graft in vitro (in the laboratory). We believe that prevascularizing the graft in the presence of the appropriate signalling molecules and cells, will allow a more rapid integration with the host tissues when transplanted. The objective will be to investigate whether cellular contribution from the transplanted mesenchymal stem cells or a growth-factor and/or pre-vascularised scaffold can survive, enhance vascularization and integrate with the host tissue in an in vivo model.

Is this research going to solve the problem?

This research project is extremely challenging, and whilst it will not offer an immediate “off-the-shelf” solution it will assist in determining whether there is any advantage in adding the patient’s own stem cells to the graft (induce osteognensis), and whether this is enhanced by the presence of specific bone growth stimulatory factors. In order to engineer viable bone grafts, it is necessary to understand the mechanisms of native bone development and growth. This project will most importantly, provide information on whether it is possible to prevascularize a graft outside the body and then transplant it and attain anastomosis between pre-formed microvasculatures inside a scaffold with host vessels. Control of bone regeneration with strategies that mimic ‘normal bone’ formation will offer successful management of conditions where bone grafts are required, which in the long term will be beneficial in treating a wide range of conditions and reducing costs.

Impact statement

- The development of bone grafts has become better understood as a result of this work
- This work has improved our understanding of how bone grafts can be enhanced outside the body using cells and stimulatory factors
- This work has resulted in a better understanding of how bone grafts can integrate with the host tissue which is vital in order to develop more effective future treatments for patients with bone related conditions

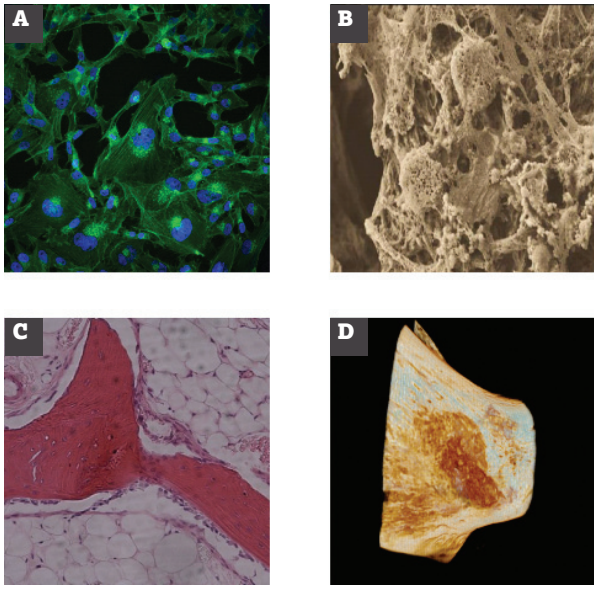


Figure:
A: Fluorescent stained stem cells
B: Cells on graft
C: Histological image of prevascularized graft
D: Integrated graft

What are the long-term benefits to patients with this problem?

The future challenges lie with survivability of grafts after implantation, which is dependent on revascularization and anastomosis of the implant with the host vasculature, otherwise ischemia and necrosis set in. The outcome from this study will provide information that could impact on design of future tissue engineered constructs, in particular, for the treatment of critical size defects and in patients with life threatening trauma or compromised patients with poor bone quality and quantity at the trauma site. In the long term, the use of a viable graft could provide a treatment modality that could significantly improve clinical outcome and reduce socio-economic health costs.

Publications

1. Buranawat, B., Di Silvio, L.*, Deb, S., Nannmark, U., Sennerby, L., Palmer, R.M* Evaluation of a ß-calcium metaphosphate bone graft containing bone morphogenetic protein-7 in rabbit maxillary defects (2014) Journal of Periodontology 85 (2) PP.298-307 doi: 10.1902/jop.2013.130159. * Joint Principle authors

2. Buranawat, Borvornwut , Palmer, Richard M., Sennerby, Lars, Nannman, Ulf., Deb, Sanjukta., Di Silvio, Lucy Development of a 'Bioengineered block graft' for Maxillofacial Reconstruction. International Poster Journal of Dentistry and Oral Medicine 15 (2013)

3. Busuttil Naudi, K, Ayoub, A, McMahon, J, Di-Silvio, L, Lappin, D, Hunter, KD & Barbenel, J 2012, 'Mandibular reconstruction in the rabbit using beta-tricalcium phosphate (ß-TCP) scaffolding and recombinant bone morphogenetic protein 7 (rhBMP-7) - histological, radiographic and mechanical evaluations' Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery, vol 40, no. 8, pp. e461-e469., 10.1016/j.jcms.2012.03.005

Impact report

Understanding mechanisms of pain and the role of glutamate in tendinopathy

Researcher Mr Benjamin Dean

Supervisor Professor Andrew Carr

Stream MD

Duration 24 months

Cost £60,000

Other funders No

Focus Shoulder, Soft tissue biology

Mr Benjamin Dean

I am an Orthopaedic specialist trainee in the Oxford region and am keen to pursue an academic career. I undertook this work as part of a DPhil in Oxford and have recently completed my viva examination. My future aim is to become a Clinical Lecturer later in my Orthopaedic training in order to enable the pursuit of my research interests which focus particularly on musculoskeletal pain.

What is the basic problem that you are trying to address?

'Wear and tear' of the key shoulder tendons ('rotator cuff tendinopathy') is common as we get older and frequently results in significant pain, however some patients experience little or no pain despite having extremely worn tendons. The role of the pain system in the process of tendon failure and pain generation is very poorly understood.

More generally the way that 'wear and tear' in other diseases of the bones and joints causes pain is also poorly understood. The results of our project will therefore not only apply to shoulder pain but also to other common causes of chronic musculoskeletal pain such as arthritis of the hip and knee.

What is the estimated incidence of this particular problem in the general population?

In adults the annual incidence of shoulder pain presenting to General Practitioners in the UK is about 1.5%, this rise to an annual incidence of over 2% in older age groups. A majority of shoulder pain is related to 'rotator cuff disease'. The overall incidence of chronic musculoskeletal pain in general is approximately 20%.

What are the aims and objectives of this research study?

The first aim of this study is to investigate how the pain system is involved in tendon failure and how this can help explain why different patients experience vastly different levels of pain despite similar looking tendons. This will be achieved by relating differences in pain to differences in shoulder tendon tissue in several groups of patients.

The second aim of this study is to investigate the impact of novel drugs targeting the pain system on cellular models of shoulder tendon disease. This has the potential of leading to valuable new treatments for chronic shoulder pain.

Is this research going to solve the problem?

This study promises to help advance our understanding of why the levels of pain experienced by patients with shoulder tendon problems are so variable and unpredictable. Understanding which tendon changes result in pain and then targeting these changes with new treatments has great potential for solving this problem for patients with chronic shoulder pain, as well as for patients with other causes of chronic musculoskeletal pain.

What are the long-term benefits to patients with this problem?

The great long-term benefits to patients are the development of new treatments for patients with chronic shoulder pain. Current treatments are limited both in terms of improving pain and in terms of complication rates. Developing more effective treatments with more acceptable levels of complications that may be used on their own or in combination with surgery promises to be a huge breakthrough for patients with chronic shoulder pain.

The results of our study are also likely to be transferable to other common causes of chronic musculoskeletal pain such as osteoarthritis and degenerative disc disease of the spine. Our results may lead to a better understanding of all chronic musculoskeletal pain in general and new drugs that may be used in many different diseases.

"Our results may lead to a better understanding of all chronic musculoskeletal pain in general and new drugs that may be used in many different diseases"

Impact statement

- The role of the glutamate in rotator cuff tendinopathy has become better understood as a result of this work
- This work has improved our understanding of what drives tendon pain, pointing to both the glutaminergic and inflammatory systems being involved
- This work has resulted in a better understanding of disease pathogenesis, which is vital in order to develop more effective future treatments for patients with tendon pain

Publications

Franklin SL, Dean BJ, Wheway K, Watkins B, Javaid MK, Carr AJ. Up-regulation of Glutamate in Painful Human Supraspinatus Tendon Tears Am J Sports Med. 2014 May 28. pii: 0363546514532754.

Glucocorticoids induce specific ion-channel-mediated toxicity in human rotator cuff tendon: a mechanism underpinning the ultimately deleterious effect of steroid injection in tendinopathy? BJF Dean, SL Franklin, RJ Murphy, MK Javaid, AJ Carr. Br J Sports Med 2014. doi:10.1136/bjsports-2013-093178

The risks and benefits of glucocorticoid treatment for tendinopathy: A systematic review of the effects of local glucocorticoid on tendon Dean BJ, Lostis E, Oakley T, Rombach I, Morrey ME, Carr AJ. Semin Arthritis Rheum. 2013 Sep 26. pii: S0049-0172(13)00173-X. doi:10.1016/j.semarthrit.2013.08.006.

The Peripheral Neuronal Phenotype is Important in the Pathogenesis of Painful Human Tendinopathy: A Systematic Review Floyd Dean BJ, Franklin SL, Carr AJ. Clin Orthop Relat Res. 2013 Apr 23. [Epub ahead of print]

Why does my shoulder hurt? A review of the neuroanatomical and biochemical basis for shoulder pain Dean BJF, Giwilyn SE, Carr AJ. Br J Sports Med. British Journal of Sports Medicine. 2013 Feb 21.

A systematic review of the histological and molecular changes in rotator cuff disease B. J. F. Dean, S. L. Franklin, and A. J. Carr. Bone Joint Res July 2012 1:158-166.

Impact report

Hypoxia inducible factor-regulating scaffolds for osteochondral regeneration

Researcher Mr Dheraj Taheem

Supervisor Dr Eileen Gentleman

Stream PhD

Duration 36 months

Cost £75,000

Other funders No

Focus Tissue engineering, stem cells

Mr Dheraj Taheem

Dr Eileen Gentleman

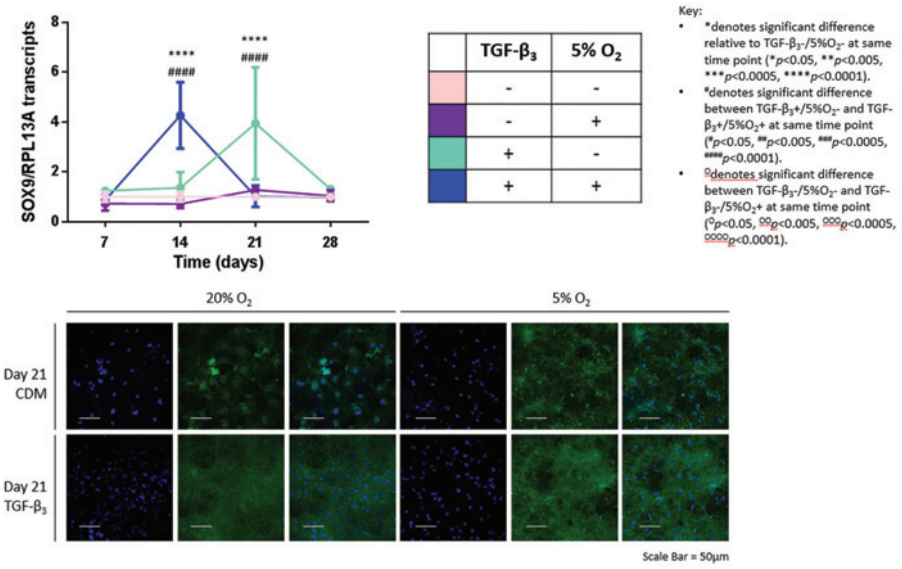
After earning a BSc in Biochemistry (2:1) from Newcastle University, I completed a Masters by Research (MRes) in Stem Cells & Regenerative Medicine (Newcastle) in 2013. My MRes research project, which focused on characterizing induced pluripotent stem cell lines, cemented my decision to pursue a career in biological research. In 2013, I moved to King's where my primary research interest is in utilizing stem cells/adult cell progenitors in tissue regeneration. I focus on using these cells to repair tissues which have been chronically or acutely damaged, and in doing so, better understand their regulation under native conditions.

What is the basic problem that you are trying to address?

Osteochondral tissue, which is composed of articular cartilage, subchondral bone and a bone-cartilage interface, is essential in joint function. Traumatic injuries, particularly in the knee, can create full thickness osteochondral defects, which penetrate through both the cartilage and bone layers and cause pain, immobility, and can progress to osteoarthritis. Current treatments often do not allow for complete, long-term healing, so more effective strategies to repair damaged osteochondral tissue are needed to prevent patients from developing painful, debilitating and costly osteoarthritis. The field of tissue engineering, which combines biomaterial scaffolds and cells, may offer a solution. One aim of tissue engineering is to replicate the signals present in the native cells' microenvironment, such as the presence of chemical factors and oxygen gradients. When such instructive cues are incorporated into a biomaterial scaffold, it can effectively instruct cells to create tissues. During normal development, the formation of bone and cartilage in one integrated tissue is partially controlled by an oxygen gradient, which signals through the hypoxia inducible factor (HIF) family of transcription factors. Therefore, by recreating this HIF gradient on a biomaterial scaffold, it may be possible to promote region-specific formation of both cartilage and bone from a single mesenchymal stem cell (MSC) population.

What is the estimated incidence of this particular problem in the general population?

In the general population, osteochondral defects are thought to occur in 15-30 people per 100,000. Injuries to osteochondral tissue may progress to osteoarthritis, which is common and one of the leading causes of disability. In the UK alone, 8.75 million people have sought treatment for osteoarthritis.



What are the aims and objectives of this research study?

The first aim of this study is to investigate the ability of HIF-activating drugs to promote MSC to differentiate to chondrocytes which can form articular cartilage, as occurs under hypoxic conditions during normal development. This will be achieved via in vitro assays, which allow us to assess the cells' gene expression by qRT-PCR and check for the presence of particular proteins (by immunostaining) such as Collagen Type II, one of the primary components of cartilage matrix.

The second aim will be to investigate the role of hypoxia and HIF-activating drugs in MSC-induced cartilage formation in 3D. This will be achieved by culturing MSC-seeded biomaterials in hypoxic conditions or co-seeding the scaffold with HIF-activating drugs. In vitro biochemical and molecular biology techniques will then we used to assess whether the cells have successfully formed bone and cartilage tissue.

Is this research going to solve the problem?

The research conducted as part of this project will go towards developing a biomaterial scaffold which will recreate the hypoxic conditions present during normal development of osteochondral tissue. Once we can effectively create cartilage and bone in the same construct, we will then need to test them in animals before they can be used in clinical trials.

What are the long-term benefits to patients with this problem?

Faithful regeneration of osteochondral tissue, which may be achieved by mimicking the region-specific hypoxic conditions present in the developing joint, may enable us to create tissue in the laboratory that can be surgically implanted to repair cartilage defects. If successful, such repairs may improve patient mobility and reduce pain after injury. More importantly, however, repairing damaged osteochondral tissue may reduce the chance that patients go on to develop painful, debilitating and costly osteoarthritis.

"This work will go towards the development of continuous osteochondral scaffolds, enabling synchronous development of articular cartilage and subchondral bone occuring during normal development"

Impact statement

- This work will increase our understanding of the role of hypoxia and its downstream factor, hypoxia inducible factor, in osteochondral tissue formation and homeostasis.
- This work will generate a new strategy for engineering articular cartilage whilst minimizing cartilage hypertrophy and fibrocartilage formation.
- This work will help us develop tissue engineering scaffolds, which may enable us to form articular cartilage and subchondral bone in a continuous construct, as occurs during in vivo development.

Impact report

The use of PEEK in uncemented shoulder arthroplasty

Researchers Miss Sara Ajami and Mr Temitope Adesina

Supervisors Dr Melanie Coathup and Professor Gordon Blunn

Stream PhD

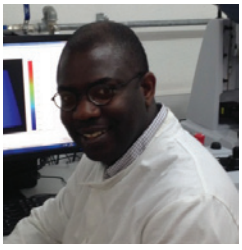
Duration 36 months

Cost £99,999

Other funders No

Focus Shoulder, bone regeneration

Miss Sara Ajami



Mr Temitope Adesina

Sara Ajami is a final year PhD student in Biomedical Engineering at the Institute of Orthopaedics and Musculoskeletal Science, University College London. She graduated from Queen Mary University of London with a BEng degree in Biomedical and Material Science Engineering and joined UCL in October 2010 to study for her Master's degree in Nanotechnology and Regenerative Medicine.

Sara's doctoral research funded by ORUK, addresses the problem of shoulder implant failure and investigates the use of a strong but lightweight polymer called Polyetheretherketone (PEEK) in uncemented shoulder arthroplasty. In particular, her research focuses on the surface modification of PEEK to improve its bioactivity and allow integration of the implant within the skeleton. Her research interests include biomaterials, orthopaedic implants, tissue engineering and regenerative medicine. Sara has presented her work at various national and international conferences

Temitope Simon Adesina obtained a primary medical degree (MBChB) from the Obafemi Awolowo University, Ile-Ife, Nigeria. He is a Member of the Royal College of Surgeons of Edinburgh and holds a Masters degree in Evidence Based Practice from the Teesside University. He is currently a PhD student at the Institute of Orthopaedics and Musculoskeletal Sciences, UCL under supervision of Dr Coathup and Professor Blunn. His research project is on assessing the suitability of polyetheretherketone (PEEK) as a bearing surface in joint replacement.

Professor Gordon Blunn is Head of the John Scales Centre for Biomedical Engineering and Dr Melanie Coathup is Head of the Centre for Cell and Tissue Research, both based within the Institute of Orthopaedics and Musculoskeletal Science. Over the years, we have undertaken studies that include wear of joints, fixation methods, biomaterials to enhance bone regeneration, tissue engineering technology to increase bone formation, and the design of implants. We have established animal models, cell models, biochemical, molecular and histological techniques for studying tissue repair and regeneration adjacent to implant materials. It is our aim to work as a translational research unit bridging clinical orthopaedics and associated areas of research to improve musculo-skeletal treatments in partnership with the Royal National Orthopaedic Hospital Trust and other Orthopaedic Centres within the UK.

"If successful, this work will have a high positive impact on the NHS as it would reduce the financial burden associated with treating failed shoulder implants"

What is the basic problem that you are trying to address?

This proposed work attempts to address the problem of shoulder implant failure. Presently, implants that re-surface worn and painful bony surfaces in the shoulder are made from cobalt chrome alloy and the stiffness of metal causes bone loss and poor integration with bone in patients, often leading to failure of the implant. Our study investigates the use of a strong lightweight polymer called polyetheretherketone (PEEK) which has a low Young's modulus.

What is the estimated incidence of this particular problem in the general population?

It has been reported that there are 100 new patient encounters per general practitioner per year with shoulder pain. Osteoarthritis is the most common reason for shoulder replacement surgery and this intervention is predicted to continue rising as demographics show that our population is living longer with a larger proportion of older people. Shoulder surgery that replaces the joint with a metal implant has increased nearly 10-fold over the last 25 years. With this older society, this equates to a rate of 11.4 surgeries per 100 000 of the population in the United States.

What are the aims and objectives of this research study?

The goal of this study is to design and test a shoulder implant manufactured from PEEK. Although PEEK has good wear properties sit does not integrate with bone and the aims are to use enhance the PEEK implant surface that enables osteointegration of the implant. Our study will first investigate the failure of metallic alloy humeral resurfacing implants form retrieval specimens. Using novel treatments on the PEEK surface we will investigate the durability of these treatments, the effect of these treatments on the proliferation, differentiation and attachment of cells in vitro and finally investigate if these coatings can enhance osteointegration.

Is this research going to solve the problem?

It is possible that the results obtained from our proposed study will result in the use of a novel implant in shoulder replacement surgery which will used as a resurfacing device and will enable greater integration and much lower revision rates. This study will be undertaken with the involvement of two specialist shoulder surgeons at the Royal National Orthopaedic Hospital and if successful after this study, the implant will be piloted at this hospital.

What are the long-term benefits to patients with this problem?

The long-term benefit to patients who require shoulder replacement surgery is the insertion of a durable and long-lasting implant that is able to integrate within the bone and maintain bone stock avoiding the current problems associated with shoulder resurfaced replacements. If successful, this work would be of international interest and will have a high positive economic impact on the NHS as it would reduce the financial burden associated with treating failed shoulder implants and will also improve the health and well-being of patients suffering from arthritis.

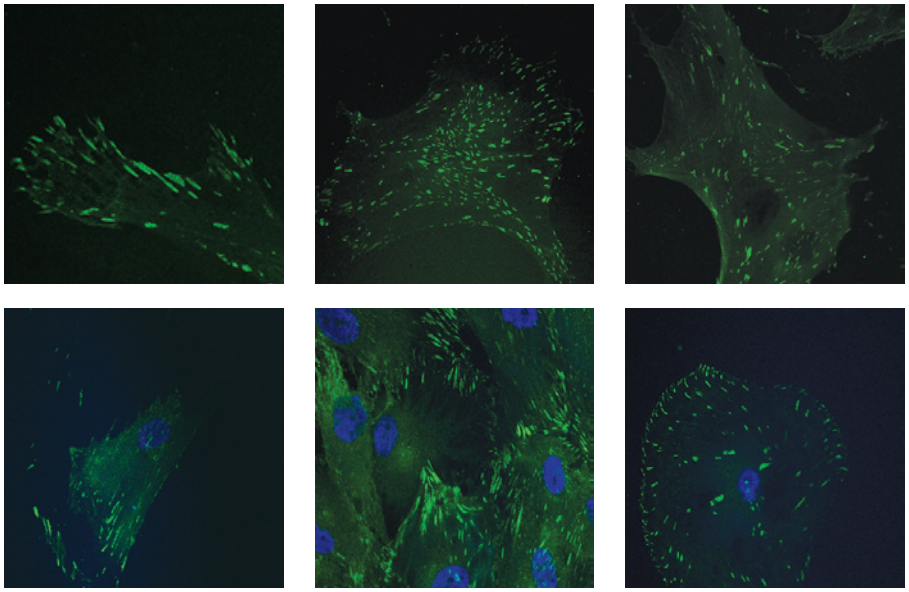


Figure:
Photomicrographs showing increased vinculin marker expression in cells when cultured on a PEEK surface treated using a novel atom beam technique (ANAB). This treatment enhanced osteoblastic attachment when compared with untreated PEEK and control (Thermanox) surfaces.

Impact statement

- This work will investigate a shoulder implant manufactured from PEEK. If successful, this novel implant may reduce failure and will improve the health and wellbeing of patients suffering from arthritis.
- This work will increase our understanding of PEEK and whether PEEK can be used as an implant bearing surface in shoulder surgery.
- This work will result in a better understanding of how to increase the biocompatibility of PEEK, to encourage bone cell attachment, bone repair, regeneration and implant integration.

Publications

1. TS Adesina, S Ajami, MJ Coathup and GW Blunn. Wear Performance Of Polyetheretherketone In An All Polymer Total Knee Replacement PEEK Conference, Philadelphia, USA, 2015.

2. S Ajami, MJ Coathup, Alexander S, Lambert S, Blunn GW. Histological and Clinical Evaluation of Failed Shoulder Surface Replacement Implants Society for Biomaterials, Boston, 2013.

Impact report

Optimising high tibial osteotomy for the treatment of early OA

Researcher Ying-chun Chen

Supervisors Dr Cameron Brown and Professor Andy Price

Stream PhD

Duration 36 months

Cost £75,000

Other funders No

Focus Osteotomy and early interventions, cartilage surface structure, spectroscopy

Ying-chun Chen

I am a DPhil student at Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford. My research focuses on developing a cartilage surface-structural model to explore the mechano-structural changes under tangential tension and also understanding what structure looks like in terms of diagnostics.

What is the basic problem that you are trying to address?

Many attempts have been developed to treat OA at early stage in recent years. Restructuring of collagen, particularly the formation of collagen bundles in the cartilage surface is a critical step in osteoarthritis progression. Lack of understanding of the balance between a tissue's structure and its ability to function limits successful early-stage treatments. Therefore, this research aims to explore the 'tipping point' at which the collagen structure does not recover and damage progresses with each application of load.

Nowadays, the relationship between structures and the spectra from diagnostic tools is still unclear. We also aim to fill this gap for better understanding of the structures with the spectra.

What is the estimated incidence of this particular problem in the general population?

Osteoarthritis is high impact global problem. According to the data from Arthritis Research UK in 2013, one-third of people aged 45 years and over, 8.75 million people, in the UK have sought treatment for osteoarthritis . In US, one-fifth of adults reported doctor-diagnosed arthritis from 2007 to 2009. In Singapore, OA is one of the five leading causes of disability.

What are the aims and objectives of this research study?

The first aim of this study is to explore the mechano-structural 'tipping point' at which the collagen structure does not recover when load is removed and damage progresses with each application of load.

The second aim of this study is to correlate the critical change in structure with its UV-VIS and Raman spectroscopy fingerprint, which are currently being developed as arthroscopic/endoscopic diagnostic tools.

Is this research going to solve the problem?

This study can help distinguishing between tissue that requires replacement or offloading, and that which is functionally viable and should be preserved, providing

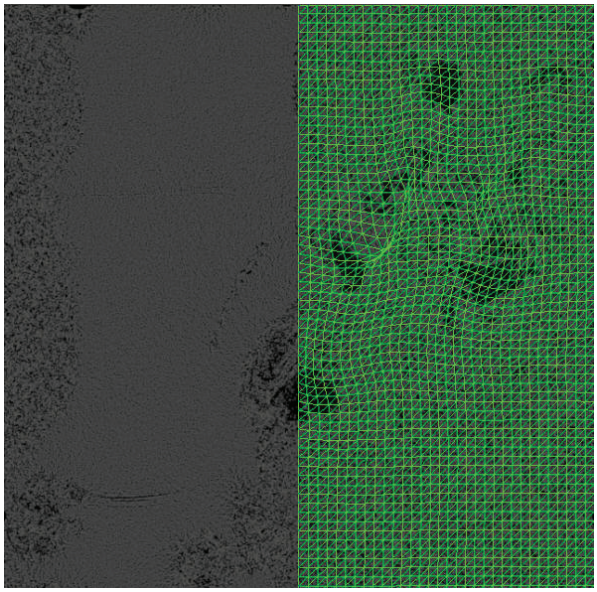


Figure:
Patterns of solid (green) and fluid (grey) deformation in the cartilage surface model under local loading.

information to design and test tissue replacements, or determine a suitable redistribution of load in osteotomy. We also provide the information to link the structures to the spectroscopy fingerprints, which are currently being developed as arthroscopic/endoscopic diagnostic tools. This information can be used for future diagnostic tool development.

What are the long-term benefits to patients with this problem?

The great long-term benefits to patients are having better OA treatment. Current treatments lack the understanding of surface structures. Providing the information can help surgeons to give better treatment to the patients, such as how much load needs to be shifted, which parts needs to be replaced or which part can be reserved. Having this information can also provide tissue engineering to produce more suitable structure artificial cartilage. In this study, filling the gap between structures and spectra form diagnostic tool can aid future diagnostic tool development.

Impact statement

- Better understanding of cartilage surface structural changes under load
- Identify early structural features of irreversible surface damage from a mechanical viewpoint
- Correlate the structural features with spectroscopy fingerprint, providing the information between structure and spectrum from diagnostic tools

“Our results may lead to a better understanding of the balance between a tissue’s structure and its ability to function, providing information for better early OA treatment”

Publications

Ying-Chun Chen, Minsi Chen, Andrew Price, Cameron Brown, Bottom-up Mechano-Structural Modeling of the Cartilage Matrix ISB conference (2015), Glasgow

Impact report

Is CD64 level an effective test for the early diagnosis and management of joint replacement infection?

Researcher Mr Ramsay Refaie

Supervisors Mr Mike Reed and Mr Kenny Rankin

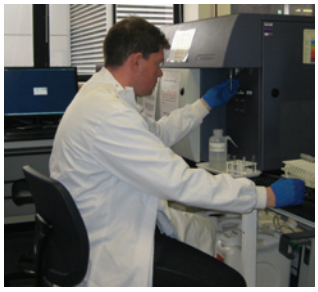
Stream MD

Duration 30 months

Cost £60,000

Other funders No

Focus Joint replacement, infection



Mr Ramsay Refaie

I am an orthopaedic surgery trainee working in the North East of England. My academic interest is in infection markers for joint replacement patients and in my spare time I enjoy reading and playing squash.

What is the basic problem that you are trying to address?

The current blood tests for joint replacement infection can be affected by many factors other than infection. They are also significantly affected by surgery itself and therefore in the early stages after joint replacement they are of little use in distinguishing infection from other causes of pain and inflammation in the joint. In many cases this can result in patients receiving antibiotics that are not required and in extreme cases can result in patients having further surgery that could have been avoided. New improved blood tests are required to help doctors make an accurate diagnosis of joint replacement infection as early as possible so that appropriate treatments can be started. This will help prevent excessive antibiotic prescription and unnecessary operations in this patient group.

What is the estimated incidence of this particular problem in the general population?

In primary joint replacement infection occurs in around 1-2% of patients. In revision surgery this number is higher 4-5%. With over 150000 joint replacement operations per year in the UK a large number of patients are unfortunately affected by this problem.

What are the aims and objectives of this research study?

To better understand the behavior of the CD64 marker around the time of surgery

To evaluate the potential of CD64 as an infection marker in patients with joint replacement infection

To compare the diagnostic accuracy of CD64 against other new and established markers for diagnosing joint replacement infection

Is this research going to solve the problem?

There is a clear need for markers that can effectively rule out infection particularly early after an operation which is when a number of patients are treated unnecessarily with antibiotics. We hope that CD64 will help guide clinicians about their decision to prescribe an antibiotic and or treat a patient with infection with further surgery. In turn this could help reduce the worldwide problem of growing antibiotic resistance as well as directly helping patients with suspected infection by preventing them from getting the side effects of antibiotic treatment and or surgical treatment.

What are the long-term benefits to patients with this problem?

Early treatment certainly provides the best chance of successful treatment of infection but early after joint replacement is precisely the time when it is hardest to diagnose joint replacement infection. Through this study we aim to validate CD64 as a marker that can predict infection or lack of in the early stages after joint replacement surgery. For patients with suspected infection this will mean far less uncertainty about the condition and the appropriate level of early treatment.

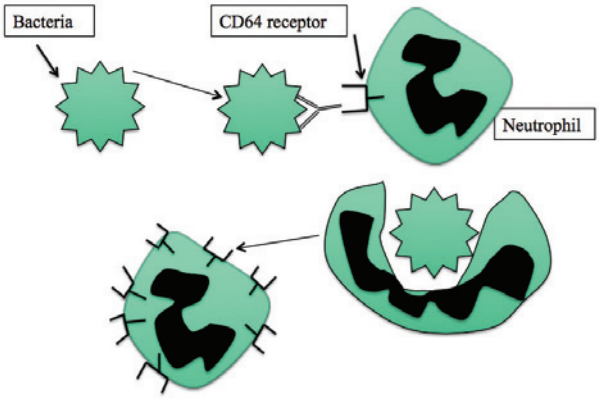


Figure:
The neutrophil CD64 response mechanism

Impact statement

- A new blood test for diagnosing joint replacement infection could help doctors in the NHS determine with higher speed and accuracy whether a patient's joint is infected or not.
- This in turn could prevent thousands of patient's each year receiving antibiotic treatment that they do not need and which could be harmful.
- Helping doctors to determine whether patients have joint replacement infection could prevent patients going through the physical and emotional stress of repeated operations and procedures on their joint.

"Our study may provide clinicians with a new improved diagnostic test that will help them determine whether joint replacement patients are developing an infection"

Publications

Arch Orthop Trauma Surg. 2013 Oct;133(10):1351-8. doi: 10.1007/s00402-013-1816-4. Epub 2013 Jul 17. The assessment of neutrophil CD64 count as an early warning marker of joint replacement infection Perry J, Reed MR, Refaie R, Sprowson AP, Rankin KS

Impact report

Adolescent hip disease: biomarkers, morphology and PROMS in a longitudinal study

Researcher Mr Avi Marks

Supervisor Mr Andreas Roposch

Stream Clinical Fellowship

Duration 24 months

Cost £99,817

Other funders No

Focus Biomechanics, computational modelling, deformities, hip, paediatric

Mr Avi Marks

Having graduated from Warwick Medical School in 2007, I was appointed to a Trauma and Orthopaedics run-through specialty training programme in 2009 in the West Midlands Deanery. I obtained membership of the Royal College of Surgeons of England and have completed five years speciality training on the Coventry and Warwickshire rotation. I have now taken three years out of clinical training to pursue a PhD in clinical epidemiology at UCL. This research project will contribute to improving prediction of outcomes in paediatric hip disease by enabling the development of novel disease severity index for patients with osteonecrosis, a complication of treatment for developmental dysplasia of the hip.

What is the basic problem that you are trying to address?

In adolescents who have hip disease that originated in childhood, the disease is defined purely by X-ray criteria. Because radiographic features cannot be directly perceived by patients, our current classification schemes are flawed. We need to find other ways to understand and define adolescent hip disease. One approach is to define it by outcomes that patients can recognise. Outcomes that patients can perceive directly are more meaningful when counselling affected patients about their prognosis or the need for treatment. This research will determine how X-ray findings correlate the real 3D structures as revealed by MRI, and how these correlate with pain, function, disability and quality of life. The research will determine in particular what findings in childhood will lead to mild and severe hip disease in adolescence/young adulthood.

What is the estimated incidence of this particular problem in the general population?

Congenital hip dysplasia occurs in 40-60/1000 newborns and, despite of treatment, it will lead to adolescent hip disease of mild or severe grade. It is a major cause of debilitating hip disease in adulthood. It underlies up to 9% of all primary hip replacements and up to 29% of those in people aged 60 years and younger. 46% of patients who had DDH in childhood had a primary hip arthroplasty done by the age of 43 years and 25% of the remaining patients suffered from osteoarthritis.

What are the aims and objectives of this research study?

We will determine what it means for affected adolescents to have hip disease, in terms of pain and disability originating from the hip; physical functioning; and in terms of quality of life. We assembled and examined a group of 88 children with this condition in 2006 ("2006 cohort") and we will examine these patients 8 years later in order to understand how much their function, pain, and quality of life has changed with increasing age.

With the 3D evidence we will develop a more powerful predictor of adolescent hip disease generating a new classification. This will drive better decisions in affected children, helping to minimize problems when they are teenagers and throughout adult life.

Is this research going to solve the problem?

Yes - the research will give us insights about how children with hip dysplasia change when they grow up and what can be expected when they are adolescents. This information is not available elsewhere.

What are the long-term benefits to patients with this problem?

The results of this study can be used to counsel parents of children with DDH at a young age about what can be expected when the children grow older. The results will clarify how adolescents with certain X-ray changes of the hip cope in terms of functioning, pain and general wellbeing.

The results will inform about the development of risk-tailored care pathways, especially in the transition from childhood to adult services, for which there are currently no agreed services in place across NHS Trusts.

"The results will clarify how adolescents with certain X-ray changes of the hip cope in terms of functioning, pain and general wellbeing"

Impact statement

- Providing novel insights into the relationship between premature degenerative arthritis and childhood hip disease.
- Focusing on patient reported outcomes, this work will replace the flawed, unreliable radiographic classification schemes with a new disease severity index based on the patient's perspective.
- Establishing outcomes patients can recognise, will enable improved counselling to families, guide patient care, guide the development of services, and educate clinicians regarding what to expect for children with developmental dysplasia of the hip.

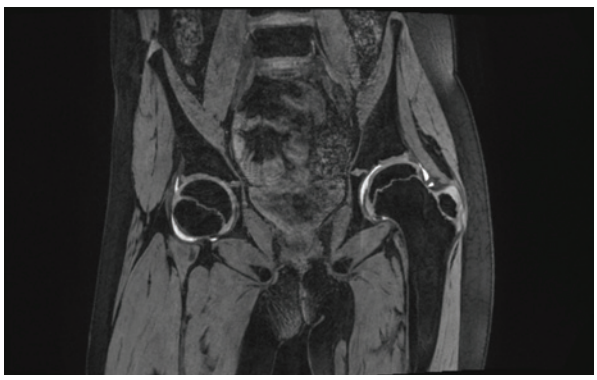


Figure:
3T magnetic resonance image of the pelvis.

Impact report

Will the intravenous adminstration of mesenchymal stem cells modified to migrate to the bone marrow increase bone formation in osteoporosis?

Researchers Dr Sorousheh Samizadeh and Miss Anita Sanghani

Supervisors Dr Melanie Coathup, Dr Jie Huas, Professor Allen Goodship and Professor Gordon Blunn

Stream Postdoctoral Fellowship

Duration 24 months

Cost £99,999

Other funders No

Focus Osteoporosis, fracture healing and bone regeneration

Dr Sorousheh Samizadeh

Anita Sanghani

Dr Sorousheh Samizadeh completed her PhD in Orthopaedic Biomaterials in 2010 at the Center for Biomedical Engineering, Institute of Orthopaedics and Musculoskeletal Science, University College London. Prior to this, and having always been keen on finding solutions for bone tissue regeneration, she studied Molecular Genetics (BSc.,) at King's College London in order to shape her knowledge of the mechanisms of gene expression and their role in tissue development and repair. The focus of Dr Samizadeh's doctoral studies was in understanding the cellular mechanisms of bone formation adjacent to bone substitute biomaterials and the role of chemical substitutions in enhancing the bioactivity of these biomaterials. This in combination with her genetics background enabled her to work as part of her post doctoral research, which is supported by ORUK, on a project focused on up regulation of the CXCR-4 gene which is involved in the homing of stem cells from the bone marrow niche to sites of bone repair. Dr Samizadeh has presented at various prestigious international and national conferences and has authored a number of publications. In addition to research she also enjoys teaching and lectures on both BSc and MSc courses run by the Institute of Orthopedics and Musculoskeletal Science, UCL.

Anita Sanghani – I qualified as a Biomedical Engineer from Queen Mary, University of London with MEng(Hons). Throughout my degree, I developed an interest in bone and joints, especially regeneration of bone. Stem cells, is another topic that fascinates me, as it is an emerging field in tissue regeneration and its application has become wider and more varied. I therefore decided to pursue a research career in bone regeneration using stem cells. I am currently studying a PhD at UCL, Institute of Orthopaedics and Musculoskeletal system. In my project I genetically manipulate stem cells, to over-express CXCR4, a chemokine that increases the migratory capacity of cells to sites of injuries, bone defect sites. Poor functional migration of stem cells in osteoporosis and non-union bone fractures is an emerging medical problem that affects millions of elderly patients worldwide. This was therefore a challenging and novel topic of research. So far my project has been very exciting as I have also had the opportunity to compare the functional differences of stem cells in osteoporosis. I have harvested stem cells from osteopenic animals and compared their migratory and differentiation differences to cells from young and adult animals. I am hoping to translate my study in vivo so that it can be applies clinically for osteoporotic patients.

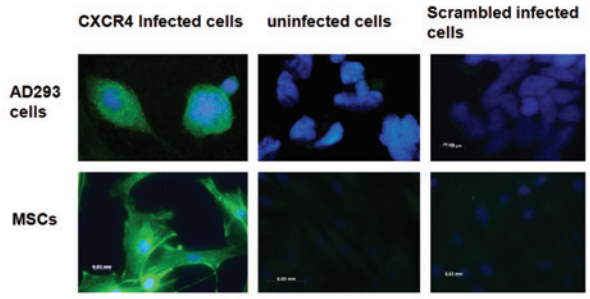


Figure 1:
Photomicrographs showing positive expression of CXCR4 in mesenchymal stem cells (MSCs) following transfection. Images show minimum expression in non-transfected cells.

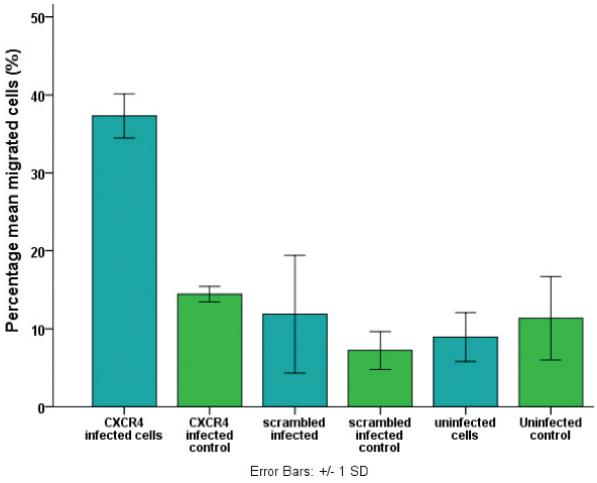


Figure 2:
Histogram to show that the migration of CXCR4 transfected stem cells significantly increased towards a chemoattractant within a Boyden chamber.

Professor Gordon Blunn is Head of the John Scales Centre for Biomedical Engineering and Dr. Melanie Coathup is Head of the Centre for Cell and Tissue Research, based within the Institute of Orthopaedics and Musculoskeletal Science. We have undertaken studies on the wear of joints, osteointegration of implants, biomaterials to enhance tissue regeneration, tissue engineering technology to increase bone formation and the design of implants. We have established in vitro and in vivo models, biochemical, molecular and histological techniques for studying tissue regeneration. We are a translational research unit bridging clinical orthopaedics and research to improve care of patients with musculoskeletal conditions.

What is the basic problem that you are trying to address?

Osteoporosis is one of the most prevalent and serious systemic diseases affecting the elderly population and constitutes a major health problem. Osteoporosis is characterised by low bone mass and a microarchitectural deterioration of bone leading to impaired skeletal strength and increased susceptibility to fractures. The conventional therapies used to prevent and treat osteoporosis have recently been questioned due to the risk/benefit ratio of prolonged treatment. Most of the treatments are aimed at reducing bone resorption, preventing further reduction in bone mass. There are very few treatments, which are aimed at increasing bone mass in osteoporosis. The goal of this study is to increase bone mass using stem cells that home to the bone marrow and have an anabolic effect on bone remodeling.

Impact statement

- This work will investigate developing a novel cell therapy that augments bone formation in osteoporosis and in fracture healing. If successful this treatment will reduce the incidence of fragility fractures and improve the health and wellbeing of patients.
- This work will increase our understanding of using gene therapy, administered locally or systemically to increase bone mass and strength.
- This work will result in a better understanding of whether stem cell therapy can be used as a new method of treatment to encourage bone repair and regeneration in osteoporosis.

What is the estimated incidence of this particular problem in the general population?

This investigation is of considerable importance because the incidence of osteoporotic hip fractures is predicted to increase worldwide from 1.66 million to 6.26 million by 2050. These fractures occur at multiple skeletal sites, most often at the spine, hip or wrist causing significant morbidity and mortality in males and females. In the UK the number of hip fractures is estimated to increase to 117,000 in 2016. The cost of treating hip fractures in the UK is £1.4bn/year and this figure will double by 2050 making osteoporosis a significant health problem of growing economic concern. In Europe, osteoporotic fractures account for more disability adjusted life years (DALYs) than any other chronic non-communicable disease. One in two women 50 years of age will have an osteoporotic fracture in their remaining lifetime; this figure in men is one in five.

What are the aims and objectives of this research study?

The aim of this study is to determine whether stem cells engineered with a gene that enhances their migration to the bone marrow and to fracture sites will increase the mass and strength of fragile osteoporotic bone and if this treatment augments fracture repair and healing. The aims of this study are to investigate if stem cells from osteopenic animals behave in the same way as those from non osteopenic animals. We are investigating cell migration, proliferation and differentiation of these cells in vitro. The over expression of the gene encoding for CXCR4 which is membrane bound factor responsible for the migration of stem cells will be investigated to see if this potentially enhances migration to the bone marrow and to sites of injury. We are then using an in vitro model to investigate the optimal strategy to increase bone strength and fracture repair in an osteopenic model where bone mass and strength are reduced to similar levels found in patients with osteoporosis.

Is this research going to solve the problem?

Currently, intravenously administered mesenchymal stem cells (MSCs) are used to treat many conditions including patients following stroke and myocardial infarction, patients with multiple sclerosis, Crohn's disease, osteoarthritis, spinal cord injury, Parkinson's disease and patients with osteogenesis imperfecta where early results have confirmed some clinical improvements following cell therapy. The mechanism of osteoporotic bone loss is not fully understood and our proposed study will provide researchers with an increased understanding of the biological mechanisms involved in osteoporosis and will also determine whether expanded MSCs can be used as a therapy in the treatment of osteoporosis and fracture repair in osteoporotic patients.

What are the long-term benefits to patients with this problem?

If successful, this work would be of international interest and will have an impact on patients suffering from osteoporosis and fragility fractures. This would potentially have an economic impact on the NHS as the further development of this technology in humans would reduce the financial burden associated with treating fragility fragility fractures. Following investigation in a rat model, it is our intention for this treatment protocol to be investigated in a larger animal model and then if successful into a phase I safety trial in humans.

"If successful, this work will impact on patients with osteoporosis and reduce the financial burden associated with treating fragility fractures"

Publications

1. Ho CY, Snaghani A, Hua J, Coathup MJ, Kalia P, Blunn GW. Mesenchymal stem cells with increased stromal cell-derived factor 1 expression enhanced fracture healing Tissue Eng A 21(3-4):594-602, 2015.

2. Lien CY, Chih-Yuan Ho K, Lee OK, Blunn GW, Su Y. Restoration of bone mass and strength in glucocorticoid-treated mice by systemic transplantation of CXCR4 and cbfa-1 co-expressing mesenchymal stem cells J Bone Miner Res 24(5):837-48, 2009.

Impact report

Does dysfunctional autophagy underlie both ageing-related and mechanical deterioration of cartilage in osteoarthritis

Researcher Dr Seint Lwin

Supervisor Dr James Edwards

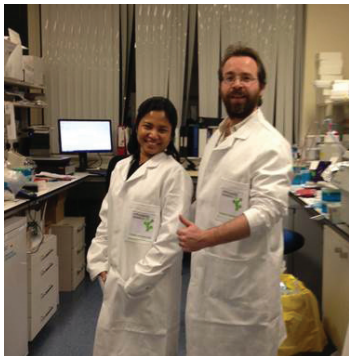
Stream Postdoctoral Fellowship

Duration 24 months

Cost £100,000

Other funders No

Focus Cartilage, arthritis, ageing



Dr Seint Lwin and Dr James Edwards

The Musculoskeletal Ageing group at Oxford, led by Dr James Edwards, is focused on the study of ageing and longevity mechanisms in health and disease. Built upon an extensive expertise in bone and joint research, including genetic modification and surgical models of ageing-related musculoskeletal disease, Dr Edwards' team uses human tissue samples and advanced cellular and molecular techniques to explore common factors linking increasing age and lifespan control with musculoskeletal decline.

Recently, novel longevity-related factors have been shown to contribute to age-related bone loss and modifications in diet quantity and quality explored as viable and effective approaches to combat bone and joint disease.

What is the basic problem that you are trying to address?

This study explores underlying mechanisms contributing to age-related musculoskeletal degeneration. Osteoarthritis (OA) results from defective and inadequate cartilage coating a joint, leading to increased bone destruction and considerable pain. It is the aim of this proposal to better understand the causes of OA, what leads to the onset of disease, and how we may be able to target this earlier and more effectively.

Our studies have linked a known regulator of longevity to the development of age-related musculoskeletal disease, including OA. This proposal addresses whether this age-related factor forms a common link between increased lifespan, and the development of OA.

What is the estimated incidence of this particular problem in the general population?

Bone and cartilage disorders are very common, affecting over 50% of adults over the age of 50 years, and their consequences represent major costs to the health services. Osteoarthritis affects over 7 million people, representing 12% of the UK population. Arthritis and related conditions are the second most common cause of days off work and the cost of OA in the UK is estimated at 1% of annual gross national product.

This proposal is focused upon Ageing, and how lifespan-regulating factors contribute to arthritis. As life expectancy and the ageing population increases, it is anticipated that the numbers of patients presenting with conditions such as OA will also increase. It is the aim of our research group to better understand the mechanisms controlling ageing and lifespan, and how they underlie age-related disorders, to more effectively target conditions such as OA before they manifest.

"Our results will improve our understanding of why ageing causes musculoskeletal disease and whether new drugs targeting lifespan-regulating factors may be beneficial for disorders such as osteoarthritis"

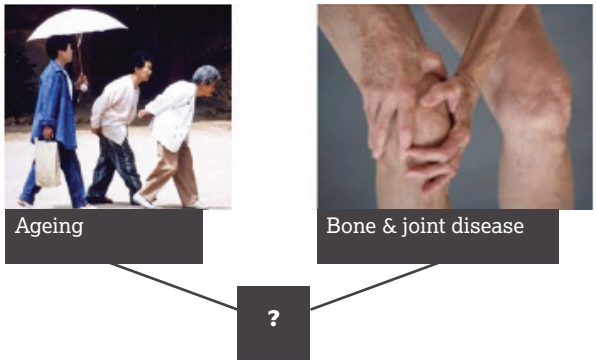


Figure: Do common factors exist which regulate both the ageing process, and the decline in musculoskeletal function?

What are the aims and objectives of this research study?

We believe that a defect in the cells which maintain articular cartilage (chondrocytes), brought about by increased age and mechanical forces, underlies the development of OA. This defect is centered upon an inability of the cartilage cells to remove unwanted waste debris (autophagy). Impaired autophagy is a well-accepted component of the ageing process and is decreased in areas subjected to accumulative mechanical forces (such as the ageing joint). It is our aim to characterize the extent of impaired autophagy in OA, and whether stimulating this process can protect against the cellular defects which lead to OA.

Is this research going to solve the problem?

This study promises to help advance our understanding of the links between getting old and skeletal diseases, specifically osteoarthritis. Why do older people develop osteoarthritis and what are the lifespan-related factors which underlie musculoskeletal disease?

In revealing novel markers of age-related musculoskeletal decline, this work aims to improve early detection and intervention in OA, and to test the potential for targeting ageing mechanisms to preserve joint health and longevity and reduce the need for surgical interventions (i.e. hip and/or knee replacements).

What are the long-term benefits to patients with this problem?

This study tests novel anti-ageing drugs currently in clinical trials for other age-related disorders (Type II diabetes). It is intended that this work will form the basis for further studies extending this research to target ageing-related factors for the treatment of OA, to not only reverse, but to protect against cartilage destruction and restore the normal biology of the cell and joint over the long term.

Impact statement

- Why does our skeleton deteriorate as we get old? The link between Ageing and Arthritis has become better understood as a result of this work.
- This work has revealed new lifespan-regulating factors as underlying mediators of musculoskeletal disease.
- Targeting novel ageing-related factors may improve early detection of osteoarthritis and reveal better treatment options for managing musculoskeletal disorders.

Publications

1. P. Sacitharan, ST. Lwin, T. Vincent, JR. Edwards. Loss of SirT1 Dysregulates Chondrocytes And Leads To An Arthritic Phenotype In Vivo Through Impaired Autophagy. BRS 2015

2. S. Lwin, JR Edwards. We Are What We Eat - How Diet Manipulation Impacts Ageing, Cancer and Skeletal Health 2015 SET for Britain Parliamentary Competition.

3. EV. Morris, P. Sacitharan, S. Lwin, V. Treasure, T. Vincent, JR. Edwards. Autophagy is Activated in Bone and Joint Cells During Lineage Commitment and is Regulated In Vivo by Diet and Ageing via SirT1 ASBMR 2014

Impact report

The investigation of radiographic measuring of femoral migration without using marker beads

Researcher Mr Tamer T Malak

Supervisors Professor Sion Glyn-Jones, Dr Cameron Brown

Stream PhD

Duration 36 months

Cost £75,000

Other funders Corin Group PLC

Focus Hip, total hip

Mr Tamer T Malak

I am an Orthopaedic Registrar currently studying for a Doctorate in Musculoskeletal Science in the University of Oxford. My programme of research investigates methods of detecting failing hip replacement devices early before many are implanted in patients.

What is the basic problem that you are trying to address?

Currently the only way of measuring the success of a hip replacement is to see how many require further surgery (revision) after ten years. However, waiting this long to see the success of the operation is too long especially to know whether a new implant will be good.

One method uses a complex 3D X-ray technique that requires small metal beads inserted into the bone at the time of surgery. It can accurately determine the success of replacement in 2 years. However, the insertion of the metal beads is unacceptable to some patients and surgeons as it can prolong surgery. It is very difficult to perform and is done in specialist centres of which there are only three in the country. We are developing a way of using X-ray but without using metal beads or specialist equipment.

What is the estimated incidence of this particular problem in the general population?

Over 80,000 hip replacements are performed in the UK per year. Over 20% devices used in hip replacements have no evidence to support their use.

What are the aims and objectives of this research study?

The aim of this study is to develop a method of measuring how a hip implant moves in the thighbone over time without using marker beads in the bone.

We will first try to achieve this using the current 3D X-ray system but no marker beads. Then we will develop a method using standard X-ray and sophisticated software. Testing will first be on models. Once successful we will test our method in a Randomised Control Trial.

Is this research going to solve the problem?

Our study can solve the problem if we show that our method is able to measure how a hip replacement moves in the bone with the same accuracy as conventional methods without marker beads.

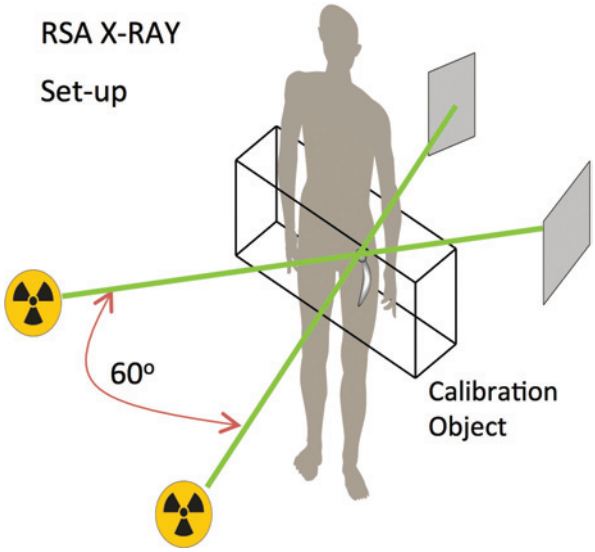


Figure:
How 3D imaging is currently performed. Two X-rays are taken at the same time with the patient in a calibration object. Metal beads are inserted into the bone, which is then marked against the calibration object

What are the long-term benefits to patients with this problem?

The great long-term benefits to patients are the development of new method to detect failing hip replacement devices early before many are implanted in patients. This is particularly important in light of recent catastrophes involving Metal-on-Metal hip replacements where over 100,000 patients were given the implant before any problems were identified.

Our study may lead to a better method of identifying failing hip implants early. We would be able to identify such devices within 2 years of the operation and only requires a small number of patients to investigate. Furthermore, our technique could be used in any hospital with standard X-ray equipment allowing for new devices to be tested earlier and quicker.

"Our study may lead to a better method of identifying failing hip implants early"

Impact statement

- The overall aim of this project is to develop a portable ultrasound device incorporating motion capture analysis that can be used to study painful joint movements in the outpatient setting

Impact report

Dynamic musculoskeletal ultrasound measurement of joint pain

Researcher Mr Paul Monk and Mr Reiv Jia

Supervisors Professor David Murray, Professor Alison Noble and Dr Mark Thompson

Stream PhD

Duration 36 months

Cost £75,000

Other funders Intelligent Ultrasound

Focus Shoulder, hip, knee

Mr Paul Monk

What is the basic problem that you are trying to address?

The current gold standard of musculoskeletal imaging are MRI, CT, with images traditionally acquired in the rested, supine position. This is clearly far from adequate for assessing their functional performance and response to loading.

This innovative technology will allow acquisition of images during dynamic movement with patients undergoing analysis whilst performing activities of daily living, in the upright position.

What is the estimated incidence of this particular problem in the general population?

Total joint replacement (TJR) has become the standard operative treatment for advanced joint diseases when conservative measures have failed. In the lower limb alone, by 2030 the estimated number of total knee replacements being performed in the US alone is 3.48 million whilst the annual predicted number of total hip replacements (THR) is 572,000 [1]. Despite significant advances in surgical technique and implant design, studies continue to report poor functional outcome or pain associated with poor range of movement, dislocation and wear [2-5]. The reason for this is not well defined, but is likely in part to be related to abnormal kinematics and implant positioning [6-7].

What are the aims and objectives of this research study?

The overall aim of this project is to complete the development of a portable ultrasound device incorporating motion capture analysis that can be used to study painful joint movements in the outpatient setting.

This will be achieved via the following objectives:

1) to develop novel, Motion Analysis and UltraSound (MAUS) methods to measure 6 degrees of freedom kinematics with greater fidelity and accuracy than previously possible.

2) to use advanced imaging methods to describe normal, painless joint kinematics followed by comparison with painful movements and adverse functional outcome following joint replacement.

This innovative technique co-registers motion analysis data with ultrasound to study everyday joint movements. Presently, functional musculo-skeletal imaging remains limited to static studies, often with patients lying in a supine position.

The main outcome of this project will be to use this new kinematic understanding to improve function following joint replacement surgery.

Is this research going to solve the problem?

In order to use ultrasound to assess kinematics we have combined it with our motion analysis system. The system has been successfully implemented in previous studies of knee kinematics in this institution, with a system error of 1.8 mm (2xSD) which, to our knowledge is currently the lowest reported error in the literature [8].

We attach retro-reflective markers to the ultrasound probe and following calibration, can determine the position of a bony landmark in three-dimensional (3D) space (fig 1). Using skin markers and ultrasound to determine the site of a series of landmarks we are able to determine the position of e.g. the hip relative to the pelvis, or humerus relative to the scapula. By repeating this at a series of flexion angles under different loads we will assess joint kinematics in 3 dimensions.

What are the long-term benefits to patients with this problem?

This device will be used to investigate unexplained pain associated with joint movements. To date using contemporary imaging techniques (radiographs/ fluorscopy, CT, MRI) there is no described method for directly imaging functional joint movements during activities of daily living (stair climbing, walking etc). Ultrasound has the great advantage over other imaging modalities in that it doesn't involve ionising radiation and imaging studies can be acquired on a portable device.

Furthermore, until now no technique has successfully described three dimensional kinematics of the patellofemoral joint in the native and replaced knee due

"This portable technology is the first to provide real-time kinematic data to a high degree of accuracy to image patients performing activities of daily living, without using ionizing radiation"

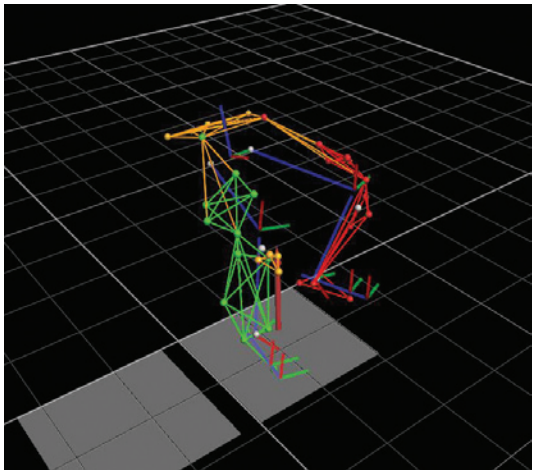
to image artefact associated with metal impants. As stated, we believe that only by understanding the full 3D kinematics will it be possible to identify the cause of poor outcomes following total knee replacement in particular anterior knee pain, and therefore to begin to address this. Potential avenues for ameliorating knee pain include: new design of knee implants, new jigs for insertion of implant, new imaging during operations to control implant position and new rehabilitation methods.

These new insights into knee joint mechanics and dynamics in healthy knees will provide base line data from which patients with developing joint disease may be assessed, and hence new understanding of the mechanical causes underlying osteoarthritis initiation and progression will be obtained.

Finally the technology developed will provide a platform for assessing kinematics of the musculoskeletal system during normal movement and will benefit musculoskeletal researchers in neighbouring groups. Potential applications could build on strong local expertise in understanding the movement of the foot, and also in the use of ultrasound for characterising hand movement in rheumatoid arthritis.

Impact statement

- The overall aim of this project is to develop a portable ultrasound device incorporating motion capture analysis that can be used to study painful joint movements in the outpatient setting



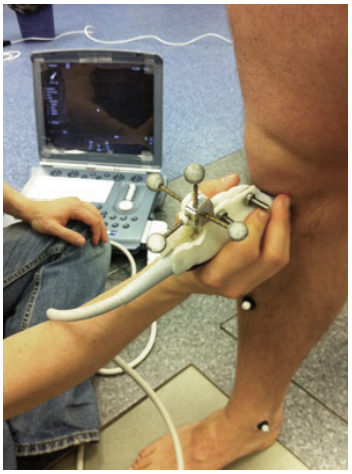


Figure:
Mapping device tracking joints movements

Publications

1.Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030 J Bone Joint Surg Am. 2007 Apr;89(4):780-5.

2. Williams D, Royle M, Norton M. Metal-on-metal hip resurfacing: the effect of cup position and component size on range of motion to impingement J Arthroplasty 2009;24-1:144-51.

3. Biedermann R, Tonin A, Krismer M, Rachbauer F, Eibl G, Stockl B. Reducing the risk of dislocation after total hip arthroplasty: the effect of orientation of the acetabular component JBJS Br 2005;87-6:762-9.

4. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol AV, De Smet KA. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear J Bone Joint Surg Br;93-2:164-71.

5. Grammatopoulos G, Thomas GE, Pandit H, Beard DJ, Gill HS, Murray DW. The effect of orientation of the acetabular component on outcome following total hip arthroplasty with small diameter hard-on-soft bearings Bone Joint J;97-B-2:164-72.

6. Grammatopoulos G, Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gill HS, Murray DW. Optimal acetabular orientation for hip resurfacing J Bone Joint Surg Br 2010;92-8:1072-8.

7. Callanan MC, Jarrett B, Bragdon CR, Zurakowski D, Rubash HE, Freiberg AA, Malchau H. The John Charnley Award: risk factors for cup malpositioning: quality improvement through a joint registry at a tertiary hospital Clin Orthop Relat Res 2011;469-2:319-29

8. Measurement of in-vivo patella kinematics using motion analysis and ultrasound (MAUS) AP Monk, M Chen, CLMH Gibbons, DJ Beard, HS Gill, DW Murray. In supplement: IEEE International Symposium on Medical Measurements and Applications, 2013: 2013-5-04

Impact report

Surgery for patellar instability: The impact of pathomorphology on kinematics and gait

Researcher Dr Arash Aframian

Supervisors Miss Caroline Hing, Professor Justin Cobb, Mr Duncan Tennent and Professor David Oliveira

Stream MD

Duration 24 months

Cost £88,868

Other funders Imperial College London

Focus Knee surgery, patellofemoral instability

Dr Arash Aframian

I studied medicine, completing my MB BS with an intercalated BSc(Hons) in 2008. I then worked as a junior doctor for five years with a focus in surgery, particularly orthopaedics. Having worked as a registrar in trauma & orthopaedics for a year in Kent, I then worked as a Junior Trauma Fellow at St George's Hospital in south-west London, one of the four major trauma centres for London, and where I am now registered for an MD(Res) at St George's University of London and collaborating with Imperial College London.

What is the basic problem that you are trying to address?

Patellofemoral Instability (PFI, dislocating kneecaps) can cause pain and lead to loss of function. The aetiology of PFI is multi-factorial [1][2][3].

The measurement of outcomes is challenging, and even some objective measurements are not always reliable [4]. Specialist PFI questionnaires have been developed and validated but the management of this complex multi-factorial problem remains challenging [5]. It is unclear from some studies if surgical management is superior to conservative management due to the way data is collected and varying methodology and surgical technique, even within studies [6][7][8].

A dysplastic or flat trochlear groove is treated with a trochleoplasty that aims to deepen the femoral trochlear groove. We plan to make objective measurements of function using a specialised treadmill before and after surgery to look at the way patients walk. By comparing this to the way 'normal' people walk we can see if patients have a stable kneecap after surgery.

What is the estimated incidence of this particular problem in the general population?

The annual incidence of patellofemoral dislocation is 77 in 100,000 with recurrence in 20-40%, or 2-3% of all acute knee injury presentations [9] [10] [11] [[12].

What are the aims and objectives of this research study?

The aim of this research is to investigate if gait studies are a valid objective measure of surgical outcome by comparing these with patient completed questionnaires, clinical examinations and radiology. This will allow us to see if surgery helps improve gait to more closely resemble normal walking patterns [13][14].

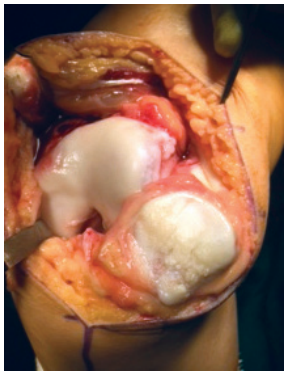


Figure:
Patellofemoral surgery: The effects of patellofemoral instability with damage to the back of the patella

Is this research going to solve the problem?

This study will advance our understanding of why the symptoms experienced by patients with PFI are so variable and unpredictable. Understanding which factors result in pain and instability, then targeting these issues directly by using new tools we are developing, can be used to assess and treat patellar instability and anterior knee pain.

What are the long-term benefits to patients with this problem?

Current treatments are limited both in terms of improving pain and in terms of complication rates, with some surgeons reporting outcomes as 54% poor, 23% fair and only 23% good [15] in a case series. Developing more effective treatments with more acceptable outcomes promises to be a huge breakthrough for patients with patellar instability. The results of our study are also likely to be transferable to other common causes of anterior knee pain. Our results may lead to a better understanding of gait analysis in anterior knee pain, and objective outcome scoring in general. The new tools may be used in other types of knee surgery.

Impact statement

- Patellofemoral instability affects up to 77/100,000 with recurrence rates nearly one in two
- There is still no clear solution to the management of this complex problem.
- The results of surgery can be difficult to assess, and there are numerous systems in existence.
- This study will look at treadmill gait analysis to see if this provides a good reflection of surgical outcomes.
- This work will improve understanding of what drives patellofemoral pain, and help to guide future treatment. We will:

- Use a specialised treadmill with force plates
- Objectively measure gait
- Change speed and inclination
- Reproduce movements usually associated with knee pain
- Compare to patient completed questionnaires
- Develop a 3D camera array to analyse gait

“Our study aims to improve the treatment of patellar instability by using gait analysis as an objective measure of outcome”

Publications in progress

Patellofemoral Instability: Operate earlier?

The relationship of pain and outcome following patellofemoral instability surgery.

References

1. Arendt EA, Fithian DC, Cohen E. Current concepts of lateral patella dislocation. Clin Sport Med Sport Med 2002;21:499–519. doi:10.1016/S0278-5919(02)00031-5.

2. Goodwin D, Postma W. Patellar instability. OA Sport Med 2013;1:1–13.

3. Dejour H, Walch G, Nove-Josserand L, Guier C. Factors of patellar instability: an anatomic radiographic study. Knee Surg Sports Traumatol Arthrosc 1994;2:19–26.

4. Smith TO, Davies L, O'Driscoll M-L, Donell ST. An evaluation of the clinical tests and outcome measures used to assess patellar instability. Knee 2008;15:255–62. doi:10.1016/j.knee.2008.02.001.

5. Smith TO, Donell ST, Clark A, Chester R, Cross J, Kader DF, et al. The development, validation and internal consistency of the Norwich Patellar Instability (NPI) score. Knee Surg Sports Traumatol Arthrosc 2014;22:324–35. doi:10.1007/s00167-012-2359-x.

6. Smith TO, Song F, Donell ST, Hing CB. Operative versus non-operative management of patellar dislocation. A meta-analysis. Knee Surgery, Sport Traumatol Arthrosc 2011;19:988–98. doi:10.1007/s00167-010-1355-2.

7. Hing CB, Smith TO, Donell ST, Song F. Surgical versus non-surgical interventions for treating patellar dislocation (Review). Cochrane Rev 2012:45.

8. Saccomanno M, Deriu L, Careri S, Ieso C De, Donati F, Milano G, et al. In-Depth Oral Presentations and Oral Communications S68: Surgical versus conservative treatment after acute patellar dislocation: a systematic review and meta-analysis. vol. 13. 2012. doi:10.1007/s10195-012-0210-2.

9. Hawkins RJ, Bell RH, Anisette G. Acute patellar dislocations. The natural history. Am J Sports Med n.d.;14:117–20.

10. Nietosvaara Y, Aalto K, Kallio PE. Acute patellar dislocation in children: incidence and associated osteochondral fractures. J Pediatr Orthop 1994;14:513–5.

11. Tjoumakaris FP, Forsythe B, Bradley JP. Patellofemoral instability in athletes: treatment via modified Fulkerson osteotomy and lateral release. Am J Sports Med 2010;38:992–9. doi:10.1177/0363546509357682.

12. Stefancin JJ, Parker RD. First-time traumatic patellar dislocation: a systematic review. Clin Orthop Relat Res 2007;455:93–101. doi:10.1097/BLO.0b013e31802eb40a.

13. Hausdorff JM, Alexander NB. Gait Disorders: Evaluation and Management. 2005.

14. Baker R. The history of gait analysis before the advent of modern computers. Gait Posture 2007;26:331–42. doi:10.1016/j.gaitpost.2006.10.014.

15. Verdonk R, Jansegers E, Stuyts B. Trochleoplasty in dysplastic knee trochlea. Knee Surg Sports Traumatol Arthrosc 2005;13:529–33. doi:10.1007/s00167-004-0570-0.

Impact report

Dispersal of clinical biofilms from titanium and cobalt chrome surfaces using a novel marine nuclease (NucB)

Researcher Andrea Pujol Nicolas

Supervisors Professor Grant Burgess and Mr Mike Reed

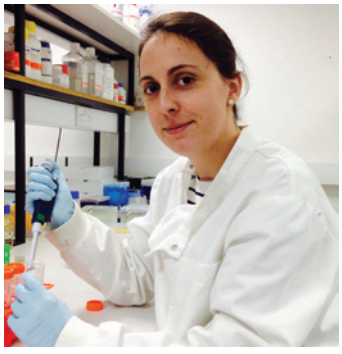
Stream MD

Duration 24 months

Cost £58,696

Other funders No

Focus Biofilms, infected hip and knee arthroplasty



Miss Andrea Pujol Nicolas

I am an Orthopaedic surgical trainee in the North East of England. Currently I am studying for a Medical Doctorate (MD) at Newcastle University and part of an award winning, multidisciplinary research team, which reflects the wide ranging problems caused by bacterial biofilms. I work in a large team of microbiologists, chemists, dentists and marine biologists. Originally from Spain, I completed my medical degree in 2007 at the University of Navarra, Spain. I moved to the UK in September of the same year to continue my specialty training in Trauma and Orthopaedics. Over the past 2 years I have participated in several national and international meetings, successfully presenting our NucB work. While continuing with my full time MD I still maintain clinical commitments at Northumbria Healthcare NHS Trust. I led the team which applied for and successfully won this support from ORUK, in collaboration with Mr Mike Reed and Professor J Grant Burgess.

What is the basic problem that you are trying to address?

Total hip or total knee replacement offers an effective treatment for osteoarthritis. It is a common operation with over 120,000 joint replacements carried out each year. Although the majority are successful, a small number are complicated by infection of the joint.

Although infection is rare, it is a serious complication requiring further surgery and antibiotic treatment. Further operations to clear infection mean that hip and knee replacements do not work as well compared to those that are not infected and there is an increased chance of other complications.

Recent work has shown that the bacteria which cause infections are able to grow on the surface of the joint replacement. To achieve this they produce a thick slime layer know as a biofilm. The biofilm protects the bacteria and reduces the effectiveness of antibiotics used.

Most bacteria that cause joint infection also produce DNA which they release into their surroundings helping form the biofilm. This DNA, called Extracellular DNA or eDNA is important as it holds the bacteria together and gives the biofilm its mechanical strength.

Our team of researchers recently discovered a novel marine enzyme that is able to break down the extracellular DNA in biofilms. This can release the bacteria, by removing the protective slime making them easier to remove and kill. We plan to develop a new treatment using this enzyme that will improve the response to antibiotic and reduce the need for further operations.

What is the estimated incidence of this particular problem in the general population?

Thankfully infections of joint replacements remain rare. However, for the foreseeable future the number of cases is expected to increase. Currently, around 1,000 to 4,000 joint replacements become infected each year in the UK.

What are the aims and objectives of this research study?

We aim to improve the current treatment for infected joint replacements. We will establish if our enzyme NucB can clear the bacteria from joint replacements. We will investigate if combining the enzyme with antibiotics may more effectively kill bacteria. Finally we will study whether our enzyme can stop the biofilm forming and therefore help prevent infections in the first place.

Is this research going to solve the problem?

Yes. Bacteria have been living in biofilms for millions of years. The process by which they are formed is complex and not yet fully understood. There are several approaches being investigated but our approach of attacking the biofilm using enzymes is novel and shows promise. This project will provide data, which will confirm the ability of NucB to break up protective biofilm from infected artificial joints adding to the knowledge of biofilm formation and their role in joint infection.

What are the long-term benefits to patients with this problem?

Prosthetic joint infection is a devastating complication for patients. If successful the use of the enzyme NucB may reduce the amount of antibiotics that are required to treat infection by increasing their effectiveness. It may reduce the number of operations that are required to clear infection and therefore the amount of time patients have to stay in hospital. The management of joint infection is costly to the NHS, and the use of NucB could reduce the cost of care, meaning more funds are available for other treatments. Furthermore NucB may have a role in preventing infection making hip and knee replacements safer in the future.

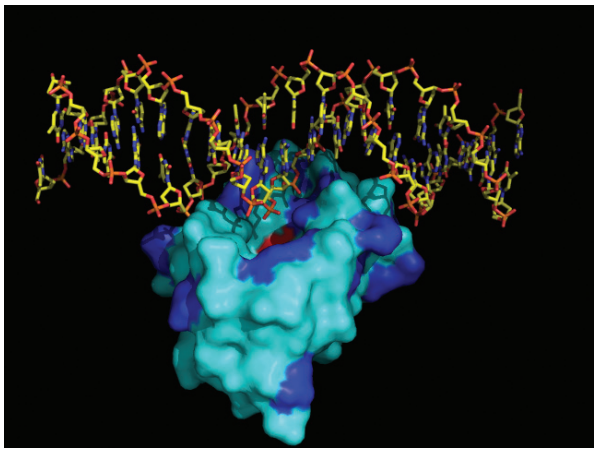


Figure:
Three dimensional structure of NucB (blue) bound to and digesting a DNA molecule (yellow) Image courtesy of Professor Rick Lewis.

“Our results may lead to the development of a new adjuvant in the treatment of infected artificial hip and knee joint, improving patient care and quality of life”

Impact statement

- This work has increased our understanding of biofilms and the important role they play in infected joint replacements
- This work has shown that NucB may improve the treatment of infected joint replacements and help to reduce the amount of antibiotics required
- We have established that NucB may help to prevent prosthetic joint infection and ultimately improve patient care.

Publications and presentations

1. The Effect of a Novel Marine Nuclease on the Removal of Biofilm: A New Approach to Periprosthetic Infection. Podium presentation at the Musculoskeletal Infection Society Meeting – North America 24th Annual Open Scientific Meeting. August 8 & 9, 2014 – Charleston, SC USA

2. Ways to minimize infection- the Northumbria Experience. Satellite Symposium, European Federation of National Associations of Orthopaedics and Traumatology (EFFORT) Prague Czech Republic 28, May 2015.

3. Enzymatic biofilm prevention and dispersal using a marine endonuclease. A new paradigm in the treatment of periprosthetic joint infections. Podium presentation 5th Oxford Bone Infection Conference (OBIC)-United Kingdom, 26th and 27th March, 2015, Oxford, UK

4. Efficacy of NucB on Staphylococcal biofilms commonly associated with periprosthetic joint infections. Pujol Nicolas A, Marsh M, Reed MR, Jakubovics N, Burgess JG. Journal of Orthopeadic Research. In preparation.

5. Biofilms: an explanatory project video for a wider non specialist audience. https://www.youtube.com/watch?v=_H-2XRbasw0

Impact report

Bioengineering the fracture callus: bone repair through fracture mimetics

Researcher Mr Wollis Vas

Supervisor Dr Scott Roberts

Stream PhD

Duration 36 months

Cost £74,994

Other funders No

Focus Non-union fractures, stem cells/tissue engineering

Mr Wollis Vas

I am a PhD student within the Institute of Orthopaedics and Musculoskeletal Science at University College London. I am currently working on developing novel bone grafts with potential applications in fracture repair.

What is the basic problem that you are trying to address?

Fracture non-union is the permanent failure of bone healing. The causes of fracture non-union are thought to relate to the severity of the initial injury, inadequate fixation, impaired blood supply, metabolic deficiencies and disease. Unfortunately, surgical intervention to re-unite the bone is often unsuccessful and in many cases relates back to the body's inability to heal the initial fracture. For this reason, we plan to develop an implant that can replicate the body's natural response to a fracture, thus kick-starting the biological cascades observed during successful tissue repair.

What is the estimated incidence of this particular problem in the general population?

Fracture non-unions occur in approximately 5-10% of the 850000 fractures seen just in the UK on a yearly basis. Costs of the treatment of non-unions within the NHS can range from £7000 -£79000 per person the higher costs are due to repeated surgeries as a result of failed interventions.

What are the aims and objectives of this research study?

Our aim is to produce a tissue engineered construct that can mimic the body's natural response to bone fracture. It is hypothesised that this will form a robust and reproducible implant that can stimulate the body's repair response. The objectives of this study will define the optimal methodology to produce a scaffold capable of directing the differentiation of adult stem cells towards fracture repairing cells. This scaffold will be produced by decellularisation of porcine cartilage, a tissue which is similar to that produced during the body's natural response to bone injury. This process of producing scaffolds has been used clinically to produce windpipes for transplantation.

Is this research going to solve the problem?

It is predicted that the technology that is developed and the knowledge gained from this proposal will contribute to a new generation of fracture repair therapeutics. Although the concepts proposed herein are aiming to replicate the natural route to fracture repair, it is impossible at this stage to comment on how this construct will integrate into the host environment. Only following the laboratory-based and preclinical work defined within this project will this become clear. If successful, it is proposed that this construct will be successful in at least a proportion of fracture non-unions. It is hypothesised that those resulting from metabolic or genetic bone disease may pose an additional level of complexity that will need to be taken into consideration.

What are the long-term benefits to patients with this problem?

The proposed construct will initiate and accelerate the skeleton's natural healing process, thus limiting any period of patient inactivity or in the worst cases disability. It is also predicted that the quality of life for patients will be considerably improved, as pain associated with current surgical techniques would no longer be present. Furthermore, the ability to have a robust one-surgery implant will have economic benefit to the NHS thus allowing for the improvement of patient services across the board.

"Our research may produce an orthopaedic implant that revolutionises fracture management and patient outcomes"

Impact statement

- This work has resulted in a decellularisation protocol for producing cell free scaffolds to mimic the fracture callus
- This work aims to produce an orthopaedic implant that overcomes current limitations of bone graft options
- It is anticipated that this implant will have applications to non-union observed as a result of, or compounded by traumatic injury or diseases such as osteogenesis imperfecta and diabetes.

Impact report

Enhanced osteointegration using a selective laser sintering solution deposited HA coating

Researchers Dr Vee San Cheong and Mr Aadil Mumith

Supervisors Professor Gordon Blunn and Dr Melanie Coathup

Stream Postdoctoral Fellowship

Duration 24 months

Cost £100,000

Other funders Skeletal Cancer Action Trust (SCAT)

Focus Arthroplasty, Biomaterials and Tissue Engineering

Dr Vee San Cheong

Mr Aadil Mumith

Vee San Cheong completed her PhD at Imperial College London, where she studied the structural failure and fracture of immature bones in bending and torsion at various strain rates. This was made possible by the financial support provided by the SIM-You Poh Seng Scholarship and the Department of Bioengineering studentship. Her keen interest in learning and education also led her to be a graduate teaching assistant during her PhD. Prior to her arrival in the UK, she worked as a research engineer for the Agency for Science, Technology and Research (A*STAR) in Singapore. Her research interests include understanding how bone fails at the structural level, and improving the design of orthopaedic implants to delay and hopefully one day prevent the onset of implant failure in patients.

Aadil Mumith qualified as a doctor from University College London Medical School with his primary medical degree (MBBS) and a BSc(Hons) in Pharmacology with Basic Medical Sciences. He completed foundation and basic surgical training as well as completing his Membership to the Royal College of Surgeons of England (MRCS) shortly afterwards. Through a rigorous national application process he attained a highly sought after post as a Trauma & Orthopaedic Specialist Registrar. Throughout his specialist training he developed an interest in lower limb arthroplasty and joint reconstruction and has elected to take time out of his training to complete a PhD under the supervision of Prof Blunn, Prof Briggs and Dr Coathup at the internationally renowned Royal National Orthopaedic Hospital, Stanmore. His work is based on the development of novel implant components and coatings to enhance osseintegration, in particular bone tumour endoprostheses. The key to this research is its possibilites to apply to a wide spectrum disciplines including joint replacement, spinal and maxillofacial surgery. He has been awarded a Research Fellowship from the Royal College of Surgeons of England for his research work as well as funding from Orthopaedic Research UK.

What is the basic problem that you are trying to address

This project aims to improve the fixation of massive segmental implants to the bony skeleton. These implants are used in the treatment of bone cancers and for the revision surgeries to replace failed total joint prostheses. These implants replace part of the bone with a titanium shaft, which is fixed into the intramedullary cavity. Figure 1 shows a distal femoral implant that is fixed into the intramedullary cavity of the reaming femur. We have used a grooved hydroxyapatite coated collar adjacent

to the implant shaft that encourages extra cortical bone bridging (Figure 1). This enhances the fixation of the prostheses to the bone.

In cases where osteointegration can be identified the survivorship at 10 years is 98%[1], however in cases where the implant is not osteointegrated the survivorship at 10 years reduces to 75%. This is due to the progressive formation of radiolucent lines at the stem bone interface[2].

What is the estimated incidence of this particular problem in the general population?

Revision hip replacements account for around 18% of all hip procedures. A similar number of of revision implants also occur in knee surgery. Surgeons in the United States perform about 432,000 spinal fusions a year. These procedures would be able to utilise the technology developed in this application.

What are the aims and objectives of this research study?

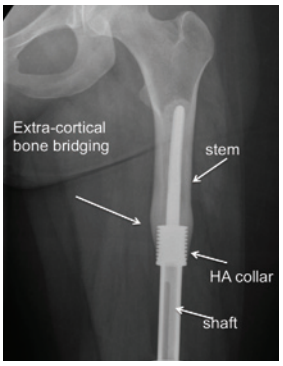
The objective of this study is to enhance fixation using a process called selective laser sintering. We have demonstrated that the role of extra cortical bone bridging is to transmit load in a more physiological manner through the cortical bone, resulting in reduced stresses at the stem implant interface, thus protecting the implant fixation (Figure 2). We have shown that this novel method of producing a porous structure at this interface results in increased osteointegration and extra-cortical bone formation (Figure3). We have also identified the structure and pore size of the implant that leads to enhanced bone formation. Work is ongoing to produce a calcium phosphate coating throughout the implant using solution deposited electrochemical method.

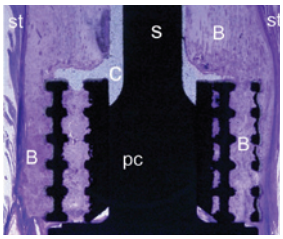
Is this research going to solve the problem?

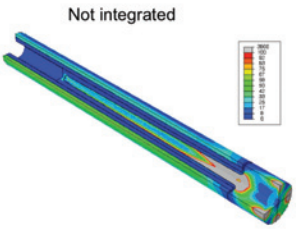
We hope that the production of an SLS region adjacent to bone will improve fixation. This is particularly important in revision implants and in young patients where the survivorship of the implant is poor.

What are the long-term benefits to patients with this problem?

The great long-term benefits to patients are the development of new implant surfaces that enhance osteointegration. The results of our study are also likely to be transferable to other implant designs.







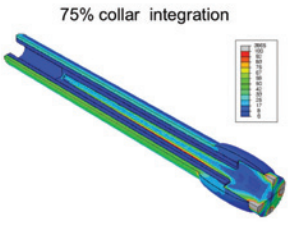


Figure 1 (top left): Radiograph of a patient with extra cortical bone growth showing osteointegration into the HA collar.

Around 10% of all hip replacements that are inserted in the UK are for revision. This accounts for over 7,000 procedures each year. These segmental implants are used in specific cases where there are large amounts of bone loss.

Figure 2 (top right): High stresses (grey) in the stem at the shoulder with no osteointegration of the collar. Lower stresess in the stem (no grey) with 75% of the collar integrated.

Figure 3 (bottom): Section through porous collar showing bone ingrowth (B), stem of the implant (S), porous collar (pc), soft tissue (st) and cement (c). Note how the porous structure is fully integrated with bone.

Impact statement

- Enhanced fixation of prostheses in patients with bone cancers and in revision implants.
- Development of novel porous structures for bone and tissue ingrowth.

Publications

1. Coathup MJ, Batta V, Pollock RC, Aston WJ, Cannon SR, Skinner JA, Briggs TW, Unwin PS, Blunn GW. Long-term survival of cemented distal femoral Endoprostheses with a hydroxyapatite-coated collar: a histological study and a radiographic follow-up. J Bone Joint Surg Am. 2013 Sep 4;95(17):1569-75

2. Coathup MJ, Sanghrajka A, Aston WJ, Gikas PD, Pollock RC, Cannon SR, Skinner JA, Briggs TW, Blunn GW. Hydroxyapatite-coated collars reduce radiolucent line progression in cemented distal femoral bone tumor implants. Clin Orthop Relat Res. 2015 Apr;473(4):1505-14

3. Mumith A, Fromme P, Blunn G, Aston W, Briggs T, Shah A, Coathup M Optimising Osteointegration of 3D Printed Components: A FEA and Histological Study. British Orthopaedic Association, Liverpool, September 2015.

Impact report

Can we improve fracture healing in the elderly by stimulating skeletal perfusion?

Researcher Dr Stephanie Gohin

Supervisor Dr Chantal Chenu

Stream Postdoctoral Fellowship

Duration 24 months

Cost £99,000

Other funders No

Focus Bone fracture repair, vascularization.

Dr Stephanie Gohin

After graduation from the University of Poitiers with a degree in Animal Physiology and Pharmacology, I conducted my PhD research in the Institute of Biology and Chemistry of Proteins in Lyon on skin neurovascular biology. I moved to England in 2012 where I did 2 years post-Doctoral at Imperial College London, studying the role of bone blood flow in the regulation of skeletal metabolism and its contribution to the effect of parathyroid hormone (PTH). I recently joined Dr Chantal Chenu's group at the Royal Veterinary College and my project aims at determining the contribution of skeletal perfusion to bone healing in young, old and osteoporotic rats using a femoral fracture model.

What is the basic problem that you are trying to address?

Our project will test whether increasing blood flow with the use of low-cost vasodilators during fracture repair helps to accelerate the slow bone healing process in elderly and osteoporotic patients.

What is the estimated incidence of this particular problem in the general population?

Osteoporotic fractures represent one of the most common causes of mortality and morbidity in older patients affecting approximately 200 million people all over the world and 3 million in the UK.

With ageing and in osteoporotic patients, fractures take longer to heal and thus the return to normal function will be delayed, with increased cost of care.

What are the aims and objectives of this research study?

The first aim of this study is to examine the acute effects of several classes of vasodilators on angiogenesis and bone blood flow in healthy mice using laser Doppler imaging.

The second aim of this study is to assess the long-term effects of the most effective vasodilators on fracture callus repair using a femoral fracture model in young, old and ovariectomised animals.

Finally, the third aim of this study is to decipher the cellular and molecular changes that take place in the fracture callus when blood flow is increased.

Is this research going to solve the problem?

If this work confirms that vasodilators are accelerating the bone ability to repair, the results have the potential to lead to a new therapeutic option for the impaired vascularisation in osteoporotic bone.

What are the long-term benefits to patients with this problem?

The great long-term benefit to patients is the improvement of osteoporotic fractures, one of the most common causes of disability in the elderly.

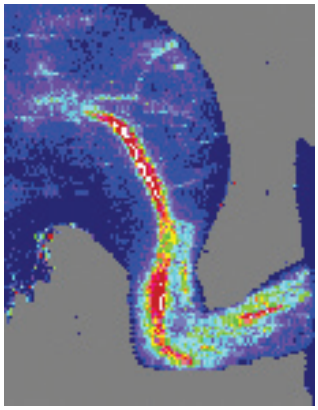


Figure:
Representative images of the bone blood flow in mouse using Laser Doppler Imaging.

Impact statement

- Better understanding of the role of vascularization during bone fracture repair
- Potential benefit of using vasodilators in fracture healing to improve blood flow in situations of compromised vascular supply such as in the elderly and in osteoporotic patients
- Possible identification of new low-cost and commercially available vasodilators for treating fractures in older patients

Impact report

Understanding biological effects of metal debris from joint prostheses on bone–microenvironment

The University Of Sheffield.

orthopaedic research UK
Postdoctoral **Fellowship**

Supervisor Prof J Mark Wilkinson

Stream Postdoctoral Fellowship

Duration 21 months

Cost £93,245

Other funders No

Focus Metal wear and corrosion, Hip replacement, Bone Biology

Prof J Mark Wilkinson

In the UK 25% of adults older than 65 years suffer pain and disability due to osteoarthritis, and over 90,000 undergo a hip replacement each year. However, 12% of joint replacements fail within 10 years, and of these 62% are due to adverse local tissue reactions (ALTR) to the prosthesis. My work has focussed on the biological effects of joint prostheses on the patient, and also on the causes and treatment of arthritis.

I am Professor of Orthopaedic Surgery at The University of Sheffield and an Honorary Consultant in Orthopaedics at Sheffield Teaching Hospitals. I am also a member of the Steering Committee of the National Joint Registry for England, Wales, and Northern Ireland.

What is the basic problem that you are trying to address?

All joint replacements create some degree of debris at the moving parts that form the joint, and at other connections that make the prostheses. With some materials, particularly with metals, the cells of the body exposed to the material can be damaged leading to failure of the joint replacement. Unfortunately at the moment we do not really understand how this damage occurs, and therefore it is difficult to prevent it.

In these studies we will use human bone cells to identify the way in which metal debris from hip prostheses causes damage to the bone surrounding the joint. We also want to understand how different prosthesis surfaces interact with human bone, and whether the metal debris released from the prostheses affects this interaction. This understanding is essential to improve the design of hip prostheses and to develop new treatments to improve the lives of patients with hip replacements.

What is the estimated incidence of this particular problem in the general population?

Over 65,000 people in England and Wales had a metal-on-metal hip replacement in the last ten years. Of these, around 1 patient in 15 will need to undergo a second surgery within 5 years to replace the prosthesis due to adverse effects, most of which cause damage to the bone surrounding the joint. An even greater number of joint replacements use other metal-to-metal connections (called modular junctions) as part of their design, and these can also cause metal release. According to the National Joint Registry, approximately 74,000 implants with modular junctions were used in patients in England and Wales over the last year; and 545,000 implanted over the last decade.

What are the aims and objectives of this research study?

The main aims of this study are to understand how the body's bone cells react to metal released from joint replacements, and identify the key chemical messengers involved in these reactions. Furthermore, we aim to understand how the bone cells interact with different surfaces of prostheses that are routinely used for replacements, and the mechanisms that govern these interactions. We believe that this knowledge is essential to developing intelligent solutions to prevent the damage caused by metals and improve the survivorship of hip implants.

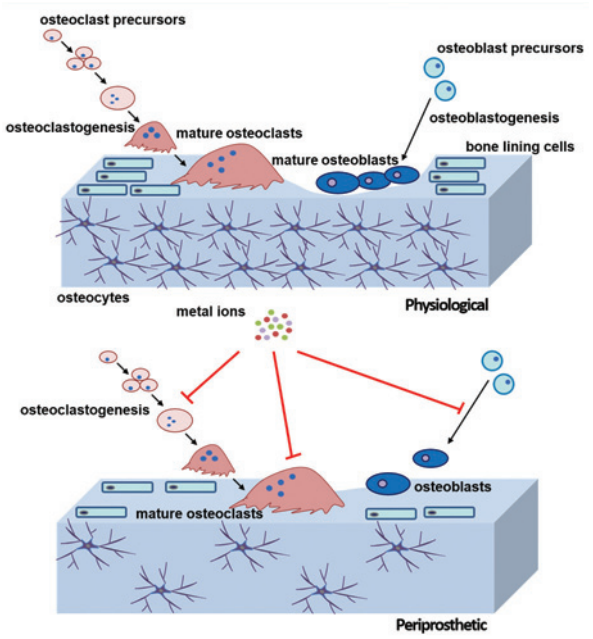
"The knowledge gained from understanding how metal debris affects bone cells is essential in developing potential clinical therapeutics which would be useful not only today, but also likely to be important in the long term."

Is this research going to solve the problem?

Knowledge of the key chemical messengers involved in these reactions is the first step towards developing new treatment strategies for these problems. Further work will be required after this step to develop and test the treatments that will, in turn, reduce the disability caused by these adverse reactions to metal debris, improve prosthesis survival, and enhance the patient experience

What are the long-term benefits to patients with this problem?

Reactions to metal materials from joint replacements are their major limitation, and developing new treatments to prevent or reduce the occurrence of this problem is a priority for joint replacement medicine. In the long-term, modular prostheses are unlikely to be phased out, and we are increasingly recognizing that similar types of debris are released from the connections within these implant types. Thus the knowledge gained from understanding how metal debris affects bone cells is essential in developing potential clinical therapeutics which would be useful not only today, but also likely to be important in the long term.



Impact statement

- A mechanistic understanding of how metal debris affects bone cells will inform therapeutic development to improve sustainability of metal prostheses
- A better clinical understanding of metal debris associated changes at bone-prostheses interface will help reduce bone-related complications through better selection of surface coatings, bearing and taper materials

Impact report

A 3D model of bone sarcoma to investigate TNT – a preconditioned bone marrow – derived mesenchymal stem cells to promote osteogenesis and induce sarcoma cell apoptosis

Researcher Mr Zakareya Gamie

Supervisors Mr Craig Gerrand, Mr Kenneth Rankin

Stream PhD

Duration 36 months

Cost £74,827

Other funders Dr William Edmund Harker Foundation

Focus Surgery, Tumour, Stem cell biology

Mr Zakareya Gamie

I am a specialty trainee in Trauma and Orthopaedic Surgery in the North East. I have completed an Academic Clinical Fellowship in Trauma and Orthopaedic Surgery with 25% protected laboratory research time from August 2011- August 2014. I aim to come out of the programme to complete a PhD in this important area of research.

What is the basic problem that you are trying to address?

The treatment of primary bone cancers involves removing the affected bone and reconstructing the defect. Present reconstructive techniques largely rely on implants made of solid titanium metal, which may not incorporate into the bone and are at risk of failure from loosening. Furthermore, these implants do not prevent local recurrence of the tumour.

Rapid manufacturing technologies mean that in future, implants may be made from biological materials including the patient's own cells. Stem cells from the bone marrow may be helpful for this as they can become any cell type, including the bone cells found in normal bone. The aim of this project is to investigate if these stem cells could be treated in such a way that they might not only be helpful in reconstructing the bone defect but might also have anti-cancer activity.

What is the estimated incidence of this particular problem in the general population?

The annual incidence of primary bone tumours is around 8-10 per million. Unfortunately, these tumours often affect teenagers and young adults, and the overall 5 year survival is around 50%. If the cancer has spread when diagnosed, the outlook is very poor, with a 5-year survival of only 20%. Surgery to remove the tumour can be challenging and the cancer returns in about 10-15%. This is associated with poorer survival and the need for further disabling surgery. Survival rates have not changed in the past 30 years and therefore new approaches which include new ways to reduce the risk of the tumour returning are desperately needed.

What are the aims and objectives of this research study?

We aim to treat stem cells with a substance known as TNF-alpha to help them become bone forming cells and express a protein known as TRAIL. Bone cancer cells are known to be sensitive to TRAIL, so this could represent a major advance. We will investigate the effect 'activated' stem cells have on tumour cells and bone growth.

We can use technology to make a 3D protein scaffold to hold stem cells and cancer cells and allow them to interact in a more realistic way than in other experiments. This interaction can be controlled, for example by making two chambers which have connecting channels. The model can then be analysed for signs of bone growth and cancer cell death using microscopic techniques. We hope this model will help us investigate this and other new treatments and act as an alternative to the use of animals in some instances.

"Our results may lead to a better understanding of the use of stem cells with 3D printed scaffolds for the reconstruction of defects resulting from bone tumours and potentially to reduce recurrence."

Is this research going to solve the problem?

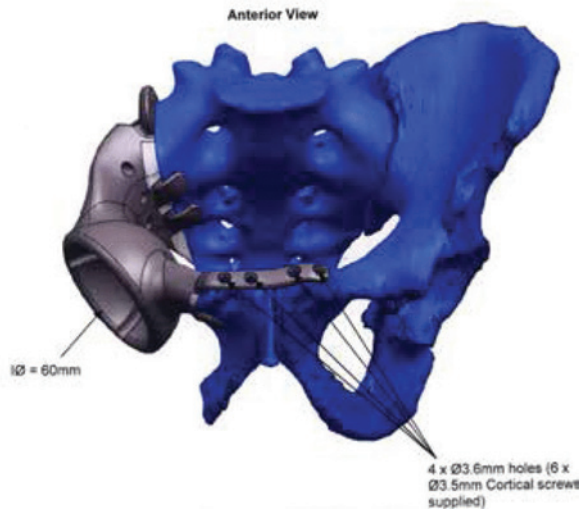
It is recognised that this proposal is an early step in solving the problems of bone reconstruction and improving outcomes for patients. If our tests show new bone growth and cancer cells dying, we would aim to repeat our experiments in mice with bone cancer, available at our institution as the next step in developing a treatment.

What are the long-term benefits to patients with this problem?

The long-term goal would be developing personalised implants for patients, fitting the defect in the bone exactly and containing activated stem cells. This new approach could provide a durable biological reconstruction for some patients, and reduce the chances of the cancer returning. If successful, this could avoid the need for further surgery and improve survival for patients.

Impact statement

- The annual incidence of primary bone tumours is around 8-10 per million. Survival has not improved for three decades and patients with metastases at presentation have a 5-year survival rate of about 20%.
- At our institution we possess the surgical expertise, basic science skills and technology to develop 3D printed culture models and shapes of defects to use with bone marrow-derived mesenchymal stem cells (BMMSCs) to investigate interactions at the cellular and molecular level and for bone tumour reconstruction.
- This work has resulted reconstruction of a pelvic defect in a patient with chondrosarcoma and further development of the use of 3D printing technology with stem cells.



Publications

1. Gerrand C. 3D Printing: a clinician's experience. Bulletin of The Royal College of Surgeons of England, Volume 96, Number 7, July 2014, pp. 230-231(2) http://www.ingentaconnect.com/content/rcse/brcs/2014/00000096/00000007/art00009XXX

2. Kwong TN, Furtado S, Gerrand C. What do we know about survivorship after treatment for extremity sarcoma? A systematic review. Eur J Surg Oncol. 2014 Sep;40(9):1109-24

3. Dyson JA, Genever PG, Dalgarno KW, Wood DJ. Development of custom-built bone scaffolds using mesenchymal stem cells and apatite-wollastonite glass-ceramics. Tissue Eng. 2007 Dec;13(12):2891-901

Impact report

The kinematics and the contact patterns of the patellofemoral joint

Researcher Dr Arash Aframian

Supervisors Miss Caroline Hing, Professor Justin Cobb, Mr Duncan Tennent, Professor David Oliveira

Collaborators Professor Andrew Amis and Mr Farhad Iranpour

Stream Postdoctoral Fellowship

Duration 24 months

Cost £100,000

Other funders Imperial College London

Focus Knee surgery, Patellofemoral Instability

Dr Arash Aframian

I studied medicine, completing my MB BS with an intercalated BSc(Hons) in 2008. I then worked as a junior doctor for five years with a focus in surgery, particularly orthopaedics. Having worked as a registrar in trauma & orthopaedics for a year in Kent, I then worked as a Junior Trauma Fellow at St George's Hospital in south-west London, one of the four major trauma centres for London, and where I am now registered for an MD(Res) at St George's University of London and collaborating with Imperial College London.

What is the basic problem that you are trying to address?

Patellofemoral Instability (PFI, dislocating kneecaps) can cause pain and lead to loss of function.Th e aetiology of PFI is multi-factorial [1-3].

The measurement of outcomes is challenging, and even some objective measurements are not always reliable [4]. Specialist PFI questionnaires have been developed and validated but the management of this complex multi-factorial problem remains challenging [5]. It is unclear from some studies if surgical management is superior to conservative management due to the way data is collected and varying methodology and surgical technique, even within studies [6-8].

A dysplastic or flat trochlear groove is treated with a trochleoplasty that aims to deepen the femoral trochlear groove. We plan to make objective measurements of function using a specialised treadmill before and after surgery to look at the way patients walk. By comparing this to the way 'normal' people walk we can see if patients have a stable kneecap after surgery.

A specialised three dimensional (3D) tracking system will also be developed to enable objective intra-operative assessment of surgical correction thus aiming to improve the accuracy of surgery, which will inform the surgeon about surface area and likely areas of high pressure.

What is the estimated incidence of this particular problem in the general population?

The annual incidence of patellofemoral dislocation is 77 in 100,000 with recurrence in 20-40%, or 2-3% of all acute knee injury presentations [9-12].

What are the aims and objectives of this research study?

This study will work to develop novel 3D patellar tracking tools, which are not currently commercially available. This has the potential of leading to valuable new ways to monitor and intra-operatively check surgical outcomes.

Is this research going to solve the problem?

This study will advance our understanding of why the symptoms experienced by patients with PFI are so variable and unpredictable by looking at areas of pressure and accurately monitoring patellar tracking intra-operatively. Understanding which factors result in pain and instability, then targeting these issues directly by using new tracking tools we are developing that can be used to assess and treat patellar instability and anterior knee pain.

What are the long-term benefits to patients with this problem?

Current treatments are limited both in terms of improving pain and in terms of complication rates, with some surgeons reporting outcomes as 54% poor, 23% fair and only 23% good [13] in a case series. Developing more effective treatments with more acceptable outcomes promises to be a huge breakthrough for patients with patellar instability. The results of our study are also likely to be transferable to other common causes of anterior knee pain. Our results may lead to a better understanding of gait analysis in anterior knee pain, and objective outcome scoring in general. The new tools may be used in other types of knee surgery.

"Our study aims to improve the treatment of patellar instability by developing new intra-operative tracking tools."

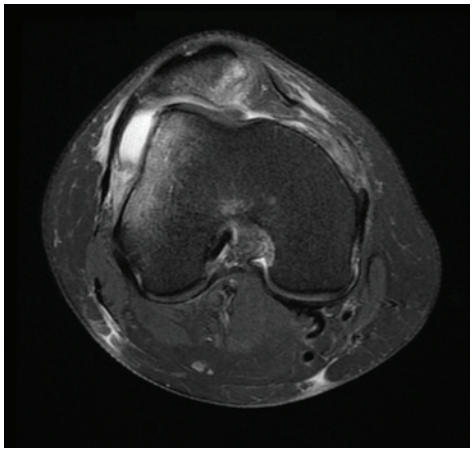


Figure:
Patellofemoral instability magnetic resonance imaging:

Pre-operative scan shows a shallow, dysplastic trochlea. There is fluid due to previous dislocation, with bruising of the patella and femoral condyle, as well as oedema of the MPFL.

Impact statement

- Patellofemoral instability affects up to 77/100,000.
- Recurrence rates one in two
- There is still no clear solution to the management of this complex problem.
- The results of surgery can be difficult to assess, and there are numerous systems in existence.
- This study will seek to develop a novel tool to track movements of the patella and further, correlate this with pre-operative scans and estimate areas of high pressure.
- The results of surgery can be difficult to assess, and there are numerous systems in existence.
- This work will improve understanding of what drives patellofemoral pain, and help to guide future treatment.
- We will develop
  - 3D computer guided patellar tracker
  - Pressure area mapping technology
  - 3D handheld scanner

  Intra-operative comparison to patient specific surgical plan

References:

1. Arendt EA, Fithian DC, Cohen E. Current concepts of lateral patella dislocation. Clin Sport Med Sport Med 2002;21:499–519. doi:10.1016/S0278-5919(02)00031-5.

2. Goodwin D, Postma W. Patellar instability. OA Sport Med 2013;1:1–13.

3. Dejour H, Walch G, Nove-Josserand L, Guier C. Factors of patellar instability: an anatomic radiographic study. Knee Surg Sports Traumatol Arthrosc 1994;2:19–26.

4. Smith TO, Davies L, O'Driscoll M-L, Donell ST. An evaluation of the clinical tests and outcome measures used to assess patellar instability. Knee 2008;15:255–62. doi:10.1016/j.knee.2008.02.001.

5. Smith TO, Donell ST, Clark A, Chester R, Cross J, Kader DF, et al. The development, validation and internal consistency of the Norwich Patellar Instability (NPI) score. Knee Surg Sports Traumatol Arthrosc 2014;22:324–35. doi:10.1007/s00167-012-2359-x.

6. Smith TO, Song F, Donell ST, Hing CB. Operative versus non-operative management of patellar dislocation. A meta-analysis. Knee Surgery, Sport Traumatol Arthrosc 2011;19:988–98. doi:10.1007/s00167-010-1355-2.

7. Hing CB, Smith TO, Donell ST, Song F. Surgical versus non-surgical interventions for treating patellar dislocation (Review). Cochrane Rev 2012:45.

8. Saccomanno M, Deriu L, Careri S, Ieso C De, Donati F, Milano G, et al. In-Depth Oral Presentations and Oral Communications S68: Surgical versus conservative treatment after acute patellar dislocation: a systematic review and meta-analysis. vol. 13. 2012. doi:10.1007/s10195-012-0210-2.

9. Hawkins RJ, Bell RH, Anisette G. Acute patellar dislocations. The natural history. Am J Sports Med n.d.;14:117–20.

10. Nietosvaara Y, Aalto K, Kallio PE. Acute patellar dislocation in children: incidence and associated osteochondral fractures. J Pediatr Orthop 1994;14:513–5.

11. Tjoumakaris FP, Forsythe B, Bradley JP. Patellofemoral instability in athletes: treatment via modified Fulkerson osteotomy and lateral release. Am J Sports Med 2010;38:992–9. doi:10.1177/0363546509357682.

12. Stefancin JJ, Parker RD. First-time traumatic patellar dislocation: a systematic review. Clin Orthop Relat Res 2007;455:93–101. doi:10.1097/BLO.0b013e31802eb40a.

13. Verdonk R, Jansegers E, Stuyts B. Trochleoplasty in dysplastic knee trochlea. Knee Surg Sports Traumatol Arthrosc 2005;13:529–33. doi:10.1007/s00167-004-0570-0.

Impact report

Developing an outcomes dashboard to improve best practice for shoulder surgery

Researcher Mr Simon Jameson

Supervisor Mr Mike Reed

Stream Clinical Fellowship

Duration 12 months

Cost £30,000

Other funders British Orthopaedic Association (BOA)

Focus Shoulder, Outcomes

Mr Simon Jameson

I am currently a British Orthopaedic Association Clinical leadership Fellow in lower limb joint replacement at South Tees NHS Foundation Trust. I completed higher specialty training in Trauma and Orthopaedic Surgery in 2014 and have recently worked at the Princess Elizabeth Orthopaedic Centre in Exeter as a hip replacement fellow. I spent 16 months employed by the National Joint Registry as a research fellow during 2011/12 where I analysed outcomes data (including Patient Reported Outcome Measures - PROMs) following hip and knee replacement surgery, and I have been involved in several projects using Hospital Episodes Statistics data. I am interested in improving outcomes after orthopaedic surgery through an evidence-based approach.

What is the basic problem that you are trying to address?

Orthopaedic surgery can offer dramatic improvements to patients' quality of life. Shoulder replacement to treat a variety of conditions is increasingly performed. There is a relative lack of data on the type of implants used nationally, and on outcomes and complications. It is believed that there is regional variation in both treatments offered for shoulder problems and the outcomes after surgery. As a group, orthopaedic surgeons should be striving to optimise the results for all our patients in line with the recently introduced initiative in the orthopaedic surgical community, 'Getting it right first time' by following an evidence-based approach to practice1. Feedback to surgical teams is critical to identify where their clinical problems lie, and to allow them to improve practice. This project allows clinical teams to see their surgical experience and results compared to others and should lead to real improvements in clinical outcomes.

What is the estimated incidence of this particular problem in the general population ?

Estimates from national data collected on NHS patients suggest around 7000 patients are undergoing shoulder replacement surgery per year in England. The number may be over 10,000 per year across all sectors in the UK. Future projections from US data predict a growth equivalent to that anticipated for hip and knee replacements. However, of particular concern is the rising burden of re-do shoulder replacements when the first replacement has failed[2].

What are the aims and objectives of this research study?

We aim to develop a group of indicators for shoulder replacement surgery based on our earlier experiences of hip and knee replacement data. The primary role of these data is to educate, based on the evidence available and best practice, and to provide national benchmarks for outcomes. These indicators have been jointly developed by the North East Quality Observatory System and clinicians from the North East and North West of England, in collaboration with the British Elbow and Shoulder Society, patient representatives and key regional representatives.

Is this research going to solve the problem?

It is hoped that this project will follow on from the success of the hip and knee dashboard, with engagement on a national level. An example of how the dashboard has led to improvements in clinical outcomes can be seen with changes made by Northumbria Healthcare NHS FT. They were identified as having below average patient-reported health gain (PROMs data) for knee replacement. Having recognised this problem, clinicians engaged in improvement so that their knee PROMS is a high outlier.

What are the long-term benefits to patients with this problem?

There are benefits for patients, surgeons, hospital Trusts, commisioners and the NHS as a whole. We anticipate improvements in patient outcomes, lower risks of further surgery, and improved cost-effectiveness. This evidence-based approach with surgeon collaboration should result in a cost-effective improvement in care for shoulder surgical patients.

Impact statement

- Compare outcomes following shoulder surgery on a national level
- Establish best practice standards which can be used to enhance patient outcomes
- Reduce variation in practice using an evidence-based approach

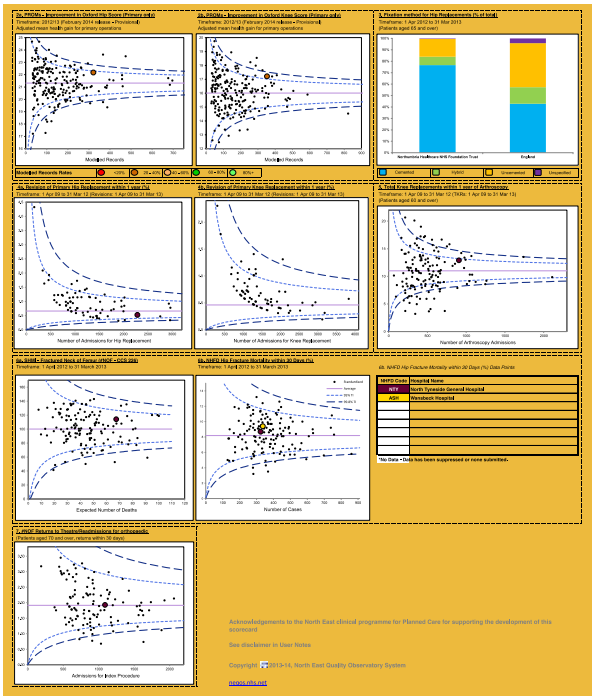


Figure:
An example of the performance outcomes 'dashboard' for hip and knee surgery

Publications

1. Briggs, T. Getting it right first time. http://www.gettingitrightfirsttime.com/ 2012

2. Day JS, Lau E, Ong KL, Williams GR, Ramsey ML, Kurtz SM. Prevalence and projections of total shoulder and elbow arthroplasty in the United States to 2015. J Shoulder Elbow Surg. 2010 Dec;19(8):1115-20

Submitting your grant applications

Translational Research Funding (TRF) and General Research Funding (GRF)

Please read our guidelines carefully before submitting your application. If you fail to follow these instructions, your proposal will be rejected and you will NOT be able to amend or re-submit your application later.

We have a four stage process for reviewing applications for both the General Research Funding (GRF) and Translational Research Funding (TRF) proposals:

Stage 1: Scientific Advisory Committee (SAC) Preliminary Review

Using the ORUK link applicants submit their Expressions of Interest (EoI) for scrutiny by our SAC committee. The maximum length of the EoI should be no more than 700 words (including references). The scientific content and quality of the EoI are carefully assessed by the SAC using a grading system, and those that are successful at this stage will be invited to submit a full proposal. The EoI can be submitted in an un-blind format.

Those not within the remits are rejected at this stage. This may be for a number of reasons: the project may not be related to orthopaedics, the study may be taking place outside the UK or the applicant may be requesting for more money than the specific call allows. Successful applicants are invited to submit their full proposal.

Stage 2: External Review

Successful applicants from Stage 1 are invited to submit their full proposal application. The full proposal must be blinded. Applicants MUST ensure that there is no mention of the names of individuals (researcher/supervisor/collaborator), institutions/places/partner organisation or any other terms or descriptions that could reveal their identity to the external reviewers (Sections 2-8). Applicants also need to blind papers published by them that have been referenced in the proposal (Section 8). In addition, all attachments apart from the CVs must be blinded. Short CVs of all the individuals involved with the project (principal investigator, co-investigator(s), and researcher) must be submitted.

The blind proposals are sent to at least three external reviewers. These reviewers may have been suggested by the applicant. The external reviewers are asked to use a scoring system to rate the scientific quality of the proposal.

Each proposal is scored based on the following assessment criteria:

1. Scientific structure of the research proposal
2. Feasibility of aims, objectives and novelty claims
3. Background to investigation
4. Methodology
5. Project timeline and deliverables
6. Clinical and research impact
7. Relevance to orthopaedics and musculoskeletal systems
8. Comments on research risk and originality
9. Requested budget, facilities and resources of the host institute
10. Support from the commercial partner organisation
11. Adequate demonstration of good research and clinical value for the benefit of patients.

Those proposals that receive top scores by the external reviewers will then be forwarded to the SAC, which acts as our internal review panel.

Stage 3: SAC Secondary Review

The SAC then convenes and views the full proposals and the opinions of the external reviewers. The SAC ranks those approved proposals, using a scoring system similar to that used by the external reviewers, and makes recommendations to the Board of Trustees.

Stage 4: Board of Trustees Review

The Board of Trustees reviews the assessment by the SAC and approves their recommendation, subject to the terms and conditions of the standard academic agreement.

The Board of Trustees reviews the assessment by the SAC and approves their recommendation, subject to the terms and conditions of the standard academic agreement.

amrc
PEER REVIEW AUDIT 2011

Best practice in medical and health research peer review

Study streams

All study streams (PhD, MD, Post-Doc, and Clinical Fellowship) are invited to submit their applications.

Partner organisation contribution

Internal or external support in the form of additional funding sources is not essential, but in the case of TRF applications, it will be taken into consideration in the assessment process as an indicator of support from a commercial partner.

ORUK contribution

The following table demonstrates the maximum grant amounts ORUK awards for each study stream per annum.

Study stream	Maximum duration	Total cost	Cost (PA)
PhD	36	£75,000	£25,000
MD	24	£60,000	£30,000
Post-Doctoral	24	£100,000	£50,000
Clinical Fellowship	24	£100,000	£50,000

Complete list of funded research projects 2004 – 2015

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
1	401	University of Oxford	PhD (36 months)	*Factors contributing to chrondoplasia in degenerate rotator cuff disease* Dr Hannah Cornell, Dr Philippa Hulley and Professor Andy Carr	£74,900
2	402	King's College London	PhD (36 months)	*Hydroxyapatite as a scaffold carrying BMPs for enhanced osseoinductivity* Dr Sofie Rebeling, Dr Sanjukta Deb and Professor Lucy Di Silvio	£62,436.82
3	403	University of Cambridge	MD (12 months)	*Carbonate substituted hydroxyapatite: is resorption responsible for increased bioactivity?* Mr Gavin Spence and Professor Neil Rushton	£35,140
4	404	Queen Mary, University of London	PhD (36 months)	*Development of a self-assembly technique for drug deliverable HA coating for Ti based implants* Dr Elnaz Ajami and Professor Xiao Guo	£54,800
5	405	University of Cambridge	PhD (36 months)	*Characteristics of the HA coated implants using high resolution imaging* Dr Patrick Marti and Professor Serena Best	£73,780
6	406	Imperial College London	PhD (36 months)	*Preclinical testing and design of shoulder prosthesis* Professor Anthony Bull and Dr Dominic Southgate	£80,590
7	407	Newcastle University and Imperial College London	PhD (36 months)	*Modelling of finite element analysis of shoulder implants* Professor Garth Johnson and Dr Milad Masjedi	£69,741
8	408	Imperial College London	Clinical Fellow (12 months)	*Three dimensional digitisation of the bones of the human elbow* Professor Srinath Kamineni	£52,995
9	409	University of Oxford	PhD (24 months)	*Blood Flow in the Femoral Head* Professor David Murray and Dr Richie Gill	£106,536
10	411	Dewsbury & District Hospital	Clinical Fellow (12 months)	*Primary total hip arthroplasty using HAC coated endoprosthesis: A study of 655 cases* Mr Raghu Raman	£12,015
11	413	University of Oxford Salisbury & District Hospital	Clinical Fellow (36 months)	Radiostereometic (RSA) analysis of 2 uncemented stems Professor David Murray, Professor Andy Carr, Dr Richie Gill, Mr Graham Rushforth	£101,095
12	414	Worthing & Southlands NHS Trust	Clinical Fellow (36 months)	Furlong Fellowship in Lower Limb Arthroplasty Mr Kerry Acton and Mr John Edge	£101,095

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
13	414a	Worthing & Southlands NHS Trust	Clinical Fellow (12 months)	*Furlong Fellowship in Lower Limb Arthroplasty* Mr Richard Hargrove and Mr John Edge	£63,225
14	415	RNOH Stanmore (UCL) and Royal Free Hospital	Clinical Fellow (12 months)	*Does hip resurfacing cause immune dysfunction?* Mr Alister Hart and Professor David Marsh	£50,000
15	416	University of Oxford	Post-Doc (24 months)	*Knee replacement kinematics* Professor David Murray and Dr Richie Gill	£93,526
16	417	University of Oxford	Post-Doc (36 months)	*Osteoclastogenic responses of patients with metal-on-metal prostheses* Dr Guillaume Mabilleau Dr Afsie Sabokbar, Professor David Murray and Dr Richie Gill	£150,208
17	418	University of Cambridge	Post-Doc (24 months)	*Drug delivery from the Furlong H-A-C Hip* Deborah Ireland, Dr Roger Brooks and Professor Neil Rushton	£121,650
18	419	University of Southampton	Post-Doc (12 months)	*Validate volumetric shape of femur using FEA, MRI, CT* Professor Mark Taylor, Mr John Shepperd	£65,766.09
19	420	Imperial College London	Clinical Fellow (6 months)	*Quantification of the Biomechanics of the arthroplasty and their relationship to functional outcome* Mr Vijayaraj Kannan and Professor Justin Cobb	£24,926
20	421	Imperial College London	Clinical Fellow (12 months)	*3-D Preoperative planning system* Professor Justin Cobb	£26,024
21	423	Imperial College London	Clinical Fellow (12 months)	*Integrity of the Repaired Rotator Cuff: A roentgen stereophotogrammetric analysis with Ultrasound comparison* Dr Toby Baring, Professor Andrew Amis and Mr Roger Emery	£53,000
22	424	Imperial College London	Clinical Fellow (36 months)	*Shockwave treatment for infected prostheses, an experimental study* Dr Moustafa Hafez and Mr Richard Coombs	£97,641
23	425	Imperial College London	Clinical Fellow (12 months)	*Computer Assisted Hip Arthroplasty* Mr Vijayaraj Kannan and Professor Justin Cobb	£50,000
24	426	University of Bath	Post-Doc (24 months)	*Fabrication and compatibility testing of a new generation of structural bioceramic bone graft substitutes* Dr Irene Turner and Professor Tony Miles	£81,266.99
25	427	University of Cambridge	MPhil (24 months)	*Reinforcing Hydroxyapatite with Carbn Nanotubes* Professor N. Rushton and Dr Osa Emohare	£93,256

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
26	429	University College London (RNOH)	Clinical Fellow (24 months)	*Whole blood metal ion levels, immune responses and chromosomal analysis in patients with MoM and MoPe hip articulations* Mr Baljinder Dhinsan, Mr Ben Spiegelberg and Professor Tim Briggs	£120,000
27	430	University of Leeds	Post-Doc (36 months)	*Tribology of bearing surfaces for hip prosthesis* Professor John Fisher, Dr Louise Jennings, Dr Alsion Galvin and Dr Mazen Al-Hajjar	£292,480
28	431	University College London	PhD (36 months)	*Electrohydrodynamic deposition of nano-sized calcium phosphate* Professor Mohan Edirisinghe and Dr Jie Huang	£90,000
29	432	Imperial College London	Clinical Fellow (12 months)	*Relationship between metal wear debris speculation and immune dysfunction in patients* Mr Alister Hart	£70,0000
30	433	Imperial College London	Clinical Fellow (24 months)	*Mapping metal nano particles in human tissues exposed to MoM hip replacement wear debris* Mr Alister Hart	£69,500
31	434	Imperial College London	PhD (24 months)	*Computer assistance in early knee disease* Dr Farhad Iranpour-Boroujeni and Professor Justin Cobb	£40,000
32	435	Imperial College London	MD (24 months)	*Minimally invasive navigated reduction and fixation of acetabular fractures* Mr Amgad Nakhla and Professor Justin Cobb	£63,000
33	436	Imperial College London	PhD (24 months)	*Navigated hip arthroplasty: image-free or CT based?* Mr Vijayaraj Kannan and Professor Justin Cobb	£40,000
34	437	University of Oxford	Post-Doc (24 months)	*Effect of cobalt chrome nanoparticles on bone volume and microarchitecture* Dr Guillaume Mabilleau and Dr Afsie Sabokbar	£30,000
35	438	The Rizolli Institute	Post-Doc (12 months)	*SA comparative study of metal ion analysis with MoM hip resurfacing and 28mm MoM THR: data at medium-term* Professor Antonio Moroni	£39,551
36	439	The Rizolli Institute	Post-Doc (12 months)	*A radiostereometric study of the effect of hydroxyapatite coating of the lag screw of the intramedullary hip screw on the fixation achieved in osteoporotic trochanteric fractures* Professor Antonio Moroni	£43,691.62
37	440	University of Strathclyde	Post-Doc (24 months)	*Finite element computer models of the load transfer characteristics in normal and pathological wrists* Dr Magnus Gislason and Professor Sandy Nicol	£89,000
38	441	University of Oxford	Clinical Fellow (24 months)	*Furlong scholars for a Tropical Orthopaedic Clinic* Miss Verona Beckles, Me Paul Harnett and Professor Chris Lavy	£75,621.54

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
39	442	University of Oxford	Clinical Fellow (12 months)	*The aetiology of tibia vara in Malawaian children and outcome following corrective surgery* Mr Robert Freeman and Professor Chris Lavy	£13,436.71
40	443	University of Aarhus	PhD (24 months)	*Long term clinical outcome of revision hip surgery* Professor Kjeld Søballe and Mette Sørensen	£122,788
41	444	University College London	Clinical Fellow (12 months)	*Study ond osteogenesis of the tibia: use of vibration therapy* Dr Ian Clark and Professor David Marsh	£23,048
42	445	London School of Hygiene and Tropical Medicine	Clinical Fellow (12 months)	*Pilot study for the development of a patient reported outcome measure (PROM) for child with musculoskeletal impairments in Malawi* Dr Yasmin Alavi, Dr C Gilbert and Professor Chris Lavy	£7,500
43	446	University of Cambridge	MD (24 months)	*A study into a novel method of impaction bone grafting* Mr Iain McNamara, Professor Serena Best and Professor Neil Rushton	£83,000
44	447	University of Cambridge	PhD (24 months)	*Evaluating cell function on Hydroxyapatite-Multiwalled Carbon Nanotubes Surfaces* Dr Osa Emohare, Dr R Brooks, Dr S Best and Prof N Rushton	£74,000
45	448	University of Oxford	PhD (24 months)	*In vitro model of distraction osteogenesis* Miss Cynthia Chang and Dr Philippa Hulley	£24,447
46	449	University of East Anglia	Post-Doc (24 months)	*The role of specific metalloproteinases in Dupuytren's disease* Dr Janine Morris , Professor Ian M Clark and Mr Adrian Chojnowski	£76,726
47	450	The Radboud University Nijmegen Medical Centre	PhD (36 months)	*Prediction of fracture risk with metastatic lesion* Ms Loes CEM Deriks, Professor Nico Verdonschot and Dr Esther Tanck	£101,809
48	451	University College London	PhD (36 months)	*Exploring the microstructure and mechanical properties of CoCrMo orthopaedic alloys* Mr Bhairav Patel and Professor Mohan Edirisinghe	£94,000
49	452	University of Oxford	Post-Doc (36 months)	*Elucidating the roles of pyrophosphate metabolism and ANKH, key factors in the regulation of calcification in health and disease* Dr Peter Cain, Dr Yun Zhang, Dr Jim Dunford, Professors Paul Wordsworth, Graham Russell and Professor Andy Carr	£155,527
50	453	University of Warwick	PhD (24 months)	*The role of platelet rich plasma in accelerating the healing of intracapsular fractures of the proximal femur* Mr Xavier Griffin, Mr Matt Costa and Professor Damian Griffin	£93,930

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
51	454	Worthing and Southlands NHS Trust	Clinical Fellow (12 months)	*Furlong Fellowship in Lower Limb Arthroplasty* Mr Nirav Shah and Mr John Edge	£84,300
52	455	University of Aarhus	Post-Doc (24 months)	*Drug delivery from the Furlong H-A.C Hip* Dr Priya Kalia, Dr Roger Brooks and Professor Neil Rushton	£105,349
53	456	University of Manchester	Post-Doc (12 months)	*Mechanisms underlying cellular sentence in degeneration of the intervertebral discimplications for novel repair strategies* Dr Sarah Heathfield and Professor Judith Hoyland	£46,527
54	457	University of Brighton	PhD (36 months)	*Nanostructured, biocompetent biomaterials for early diagnosis & treatment of osteoporotic fractures* Mr Lubinda Mbundi and Professor Matteo Santin	£89,000
55	458	University of Oxford	PhD (36 months)	*Correlating mechanical properties and matrix biology of articular cartilage in the knee* Ms Monica Armengol and Dr Richie Gill	£73,129
56	459	Western Sussex Hospitals NHS	Clinical Fellow (12 months)	*Furlong Fellowship in Lower Limb Arthroplasty* Mr Nirav Shah and Mr John Edge	£84,300
57	460	University of Oxford (Furlong-BOTA Fellowship)	PhD (24 months)	*The patho-aetiology of hip osteoarthritis* Mr Geraint Thomas and Mr Sion Glyn-Jones	£22,322.09
58	461	University College London	PhD (18 months)	*Functional smart deposition of nano-sized calcium phosphate for medical applications* Mrs Gillian Munir, Dr Jie Huang and Professor Mohan Edirisinghe	£30,000
59	462	Western Sussex Hospitals NHS Trust	Clinical Fellow (12 months)	*Furlong Fellowship in Lower Limb Arthroplasty* Mr George Joseph and Mr Nirav Shah	£47,000
60	463	University of Bristol	PhD (36 months)	*Could physiologically relevant orthopaedic ions cause indirect DNA and chromosome damage to human embryonic stem cells across a trophoblast cell barrier?* Miss Anna Rogers and Dr Patrick Case	£60,000
61	464	Imperial College London	PhD (36 months)	*Injectable cellular constructs from human mesenchymal stem cells for translational bone tissue engineering* Miss Anastasia Georgion and Professor Sakis Mantalaris	£60,000

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
62	465	Queen Mary, University of London University College London	PhD (36 months)	*The use of antimicrobial nanomaterials as coatings for the next generation of prostheses* Mr Kaveh Memarzadeh, Dr Rob Allaker and Dr Jie Huang	£60,000
63	466	University of Sheffield	PhD (36 months)	*Porous metal implants for enhanced bone in-growth and stability* Mr William van Grunsven, Dr Gwendolen Reilly and Dr Russell Goodall	£59,209
64	467	Queen Mary, University of London	PhD (36 months)	*Complex mechanical loading of cell-seeded constructs can lead to functional repair of cartilage defects* Ms Erica Di Federico and Professor Julia Shelton	£60,000
65	468	University of Manchester	PhD (36 months)	*Effect of Mesenchymal Stem Cell Ageing on the Efficacy of Musculoskeletal Tissue Engineering /Regeneration Strategies* Miss Kimberley Swinton, Dr Stephen Richardson and Professor Judith Hoyland	£60,000
66	469	University of Edinburgh	PhD (36 months)	*Optimising fixation in osteoporotic bone fractures* Mr Alisdair MacLeod, Dr Pankaj Pankaj and Professor Hamish Simpson	£60,000
67	470	University of Oxford	Post-Doc (12 months)	*Bone activity of vitamin D2 vs. D3* Mr Ali Zarei and Dr Afsie Sabokbar	£57,885
68	471	Royal Veterinary College	Post-Doc (24 months)	*Optimising shoulder replacement by selecting ideal target bone for fixation* Dr Mittal Shah, Professor Andrew Pitsillides and Professor Roger Emery	£80,000
69	472	University of Birmingham	Post-Doc (24 months)	*Development of tissue engineered ligaments with titanium spring reinforcement* Dr Neeraj Jumbu, Dr Rachel Sammons and Dr Liam Grover	£72,774
70	473	King's College London University College London	Post-Doc (24 months)	*Development of a 'bioconnecting' nanoscomposite scaffold for hard and soft tissue repair and regeneration* Dr Priya Kalia, Professor Lucy Di Silvio and Dr Jie Huang	£80,000
71	474	University College London	Post-Doc (24 months)	*Investigation of interlocked bioactive coating for orthopaedic applications* Dr M Rafique Nangrejo and Professor Mohan Edirisinghe	£40,000
72	475	Cardiff University	Post-Doc (24 months)	*Why is post-traumatic arthritis more common than primary arthritis in the ankle?* Dr Emma Blain and Professor Victor Duance	£24,000
73	476	Cardiff University	Post-Doc (12 months)	*The Relationship between Alignment, Function and Loading in Total Knee Replacement: In-Vivo Analysis of a Unique Patient Population* Mr Andrew Metcalf and Dr Cathy Holt	£39,416

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
74	477	University of Edinburgh	Clinical Fellow (24 months)	*Investigation into synovial fluid markers of disease activity in knee osteoarthritis* Mr Chethan Jayadev, Professor Andrew Price and Dr Philippa Hulley	£44,881
75	478	University of Oxford	Post-Doc (24 months)	*Modelling mechanical signalling at the bone-tendon interface* Dr Andy Jones and Maria Kuzma-Kuzniarska, Dr Philippa Hulley	£80,000
76	479	University of Oxford	Clinical Fellow (12 months)	*Investigation into synovial fluid markers of disease activity in knee osteoarthritis* Mr Chethan Jayadev, Professor Andrew Price and Dr Philippa Hulley	£44,881
77	480	Queen's University Belfast	Post-Doc (24 months)	*A Minimally Invasive Solution for the Treatment of Spinal Fractures* Dr Nicholas Dunne, Professor Fraser Buchanan, Professor Serena Best and Professor Ruth Cameron	£79,592
78	481	University of Oxford	Post-Doc (12 months)	*Is HLA-B27 expression abnormal in Ankylosing Spondylitis joints?* Ms Kirsty McHugh and Dr Paul Bowness	£40,000
79	482	Sheffield Children's NHS Foundation Trust	Clinical Fellow (24 months)	*Acute response of bone to vibration in boys who have previously fractured* Ms Rachel Harrison and Professor Nick Bishop	£73,042
80	483	Royal Veterinary College	Post-Doc (24 months)	*Identification of Optimal Clonal Subpopulations Within Bone Marrow Derived Mesenchymal Stem Cells for Bone and Cartilage Repair* Mr Wasim Khan, Professor David Marsh and Dr Jay Dudhia	£36,700
81	484	University of Sheffield The National Osteoporosis Society	PhD (24 months)	*The effects of obesity on bone structure and strength* Dr Jennifer Walsh and Professor Richard Eastell	£24,203
82	485	University College London	Post-Doc (24 months)	*The Effect of Head Size, Torsion, Surface Finish and Material Composition on the Corrosion of Modular Tapers in Large Head Metal on Metal Total Hip Replacements* Dr Anna Panagiotidou, Professor Gordon Blunn, Mr John Skinner, Professor Alister Hart	£79,967
83	486	University of Cambridge	Post-Doc (12 months)	*In vitro investigation of plasma sprayed zinc substituted hydroxyapatite* Dr David Shepherd, Professor Serena Best and Dr Roger Brooks	£39,323
84	487	University of East Anglia	Post-Doc (24 months)	*Dietary-derived diallyl disulphide as a chondroprotective agent in osteoarthritis* Miss Sarah Gardner, Professor Ian Clark, Professor Aedin Cassidy and Professor Simon Donell	£79,319

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
85	488	University of Manchester	PhD (24 months)	*Optimised electrical stimulation for bone tissue engineering* Mr Richard Balint and Dr Sarah Cartmell	£50,000
86	489	University of East Anglia	MD (24 months)	*Role of Metal Ions in Metal on Metal Hip Arthroplasty* Mr Darren Ebreo, Professor Simon Donell and Professor Ian Clark	£59,924.33
87	490	Queen Mary, University of London University of East Anglia	PhD (36 months)	*The role of high frequency loading in the treatment of tendinopathy* Miss Chineye Princess Udeze, Dr Hazel Screen, Dr Dylan Morrissey and Dr Graham Riley	£72,913
88	491	St George's, University of London	PhD (36 months)	*The management of early stage degenerative disease of the hip joint. Evaluation of synthetic labro-chondral graft implantation* Mr Francesco Strambi, Mr Richard Field and Dr Andrea Fontana	£75,000
89	492	University of Oxford	PhD (36 months)	*Protecting tendon from lifestyle-induced epigenetic and metabolic alterations* Miss Zozana Kalivodova, Dr Philippa Hulley, Dr Mark Thompson and Dr Raewyn Poulsen	£75,000
90	493	University of East Anglia Queen Mary, University of London	Post-Doc (18 months)	*Is IL6 a target for therapy of tendinopathy?* Miss Eleanor Jones, Dr Graham Riley, Mr Simon Donell and Dr Hazel Screen	£79,337
91	494	University College London	Post-Doc (12 months)	*TAEA deposition of multifunctional nanoCalcium Phosphate with controlled release of drugs for skeletal tissue repair* Dr Gillian Munir, Dr Jie Huang and Dr Junwang Tang	£39,936
92	495	University of Leeds	Clinical Fellow (24 months)	*Understanding the biology of bone fracture healing: The role of immunoregulatory and regenerative cells as basis of poor prognostic biomarker development* Mr Hiang Boon Tan, Mr Hiang Boon Tan, Dr Elena Jones, Dr Frederique Ponchel, Professor Peter Giannoudis	£80,000
93	496	North Bristol NHS Trust	Post-Doc (12 months)	*Developing a dual-action titanium surface to deter bacteria and enhance osteoblastogenesis* Dr Jason Mansell and Professor Ashley Blom	£47,657
94	497	University of Birmingham	Post-Doc (24 months)	*Designing a robust process for clinical translation of tissue engineered bone to bone ligament replacements* Dr Jennifer Paxton and Dr Liam Grover	£80,000

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
95	498	Cardiff University	Post-Doc (18 months)	*Can activation of lysyl oxidase-like 1 induce repair of osteoarthritic cartilage?* Dr Yadan Zhang, Dr Ilyas M Khan and Professor Charles W Archer	£68,549
96	499	King's College London	Post-Doc (18 months)	*Stem cell based bone engineered vascular grafts* Dr Priya Kalia and Professor Lucy Di Silvio	£80,000
97	500	The Royal College of Surgeons of England	Clinical Fellow (36 months)	*Surgical Speciality Leads* Professor Matt Costa and Professor Amar Rangan	£45,000
98	501	University of Oxford	MD (24 months)	*Understanding mechanisms of pain and neuronal regulation in tendinopathy* Benjamin Dean, Dr Sarah Franklin and Professor Andrew Carr	£60,000
99	502	King's College London	PhD (36 months)	*HIF-regulating scaffolds for osteochondral regeneration* Dheraj Kumar Taheem, Dr Eileen Gentleman and Dr Gavin Jell	£75,000
100	503	University College London	Post-Doc (36 months)	*The Use of PEEK in Uncemented Shoulder Arthroplasty* Miss Sara Ajami, Dr Melanie Coathup and Professor Gordon Blunn	£75,000
101	504	University of Oxford	Post-Doc (36 months)	*Optimising high tibial osteotomy for the treatment of early OA* Dr Cameron Brown, Professor Andrew Price and Dr Amy Zavatsky	£75,000
102	505	Newcastle University	MD (24 months)	*Is CD64 level an effective test for the early diagnosis and management of joint replacement infection?* Mr Kenneth Rankin and Mr Mike Reed	£59,145
103	506	University of Oxford	Clinical Fellow (24 months)	*Biochemical Markers for the Identification of Individuals at Risk of Developing Osteoarthritis* Mr Antony Palmer, Mr Sion Glyn-Jones, Dr Philippa Hulley and Professor Andrew Carr	£22,740
104	507	University College London Imperial College London	Clinical Fellow (24 months)	*Adolescent hip disease: biomarkers, morphology and PROMS in a longitudinal study* Mr Andreas Roposch, Professor Justin Cobb, Dr Milad Masjedi and Mr Aresh Hashemi-Nejad	£99,817
105	508	University College London	Post-Doc (24 months)	*Will the Intravenous Administration of Mesenchymal Stem Cells Modified to Migrate to the Bone Marrow Increase Bone Formation in Osteoporosis?* Dr Melanie Coathup, Prof Gordon Blunn, Dr Jia Hua and Professor Allen Goodship	£100,000
106	509	University of Oxford	Post-Doc (24 months)	*Does dysfunctional autophagy underlie both ageing-related and mechanical deterioration of cartilage in osteoarthritis* Dr James Edwards, Professor Andrew Price, Dr Sarah Snelling and Dr Mark Thompson	£100,000

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
107	510	University of Oxford	PhD (36 months)	*The in-vitro and in-vivo investigation of measuring outcome in Total Hip Arthroplasty using marker-less Radiostereometric Analysis (RSA)* Tamer Malak, Mr Sion Glyn-Jones (Supervisor) and Dr Cameron Brown	£56,250
108	511	University of Oxford	PhD (36 months)	*Dynamic musculo-skeletal ultrasound measurement of joint pain* Andrew Paul Monk, Professor David Murray, Alison Noble and Mark Thompson	£56,250
109	512	St George's, University of London Imperial College London	MD (24 months)	*Surgery for patellar instability: the impact of pathomorphology on kinematics and gait* Arash Aframian, Miss Caroline Hing and Professor Justin Cobb	£45,000
110	513	Newcastle University	MD (24 months)	*Dispersal of Clinical Biofilms from Titanium and Cobalt Chrome Surfaces Using a Novel Marine Nuclease* Andrea Pujol Nicolas, Professor Grant Burgess and Mr Mike Reed	£58,696.90
111	514	University College London	PhD (36 months)	*Bioengineering the Fracture Callus: Bone Repair through Fracture Mimetics* Mr Wollis Vas, Dr Scott Roberts, Professor Paul Sibbons and Dr Tahera Ansari	£74,994
112	515	University of Leeds	Post-Doc (24 months)	*Enhanced Osteointegration Using a Selective Laser Sintering Solution Deposited HA coating* Dr Vee San Cheong, Dr Melanie Coathup and Professor Gordon Blunn	£99,999
113	516	North Bristol NHS Trust	Post-Doc (12 months)	*Can we improve fracture healing in the elderly by stimulating skeletal perfusion?* Dr Stephanie Gohin, Dr Chantal Chenu, Professor Tim Arnett and Mr Peter Smitham	£99,055
114	517	University of Sheffield	Post-Doc (21 months)	*Biological effects of tribocorrosion products on the bone micro-environment and prosthesis osseo-integration* Karan Mehul Shah, Professor Jeremy Mark Wilkinson and Dr Alison Gartland	£93,245
115	518	Newcastle University	PhD (36 months)	*Development of a novel 3D printed co-culture model of bone sarcoma to investigate the use of TNF-alpha preconditioned bone marrow-derived mesenchymal stem cells (BMMSCs) to promote osteogenesis and induce sarcoma cell apoptosis* Mr Zakareya Gamie, Mr Kenneth Rankin, Mrs Katherine Rennie, Mr Craig Gerrand, Dr Anja Kripppner-Heidenreich, Dr Mark Birch, Professor Kenneth Dalgarno and Professor Andrew McCaskie	£74,827.41

No	ORUK ref.	Institution	Study Stream (Duration)	Research Project Title	Amount
116	519	University of York British Orthopaedic Association	Clinical Fellow (24 months)	*ORUK Clinical Fellow at the BOA Orthopaedic Surgery Research Centre (BOSRC) in York* Professor Amar Rangan	£94,000
117	520	Imperial College London St George's, University of London	Post-Doc (24 months)	*The kinematics and the contact patterns of the patellofemoral joint* Mr Arash Aframian, Professor Justin Cobb, Professor Andrew Amis, Mr Farhad Iranpour, Miss Caroline Blanca Hing	£75,000
118	521	Northumbria Healthcare NHS Foundation	Clinical Fellow (21 months)	*An interactive musculoskeletal dashboard to inform best practice* Mr Simon Jameson, Mr Mike Reed, Professor Philip Turner, Mr David Johnson, Professor Amar Rangan, Liz Lingard, Valerie Corris and Gary Cook	£29,875

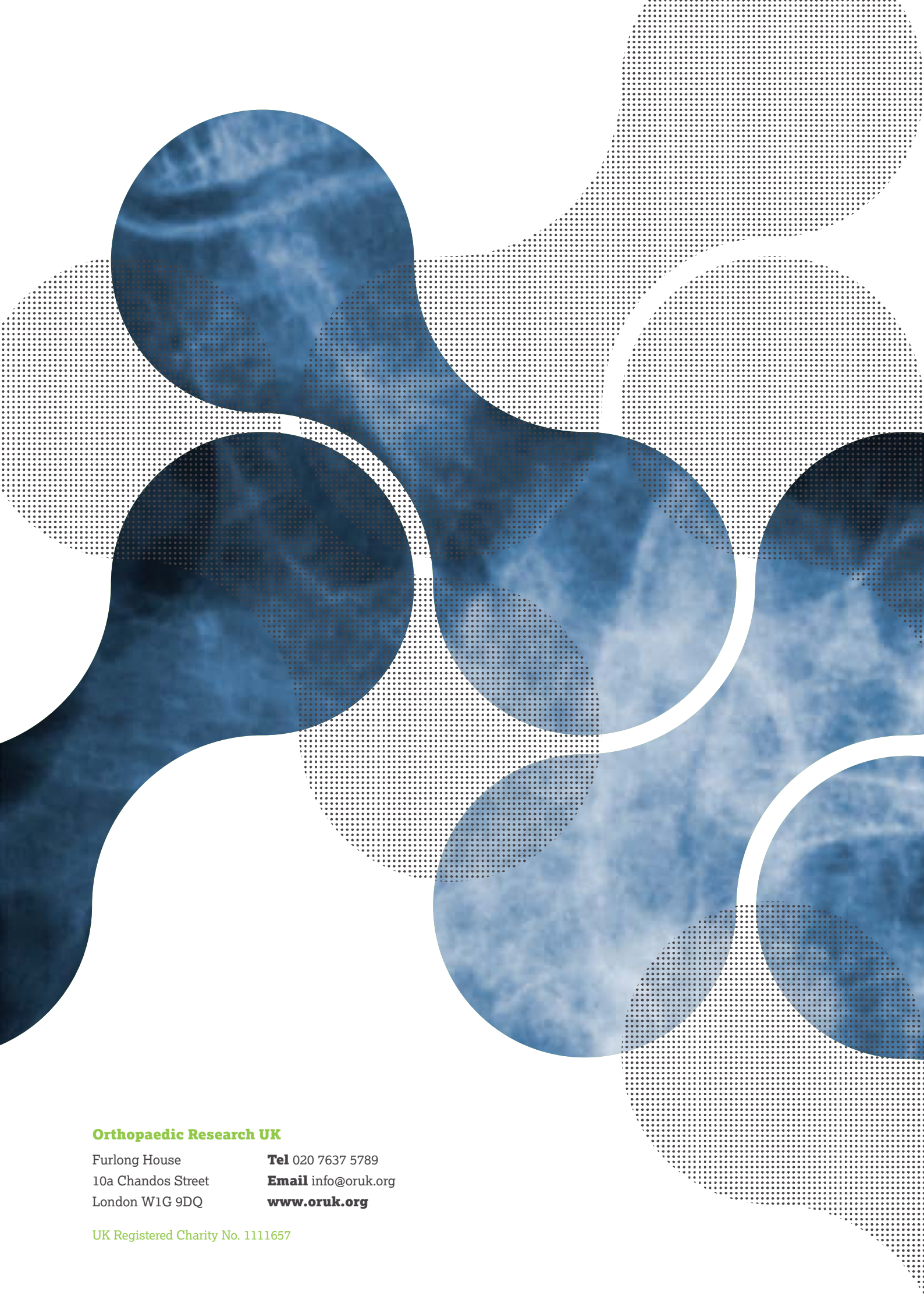
Notes

Acknowledgements

We would like to sincerely thank our reviewers for their unconditional support:

Mr John Edge | Prof Neil Rushton | Prof Lucy DiSilvio | Prof Julia Shelton | Prof Victor Duance | Prof Damian Griffin
Dr Ralf Kettner | Mr Vikas Khanduja | Prof Matteo Santin | Prof Gordon Blunn | Prof Justin Cobb | Dr John Egan
Prof Ian Clark | Mr Ben Ollivere | Prof Jeremy Fairbank | Prof Chris Lavy | Prof Tim Briggs | Dr Graham Riley
Prof Catherine Holt | Prof Roger Emery | Prof Tony Miles | Dr Eileen Gentleman | Dr Nicole Horwood | Dr Roger Brooks
Prof Afsie Sabokbar | Prof Richie Gill | Dr Anwen Williams | Dr George Burke | Dr Aileen Crawford | Prof Richard Hall
Dr Marianne Ellis | Prof Richard Oreffo | Dr Adrian Boyd | Dr Caroline Milner | Dr Hazel Screen | Dr Jie Huang
Dr Peter Laz | Prof Sarah Cartmell | Mr Michael Whitehouse | Prof Serena Best | Dr Anne Young | Dr Dick Shelton
Dr Emma Blain | Dr Julie Gough | Prof Liam Grover | Dr Milad Masjedi | Prof Andrew Carr | Prof Martin Knight
Dr Cheryl Miller | Prof Andrew Pitsillides | Prof Andrew Price | Prof Richard Field | Dr Deborah Mason | Mr Johan Witt
Dr Andreas Roposch | Dr Chantal Chenu | Dr Ilyas Khan | Dr James Edwards | Dr Jay Dudhia | Dr Lindsay Smith
Dr Priya Kalia | Dr Rachel Sammons | Prof Alison McGregor | Prof Rob Allaker | Prof Simon Donell | Dr Claire Brockett
Dr Nigel Loveridge | Dr Rachel Allen | Dr Vehid Salih | Mr Iain McNamara | Mr Sebastian Dawson-Bowling
Prof Richard Aspden | Dr Alexandra Porter | Dr Catherine Dobson | Dr Rahul Tare | Dr Sanjukta Deb | Miss Caroline Hing
Prof Elizabeth Tanner | Prof Hamish Simpson | Prof Joost de Bruijn | Prof Matthew Dalby | Dr Agi Grigoriadis
Dr Alison Hayman | Dr Alison Tyson-Capper | Dr Ben Scheven | Dr Martin Beck | Dr Simon Harris | Miss Leela Biant
Mr Ben Bolland | Mr Paul Manning | Prof Andrew McCaskie | Prof James Hutchison | Prof Jonathan Knowles
Prof Matthew Costa | Prof Paul Hatton | Prof Robert Hill | Dr Alan Smith | Dr Alessandra Carriero | Prof Ali Mobasheri
Dr Antti Eskelinen | Dr Claire Clarkin | Dr Daniel Boyd | Dr Duncan Shepherd | Dr Elise Pegg | Dr Francesco Dell'Accio
Dr Gwendolen Reilly | Dr Helen Chappell | Dr Ifty Ahmed | Dr Irene Turner | Dr Judith Meakin | Dr Lee Buttery
Dr Paul Stoodley | Prof Philippa Hulley | Dr Polina Prokopovich | Dr Russell Goodall | Dr Stephanie Dakin
Mr Ajay Malviya | Mr Andy Sprowson | Mr Jeremy Latham | Mr Peter Smitham | Prof Giandomenico Logroscino
Prof Judith Hoyland | Prof Martin Beck | Prof Mohan Edirisinghe | Prof Ravichandran Subbaraj | Prof Sandy Cochran
Dr Alison Gartland | Dr Anastasios Chanalaris | Dr Aram Saeed | Dr Charlie Waugh | Dr Colin Scotchford
Dr David Hamilton | Dr David Young | Dr Donal McNally | Dr Hannah Moir | Dr Ines Reichert | Dr Ivan Wall
Dr Jim Ralphs | Dr Mike Rodger | Dr Nicholas Evans | Dr Osnat Hakimi | Dr Owen Addison | Dr Paul Genever
Dr Tina Chowdhury | Dr Xuebin Yang | Prof Alastair Sloan | Prof Bruce Drinkwater | Prof Cosimo De Bari
Prof Heikki Kroger | Prof Nicola Maffulli | Prof Sally Roberts | Prof Thomas Joyce | Dr Alex Lennon | Dr Amer Arslanagic
Dr Catherine Boulter | Dr Anita Ghag | Dr Benjamin Fisher | Dr Blandine Poulet | Dr Carl Goodyear | Dr Chaozong Liu
Dr Chrissy Hammond | Dr David Buttle | Dr David Shepherd | Dr Deepak Kalaskar | Dr Dong Barraclough
Dr Edward Chadwick | Dr Edward Purdue | Dr Elena Jones | Dr Elizabeth Laird | Dr Emma Williams
Dr Emmanuel Audenaert | Dr Eric Downer | Dr Fintan Mority | Dr Frank Petrigliano | Dr Gary Shum | Dr Georges Limbert
Dr Glen Turley | Dr Helen Birch | Dr Ian McCarthy | Dr Jennifer Paxton | Dr Jill Urban | Dr Jonathan Jeffers
Dr Jonny Blaker | Dr Kim Midwood | Dr Lang Yang | Dr Lee Herrington | Dr Marcello Riggio | Dr Marietta van der Linden
Dr Martin Warner | Dr Melanie Coathup | Dr Michael Doube | Dr Mittal Shah | Dr Natalia Karpukhina | Dr Nathan Jeffery
Dr Neil Artz | Dr Neil Reeves | Dr Nicola Hunt | Dr Nidhi Sofat | Dr Patrick Case | Dr Paul Genever | Dr Peter Coussons
Dr Peter Dabnichki | Dr Piergiorgio Gentile | Dr Rajeev Gupta | Dr Richard Barrett-Jolley | Dr Sarah Shultz
Dr Sarah Snelling | Dr Scott Roberts | Dr Simon Ostlere | Dr Simon Rawlinson | Dr Simon Tew | Dr Sunthar Mahalingam
Dr Susan Clarke | Dr Tom Kelly | Dr Vesa Saikko | Dr Xize Niu | Dr Yang Liu | Mr Andrew Metcalf | Mr Andrew Sankey
Mr Andrew Sprowson | Mr Andy Goldberg | Mr Benjamin Ollivere | Mr Craig Gerrand | Mr Dominic Meek
Mr Frederic Picard | Mr Gareth Stables | Mr H K Sharma | Mr Hemant Pandit | Mr Ian Bacarese- Hamilton
Mr Masood Shafafy | Mr Michael Thomas | Mr Mike Kelly | Mr Norbert Kang | Mr Oday Al-Dadah | Mr Peter Young
Mr Rhidian Morgan Jones | Mr Stephen Jones | Mr Tim Board | Prof Alister Hart | Prof Amar Rangan
Prof Andrew Pitsillides | Prof Bill Baltzopoulos | Prof Bo Su | Prof Catherine Van Der Straeten | Prof Charles Archer
Prof David Hukins | Prof David Williams | Prof David Young | Prof Dong-Woo Cho | Prof Fares Haddad
Prof Fraser Buchanan | Prof Gabor Tigyi | Prof Georg Bergmann | Prof Gladius Lewis | Prof Grant Burgess
Prof Ian McDermot | Prof J Mark Wilkinson | Prof Jagdeep Nanchahal | Prof James Wang | Prof James Wright
Prof Janet Patterson-Kane | Prof Jeffrey Gimble | Prof Joanna Verran | Prof John Loughlin | Prof Kenneth Dalgarno
Prof Kevin Shakesheff | Prof Mark Rainforth | Prof Markus Heller | Prof Mats Brittberg | Prof Michael Kjaer
Prof Paul Ackermann | Prof Paul Ackermann | Prof Peter Clegg | Prof Philippe Young | Prof Raymond Lee
Prof Shaowei Zhang | Prof Tim Cawston | Prof Tony Anson | Prof Vehid Salih | Prof Yiannis Koutedakis

Design and production: chacha.co.uk



Orthopaedic Research UK

Furlong House
10a Chandos Street
London W1G 9DQ

Tel 020 7637 5789
Email info@oruk.org
www.oruk.org

UK Registered Charity No. 1111657