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

UNIVERSITY OF LEEDS

BRITISH ORTHOPAEDIC RESEARCH SOCIETY

CONFERENCE 2018

10 - 11 September 2018
University of Leeds
Maurice Keyworth Building

With thanks to our sponsors

Welcome

On behalf of the local organisers we would like to welcome you to the 2018 British Orthopaedic Research Society annual meeting.

We are delighted to be hosting you at the University of Leeds and hope that you find the next few days stimulating academically as we hear from orthopaedic researchers around the UK (and further afield). As we have developed the programme we have been keen to make this annual meeting as inclusive and diverse as possible. Invited talks are from colleagues from a wide range of backgrounds, including a focus on education and engagement in our community. We are delighted that scientific sessions will be chaired by PhD students or early career researchers alongside last year's BORS travelling fellows and have strived to achieve gender balance across all aspects of the conference. Please read the equality and diversity to statement to find out more.

We are also excited about the poster teaser session, a first for a BORS annual meeting and an opportunity for poster presenters to showcase their research.

We would also like to take this opportunity to thank all our keynote speakers for supporting the conference and helping us to provide such a varied programme. Additionally, thank you to our sponsors for their valuable support and contribution to this annual meeting.

Throughout the meeting we hope you enjoy opportunities to network with existing collaborators and friends, as well as future ones.

All the very best for a stimulating and fruitful conference.

Prof Sophie Williams   Dr Claire Brockett
On behalf of the local organising team

Welcome from the President of the British Orthopaedic Research Society

Welcome to Leeds and to the British Orthopaedic Research Society 2018 Annual Meeting. I would like to extend my thanks to Claire, Sophie, and the organising committee for putting together such a stimulating scientific and social programme. We look forward to keynote speakers and themed areas from orthopaedic biomechanics, manufacturing and regulation, trauma, the OA-tech network, translation of basic and translational science to the clinic, orthopaedic outreach and patient outcomes. We also Welcome Prof Kate Robson-Brown from the University Bristol who will deliver our open Public Engagement Lecture and Professor Paul Gregg who will deliver this year's President's Prize Lecture.

The diversity of our invited speaker programme is also reflected within the abstracted podium and poster presentations, underlining the breadth of our membership and collaborative expertise. Our conference Dinner will be held on Monday evening at the Thackray Medical Museum, a great opportunity to immerse yourself in some of the manufacturing heritage of our field!

On behalf of the British Orthopaedic Research Society, I hope you have a very fruitful meeting here in Leeds!

Prof J Mark Wilkinson
BORS President

Annual meeting presentation and poster prizes

Further details of prizes that will be awarded during the meeting are below:

- New Investigator Award: Award for best podium presentation from a new investigator. New investigators are considered to be early career researchers who have not previously presented research at a BORS conference. Presenters were asked to indicate if they wish to be considered for this award when submitting their abstract.
- Andrew Sprowson Award for Translational Research: Award for best podium presentation detailing translational research. Presenters were asked to indicate if they wish to be considered for this award when submitting their abstract.
- Best Poster: Award for best poster this year will be selected by delegates. During registration you will have been given two "sticky dots!" Please adhere these to the two posters you consider worthy of this prize. You are free to set your own criteria; for example most exciting science, best presented poster.
- Best Paper: Award for the best overall paper. This is awarded to the best research presented through a podium presentation during the conference.
- Public engagement award: Award for the best tweet. Follow the @BritishORS twitter feed for more details. The criteria are published on the twitter feed, and the winner will be determined by the end of the conference.

In addition to the BORS prizes awarded during the meeting, all prize winners will be granted free registration for BORS 2019.

Equality and diversity statement

In developing the programme for this annual meeting, the organising team have undertaken to consider equality and diversity across different aspects of the conference. We have considered gender, geographical diversity and opportunities for researchers at all stages of their careers. Our intention was to ensure the programme reflected the breadth and diversity of our research community.

To achieve this we have taken the following steps:

- Reviewed gender balance data from the 2017 annual meeting, in terms of registered delegates, invited speakers, podium presentations, and awarded prizes to enable the impact of changes to be monitored.
- Ensured a diverse organising committee
- Developed a plan whereby we considered equality and diversity across the programme.
- Invited BORS travelling fellows from 2017 to chair sessions, and asked them to invite a PhD student / early career researcher to co-chair the session.
- Invited keynote speakers to provide a varied programme across the breadth of orthopaedic research who are leaders in their field, while being mindful of ensuring a gender balance that is representative of the society, and geographical diversity in invited speakers.
- Avoided the first week in September for the conference (anecdotal evidence told us this week is unpopular, it clashes with return to schools for families that can make travel difficult and in terms of work-life balance is unpopular due to the proximity to the bank holiday when delegates may take annual leave).
- Commit to publishing the results (this information will be presented during the meeting)

CONFERENCE PROGRAMME

Accredited by the Royal College of Surgeons of England for up to 10.5 CPD points

Monday 10th September

0815 onwards	Registration and coffee
0900	Welcome to BORS 2018, Prof Mark Wilkinson, BORS President and Prof Sophie Williams for the local organising team

0915-1045 Session 1: Orthopaedic Biomechanics
Chairs Dr Richard van Akel and Amy Garner

0915 — *Keynote presentation*: Modelling Knee Mechanics for TKR Design and Patient Monitoring
Prof Paul Rullkoetter, University of Denver

0945-1045
1. Hip capsular function after arthroplasty
Dr Richard van Arkel, Imperial College
2. Cortical Bone Spherical Indentation Modulus Correlates with the Elastic Modulus from Compression Testing and CT-measured Porosity
Mr Oliver Boughton, Imperial College
3. Decellularisation affects the strain rate dependent and dynamic mechanical properties of a xenogeneic anterior cruciate ligament graft Dr Jennifer Edwards, University of Leeds
4. Biomechanical Testing for the in vitro Testing of Intervertebral Disc Nucleus Augmentation Devices
Dr James Warren, University of Leeds
5. Estimation of viscoelastic bushing parameters of a musculoskeletal cervical spine model in impact scenarios
Dr Sabina Gheduzzi, University of Bath
6. Physiological mechanical loading from voluntary wheel running promotes increased plasma membrane disruptions in osteocytes
Dr Meghan McGee-Lawrence Medical College of Georgia, Augusta University

1045-1200 Session 2: Poster teaser presentations (2 minute pitch + transition)
Chair Dr Marlene Mengoni

1200-1315 Lunch and BORS AGM (1215-1300), Poster viewing

1315-1445 Session 3: Translation of Orthopaedic Research into Clinic
Chairs Mr Tom Kurien and Jake Bowd

1315-1340 — *Keynote presentation:* Impact of MDR on evidence requirements
Dr John Wilkinson, MHRA

1340-1430
1. A Collagen-Based Soft Tissue Barrier Membrane with Periosteal Mesenchymal Stem Cell Homing Capability for Bone Defect Repair Ms Heather Owston, University of Leeds
2. Introducing the Z-track method for cells-delivery injection in a model of atrophic non-union to prevent backflow leakage
Dr Murthadah Jalal, University of Edinburgh
3. Comparison of Different Tissue Processing Methods for Maximization of Bacterial Recovery
Mr Mohamed Askar, University of Nottingham
4. Genome-wide Expression Analysis of Human Osteoblasts on Prosthesis Surfaces following Clinically Relevant Cobalt and Chromium Exposure
Dr Karan Shah, University of Sheffield
5. Nanotubes improve Human Dermal Fibroblasts and Keratinocytes attachment on Intraosseous Transcutaneous Amputation prosthesis
Ms Elena Giusto, UCL

1430-1505 Session 4: Orthopaedic Research Outreach
Chair Dr Susan Clarke

1430-1450 — *Keynote presentation:* How orthopaedic research can influence Engineering Education
Prof Julia Shelton, QMUL

1450-1505 — **Discussion:** Patient involvement in orthopaedic research led by Dr Claire Brockett

1505-1540 Coffee, Mini science-fair

1540-1630 Session 5: Manufacturing in Orthopaedics
Chairs Dr Tony Herbert and Lekha Koria

1540 — *Combined keynote presentation*: An Innovative Multidisciplinary Approach to Optimising Knee Therapies
Prof Eileen Ingham and Prof Ruth Wilcox, Leeds

1610 -1640
1. The effect of pore size on bone marrow mesenchymal stem cell morphology, proliferation and mineralisation of bone in vitro.
Dr Anita Sanghani Kerai UCL
2. Nanotechnology based antimicrobial drug delivery system for orthopaedic application
Dr Polina Prokopovich, Cardiff
3. A biomimetic peptide/glycosaminoglycan hybrid hydrogel for nucleus pulposus augmentation therapy utilising minimally invasive methods
Dr James Warren, University of Leeds

1645-1715 Presidential Prize Lecture – Professor Paul Gregg
Chair Prof Mark Wilkinson

1720-1750 Public Engagement Lecture:
The microstructure of bones and teeth as a signature of human experience: from australopithecines to astronauts
Prof Kate Robson-Brown, University of Bristol
Chairs Dr Robert Wallace, Dr Claire Brockett

1845 Coach pick up for dinner*
1900 Conference dinner, Thackray Medical Museum

Tuesday 11ᵗʰ September

0900-1030   Session 6: Trauma
Chairs Dr Jerry Tsang and Alex Seghal

0900   *Keynote presentation:* Trauma Research - current scope and future horizons.
Prof Ian Pallister, Swansea

0930-1030   1. Mechanical Characterisation of the Lateral Collateral Ankle Ligaments Under Sprain-like Conditions
Dr Anthony Herbert, University of Leeds
2. Stratification of decellularised porcine super flexor tendon for replacement of the anterior cruciate ligament
Mr Samuel Whitaker, Leeds General Infirmary
3. Development of a method for proper X-ray viewing of the leg in a clinically-relevant model of atrophic non-union
Dr Murtadah Jalal, University of Edinburgh
4. Comparison of vertebral body displacements obtained by DIC and motion capture in a cervical spine impact experiment
Mr Stuart Boyd, University of Bath
5. Computational modelling of tendons and ligaments, a pathway to understand damage mechanisms
Dr Marlene Mengoni, University of Leeds

1030-1100   Coffee break, Poster viewing

1100-1250   Session 7: OATech Network
Chair Prof Cathy Holt and Prof Philip Rowe

1100-1115   The OATECH+ Network of the EPSRC
Prof Cathy Holt, University of Cardiff
1115-1130   Future Perspectives for Biomechanical Motion Analysis in OA
Prof Philip Rowe, University of Strathclyde
1130-1145   Future Perspectives for Biological Phenotyping in OA
Prof Sally Roberts, Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry.
1145-1200   General discussion on the OATECH Network

1200-1250   1. The Biomechanical Characterisation of Subjects with Medial and Lateral Knee Focal Cartilage Defects
Mr Nidal Khatib, University of Cardiff
2. Epigenetic drugs as potent modulators in osteoarthritis
Ms Namrata Madhusudan, University of Southampton
3. The in vivo compatibility, integration and regeneration of a decellularised porcine bone scaffold in an ovine model
Dr Hazel Fermor, University of Leeds
4. Universal drug delivery platform into cartilage
Dr Polina Prokopovich, University of Cardiff

1250   BORS/BJR Travelling Fellowships
Chair Prof Hamish Simpson

1300-1410   Lunch, Poster viewing

1410-1530   Session 8: Orthopaedic Outcomes
Chairs Mr Oliver Broughton and Ruben Doyle

1410   *Keynote presentation:* Measuring success and failure after hip and knee replacement
Prof Ashley Blom, University of Bristol
1440-1530   1. Bone Ageing Atlas Development: The UK Biobank Study
Mr Moshen Farzi, University of Sheffield
2. Combining inertial sensors and principle component analysis to distinguish between knee rehabilitation exercises
Dr Philippa Jones, University of Cardiff
3. Patellofemoral-arthroplasty improves gait in isolated patellofemoral-arthritis, a prospective cohort gait analysis study
Dr Aliya Choudury, St Georges
4. An evaluation of survival modelling approaches for personalised risk prediction after hip replacement for osteoarthritis
Prof Mark Wilkinson, University of Sheffield
5. Stratifying the immune response to biomaterials: can cobalt-mediated inflammation be prevented?
Ms Amy Mawdesley, University of Newcastle

1530 -1600   Awards, Presidential Handover & thank yous - pass on to BORS2019
Chair Prof Mark Wilkinson

1600   CLOSE

*The BORS 2018 Conference Dinner will take place at the Thackray Medical Museum. Coaches to the museum will depart at 18:45 from outside Charles Morris Hall and return at 22:15. For those wishing to go into town after dinner, a taxi will cost approximately £5.00.

Poster Presentations

Manufacturing in orthopaedics

ID	Title
39	In vitro 3D model for bone tissue: a bioelectronics approach.
	Dr Donata Iandolo, University of Cambridge, UK
86	Radiopaque Unicompartmental Knee Bearing for Direct Wear Measurement
	Ms Fedra Zaribaf, University of Bath, UK

Orthopaedic biomechanics

ID	Title
10	Visualisation and quantification of in situ porcine acetabular soft tissue deformation
	Dr Alison Jones, University of Leeds, UK
27	Factors affecting the mechanical stability of impacted morsellised bone graft
	Mr Andy Craig, Bradford Teaching Hospitals NHS Foundation Trust/University of Leeds, UK
33	Biomechanical properties of intramedullary nail reveal more stable fixation than external fixator and compression plate in a clinically-relevant model of atrophic non-union
	Dr Murtadhah Jalal, University of Edinburgh, UK
42	Contact and Wear Mechanics of Dynamic Separation in Hip Arthroplasty
	Dr Lin Wang, DePuy Synthes Joint Reconstruction, UK
43	Development of a porcine knee model for pre-clinical tribological assessment of early stage knee therapies
	Dr Aiqin Liu, Unversity Of Leeds, UK
46	The effect of varying implant size on the wear performance of total ankle replacements
	Mr James Hopwood, University of Leeds, UK
59	Feasibility of pressure mat analyses during simple clinical tests in detecting instability in total knee arthroplasty: a proof of concept examination
	Ms Alexandria Sehgal, University of Edinburgh, UK
62	On the validity of computational modelling for intervertebral disc interventions
	Dr Marlene Mengoni, University of Leeds, UK
63	Investigation of the Influence of Material Properties on Osteochondral Graft Fixation: A Finite Element Analysis
	Dr Michelle Casper Taylor, University of Leeds, UK
66	Evaluation of the Mechanical Behaviour of Osteochondral Grafts and their Composite Parts: Naturally Variable Tissues
	Dr Michelle Casper Taylor, University of Leeds, UK
67	Exploring the Mechanisms of Head-Trunnion Mechanics in Modular Hip Prostheses: The Influence of Material and Structural Stiffness
	Dr Alisdair MacLeod, University of Bath, UK
72	DIC affords better validation of predictive specimen specific finite element vertebral models than load displacement curves alone
	Mr Bruno Agostinho Hernandez, University of Bath, UK
76	What is the influence of frontal plane surgical alignment on TKR in-vivo kinematics?
	Mr David Williams, Cardiff University, UK

Orthopaedic outcomes

ID	Title
16	Combining Metrology Data for Detailed Wear Characterisation of Hip Implants
	Mr Joe Pashley, Future Metrology Hub, UK
20	Methodology for Assessment of Surgically Induced Stem Taper Distortion
	Mr Karl Dransfield, University of Huddersfield, UK
24	Relationship Between Differing Measures of Function Following Total Knee Arthroplasty
	Prof Hamish Simpson, University of Edinburgh, UK
61	MRI MEASUREMENTS PRE AND POST TROCHLEOPLASTY : Functional outcomes in Trochlear Dysplasia
	Dr Aliya Choudhury, St. Georges University, UK
65	Development of Methods to Characterise UHMWPE Edge Wear
	Mr Ameer Hussain, University of Huddersfield, UK
70	A comparison of outcomes in metastatic proximal femoral fractures between an MSK-oncology centre and a non tumour-specialist university hospital
	Mrs Samantha Downie, NHS Tayside, UK
84	Measurement of two-dimensional linear wear on Total Knee Replacement prostheses using co-ordinate metrology and fitting techniques
	Mr Matthew Holland, University of Huddersfield, UK

Osteoarthritis (Session sponsored by OATech+)

ID	Title
29	Characterising the mechanical properties in the ankle
	Ms Lekha Koria, University of Leeds, UK
47	Anti-inflammatory drug-eluting implant model system to prevent wear particles induced osteolysis
	Dr Polina Prokopovich, Cardiff University, UK
78	Can Surface Engineered Coatings Improve the Biocompatibility of Metals for Biomedical Applications?
	Dr Saurabh Lal, University of Leeds, UK
82	Does gait retraining have the potential of reducing medial knee loading and force in individuals with osteoarthritis whilst not adversely affecting the hip and ankle joints? Prospective systematic review
	Mr Jake Bowd, Cardiff University, UK

Translation of orthopaedic research into the clinic

ID	Title
11	Effect of Low Intensity Pulsed Ultrasound Therapy on Staphylococcus Aureus Biofilms
	Dr Jerry Tsang, University of Edinburgh, UK
32	Validation of a Novel Method for Bone Marrow Collection for Autologous MSCs Transplantation in Murine
	Dr Murtadhah Jalal, University of Edinburgh, UK
40	Improved Laboratory Methods for Diagnosis of Infection in Spinal Instrumentation
	Ms Rachel Thavayogan, University of Nottingham, UK
45	The Long Non-Coding RNA CASC20 is a Susceptibility Locus for Heterotopic Ossification: Results of a Genome-Wide Association Study
	Mr Matthew Clark, University of Sheffield, UK
56	A Combined Computational and Experimental Approach for Pre-clinical Simulation of Total Knee Replacements
	Dr Abdellatif Abdelgaied, University of Leeds, UK

Hip capsular function after arthroplasty

Kartik LOGISHETTY[1], Richard VAN ARKEL[1], Sarah MUIRHEAD-ALLWOOD[2], Geoffrey NG[1], Justin COBB[1], Jonathan JEFFERS[1]

[1] Imperial College London, London, United Kingdom (Institution, City, Country)

[2] London Hip Unit, London, United Kingdom

Background

The hip's capsular ligaments (CL) passively restrain extreme range of motion (ROM) by wrapping around the native femoral head/neck, and protect against impingement and instability. We compared how CL function was affected by device (hip resurfacing arthroplasty, HRA; dual mobility total hip arthroplasty, DM-THA; and conventional THA, C-THA), and surgical approach (anterior and posterior), with and without CL surgical-repair. We hypothesized that CL function would only be preserved when native head-size (HRA/DM-THA) was restored.

Methods

CL function was quantified on sixteen cadaveric hips, by measuring ROM by internally (IR) and externally rotating (ER) the hip in six functional positions, ranging from full extension with abduction to full flexion with adduction (squatting). Native ROM was compared to ROM after posterior capsulotomy (right hips) or anterior capsulotomy (left hips), and HRA, and C-THA and DM-THA, before and after CL repair.

Results

Independent of approach, ROM increased most following C-THA (max 62°), then DM-THA (max 40°), then HRA (max 19°), indicating later CL engagement and reduced biomechanical function with smaller head-size. Dislocations also occurred in *squatting* after C-THA and DM-THA. CL-repair following HRA restored ROM to the native hip (max 8°). CL-repair following DM-THA reduced ROM hypermobility in flexed positions only and prevented dislocation (max 36°). CL-repair following C-THA did not reduce ROM or prevent dislocation.

Discussion

For HRA and repair, native anatomy was preserved and ligament function was restored. For DM-THA with repair, ligament function depended on the movement of the mobile-bearing, with increased ROM in positions when ligaments could not wrap around head/neck. For C-THA, the reduced head-size resulted in inferior capsular mechanics in all positions as the ligaments remained slack, irrespective of repair.

Relevance

Choosing devices with anatomic head-sizes (HRA/DM-THA) with capsular repair may have greater effect than surgical approach to protect against instability in the early postoperative period.

Cortical bone spherical indentation modulus correlates with the elastic modulus from compression testing and CT-measured porosity

Oliver BOUGHTON[1], Liye YAN[2], Shaocheng MA[1], Ulrich HANSEN[1], Finn GIULIANI[1], Justin COBB, James MARROW[2], Richard ABEL[1]

[1] Imperial College London, London, United Kingdom

[2] Department of Materials, University of Oxford, Oxford, United Kingdom

Introduction: With information about a patient's bone mechanical properties orthopaedic operations could be optimised to reduce intra- and post-operative complications. However, there is currently no reliable method of measuring a patient's bone mechanical properties in vivo. We have previously investigated microindentation, using a 1.5mm diameter spherical indenter tip, and found no correlation between these measurements and compression testing measurements (Boughton et al., BORS, 2016). We hypothesised that by using a larger diameter indenter tip we would closer match bone millimetre-scale mechanical properties.

Method: 20 bone samples were taken from 20 patients undergoing hip replacement surgery. The samples were machined from the femoral neck calcar cortical bone into 6x3x3mm parallelepiped specimens, aligned with the osteons along the long axis. The samples were micro-computed tomography (CT) scanned to calculate porosity. Microindentation was performed using a 6mm diameter, sapphire, spherical indenter tip. 12 indentations were performed in a grid and the reduced moduli were calculated using the Oliver-Pharr method. Compression testing was then performed to failure and the apparent elastic modulus was calculated for each sample.

Results: The mean indentation reduced modulus was plotted against the compression apparent elastic modulus in Figure 1. A moderate correlation was found between the indentation reduced moduli and compression testing elastic moduli (r=0.52, r^2=0.275, p=0.018). In addition, a moderate correlation was found between the indentation reduced moduli and CT-measured porosity (r=0.5, r^2=0.251, p=0.025) and a strong correlation was found between compression testing moduli and porosity (r=0.75, r^2=0.568, p<0.001, Figure 2).

Conclusion: Using large-tip spherical microindentation, indentation reduced moduli correlated significantly with compression testing apparent elastic moduli in these 20 cortical bone specimens. Microindentation using a large, spherical indenter tip may predict the mechanical properties of bone at the millimetre length scale and shows promise as a potential future clinical decision aid in surgery.
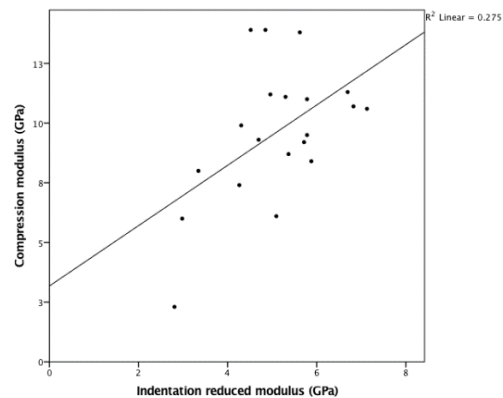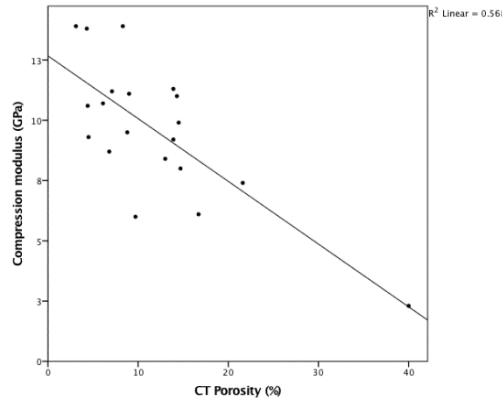
Figure 1.   Figure 2.

Decellularisation affects the strain rate dependent and dynamic mechanical properties of a xenogeneic anterior cruciate ligament graft

Jennifer EDWARDS [1], Eileen INGHAM [1], John FISHER, Anthony HERBERT [1]

[1] Institute of Medical and Biological Engineering, University of Leeds, Leeds, UK.

Introduction: We have developed a decellularised porcine superflexor tendon (pSFT), which has shown promising regenerative capacity in an ovine model of anterior cruciate ligament (ACL) repair. This study investigated the strain rate dependent and dynamic mechanical properties of native and decellularised pSFTs.

Methods: Decellularisation was carried out using a previously established procedure, including antibiotic washes, low concentration detergent (0.1% sodium dodecyl sulphate) washes and nuclease treatments.

Three different strain rates were employed: 1, 10 & 100%s^{-1} (n=6 for all groups). Toe-region modulus (E0), linear-region modulus (E1), transition coordinates (εT, σT), tensile strength (UTS) and failure strain were calculated. For DMA, specimens were loaded between 1 & 5MPa with increasing frequency up to 2Hz. Dynamic (E*), storage (E') and loss (E'') moduli, and tan delta were calculated for native and decellularised groups (n=6). Data was analysed by 2-way ANOVA and Tukey post-hoc test (p<0.05).

Results: For decellularised tendons, altering the strain rate did not affect any of the static tensile properties. For native pSFTs, the UTS, failure strain and E1 were not affected by changing the strain rate. Increasing the strain rate significantly increased E0 (1% vs 10% and 1% vs 100%) and σT (1% vs 100%) and decreased εT (1% vs 10% and 1% vs 100%) for native pSFT. E*, E' and E'' were all significantly reduced in decellularised specimens compared to native controls across all frequencies investigated. No significant differences were found for tan delta (figure 1).

Discussion: Evidence of strain rate dependency was witnessed in the native pSFTs by increase of the toe region modulus and displacements of the transition point coordinates. This response was not seen in the tissue following decellularisation. DMA demonstrated a reduction in dynamic, storage and loss moduli. Tan delta (E''/E') remained unchanged, indicating reductions in solid and fluid components are interlinked.
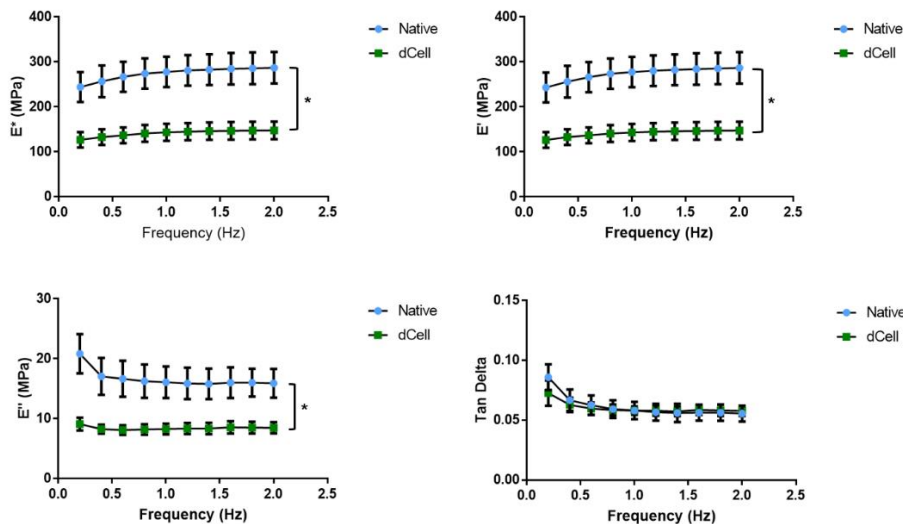

Figure 1.

Biomechanical Testing for the *in vitro* Testing of Intervertebral Disc Nucleus Augmentation Devices

Ruth COE[1], James WARREN, Sebastien SIKORA[1], Danielle MILES[1], Marlène MENGONI, Ruth WILCOX[1]

[1] IMBE, University of Leeds, Leeds, UK

Intervertebral disc (IVD) degeneration is one of the major causes of back pain. A number of emerging treatments for the condition have failed during clinical trial due to the lack of robust biomechanical testing during product development. The aim of this work was to develop improved in-vitro testing methods to enable new therapeutic approaches to be examined pre-clinically. It forms part of a wider programme of research to develop a minimally invasive nucleus augmentation procedure using self-assembling hydrogels.

Previous static testing on extracted IVDs have shown large inter-specimen variation in the measured stiffness when specimen hydration and fluid flow were not well controlled. In this work, a method of normalising the hydration state of IVDs prior-to and during compressive testing was developed.

Excised adult bovine IVDs underwent water-pik treatment and a 24-hour agitated bath in monosodium citrate solution to maximise fluid mobility. Specimens were submerged in a saline bath and held under constant pressure for 24 hours, after which the rate of change of displacement was low. Specimens were then cyclically loaded, from which the normalised specimen stiffness was determined. A degenerate disc model was developed with the use of enzymatic degeneration, allowing specimens to be tested sequentially in a healthy, degenerate, and then treated state. Self-assembling peptide-GAG hydrogels were tested using the developed method and the effect of treatment on stiffness and disc height were assessed.

Compared to previous static tests, the improved method reduced the variation in the normalised specimen stiffness. In addition, statistically significant differences were seen before and after enzymatic degradation to simulate degeneration, thus providing controls against which to evaluate treatments. The augmentation of the nucleus with the hydrogel intervention reduces the stiffness of the degenerate disc towards that of the healthy disc. This method is now being used to further investigate nucleus augmentation devices.
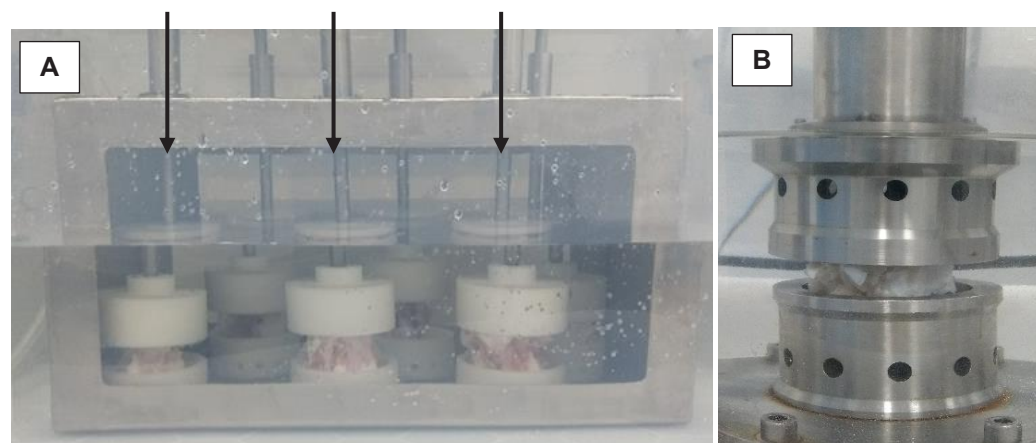

Figure 1 A) Disc specimens in PBS soak under load (black arrows show load application locations) and B) Specimen in materials testing machine for dynamic loading tests.

Estimation of viscoelastic bushing parameters of a musculoskeletal cervical spine model in impact scenarios

Pavlos SILVESTROS[1], Stuart BOYD[2], Bruno AGOSTINHO HERNANDEZ[2], Sabina GHEDUZZI[2], Harinderjit S. GILL[2], Ezio PREATONI[1], and Dario CAZZOLA[1]

[1] Department for Health (University of Bath, Bath, UK)

[2] Centre for Orthopaedic Biomechanics, Department of Mechanical Engineering (University of Bath, Bath, UK)

Head collisions in sport can result in catastrophic cervical spine injuries. Musculo-skeletal (MSK) modelling can help analyse the relationship between players' motion, external loading and internal stresses that lead to injury. However, the literature lacks sport specific MSK models. In automotive research the intervertebral disc behaviour has been represented as viscoelastic elements ("bushing"), whose stiffness and damping parameters are often estimated under quasi-static conditions and may lack validity in dynamic impacts.

The aim of this study was to develop a validated cervical spine model for axial impacts for future use in the analysis of head-first rugby collisions.

A drop test rig was used to replicate a sub-catastrophic axial head impact. A load of 80 N from 0.5 m was applied to the cranial aspect of a C2-C6 porcine spinal specimen mounted in the neutral position. The 3D motion of C3-C5 vertebras (4 kHz) and the cranial axial load (1 MHz) were measured via motion capture (Qualysis, Sweden) and a uniaxial load cell (RDP Electronics Ltd, UK). Specimen specific models were created in NMSBuilder and OpenSim after the vertebrae geometries were obtained from the segmentation of micro-CT images of the specimens. The compressive viscoelastic properties of four vertebral joints (C2-C3 through to C5-C6) were optimised via a Genetic Algorithm (MATLAB v2016b, The Mathworks Inc) to minimise tracking errors.

The optimisation converged to a solution of 140-49000 kN/m and 2000-8000 Ns/m for stiffness and damping respectively (RMSE=5.1 mm). Simulated joint displacements ranged between $0.09 - 1.75$ mm compared to experimental $0.1 - 0.8$ mm.

Optimal bushing parameters were higher than previously reported values measured through quasi-static testing [1]. Higher stiffness and damping values could be explained by the higher-dynamics nature of the event analysed related to a different part of the non-linear intervertebral disc load-displacement curve.
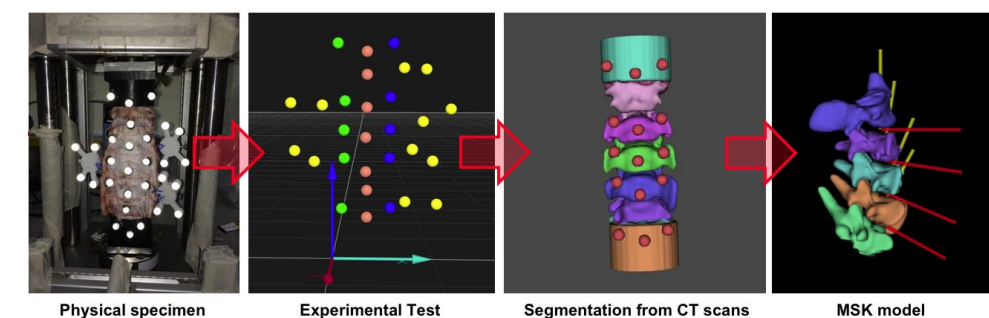

Physical specimen   Experimental Test   Segmentation from CT scans   MSK model

Figure 1: Modelling workflow used for the creation of the musculoskeletal model of the porcine specimen in OpenSim.

References:
1. Moroney et al.; (1998). JBiomech, **21**(9)

Physiological mechanical loading from voluntary wheel running promotes increased plasma membrane disruptions in osteocytes

Kanglun YU[1], Daniel BLUMENTHAL[1], Sarah BASS[1], Mackenzie L. HAGAN[1], Alberto CASTRO[2], Theodore GARLAND Jr.[2], Paul L. MCNEIL[1], Meghan E. MCGEE-LAWRENCE[1]

[1] Medical College of Georgia, Augusta University, Augusta GA USA

[2] UC Riverside, Riverside CA USA

Osteocytes direct bone adaptation to mechanical loading (e.g., exercise), but the ways in which osteocytes detect loading remain unclear. We recently showed that osteocytes develop repairable plasma membrane disruptions (PMD) in response to treadmill-running exercise, and that these PMD initiate mechanotransduction. As treadmill running is a non-voluntary activity for rodents, our current goal was to determine whether osteocytes develop PMD with voluntary wheel running as a better model of physiological exercise.

Male and female Hsd:ICR mice from lines selectively bred (>75 generations) to demonstrate high voluntary wheel running ("High Runners") or non-selected control lines ("Control") were studied (n=9 to 12 mice per sex per line, 4 lines each). At 12 weeks of age, half of the animals within each group were provided access to running wheels for 6 days while remaining mice had no wheel access.   Tibias were collected at sacrifice and bone mineral density was analyzed by DXA. Osteocyte PMD were quantified by immunochemistry for intracellular albumin. Groups were compared with 3-factor ANOVA.

Voluntary exercise (wheel access) significantly increased osteocyte PMD (+16.4%, p=0.013). PMD-labelled osteocytes did not differ between sexes (p=0.415). Male mice had significantly greater BMD (p=0.0007) and BMC (<0.0001) than females. Interestingly, mice with wheel access had significantly lower BMD and BMC compared to mice without wheel access (p<0.004), and high runner lines had significantly lower BMD (p=0.001) and BMC (p<0.0001) than control lines. This may reflect new bone formation in the exercising mice, as newly formed bone is less mineralized than older bone.

Data from this experiment support the idea that loading-induced disruptions develop in the osteocyte plasma membrane during both voluntary (wheel running) and forced (treadmill, shown previously) physical activity. These studies support the role of plasma membrane disruptions as a mechanosensation mechanism in osteocytes.

13:15 - 14:45 Session 3: Translation of Orthopaedic Research into Clinic

Chairs Mr Tom Kurien and Jake Bowd

13:15 -13:40 Keynote presentation – Dr John Wilkinson, MHRA

13:40 - 14:30 Free Papers

A Collagen-Based Soft Tissue Barrier Membrane with Periosteal Mesenchymal Stem Cell Homing Capability for Bone Defect Repair

Heather OWSTON[1,2], Katrina MOISLEY[1,2], Guiseppe TRONCI[3], Peter GIANNOUDIS[2], Stephen RUSSELL[3] and Elena JONES[2]

[1] Institute of Medical and Biological Engineering, School of Mechanical Engineering, University of Leeds, UK

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[3] Nonwovens Research Group, School of Design, University of Leeds, UK

The current 'gold' standard surgical intervention for critical size bone defect repair involves autologous bone grafting, that risks inadequate graft containment and soft tissue invasion[1]. Here, a new regenerative strategy was explored, that uses a barrier membrane to contain bone graft. The membrane is designed to prevent soft tissue ingrowth, whilst supporting periosteal regrowth, an important component to bone regeneration[2]. This study shows the development of a collagen-based barrier membrane supportive of periosteal-derived mesenchymal stem cell (P-MSC) growth.

P-MSC-homing barrier membranes were successfully obtained with nonaligned fibres, via free-surface electrospinning using type I collagen and poly(ϵ-caprolactone) in 1,1,1,3,3,3-Hexafluoro-2-propanol. Introduction of collagen in the electrospinning mixture was correlated with decreased mean fibre diameter (d: 319 nm) and pore size (p: 0.2-0.6 µm), with respect to collagen-free membrane controls (d: 372 nm; p: 1-2 µm). Consequently, as the average MSC diameter is 20 µm, this provides convincing evidence of the creation of a MSC containment membrane[3].

SEM-EDX confirmed Nitrogen and therefore collagen fibre localisation. Quantification of collagen content, using Picro Sirius Red dye, showed a 50% reduction after 24 hours (PBS, 37 °C), followed by a drop to 25% at week 3. The collagen-based membrane has a significantly higher elastic modulus compared to collagen-free control membranes. P-MSCs attached and proliferated when grown onto collagen-based membranes, imaged using confocal microscopy over 3 weeks. A modified transwell cell migration assay was developed, using MINUSHEET® tissue carriers to assess barrier functionality. In line with the matrix architecture, the collagen-based membrane proved to prevent cell migration (via confocal microscopy) in comparison to the migration facilitating positive control.

The aforementioned results obtained at molecular, cellular and macroscopic scales, highlight the applicability of this barrier membrane in a new 'hybrid graft' regenerative approach for the surgical treatment of critical size bone defects.

References

1   Dimitriou et al. BMC Med. 10(81):1-24, 2012

2   Chang & Knothe. Stem Cells Transl Med. 1(1):480-91, 2012

3   Siegel et al. BMC Med. 11(146):1-20, 2013

Introducing the Z-track method for cells-delivery injection in a model of atrophic non-union to prevent backflow leakage

Murtadhah JALAL[1], Hamish SIMPSON[1], Robert WALLACE[1], Bruno PEAULT[2]

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In atrophic non-union models, a minimally invasive technique is used to deliver stem cells into the fracture site via percutaneous injection. This technique is significantly affected by a backflow leakage and the net number of cells might be reduced. The Z-track method is a technique used in clinical practice for intramuscular injections to prevent backflow leakage. We evaluated the potential of the Z-track injection technique for preventing cell loss in non-union models by determining the behaviour of observable marker fluids. Firstly, toluene blue stain was used as an injection material to allow visual detection of its distribution. Rat's cadaver legs were used and tibias were kept unbroken to ensure intact skin and overlying soft tissue. Technique includes pulling the skin over the shin of tibia towards the ankle and injection of the dye around the mid-shaft *fig*.1(b, c&d). The needle was then partially pulled back, the skin was returned to its normal position and a complete extraction of the needle was followed *fig*.1(e). Secondly, a mixture of contrast material and toluene blue was used to allow direct visual and radiological detection of the injected material into the fracture site. Ante-grade nailing of tibia via tibial tuberosity was carried out followed by a 3 point closed fracture. Injection was performed into the fracture gap similarly to the steps above. X-rays were taken to visualise the location and distribution of the injected material, *fig*.1(g&h).
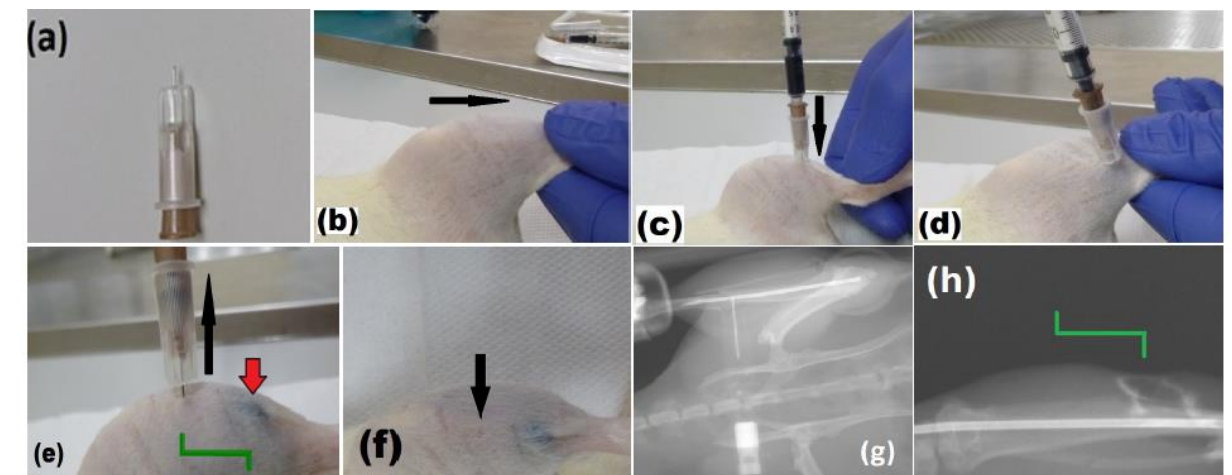
Observation revealed no blue stain could be detected over the skin *fig*.1(f), X -rays revealed that the radiopaque dye remained around the tibia with no escape of the material into the superficial layers or onto the skin surface, *fig*.1(h). Therefore, the number of cells delivered and maintained at a target site could be increased by the Z-track method and therefore, the therapeutic benefit of stem cell injections could be optimised with this simple technique.

Comparison of different tissue processing methods for maximization of bacterial recovery

Mohamed Askar[1], Waheed Ashraf[1], Brigitte Scammell[1], Roger Bayston[1]

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Introduction: Protocols for processing of tissue from arthroplasty infections vary and might affect the recovery of bacteria. We compared homogenization, bead beating and enzymatic disruption for recovery of live bacteria from tissue samples.

Methods: Suspensions of *Staphylococcus aureus* and *Escherichia coli* were prepared as controls. Three samples were taken from each and the first was bead beaten, the second homogenized, and Proteinase K was added for 10 and 30 minutes to the third sample before culturing. In addition, artificially inoculated pork tissue and known infected human tissue samples were processed by either homogenization or bead beating prior to cultures and results were compared.

Results: Number of cycles of bead beating and homogenization and duration of Proteinase K treatment had significant effects. Bead beating for 2 and 4 cycles reduced the yield of *S.aureus* to 52% and 20% of control, and *E.coli* to 33% and 8%. Homogenization for 2 and 4 cycles reduced *S.aureus* to 86% and 65% of control, and *E.coli* to 90% and 87%. Proteinase K for 10 minutes and 30 minutes reduced the yield of *S.aureus* to 75% and 33% of control, and *E.coli* to 91% and 49% respectively. Inoculated Pork tissue showed a reduction in *S.aureus* recovery of 90% for bead beating compared to homogenization, and 80% in the case of *E.coli*. Bead beating of infected human tissue samples reduced the yield by 58% compared to homogenization.

Conclusions: Bead-beating is a common recommended method of processing tissue from arthroplasty cases. However, even though it produces a homogeneous sample, it does so at the cost of significant loss of viable bacteria. Homogenization and 10 minutes of Proteinase K incubation are almost equivalent, but the homogenizer is preferred being more controllable and cheaper. This should help to define guidelines for diagnosing infections using tissue samples.

Genome-wide expression analysis of human osteoblasts on prosthesis surfaces following clinically relevant cobalt and chromium exposure

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Commonly used alterations of prosthetic surfaces include grit-blasting (GB), plasma-sprayed titanium (Ti) or hydroxyapatite (HA) coating. Systemic concentrations of cobalt (Co) and chromium (Cr) are elevated in patients with metal-on-metal hip replacement, but can occur for all modular hip replacements. Here, we use whole genome microarrays to assess differential gene expression in primary human osteoblasts grown *in vitro* and on these prosthesis surfaces following exposure to clinically relevant concentrations of Co and Cr.

Mesenchymal cells obtained from bone-fragments of 3 patients undergoing joint replacement surgery were differentiated into osteoblasts. Subsequently, cells were cultured *in vitro* on tissue-culture plates (TCP), or on GB, Ti and HA surfaces (JRI Orthopaedics Ltd, Sheffield, UK). Following 24hr exposure to a combination of clinically equivalent concentrations of $Co^{2+}:Cr^{3+}$, RNA was extracted and hybridized to SurePrint-G3 Gene Expression Microarray. Probe signals were normalised using 'Limma' package on R-Bioconductor and differential gene expression assessed with empirical Bayes approach ($Log_2FC>1.00$, $P<0.001$ for differentially expressed genes).

For cells grown on TCP, 11 genes were upregulated with 500µg/L $Co^{2+}:Cr^{3+}$. Of these, 4 were associated to HIF-1 signalling based on KEGG pathway analysis ($P=5.4e^{-5}$). Exposure to 1000µg/L $Co^{2+}:Cr^{3+}$ altered expression at 164 loci for HA surfaces, and a separate 50 loci for Ti surfaces compared to GB surfaces. Genes for osteoblast differentiation (*BMP2* and *RGS2)* were downregulated on HA surfaces compared to GB, whilst genes for cell-adhesion (*ESAM*), vesicular trafficking (*RAB37*) and protection against oxidative damage (*NRF2*) were upregulated. Ti surfaces caused an upregulation in *ERBB3* and *CNTF*, which are associated with inhibition of osteoblast differentiation and mineralisation, when compared to GB surfaces.

This study confirms the role of HIF-1 signalling in response to prosthesis generated metal ions, and is the first to provide a comprehensive genome-wide insight into transcriptional response of osteoblasts at prosthesis surface to clinically equivalent metal exposure.

Nanotubes improve Human Dermal Fibroblasts and Keratinocytes attachment on Intraosseous Transcutaneous Amputation prosthesis

Elena GIUSTO [1], Catherine PENDEGRASS[1], Chaozong LIU[2], Gordon BLUNN

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Intraosseous Transcutaneous Amputation Prosthesis (ITAP) is a new generation of limb replacements that can provide to amputees, an alternative solution to the main problems caused by the most common used external prosthesis such as pressure sores, infections and unnatural gait. ITAP is designed as one pylon osteointegrated into the bone and protruding through the skin, allowing both the mechanical forces to be directly transferred to the skeleton and the external skin being free from frictions and infections. The skin attachment to the implant is fundamental for the success of the ITAP, as it prevents the implant to move and consequently fail.

In this study we wanted to test if cell viability and attachment was improved using TiO_2 nanotubes.

Human keratinocytes and human dermal fibroblasts were seeded for three days on TiO_2 nanotubes with different sizes (18-30nm, 40-60nm and 60-110nm), compared with controls (smooth titanium) and tested for viability and attachment. A Mann-Whitney U test was used to compare groups where p values < 0.05 were considered significant. The results showed that the viability and cell attachment for keratinocytes were significantly higher after three days on controls comparing with all nanotubes (p=0.02), while attachment was higher on bigger nanotubes and controls. Cell viability for fibroblasts was significantly higher on nanotubes between 40 and 110nm comparing with smaller size and controls (p=0.03), while investigation of cell attachment is ongoing. From these early results, we can say that TiO_2 nanotubes can improve the soft tissue attachment on ITAP. Further *in-vitro* and *ex-vivo* experiments on cell attachment will be carried out.
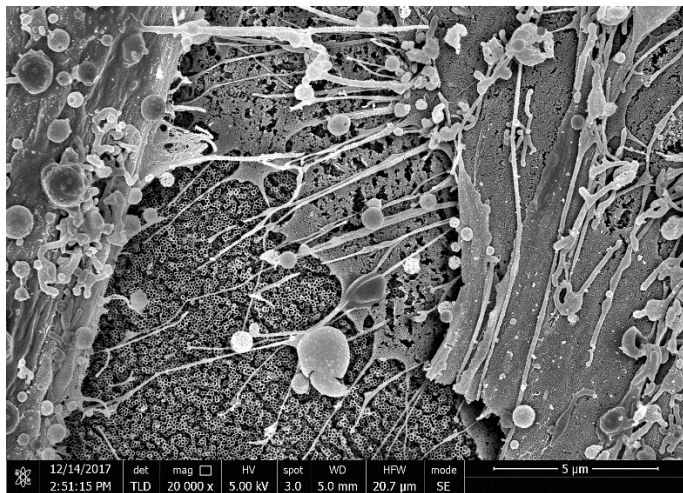

Figure 1: example of HDF on 20nm nanotubes

15:40 - 16:30 Session 5: Manufacturing in Orthopaedics

Chairs Dr Tony Herbert and Lekha Koria

15:40 Combined Keynote – Prof Eileen Ingham and Prof Ruth Wilcox, Leeds

16:10 - 16:40 Free Papers

The effect of pore size on bone marrow mesenchymal stem cell morphology, proliferation and mineralisation of bone in vitro.

Anita Sanghani-Kerai[1], Anthoulla Achilleos[1], Henry Lanchashire[1], Melanie Coathup[1], Gordon Blunn[2]

[1] University College London, United Kingdom

[2] University of Portsmouth, United Kingdom

Introduction: During remodelling, osteoclasts produce discrete bone cavities filled with bone and this is associated with the dimensions of the cavity. The aim of this study is to investigate the effect of pores of similar size to those produced by osteoclasts on the morphology, proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) in vitro. The hypothesis is that a porous surface similar in morphology to a bone surface prepared by osteoclasts will increase cell proliferation and osteogenic differentiation of MSCs.

Materials and methods: Sheep BMSCs were seeded onto plain titanium surfaces and 100μm, 250μm and 500μm discrete pores surfaces. Cell metabolic activity was investigated using Presto Blue on days 3, 7 and 10. Bone mineralisation was quantified by Alizarin red staining at days 3, 7 and 14. Cell morphology was observed by scanning electron microscopy (SEM). Data was statistically analysed using one-way analysis of variance and a Bonferroni correction method.

Results: Cells on porous discs had a three dimensional phenotype and aligned on the circumference of each pore. Metabolic activity was significantly higher by day 10 on plain discs compared to all porous discs. Bone mineralization was significantly higher on 100μm pores by day 3 (0.545mM±0.66; p=0.047) than plain discs and significantly higher on both 100μm and 250μm pores by day 7(p=0.000 and p=0.005) than plain discs. Substantial mineralised bone matrix was found on 100μm discs without being treated with osteogenic supplements, compared to other control disc types (p=0.043, p=0.003, p=0.000).

Conclusions: The different topographies altered cell behaviour and migration.100μm pores demonstrated earlier and enhanced bone mineralisation even in the absence of osteogenic supplements. This pore size is aligned to the size of individual resorption bays that osteoclasts produce on bone surfaces and is considerably lower than the pore sizes used to enhance osteo-integration of implant surfaces.

Nanotechnology based antimicrobial drug delivery system for orthopaedic application

Yazan Al Thaher[1], Stefano Perni[1], Polina Prokopovich[1].

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Total joint replacement (TJR), such as hip and knee replacement, is commonly used for the treatment of end stage arthritis. The use of Poly (methylmethacrylate) bone cement is a gold standard in such replacement, where it fixes the implant in place and transfer stresses between bone and implant, and frequently used for local delivery of drugs such as antibiotics. The use of antibiotic loaded bone cement is considered a well-established standard in the treatment and prophylaxis of Prosthetic joint infections (PJI). PJIs is a serious problem that decreases success rate of surgery and can be life threatening to patients, where the incidence can reach up 2% in total and hip replacements and up to 40% for revision surgery. Currently used antibiotic loaded bone cements have many limitations, including burst release of < 10% of antibiotic added. This burst release falls rapidly below inhibitory level within few days, which leads to selection of resistant antimicrobial strains and does not provide prophylaxis from early and delayed stage infection. This study aims to provide a controlled release for gentamicin when loaded on Silica nanoparticles (NP) using layer-by-layer technique (LbL) to provide prophylaxis and treatment from postsurgical infections. The gentamicin loaded NPs were incorporated into PMMA bone cement and the new nanocomposite is characterized for gentamicin release, antimicrobial and mechanical properties.

Our results showed that the nanocomposite gentamicin release continued for 30 days at concentration 3 times higher than the commercial formulation containing the same amount of gentamicin, where burst release for few days were observed. Moreover, the nanocomposite showed superior antimicrobial inhibition for bacterial growth and good cytocompatibility without adversely affecting the cement compressive strength, bending and fracture toughness properties.

A biomimetic peptide/glycosaminoglycan hybrid hydrogel for nucleus pulposus augmentation therapy utilising minimally invasive methods

James P WARREN[1,2*], Ruth COE[1], Sebastien SIKORA[3], Danielle E MILES[4], Paul BEALES[2] and Ruth K WILCOX[1]

[1]Institute of Medical and Biological Engineering, [2]School of Chemistry, [3]School of Earth and Environment, [4]Innovation and Knowledge Centre, University of Leeds, UK

Purpose: To develop a novel, minimally invasive therapy for nucleus pulposus augmentation without the need for major surgical incision.

Methods: Two optimum patented self-assembling peptides based on natural amino acids were mixed with glycosaminoglycans (GAGs) to form reversible, tunable hydrogels that mimic the vital biological osmotic pumping action and aid in swelling pressure of the intervertebral disc (IVD). Separate peptide and GAG solutions can be switched from fluid to gel upon mixing inside the body. The gels were analysed using a series of complementary techniques (FTIR, TEM & rheometry) to determine their cross-length scale structure and properties. Approaches to developing a clinical product were then developed including the incorporation of a fluorescent probe and a CT contrast agents to aid visualization of the gels, and a semi-automatic syringe driver rig, incorporating a pressure sensor, for the delivery of the solutions into the intervertebral discs. The efficacy of the procedure in restoring disc height and biomechanics was examined using chemically degenerated bovine caudal samples.

Results: It was found the presence of the GAGs stabilized the peptides forming stiffer gels, even upon injection through a long (~10cm) small gauge needle. The injected gels were easily visualized post injection by microCT and by eye during dissection under visible and UV light. It was also noted that following injection, the disc height of the degenerated samples was restored to a similar level of that observed for native discs.

Conclusion: A hydrogel has been developed that is injected through a narrow bore needle using a semi-automatic delivery rig and forms a self-assembled gel *in situ* which has shown to restore the disc height. Further tests are now underway to examine their biomechanical performance across more physiological time periods.

Tuesday 11 September 2018

09:00 - 10:30 Session 6: Trauma

Chairs Dr Jerry Tsang and Alex Seghal

09:00 Keynote presentation: Trauma Research - current scope and future horizons.

Prof Ian Pallister, Swansea

09:30 - 10:30 Free Papers

Mechanical characterisation of the lateral collateral ankle ligaments under sprain-like conditions

David ROCHELLE[1], Anthony HERBERT[1], Ioannis KTISTAKIS[2], Anthony REDMOND[2], Graham CHAPMAN[2], Claire BROCKETT[1]

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[2] Chapel Allerton Hospital, Leeds, England

Whilst lateral ankle sprain is often considered a benign injury it represents between 3-5% of all A&E visits in the UK. The mechanical characteristics of ankle ligaments under sprain-like conditions are scarcely reported. The lateral collateral ankle ligaments were dissected from n=6 human cadaveric specimens to produce individual bone-ligament-bone specimens. An Instron Electropuls E10000 was used to uni-axially load the ankle ligaments in tension. The ligaments were first preconditioned between 2 N and a load value corresponding to 3.5% strain for 15 cycles and then strained to failure at a rate of 100%/s. The mean ultimate failure loads and their standard deviations for the anterior talofibular (ATFL), calcaneofibular (CFL) and posterior talofibular (PTFL) ligaments are 351.4±105.6 N, 367.8±76.1 N and 263.6±156.6 N, respectively. Whilst the standard deviation values are high they align with those previously reported for ankle ligament characterisation. The large standard deviations are partly due to the inherent variability of human cadaveric tissue but could also be due to varying previous activity levels of participants or a prior unreported ankle sprain. Although the sample size is relatively small the results were stratified to identify any potential correlations of age, BMI and weight with ultimate load. A strong Pearson correlation (r=0.919) was found between BMI and ultimate load of the CFL but a larger sample size is required to confirm a link. The ligament failure modes were observed and categorised as avulsion or intra-ligamentous failure. The ATFL avulsed from the fibula in five instances and intra-ligamentous failure occurred once. The CFL avulsed from the fibula twice and failed four times through intra-ligamentous failure. Finally, the PTFL avulsed from the fibula once, avulsed from the talus once and failed through intra-ligamentous failure in four instances. The results identify the forces required to severely sprain the lateral collateral ankle ligaments and their failure modes.

Stratification of decellularised porcine super flexor tendon for replacement of the anterior cruciate ligament

Samuel WHITAKER [1] Jennifer EDWARDS [2], Stephen GUY [3], Eileen INGHAM [2], John FISHER [2], Anthony HERBERT [2]

[1] Leeds General Infirmary, Leeds, UK

[2] Institute of Medical and Biological Engineering, University of Leeds, Leeds, UK

[3] Bradford Royal Infirmary, Bradford, UK

Introduction: The concept of decellularised xenografts as a basis for anterior cruciate ligament (ACL) reconstruction was introduced to overcome limitations in alternative graft sources such as substantial remodelling delaying recovery and donor site morbidity. This study aimed to measure the biomechanical properties of decellularised porcine super flexor tendon (pSFT) processed to create ACL grafts of varying diameters, with a view to facilitating production of stratified 'off the shelf' products with specified functional properties for use in ACL reconstructive surgery.

Methods: Decellularisation was carried out using a previously established procedure, including antibiotic washes, low concentration detergent (0.1% sodium dodecyl sulphate) washes and nuclease treatments. Decellularised pSFTs were prepared to create double-bundle grafts of 7, 8 and 9mm diameter (n=6 in each group). Femoral and tibial fixations were simulated utilising Arthrex suspension devices (Tightrope®) and interference screws in bovine bone respectively.

Dynamic stiffness and creep were measured under cyclic loading between 50-250N for 1000 cycles at 1Hz. This was followed by ramp to failure at 200mm/min from which linear stiffness and load at failure were measured. Data were analysed using either 1- or 2-way ANOVA as appropriate with Tukey post-hoc analysis (p<0.05).

Results: Significant differences were found between all groups for dynamic stiffness (figure 1a) and between 7 & 9mm and 8 & 9mm groups for dynamic creep (figure 1b). Significant differences were also found between 7, 8 & 9mm groups for linear stiffness (167.8±4.9, 186.9±16.6 & 216.3±12.4N/mm respectively), but no significant differences were found between groups for load at failure (531.5±58.9, 604.1±183.3 & 627.9±72.4N respectively).

Discussion: This study demonstrated that decellularised pSFTs possess comparable biomechanical properties to other ACL graft options (autografts and allografts). Furthermore, grafts can be stratified by their diameter to provide varying biomechanical profiles depending on the anatomy and individual needs of the recipient.
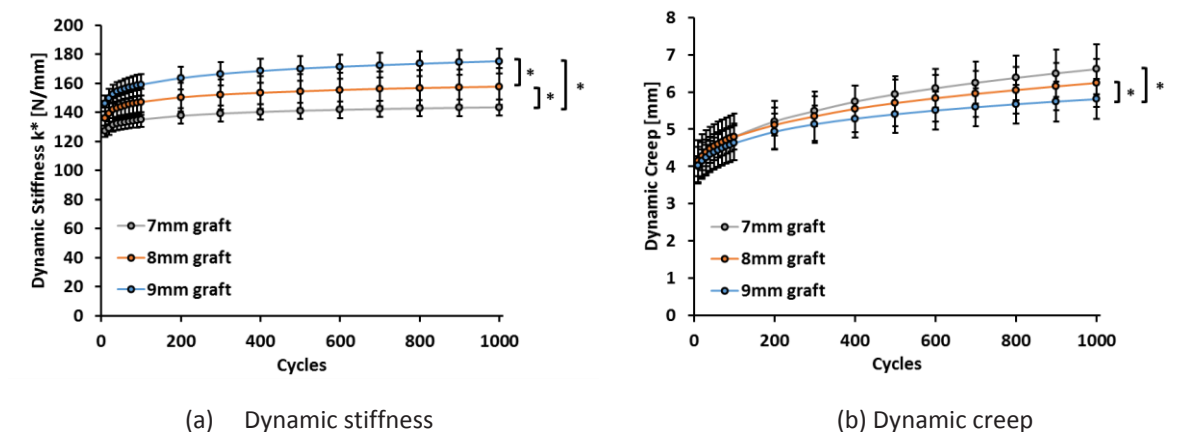

(a) Dynamic stiffness (b) Dynamic creep

Development of a method for proper X-ray viewing of the leg in a clinically-relevant model of atrophic non-union

Murtadhah JALAL[1], Hamish SIMPSON[1], Robert WALLACE[1]

[1] Orthopaedics Department, School of Clinical Sciences, University of Edinburgh, Edinburgh, UK

ABSTRACT: Appropriate in vivo models can be used to understand atrophic non-union pathophysiology. In these models, X-ray assessment is essential and a reliable good quality images are vital in order to detect any hidden callus formation or deficiency. However, the radiographic results are often variable and highly dependent on rotation and positioning from the detector/film. Therefore, standardised A-P and lateral x-ray views are essential for providing a full radiological picture and for reliably assessing the degree of fracture union.

We established and evaluated a method for standardised imaging of the lower limb and for reliably obtaining two perpendicular views (e.g. true A-P and true lateral views). The normal position of fibula in murine models is posterolateral to the tibia, therefore, a proper technique must show fibula in both views. In order to obtain the correct position, the knee joint and ankle joints were flexed to 90 degrees and the foot was placed in a perpendicular direction with the x-ray film. To achieve this, a leg holder was made and used to hold the foot and the knee while the body was in the supine position, *fig.*(c). Lateral views were obtained by putting the foot parallel to the x-ray film. Adult Wister rat cadavers were used and serial x-rays were taken *fig.*(a&b).
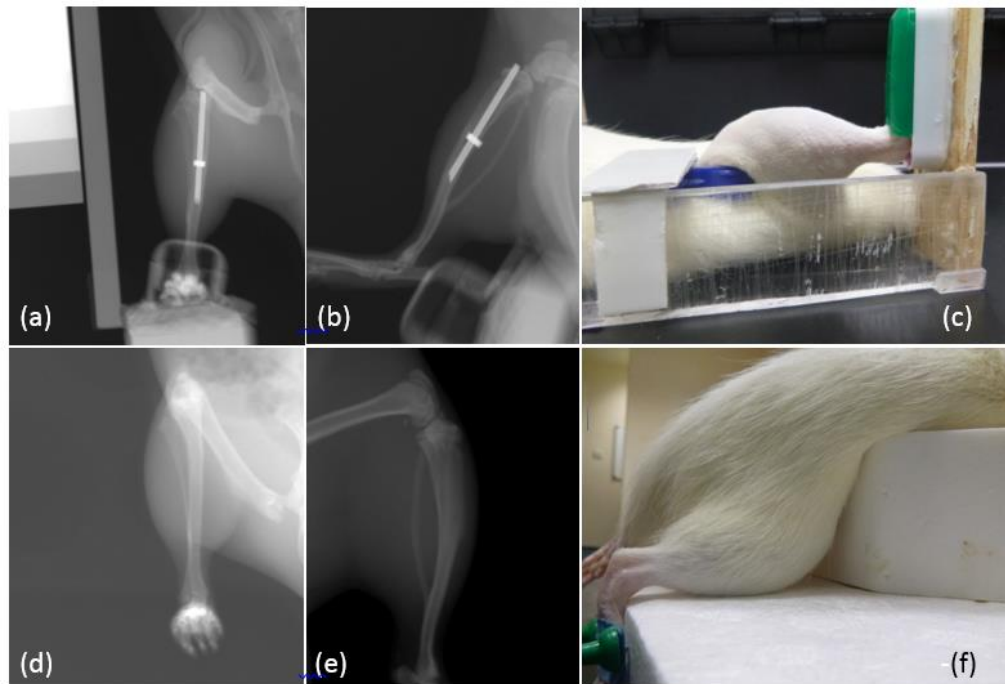
A-P view in supine position showed the upper part of the fibula clearly, however, there was an unavoidable degree of external rotation in the whole lower limb, and the lower part of the fibula appeared behind the tibia. Therefore, a true A-P view whilst the body was in the supine position was difficult. To overcome this, a P-A view of the leg was performed with the body prone position, *fig.*(f), this allowed both upper and lower parts of the fibula to appear clearly in both views *fig.*(d&e). This method provides two true perpendicular views (P-A and lateral) and helped to optimise radiological assessment.

Comparison of vertebral body displacements obtained by DIC and motion capture in a cervical spine impact experiment

Stuart BOYD[1], Pavlos SILVESTROS[2], Bruno AGOSTINHO HERNANDEZ[1], Dario CAZZOLA[2], Ezio PREATONI[2], Harinderjit S. GILL[1] and Sabina GHEDUZZI [1]

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Digital image correlation (DIC) is rapidly increasing in popularity in biomechanical studies of the musculoskeletal system. DIC allows the re-construction of full field displacement and/or strain maps of the surface of an object. DIC systems typically consist of two cameras focussing on the same region of interest. This constrains the angle between the cameras to be relatively narrow when studying specimens characterised by complex geometrical features, giving rise to concerns on the accuracy of the out of plane estimates of movement.

The aim of this research was to compare the movement profiles of bony segments measured by DIC and by an optoelectronic motion capture system.

Five porcine cervical spine segments (C2-C6) were obtained from the local butcher. These were stripped of all anterior soft tissues while the posterior structures were left intact. A speckle pattern was applied to the anterior aspect of the specimens, while custom made infrared clusters were rigidly attached to the 3 middle vertebral bodies (C3-C5). The specimens were mounted in a custom made impact rig which fully constrained C6 but allowed C2 to translate in the axial direction of the segment. Images were acquired at 4kHz, both for the DIC (Photron Europe Ltd, UK) and motion capture cameras (Qualisys Oqus 400, Sweden). The in-plane and out of plane displacements of each of the VBs were plotted as a function of time and the similarity between the curves thus obtained was analysed using the SPM1D technique which allowed a comparison to be made in terms of t-statistics. No statistical differences were found between the two techniques in all axis of movement, however the out of plane movements were characterised by higher variance which is attributed to the uncertainty arising from the near parallel positioning of the cameras in the experimental set-up.

Figure 1: experiment set up and coordinate system

Figure 2: SPM statistics output for the dataset considered
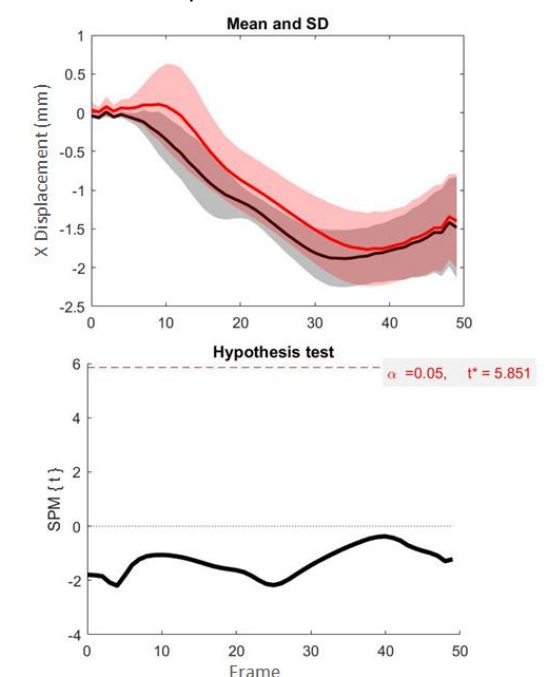
Computational modelling of tendons and ligaments, a pathway to understand damage mechanisms

Marlène MENGONI

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INTRODUCTION: Ligaments and tendons are connective tissues with a highly hierarchical structure, from collagen fibres, to fibrils and fascicules. Their intricate structural arrangement produces an anisotropic non-linear elastic mechanical behaviour and a complex damage pattern before failure. Recent constitutive models have been developed with all parameters describing the structure of the tissue, with the advantage that they can in theory be measured on the tissue rather than being phenomenologically-derived. This is an ideal framework to model damage as its onset and propagation can be associated to changes in the structure directly.

METHODS: In this preliminary study, the possibility to identify damage mechanisms in the tissue structure using in silico models was analysed for both the anterior cruciate ligament, with fascicules forming a helix with its longitudinal axis, and the patellar tendon, with fascicules co-aligned with its longitudinal axis. Tissues of interest were modelled as cylinders submitted to uniaxial tension. Damage was modelled as either a reduction of collagen volume fraction with increased strain, assuming the number of collagen fibres sustaining load decreases as fibres fail, or a reduction of the modulus of the fibres, assuming pre-failure damage of the fibres. Each damage mechanism was associated with a damage variable with different fibre stretch threshold for damage initiation and assuming linear variation of damage until an arbitrary failure point.

RESULTS: The apparent behaviour of the modelled tissues was significantly different as damage thresholds (see figure 1), damage mechanisms, type of fascicules were varied.

DISCUSSION: This preliminary work showed that using a structural constitutive model to describe occurrence and propagation of structural damage in an *in silico* model of hierarchical connective tissues is a framework that can clearly differentiate at a macroscopic level between different values of damage threshold and different damage mechanisms for tissue with co-aligned or helical fascicules.
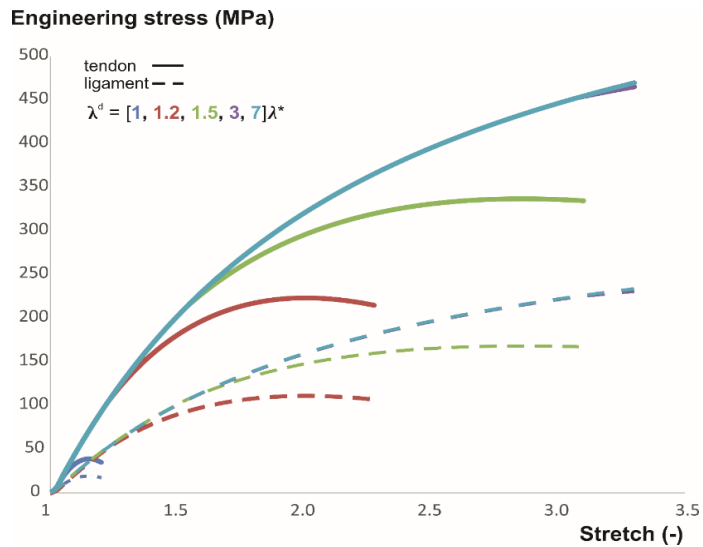

Figure 1. Variation in apparent behaviour of the tissues with different damage threshold in a model of damage as reduction of the volume fraction of the collagen fibres bearing load

11:00-12:50 Session 7: OATech Network

Chair Prof Cathy Holt and Prof Philip Rowe

11:00 - 12:00 OATech+ Research Presentations

The biomechanical characterisation of subjects with medial and lateral knee focal cartilage defects

Nidal KHATIB[1], Christopher WILSON[2], Deborah J MASON[1], Cathy A HOLT[1]

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Introduction: Focal cartilage defects (FCDs) found in medial and lateral compartments of the knee are accompanied with patient-reported pain and loss of joint function. There is a deficit of evidence to explain why they occur. We hypothesise that aberrant knee joint loading may be partially responsible for FCD pathology, therefore this study aims to use 3-dimensional motion capture (MoCap) analysis methods to investigate differences in gait biomechanics of subjects with symptomatic FCDs.
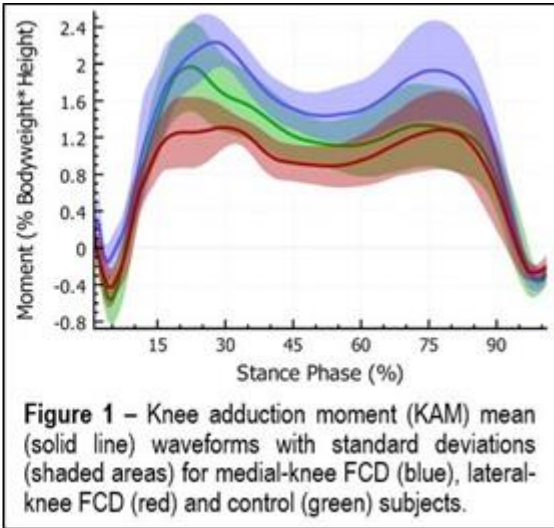
Methods: 11 subjects with Outerbridge grade II FCDs of the tibiofemoral joint (5 medial compartment, 6 lateral compartment) and 10 non-pathological controls underwent level-gait MoCap analysis using an infra-red camera (Qualisys) and force-plate (Bertec) passive marker system. 6-degree of freedom models were generated and used to calculate spatio-temporal measures, and frontal and sagittal plane knee, hip and ankle rotation and moment waveforms (Visual 3D). Principle component analysis (PCA) was used to score subjects based on common waveform features, and PC scores were tested for differences using Mann-Whitney tests (SPSS).

Results and Discussion: No group differences were found in BMI, age or spatio-temporal measures. Medial-knee FCD subjects experienced higher (p=0.05) overall knee adduction moments (KAMs) compared to controls. Conversely, lateral-knee FCD subjects found lower (p=0.031) overall KAMs. Knee flexion and extension moments (KFMs/KEMs) were relatively reduced (p=0.013), but only in medial FCD subjects. This was accompanied by a significantly (p=0.019) higher knee flexion angle (KFA) during late-stance.

Significance: KAMs have been shown to be predictive of frontal plane joint contact forces, and therefore our results may be reflective of FCD subjects overloading their respective diseased knee condyles. The differences in knee sagittal plane knee moments (KFMs/KEMs) and angles (KFA) seen in medial FCD subjects are suggestive of gait adaptations to pain. Overall these results suggest treatments of FCDs should consider offloading the respective affected condyle for better surgical outcomes.

Table 1 – Principle component features of gait waveforms that significantly differed (p<0.05) between medial-knee FCD group (blue), lateral-knee FCD group (orange) and controls.

Figure 1 – Knee adduction moment (KAM) mean (solid line) waveforms with standard deviations (shaded areas) for medial-knee FCD (blue), lateral-knee FCD (red) and control (green) subjects.

Epigenetic drugs as potent modulators in osteoarthritis

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Introduction: Osteoarthritis (OA) is a leading cause of joint pain, deformity and functional limitation. An imbalance of anabolic and catabolic activity results in destruction of the extracellular matrix of articular cartilage. While there is evidence to support the role of DNA methylation in the pathogenesis of OA, the effect of other epigenetic modifications is yet to be described. This study looks at the effect of two novel epigenetic modifiers, PFI-1, a bromodomain inhibitor, and SGC707, a histone methytransferase inhibitor, on gene expression in the pathogenesis of OA.

Methods: Chondrocytes were extracted from OA femoral heads (n=6), cultured and incubated with increasing concentrations of the compounds. Cells were treated with media alone (control), interleukin 1-beta (IL-1β) plus oncostatin M (OSM) alone, or in combination with PFI-1 or SGC707. Levels of expression of *iNOS*, *COX2*, *IL8*, *IL1B*, matrix metalloproteinase-13 (*MMP13*), *RUNX2* and *COL9A1* were measured using qRT-PCR.

Results: PFI-1 (0.5 and 5μM) suppressed expression of catabolic genes in OA chondrocytes, at basal levels and when co-stimulated with IL-1β+OSM. While there was a decrease in catabolic gene expression (*iNOS*, *COX2*, *IL8*, *IL1B* and *MMP13*), *RUNX2* expression was also supressed. There was no effect on expression of *COL9A1*, an anabolic chondrocytic gene. SGC707 (0.1 and 1μM) did not induce a reduction in expression of all the catabolic genes, with a less predictable effect on gene expression than PFI-1.

Conclusions: This study has demonstrated that the BET inhibitor PFI-1 has a potent protective effect against cartilage degradation, through its action as an epigenetic modifier in modulating the expression of catabolic genes in OA chondrocytes. This further validates the role of epigenetics in OA, with potential implications for therapeutic interventions.
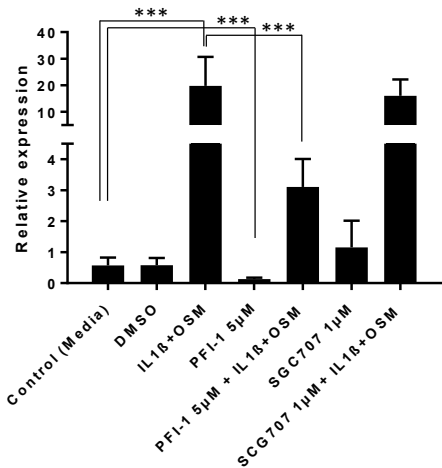

Figure. The effect of PFI-1 and SGC707 on *MMP13* expression relative to *GAPDH* when stimulated with IL-1ß plus OSM in OA chondrocytes. p<0.0001

The *in vivo* compatibility, integration and regeneration of a decellularised porcine bone scaffold in an ovine model

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Decellularised extracellular matrix scaffolds show great promise for the regeneration of damaged musculoskeletal tissues (cartilage, ligament, meniscus), however, adequate fixation into the joint remains a challenge. Here, we assess the osseo-integration of decellularised porcine bone in a sheep model. This proof-of-concept study supports the overall objective to create composite decellularised tissue scaffolds with bony attachment sites to enable superior fixation and regeneration.

Porcine trabecular bone plugs (6mm diameter, 10mm long) were decellularised using a novel bioprocess incorporating low-concentration sodium dodecyl sulphate with protease inhibitors. Decellularised bone scaffolds (n=6) and ovine allograft controls (n=6) were implanted into the condyle of skeletally mature sheep for 4 and 12 weeks. New bone growth was visualised by oxytetracycline fluorescence and standard resin semi-quantitative histopathology.

Scaffolds were found to be fully decellularised and maintained the native microarchitecture. Following 4-week implantation in sheep, both scaffold and allograft appeared well integrated. The trabecular spaces of the scaffold were filled with a fibro-mesenchymal infiltrate, but some areas showed a marked focal lymphocytic response, associated with reduced bone deposition. A lesser lymphocytic response was observed in the allograft control. After 12-weeks the lymphocytic reaction was minimised in the scaffold and absent in allografts. The scaffold showed a higher density of new mineralized bone deposition compared to allograft. New marrow had formed in both the scaffold and allografts.

Following the demonstration of osteointegration this bioprocess can now be transferred to develop decellularised composite musculoskeletal tissue scaffolds and decellularised bone scaffolds for clinical regeneration of musculoskeletal tissues.

Figure 1. Fluorescently labelled newly deposited mineralized bone. Resin embedded explants of decellularised porcine or allograft ovine bone before implantation (T=0) and following 4 and 12 week implantation in sheep. Dotted line indicates host-graft interface. Scale bar = 1000 μm.

Universal drug delivery platform into cartilage

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The efficient delivery of therapeutic molecules to the cartilage of joints is major obstacle in developing useful therapeutic interventions; hence, a targeted drug delivery system for this tissue is critical. We have overcome the challenge by developing a system that employs electrostatic attraction between the negatively charged constituents of cartilage and a positively charged polymer, poly-beta amino esters (PBAEs). We have demonstrated cartilage uptake of dexamethasone (DEX) covalently bound to the PBAE was doubled and retention in tissues prolonged compared to the equivalent dose of the commercial drug formulation. Moreover, no adverse effects on chondrocytes were found. Our data also show [1, 2] that PBAEs can bind not only healthy cartilage tissues but also enzymatically treated cartilage mimicking early stages of OA. Our PBAEs-prodrug technology's advantages are fourfold; the specificity and efficacy of its targeting mechanism for cartilage, the ease of its production and the low-cost nature of the delivery system

References:

1. Perni, Stefano and Prokopovich, Polina 2017. Poly-beta-amino-esters nano-vehicles based drug delivery system for cartilage. Nanomedicine: Nanotechnology, Biology and Medicine 13 (2) , pp. 539-548. 10.1016/j.nano.2016.10.001

2. Prokopovich and Perni. Patent: POLY(BETA-AMINO ESTER) CONJUGATES FOR CARTILAGE AGENT DELIVERY AND METHODS, PCT/GB2015/052028
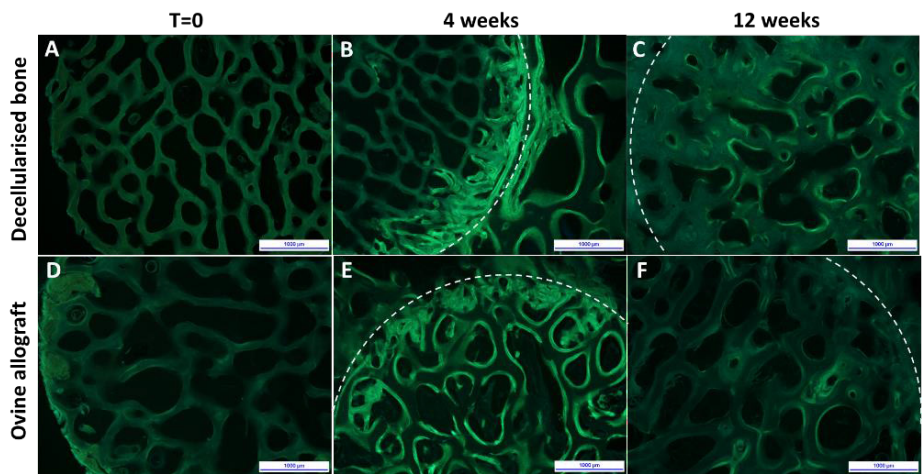
14:10 - 15:40 Session 8: Orthopaedic Outcomes

Chairs Mr Oliver Broughton and Ruben Doyle

14:10 Keynote presentation – Prof Ashley Blom, University of Bristol

14:40 - 15:40 Free Papers

Bone Ageing Atlas Development: The UK Biobank Study

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Ageing is associated with a gradual and progressive bone loss, which predisposes to osteoporosis. Given the close relationship between the involutional bone loss and the underlying mechanism of osteoporosis, improving the understanding of the bone ageing process can lead to enhanced preventive and therapeutic strategies for osteoporosis. To facilitate this understanding, we develop a spatio-temporal atlas of ageing bone in the femur.

We applied our method to a cohort of 11,576 Caucasian women (20-97 years). We amalgamated data from three different studies: 5095 women from the UK Biobank study, 1609 women from the OPUS study, and 5112 women from the MRC-Hip study. The scans are collected using either a Hologic QDR 4500A (Waltham, MA), a Lunar GE iDXA (Madison, WI), or a Lunar GE Prodigy (Madison, WI). Pixel BMD maps were exported using APEX v3.2 and Encore v16 for scans collected on Hologic Inc. and Lunar Corp., respectively. The method utilises a thin plate spline (TPS) registration to warp each scan to a reference mean shape. This image warping, termed Region Free Analysis (RFA), aims to eliminate morphological variation and establish a correspondence between pixel coordinates. At each pixel coordinate, the BMD evolution with ageing was modelled using smooth quantile curves. We deployed the R-package 'VGAM' to fit the smooth quantile curves.

Fig. 1a shows the constructed atlas. Cortical thinning was observed consistently with ageing around the shaft from the 60th onwards. A widespread bone loss was also observed in the trochanteric area. Quantile regression curves demonstrated different rates of bone loss at different anatomic locations (Fig. 1b-d). For example, bone loss was observed consistently in the mid-femoral neck, while bone mass was preserved the most in the inferior cortex. The developed atlas provides new insights into the spatial bone loss patterns, for which the conventional DXA analysis is insensitive.
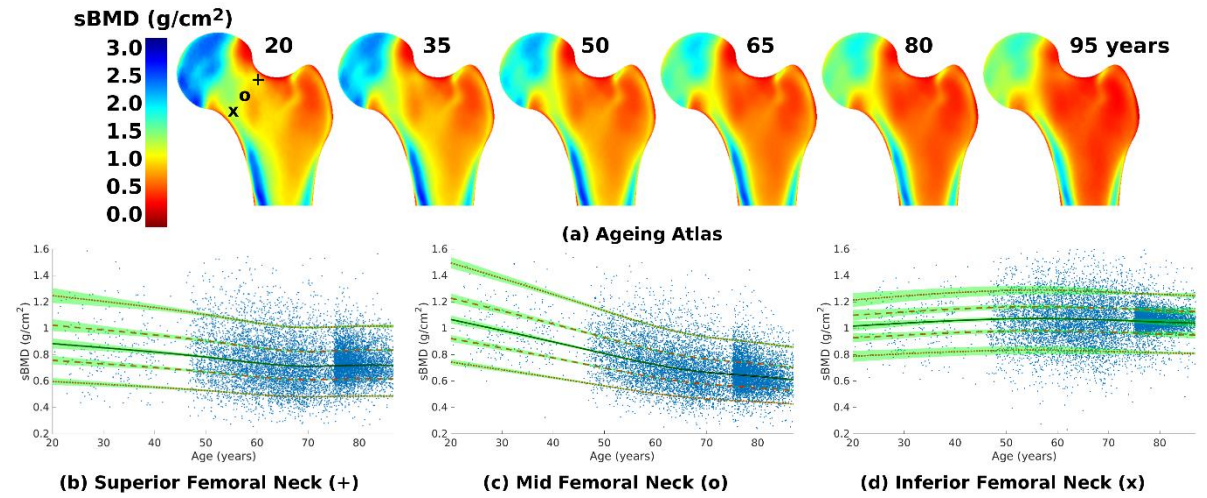

Fig 1. Bone Ageing Atlas. (a) The median BMD maps as a function of age (b, c, d) The solid, dashed, and dotted lines show the median, the 50% and the 90% quantile ranges, respectively. The green shadow shows the 95% confidence interval using the bootstrap technique.

Combining inertial sensors and principle component analysis to distinguish between knee rehabilitation exercises

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Introduction/Aim: Whilst home-based exercise rehabilitation plays a key role in determining patient outcomes following orthopaedic intervention (e.g. total knee replacement), it is very challenging for clinicians to objectively monitor patient progress, attribute functional improvement (or lack of) to adherence/non-adherence and ultimately prescribe personalised interventions. This research aimed to identify whether 4 knee rehabilitation exercises could be objectively distinguished from each other using lower body inertial measurement units (IMUs) and principle components analysis (PCA) in the hope to facilitate objective home monitoring of exercise rehabilitation. **Methods:** 5 healthy participants performed 4 repetitions of 4 exercises (knee flexion in sitting, knee extension, single leg step down and sit to stand) whilst wearing lower body IMU sensors (Xsens, Holland; sampling at 60 Hz). Anthropometric measurements and a static calibration were combined to create the biomechanical model, with 3D hip, knee and ankle angles computed using the Euler sequence ZXY. PCA was performed on time normalised (101 points) 3D joint angle data which reduced all joint angle waveforms into new uncorrelated PCs via an orthogonal transformation. Scatterplots of PC1 versus PC2 were used to visually inspect for clustering between the PC values for the 4 exercises. A one-way ANOVA was performed on the first 3 PC values for the 9 variables under analysis. Games-Howell post hoc tests identified variables that were significantly different between exercises. **Results**: All exercises were clearly distinguishable using the PC scatterplot representing hip flexion-extension waveforms (Figure 1). ANOVA results revealed that PC1 for the knee flexion angle waveform was the only PC value statistically different across all exercises. **Discussion/Conclusion**: Findings demonstrate clear potential to objectively distinguish between different knee rehabilitation exercises using IMU sensors and PCA. Flexion-extension angles at the hip and knee appear most suited for accurate separation, which will be further investigated on patient data and additional exercises.
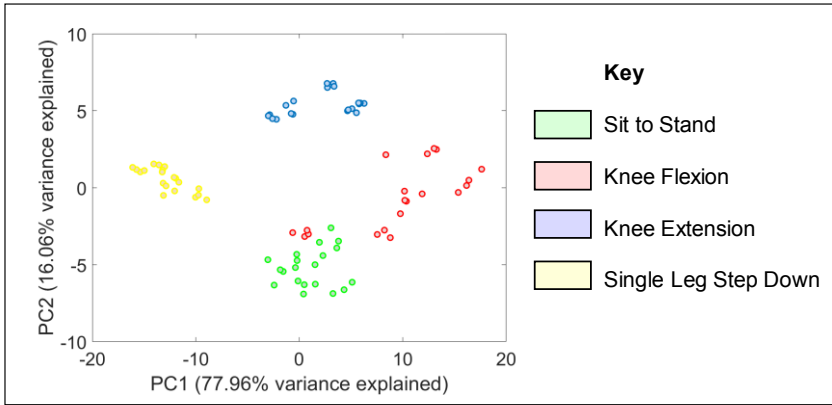

Figure 1: Flexion-extension hip angle scatterplot PC1 v PC2.

Patellofemoral-arthroplasty improves gait in isolated patellofemoral-arthritis, a prospective cohort gait analysis study

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(Caroline HING) [3], (Justin COBB) [2]

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Patellofemoral osteoarthritis (PFOA) affects 32% men and 36% women over the age of 60years and is associated with anterior knee pain, stiffness, and poor mobility. Patellofemoral arthroplasty (PFA) is a bone-sparing treatment for isolated PFOA. This study set out to investigate the relationship between patient-related outcome measures (PROMs) and measurements obtained from gait analysis before and after PFA. There are currently no studies relating to gait analysis and PFA available in the literature

A prospective cohort study was conducted of ten patients known to have isolated PFOA who had undergone PFA compared to a gender and age matched control group. The patients were also asked to complete questionnaires (Oxford knee score (OKS), EQ-5D-5L) before surgery and one year after surgery. Gait analysis was done on an instrumented treadmill comparing Ground reaction force parameters between the control and pre and post-operative PFA patients

The average age 60 (49-69) years with a female to male ratio of 9:1. Patient and healthy subjects were matched for age and gender, with no significant difference in BMI. Post-op PFA improvement in gait seen in ground reaction force at 6.5km/h. Base support difference was statistically significant both on the flat P=0.0001 and uphill P=0.429 (5% inclination) and P=0.0062 (10% inclination). PROMS response rate was 70%(7/10) pre-operative and 60%(6/10) post-operative. EQ-5D-5L scores reflected patient health state was better post-operatively.

This study found that gait analysis provides an objective measure of functional gait and reflected by significant quality-of-life improvement of patients post PFA. Literature lacks studies relating to gait-analysis and PFA. Valuable information provided by this study highlights that PFA has a beneficial outcome reflected by PROMs and improvement in vertical ground reaction force and gait (Fig.3)

Further research is needed to assess how care-providers may use gait-analysis as part of patient care plans for PFOA patients.
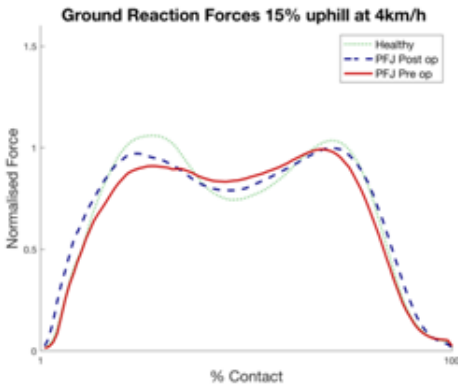

Fig 3. Ground reaction force at 15% uphill.

An evaluation of survival modelling approaches for personalised risk prediction after hip replacement for osteoarthritis

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Introduction The development of an algorithm that provides accurate individualised estimates of revision risk could help patients make informed surgical treatment choices. This requires building a survival model based on fixed and modifiable risk factors that predict outcome at the individual level. Here we compare different survival models for predicting prosthesis survivorship after hip replacement for osteoarthritis using data from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man.

Methods In this comparative study we implemented parametric and flexible parametric (FP) methods and random survival forests (RSF). The overall performance of the parametric models was compared using Akaike information criterion (AIC). The preferred parametric model and the RSF algorithm were further compared in terms of the Brier score, concordance index (C index) and calibration.

Results The dataset contains 327 238 hip replacements for osteoarthritis carried out in England and Wales between 2003 and 2015. The AIC value for the FP model was the lowest. The averages of survival probability estimates were in good agreement with the observed values for the FP model and the RSF algorithm as shown in Figure 1. The integrated Brier score of the FP model and the RSF approach over 10 years were similar: 0.011 (95% confidence interval: 0.011–0.011). The C index of the FP model at 10 years was 59.4% (95% confidence interval: 59.4%–59.4%). This was 56.2% (56.1%–56.3%) for the RSF method. Calibration plots for the FP model and the RSF algorithm are presented in Figure 2.

Conclusion The FP model outperformed other commonly used survival models across chosen validation criteria. However, it does not provide high discriminatory power at the individual level. Models with more comprehensive risk adjustment may provide additional insights for individual risk.
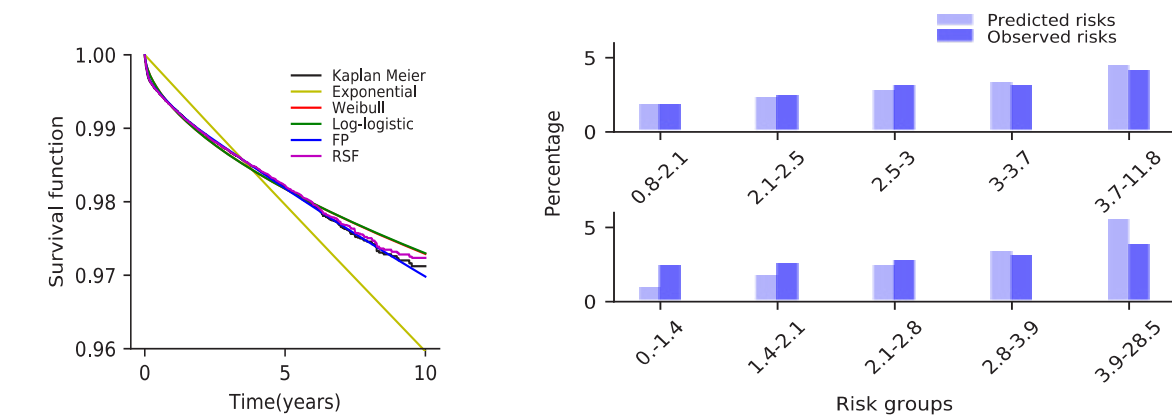

*Figure 2 **Observed and predicted probabilities from different models.***

*Figure 2 **Calibration plot of prosthesis failure for hip replacement. Top and bottom panels show the results for FP model and RSF method respectively.***

Stratifying the immune response to biomaterials: can cobalt-mediated inflammation be prevented?

Amy MAWDESLEY[1], Alison TYSON-CAPPER[1], John KIRBY[1], Joanne TIPPER[2]

[1] Newcastle University, Newcastle upon Tyne, United Kingdom

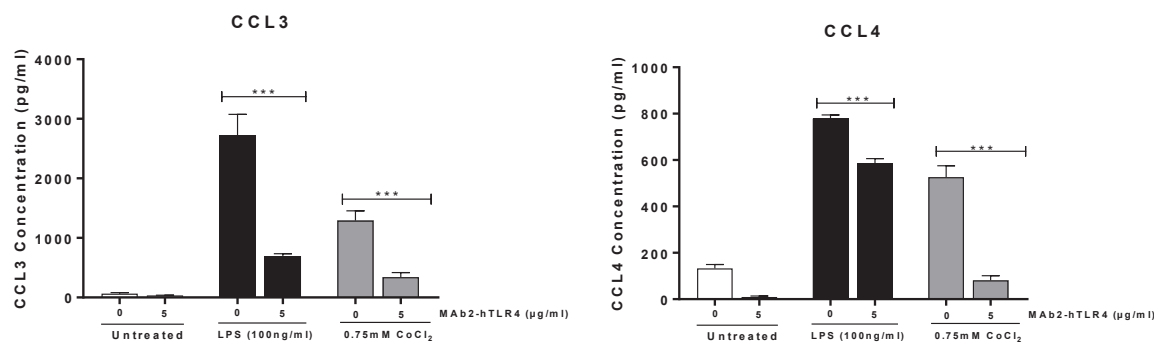[2] Leeds University, Leeds, United Kingdom

Background: Increased revision rates and early failure of Metal-on-Metal (MoM) hip replacements are often due to adverse reaction to metal debris (ARMD). Cobalt is a major component of MoM joints and can initiate an immune response via activation of the innate immune receptor Toll-like receptor 4 (TLR4). This leads to increased secretion of inflammatory cytokines/chemokines e.g. CCL3 and CCL4.

Aim: To evaluate whether TLR4-specific neutralising antibodies can prevent cobalt-mediated activation of TLR4.
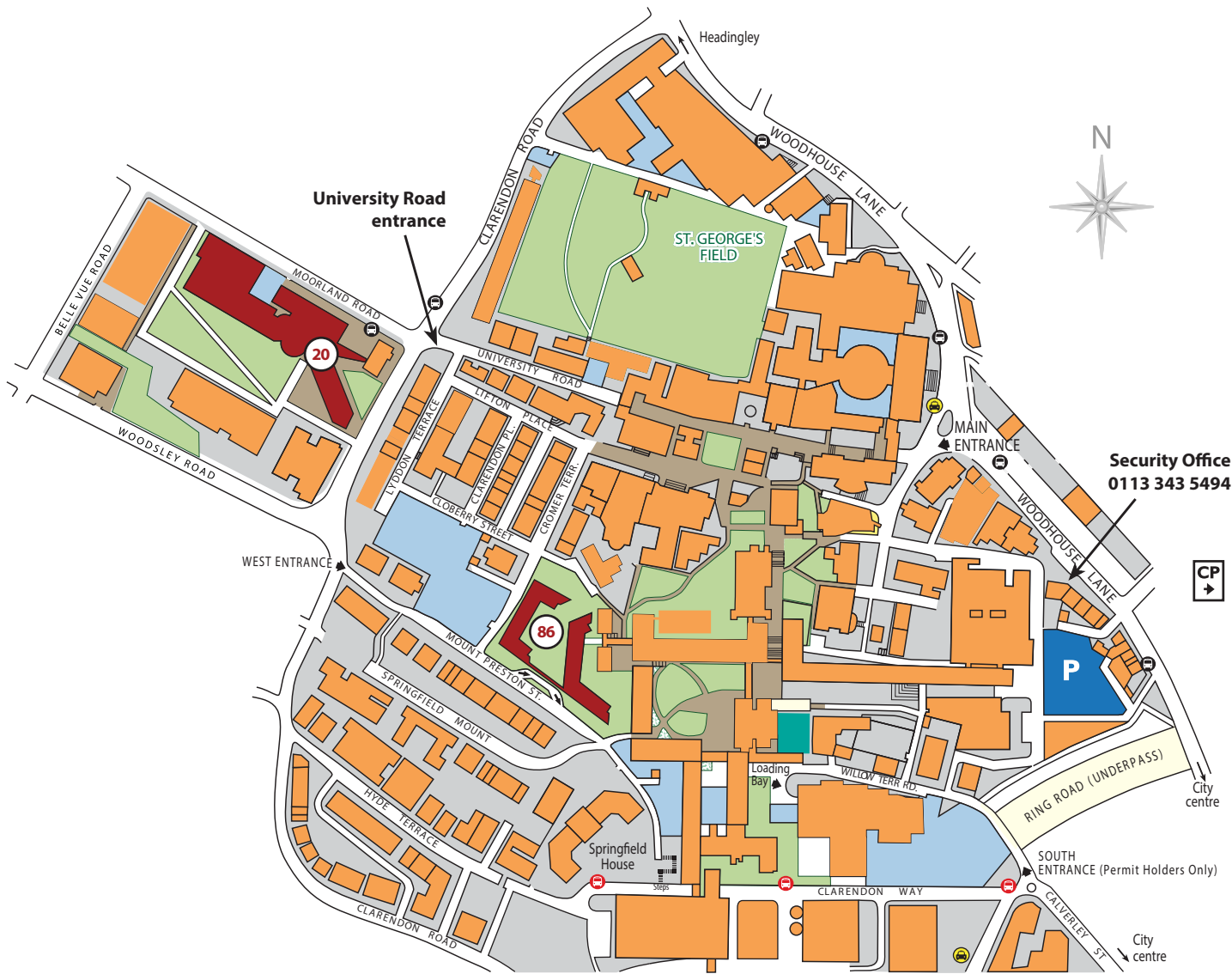
Methods: MonoMac 6 (MM6) cells, a human macrophage cell line, were treated with two different TLR4-specific monoclonal antibodies followed by 0.75mM of cobalt chloride (CoCl2). Lipopolysaccharide (LPS), a known TLR4 agonist was used as a positive control. Enzyme-linked immunosorbent assay (ELISA) was used to assess CCL3/CCL4 protein secretion and real time-polymerase chain reaction (RT-PCR) allowed quantification of CCL3/CCL4 gene expression.

Results: MM6 cells treated with cobalt and LPS up-regulate CCL3 and CCL4 gene expression and protein secretion. MM6 cells pre-treated with both monoclonal antibodies prior to stimulation with 0.75mM CoCl2 for 16 hours demonstrated significant inhibition of both CCL3 and CCL4 secretion as well as gene expression (both p=<0.0001).One of the antibodies failed to inhibit chemokine expression and secretion in LPS treated cells.

Conclusion: This study identifies for the first time the use of TLR4-specific monoclonal antibodies to prevent cobalt activation of TLR4 and subsequent inflammatory response. This finding demonstrates the potential to exploit TLR4 inhibition in the context of MoM joint replacements by contributing to the development of novel therapeutics designed to reduce the incidence of ARMD.

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