TENDON UK

EMERGING THEMES IN TRANSLATIONAL TENDON SCIENCE

11th -12th April 2018 Worcester College, University of Oxford

https://www.ndorms.ox.ac.uk/events/tendon-uk

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NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES
Medical Sciences Division

UNIVERSITY OF OXFORD

Welcome to Tendon UK

A very warm welcome to the 1st Tendon UK meeting, hosted by the University of Oxford at Worcester College. The focus of the meeting is translational, so topics will range from pathogenic mechanisms of tendon disease through physics and mechanics of tendon, biomaterials, bioreactors and the state of play in clinical trials.

Abstracts will kindly be published in Translational Sports Medicine, edited by Professor Michael Kjaer. Translational Sports Medicine promotes all aspects of sports medicine that combine basic science with clinical science by exploring the translational pathway between mechanistic research and conceptually novel insight into human exercise activities, either in relation to diagnosis, treatment, performance or prevention of diseases or sports injuries.

Please note that talks by young investigators are indicated in the programme and are entered into the competition for best podium presentation. These talks are scattered throughout the sessions as well as in the main young investigator session. A panel of eminent scientists from the audience will judge the talks

We hope Tendon UK will allow friendly and productive networking and collaboration to enable advances in this exciting field!

Andrew Carr

on behalf of the Tendon UK Organising Committee:

Stephanie Dakin
NDORMS,
University of Oxford

Sarah Snelling
NDORMS,
University of Oxford

Pierre-Alexis Mouthuy
NDORMS,
University of Oxford

And the Tendon UK Programme Committee:

Mark Thompson - IBME, University of Oxford
Jonathan Cook - NDORMS, University of Oxford
Philippa Hulley - NDORMS, University of Oxford
Graham Riley – University of East Anglia

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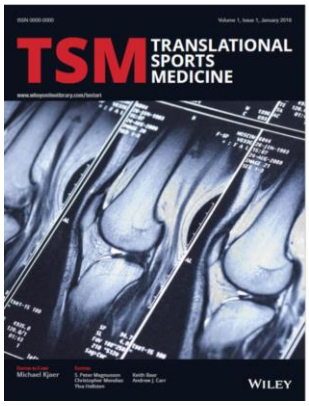


The Company of Biologists

How to get to: Worcester College

Worcester College is located in the centre of Oxford on the junction of Beaumont Street, Walton Street and Worcester Street. The college is just across the road from the main bus and coach station, and is a 10 minute walk from the railway station and main shopping areas. Maps showing the location and the grounds of Worcester College can be seen below.

Please note that there is no parking available at Worcester College.

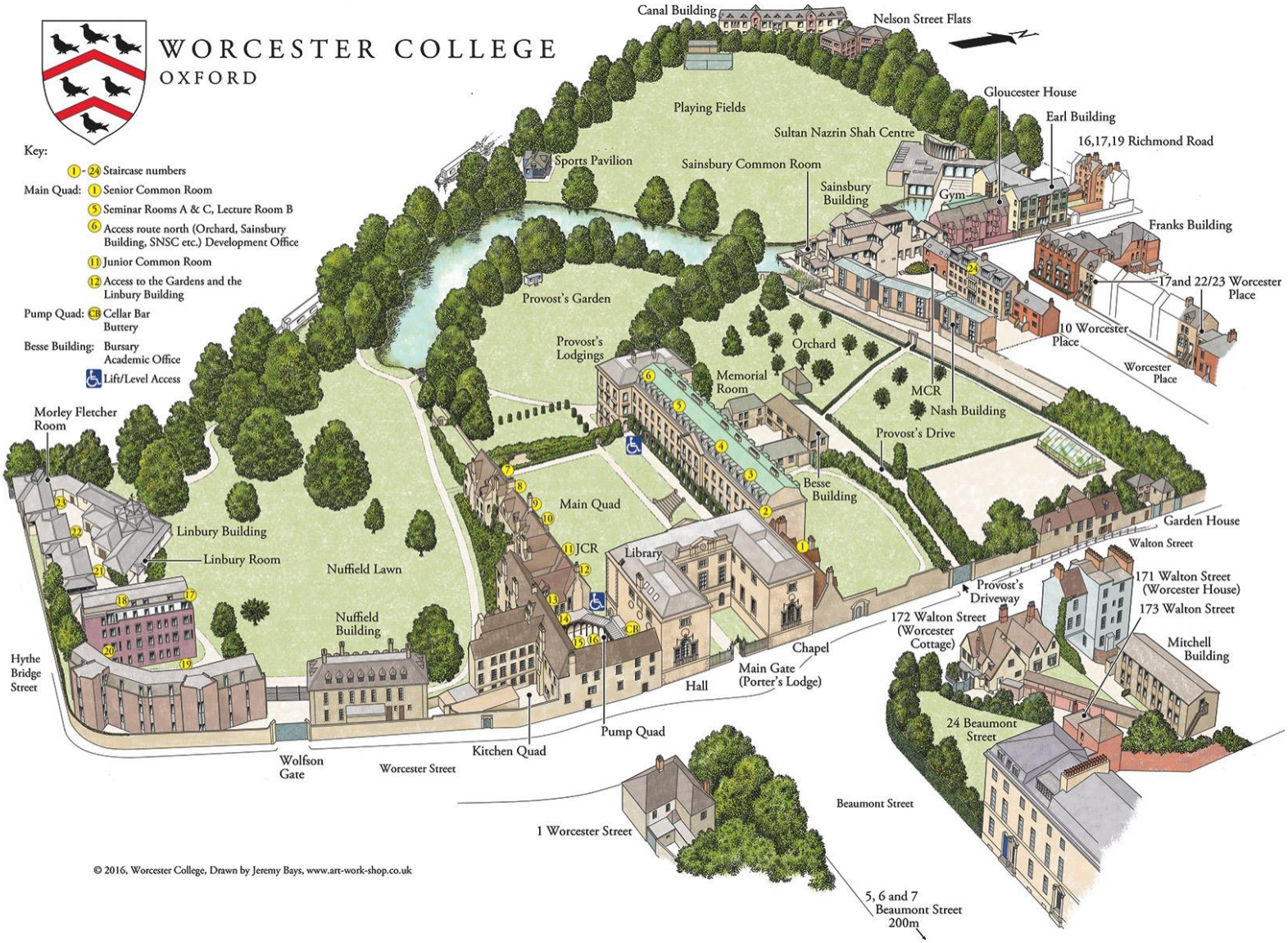
Information about how to get to Oxford is available on the University website here.

On arrival:

When arriving at Worcester College, please report to the Porters' Lodge, on the right just inside the main entrance. If you have booked a room, they will provide you with keys and instructions for you to access it. Rooms will be available from 2pm on the day of your arrival.

Assistance and/or advice for visitors with disabilities can be sought from the Porters' Lodge.

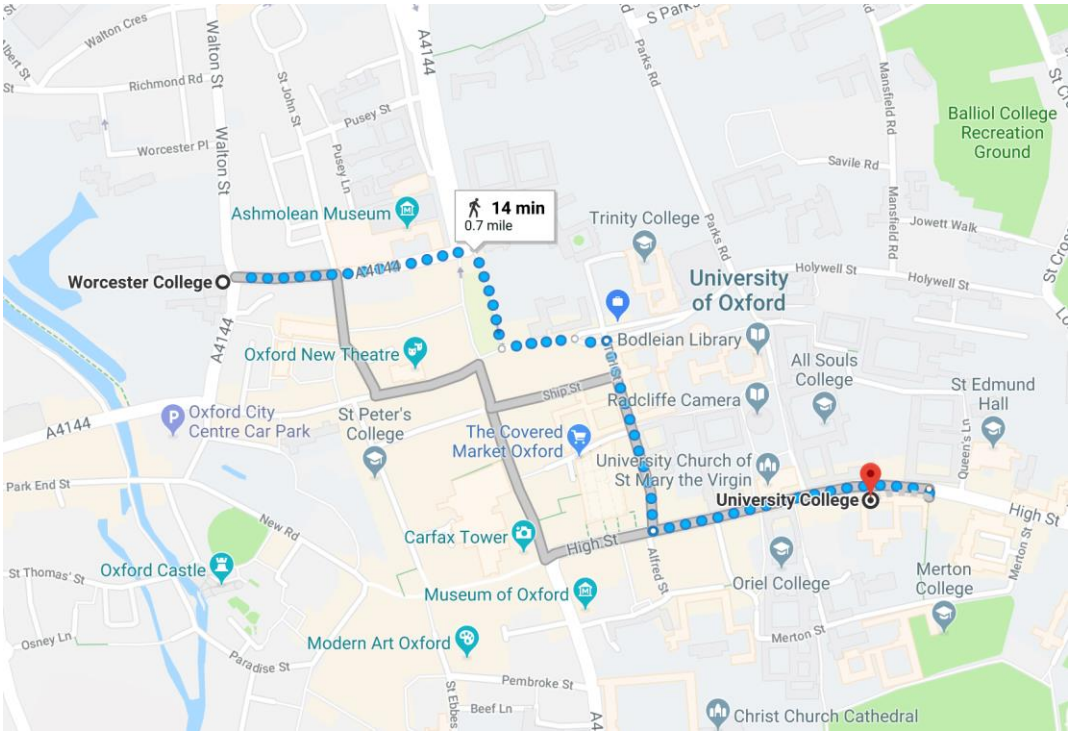
We look forward to seeing you there!


WORCESTER COLLEGE
OXFORD
Key:
1 - 24 Staircase numbers
Main Quad: 1 Senior Common Room
5 Seminar Rooms A & C, Lecture Room B
6 Access route north (Orchard, Sainsbury Building, SNSC etc.) Development Office
11 Junior Common Room
12 Access to the Gardens and the Linbury Building
Pump Quad: CB Cellar Bar Buttery
Besse Building: Bursary Academic Office
Lift/Level Access
Canal Building
Nelson Street Flats
Playing Fields
Sports Pavilion
Sultan Nazrin Shah Centre
Sainsbury Common Room
Sainsbury Building
Gym
Gloucester House
Earl Building
16,17,19 Richmond Road
Franks Building
17and 22/23 Worcester Place
10 Worcester Place
Worcester Place
Provost's Garden
Provost's Lodgings
Orchard
Memorial Room
MCR
Nash Building
Provost's Drive
Besse Building
Morley Fletcher Room
Linbury Building
Linbury Room
Nuffield Lawn
Main Quad
JCR
Library
Garden House
Walton Street
Provost's Driveway
171 Walton Street (Worcester House)
173 Walton Street
172 Walton Street (Worcester Cottage)
Mitchell Building
Chapel
Main Gate (Porter's Lodge)
Hall
Nuffield Building
Hythe Bridge Street
Pump Quad
Kitchen Quad
Wolfson Gate
Worcester Street
24 Beaumont Street
Beaumont Street
1 Worcester Street
5, 6 and 7 Beaumont Street
200m
© 2016, Worcester College, Drawn by Jeremy Bays, www.art-work-shop.co.uk

Dinner on Wednesday 11th April

The dinner on **Wednesday 11th April** will be held at **University College**, which is a short walk from the conference venue**.**

Pre-drinks will be served at 6:30pm and dinner will start at 7:30pm. Please bring your conference badge.



Tendon UK – at a glance

https://www.ndorms.ox.ac.uk/events/tendon-uk

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Wednesday 11th April 2018

10-11 am	Registration, coffee
11.15-11.30am	Welcome
11.30am-1pm	Session 1: Disease Mechanism
1-2pm	Lunch break and posters
2-3.30pm	Session 2: Tendon Physics and Mechanics
3.30- 4.15pm	Coffee break and posters
4.15-5.30pm	Session 3: Young Investigator Session
6.30- 7.30pm	Pre-dinner drinks at University College
7.30pm	Dinner at University College

Thursday 12th April 2018

9-10.30am	Session 4: Biomaterials and cell-matrix interactions
10.30-11.15am	Coffee break and posters
11.15am-12.45pm	Session 5: Bioreactors in Tendon Tissue Engineering
12.45-2pm	Lunch break and posters
2-3.30pm	Session 6: Clinical Trials and Translating Science to the Clinic
3.30pm	Final discussion, prize giving and close of conference.

Instructions for Podium and Poster presentations

All abstracts submitted for selection as podium or poster presentations will be published in Translational Sports Medicine. Abstracts and biographies from invited speakers are available in this booklet.

Podium presentations
All invited speaker presentations are 20 minutes long with time afterwards for discussion. All abstract presentations are 8 minutes long followed by 2 minutes of discussion. A computer is provided for your presentation. Please ensure your talk is uploaded prior to the start of your session. A member of the Tendon UK team will be available to help upload your talk and to answer any queries.

Poster presentations
The poster sessions will be held in the foyer during lunch and coffee breaks. Please put your poster up before the first poster session which will be held on Wednesday 11th April 1-2pm. Poster boards will be numbered with your poster number (see table overleaf). Posters should be taken down at the end of the final poster session (1245-2pm on Thursday 12th April).

Poster No.	Author	Poster title
1	Akbar	The role of interleukin-13 in tendinopathy
2	Baldwin	Exploring the role of endothelial cells in the progression and treatment of human tendon disease
3	Bayer	The exudate after muscle strain injuries in humans stimulates connective tissue synthesis
4	Bogaerts	Non-uniform deformation in Achilles tendon is not influenced by a change in knee angle or level of force production
5	Bogaerts	Healthy and pathological Achilles tendon mechanics assessment using quantitative ultrasound – exploratory study
6	Challoumas	Short and midterm effects of topical glyceryl trinitrate on tendinopathy: a systematic review of randomised controlled trials
7	Couppe	Habitual loading leads to tendon hypertrophy in the elderly and young human patellar tendon
8	Couppe	Ultrasound speckle assessment of tendon in individuals with unilateral Achilles tendinopathy
9	Francois	Standardised histopathologic scoring system to assess tendon healing
10	Kharaz	Age-related changes in microRNAs expression mouse cruciate ligament
11	Marr	Tendon stem/progenitor cells decline with ageing
12	McLean	Toxicity of tranexamic acid to human tendon: caution in clinical practice
13	Mimpen	IL-17 as a potential target in tendinopathy
14	Mortimer	Designing clinically-relevant tissue-engineered models of the tendon-bone interface
15	Nagra	The role of the microbiome in tendinopathy
16	Peffers	The tendon proteome and inflammation: an in vitro analysis
17	Sivelli	Characterisation of extracellular vesicles derived from equine mesenchymal stem cells and tenocytes
18	Stauber	A novel ex-vivo tendon injury model for longitudinal monitoring of the healing process
19	Tran	Marfan syndrome mice as a potential model for Achilles tendinopathy
20	Turlo	Changes in Achilles tendon morphology in a non- invasive mouse joint loading model
21	Yeung	Understanding the circadian clock as a therapeutic target for tendinopathies
22	Zamboulis	Development of the inter-fascicular matrix in the equine superficial digital flexor tendon
23	Zhang	Regional differences in collagen content and tendon mechanics

Tendon UK meeting – Full Programme

'Emerging themes in translational tendon science'
11th -12th April 2018 Worcester College, University of Oxford

Wednesday 11th April 2018

10-11 am Registration, coffee

11.15-11.30am Welcome (Prof Andrew Carr, Oxford)

11.30am-1pm Session 1: Disease Mechanism
Chair: Prof Stephanie Dakin

The aim of this session is to highlight the recent advances in understanding the disease mechanisms underpinning tendon disorders. The complex and multifactorial nature of tendinopathy remains to be fully elucidated and has hampered efforts to develop new and efficacious therapies. This session will highlight recent research on the physiology and pathology of tendon disorders, with a particular focus on exercise and inflammation. These recent advances help to inform the development of rehabilitation regimes and new pharmacological approaches that address the underlying pathobiology of tendon disorders.

Invited talks:
Dr Neal Millar (Glasgow) (20 minutes) *Translational targets in tendinopathy: microRNA29a and Interleukin 17*
Prof Michael Kjaer (Copenhagen) (20 minutes) *Regulation of physiological and pathological tendon adaptation to exercise*
Prof Stephanie Dakin (Oxford) (20 minutes) *Inflammation and resolution in human tendon disease*

2 x 8 min presentations from selected abstracts
Young Investigator - Lindsay Crowe (Glasgow) *Alarmins S100A8 & S100A9 modulate the inflammatory microenvironment in early tendinopathy*
Young Investigator - Adam EM Jørgensen (Copenhagen) *Carbon-14 bomb pulse reveals abnormal tendon collagen turnover before symptoms of tendinopathy*

1-2pm Lunch break and posters

2-3.30pm Session 2 Tendon Physics and Mechanics
Chair: Prof Mark Thompson

The aim of this session is to highlight recent progress in understanding the fundamental physics and mechanics of tendon damage and homeostasis. We will bring together expertise on microstructural mechanisms for mechanical damage, on microstructural modification in disease and on collagen formation to provide novel insight into disease aetiology and the potential for mechanobiologically inspired disease modifying therapies.

Invited talks:
Prof Dawn Elliott (University of Delaware) *Multi scale biomechanics of tendon damage*
Prof Jess Snedeker (Zurich) *Biomechanics of AGE cross links in tendon*
Prof Karl Kadler (Manchester) (20 minutes) *Collagen fibrillar formation and structure*

2 x 8 min presentations from selected abstracts:
Rene Svensson (Copenhagen) *Multiscale force transmission in tendon collagen*
Nathalie Crevier-Denoix (Alfort) *Tendon speed of sound changes with training: preliminary study in 9 trotters*

3.30- 4.15pm Coffee break and posters

4.15-5.30pm Session 3: Young Investigator Session
Chairs: Prof Philippa Hulley (Oxford) and Prof Graham Riley (Norwich)

6 x 8 min presentations from selected abstracts:
Young Investigator - Angelina D. Schoenenberger (Zurich) *Impact of mechanical load on the cell response to inflammatory signals in a tendinopathy model*
Young Investigator - Wataru Morita (Oxford) *Differential expression of TGF-beta and BMPs in healthy and diseased tendon stromal cells*
Young Investigator - Stefania Wunderli (Zurich) *Maintenance or loss of extracellular matrix mechanical integrity in tendon is niche-dependent*
Young Investigator - Fabian Passini (Zurich) *Quantification of mechanically-triggered calcium signalling in tendons*
Young Investigator - Antonis Giannopoulos (Copenhagen) *Altered viscoelastic properties and cell responses in human tendon constructs*
Young Investigator - Adam Janvier (Liverpool) *3D printed bioreactors for tendon engineering: characterising load induced changes by the 'collagen barcode'*

6.30- 7.30pm Pre-dinner drinks at University College

7.30pm Dinner at University College

Thursday 12th April 2018

9-10.30am Session 4: Biomaterials and cell-matrix interactions
Chair: Dr Sarah Snelling

Successful repair of tendon tears requires structural as well as biological support. This session will highlight the ability of biomaterials to regulate cell behaviour and the ability of cells to respond to these biomaterial-based cues. We aim to discuss the utility of biomaterials in tendon repair and some of the key considerations to aid their successful translation.

Prof Matt Dalby (Glasgow) (20 minutes) *Nanoscale control of Mesenchymal Stem Cell Differentiation*

2 x 8 min presentations from selected abstracts:
Young Investigator - Edward Stace (Oxford) *Healthy and diseased tendon fibroblasts respond differently to electrospun biomaterials*
Young Investigator – Amro Hussein (Zurich) *Elevated matrix tension drives a myofibroblastic phenotype in tissue engineered tendons*

Dr Sarah Snelling (Oxford) (20 minutes) *Biomaterials & Tendon - past, present and future perspectives*

10.30 -11.15am Coffee break and posters

11.15am – 12.45pm Session 5: Bioreactors in Tendon Tissue Engineering Chair: Dr Pierre-Alexis Mouthuy

Tissue engineering is a promising strategy for the repair of tendon defects and it is enabled by the development of bioreactors, which are controlled environments maintaining suitable culture conditions for tissue constructs. The aim of this session is to discuss the existing bioreactor designs used in tendon tissue engineering and to identify aspects requiring improvements for producing grafts that are clinically relevant. In particular, we will highlight the role of mechanical stimulation and mass transfer in the bioreactor chamber. We will also stress the importance of mathematical and computational modelling to accelerate the development of bioreactors.

Invited talks:
Prof David Butler (Cincinnati) (20 minutes) *History, rationale and prospects for tendon bioreactors*
Prof Hazel Screen (London) (20 minutes) *Mechanobiology in tendon tissue engineering: identifying & recapitulating cellular strains*
Prof Sarah Walters (Oxford) (20 minutes) *Mathematical modeling for bioreactor design*

12.45-2pm Lunch break and posters

2pm-3.30pm Session 6: Clinical Trials and Translating Science to the Clinic
Chair: Prof Jonathan Cook

The aim of this session is to consider clinical evidence on the use of novel medical devices in the treatment of tendinopathy. This will be mainly be through presenting the findings of a recent systematic review of clinical studies of patch augmented rotator cuff surgery and also by presenting an overview of the considerations for conducting a first in human trials of new bioactive impacts in this area.

Prof Jonathan Cook (Oxford) (20 minutes) *Systematic review of clinical studies of patch augmented rotator cuff surgery*

2 x 8 min presentations from selected abstracts:
Hayley Morris (Oxford) *Translation of tendon biomaterials to the clinic: Bioyarn case study*
Young Investigator - Jacqueline Thompson (Oxford) *Objective muscle test in a multi-centre trial on platelet-rich plasma in Achilles tendon injury*

Prof Andrew Carr (Oxford) (20 minutes) *First in man trials of bioactive implants for tendon repair*

3.30pm Final Discussion, prizegiving and close of meeting

Invited Speaker Biographies and Abstracts

Wednesday 11th April 2018

11.30-1pm Session 1 Disease Mechanism

Prof Michael Kjaer is Head of Department at the Institute of Sports Medicine, Copenhagen. His programme of research focuses on investigating how skeletal connective tissues undergo adaptation in response to mechanical loading, the pathogenesis of tendon disorders and the effects of aging-related adaptation of skeletal soft tissues to exercise and disuse. Prof Kjaer has published internationally on these topics, and is the founding Editor-in-Chief of the recently launched journal Translational Sports Medicine.
http://research.ku.dk/search/?pure=en/persons/30565

REGULATION OF PHYSIOLOGICAL AND PATHOLOGICAL TENDON ADAPTATION TO EXERCISE

Michael Kjaer

Institute of Sports Medicine, Dept Orthopedic Surgery, Bispebjerg Hospital, and Center for Healthy Aging, University of Copenhagen, Denmark

The adaptive capacity of the human tendon to exercise has been studied in several ways using various techniques. Whereas determination of precursor or breakdown cleavage products or incorporation of stable isotopes into tissue indicates a relatively fast dynamics in tendon connective tissue that accelerates with exercise, other methods using racemization or detection of 14C incorporation indicate very little tissue dynamics, especially after adolescence. Comparing tissue turnover in different tissues simultaneously suggests that a combination of a more basic structure that remains relatively unchanged through adult life, and a smaller pool of collagen that is more quickly turned over and can be influenced by mechanical loading. Mechanical loading of adult human tendon results in release of tendon tissue stimulating factors, whereas inactivity down regulates phenotypic tendon characteristics. Adjustment of the tendon mechanical properties in the form of increased stiffness and modulus after strength training, and the reverse after period of immobilization occurs relatively fast and is potentially coupled to molecular changes in relation to e.g. cross link formation. Mechanical loading improved function in tendinopathic tendons better than other non-exercise pharmacological interventions, but potentially combinations could be of additional value for treatment of tendinopathy.

Dr Neal Millar (Glasgow) is an Academic Consultant Orthopaedic Surgeon specializing in shoulder surgery having completed shoulder fellowships in Sydney and New York. His research interest lies in investigating the molecular pathophysiology of tendinopathy, his previous work has highlighted the role of inflammation and cytokines in tendon disease. His current research focuses on understanding the role of microRNA in the post transcriptional regulation of collagen synthesis and immediate tissue repair processes implicated in tendinopathy.
http://www.gla.ac.uk/researchinstitutes/iii/staff/nealmillar/

TRANSLATIONAL TARGETS IN TENDINOPATHY- *MICRORNA 29A AND INTERLEUKIN 17*

Neal L Millar PhD FRCSEd(Tr&Orth)

Senior Clinical Lecturer in Orthopaedics, Honorary Consultant Orthopaedic Surgeon
Institute of Infection,Immunity and Inflammation College of Medicine,Veterinary and Life Sciences, University Of Glasgow, Glasgow

The advent of modern molecular techniques has highlighted the presence of immune cells and inflammatory mechanisms throughout the spectrum of tendinopathy in both animal and human models of disease. Detailed mechanistic investigation of inflammatory pathways using the 'molecule to clinical' intervention paradigm has been remarkably successful in other areas of musculoskeletal therapeutics, most notably in inflammatory arthropathies. Appreciation of the finely balanced 'reparative' versus 'degenerative' inflammatory response in tendon damage is required to identify the molecular checkpoints that modify a homeostatic inflammatory response toward aberrant matrix/inflammatory remodeling and the chronic degenerative picture seen in clinical tendinopathy.

This talk will highlight the role of two novel mediators, namely microRNA 29a and interleukin-17 in tendon disease detail how mechanistic dissection of the pathways involved has led to two novel translational tendon therapies which will enter human clinical trials.

References

Millar, N.L.,*et al.* MicroRNA29a regulates IL-33-mediated tissue remodelling in tendon disease. Nat Comms 6, 6774 (2015).
Millar, N.L.,*et al* Inflammatory mechanisms in tendinopathy:toward translation *Nature Reviews Rheumatology* (2017).
Millar, N.L.,*et al.* IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. *Sci Rep* (2016)
Watts, A.E.,*et al.* MicroRNA29a Treatment Improves Early Tendon Injury. *Mol Ther* (2017)

Prof Stephanie Dakin is an Associate Professor at NDORMS, University of Oxford. Her background and experience as an equine veterinary surgeon provided the incentive for her programme of research, to improve understanding of chronic inflammation and fibrosis in disorders of musculoskeletal soft tissues. Stephanie's research focuses on understanding the mechanisms underpinning the development of chronic of inflammation, and investigating the inter-relationships between pain, inflammation and tissue damage. Her aim is to identify novel therapeutic strategies that address the pathobiology of musculoskeletal soft tissue disorders.
https://www.ndorms.ox.ac.uk/team/stephanie-dakin

INFLAMMATION AND RESOLUTION IN HUMAN TENDON DISEASE

Stephanie G Dakin PhD BVetMed MRCVS (1)

1. Associate Professor, NDORMS, University of Oxford, United Kingdom

The importance of inflammation as a contributor to the development of tendon disease has been contentious in recent years. Growing evidence supports the contribution of inflammation to the onset and progression of tendinopathy, however the mechanisms underpinning development of chronic tendon inflammation are not fully elucidated. Improved understanding of the cellular and molecular processes orchestrating tendon inflammation is essential to identify therapeutic targets that address the underlying pathobiology. Recent work has identified the complex activation states of macrophages populating diseased human tendon tissues, highlighting phenotypic changes occur between early and advanced disease stages (Dakin *et al.* 2015). We also report that resident tendon stromal cells undergo phenotypic changes as a consequence of exposure to inflammation, and act as niche conducive to sustaining inflammation (Dakin *et al.* 2017a). Using bioactive lipid mediator profiling, we demonstrate that chronic inflammation arises from dysregulated resolution responses of stromal cells isolated from patients with tendinopathy (Dakin *et al*. 2017b). This talk will discuss these recent advances which add to our understanding of the mechanisms underpinning the development and persistence of inflammation, and importantly how this may inform future novel therapeutic strategies to treat tendon disease.

References

Dakin, SG *et al*, *Sci Translational Med* 7: 311ra173, 2015
Dakin, SG *et al*, *Arthritis Res Ther* Jan 25, 2017a
Dakin, SG *et al*, *Sci Rep* 7: 11009, 2017b

Session 2 Tendon Physics and Mechanics

Prof Dawn M. Elliott, PhD
Dawn Elliott is the Blue and Gold Professor and founding department chair of Biomedical Engineering at the University of Delaware. Prior to joining Delaware in 2011, she spent 12 years in the University of Pennsylvania's Departments of Orthopaedic Surgery and Bioengineering. Her research focus is musculoskeletal biomechanics to study disc, meniscus, and tendon with degeneration, injury and therapy. Her multi-scale approach, from the entire joint-level, to the tissue-scale, and to the micro-scale, integrates mechanical testing, mathematical modeling, and multi-modal imaging. Dr. Elliott earned a PhD from Duke and a BS in ME from Michigan. She was awarded the American Society of Mechanical Engineers (ASME) Van C. Mow Medal for significant contributions to the field of bioengineering and the inaugural Outstanding Achievement in Mentoring Award from the Orthopaedic Research Society. Dr. Elliott is a Fellow of the American Institute for Medical and Biological Engineering (AIMBE) and of ASME. She is president-elect of the Biomedical Engineering Society (BMES).
http://www.bme.udel.edu/people/dawn-elliott/

MICROSCALE STRUCTURE, MECHANICS, AND DAMAGE OF TENDON

Dawn M Elliott, Andrea Lee, Babak Safa

University of Delaware, United States

Tendon's load carrying function is provided by its complex hierarchical structure. Within this hierarchical structure, interfibrillar shear, measured by relative sliding between fibrils, is a major mechanism in transmitting loads from the micro-scale to the macro- or tissue-scale. This presentation will describe the complex three-dimensional microstructure of the tendon fibril and the fibril-cell interface [Szczesny 2017]. It will also demonstrate load transfer mechanisms in tendon from the micro- to the macro-scale and how the load transfer is altered with mechanical damage [Lee 2017, Szczesny 2015, Safa 2017]. A theoretical constitutive model of reactive inelasticity will be presented. Damage, permanent structural changes that result in decreased mechanical properties, occurs due to over-loading. Following over-load induced damage, the altered structure and mechanics in a damaged tendon will then either progress toward advanced degeneration and tendinopathy, or will remodel toward healing. Studies of tendon mechanobiology should be informed by the tissue's structure and mechanical local micro-environment at the scale of the cell.

References

Lee AH, Szczesny SE, Santare MH, Elliott DM. Investigating mechanisms of tendon damage by measuring multi-scale recovery following tensile loading. *Acta Biomater*. 2017 Apr 20. pii: S1742-7061(17)30238-6. doi: 10.1016/j.actbio.2017.04.011.
Safa BN, Meadows KD, Szczesny SE, Elliott DM. Exposure to buffer solution alters tendon hydration and mechanics. J Biomech. 2017 Aug 16;61:18-25. doi: 10.1016/j.jbiomech.2017.06.045.
Szczesny SE, Caplan JL, Pedersen P, Elliott DM, Quantification of interfibrillar shear stress in aligned soft collagenous tissues via notch tension testing, *Sci Rep* 5:14649, 2015, doi: 10.1038/srep14649
Szczesny SE, Fetchko KL, Dodge GR, Elliott DM. Evidence that interfibrillar load transfer in tendon is supported by small diameter fibrils and not extrafibrillar tissue components. *J Orthop Res*. 2017 Jan 10. doi: 10.1002/jor.23517.

Prof Jess Snedeker The Orthopedic Biomechanics laboratory at ETH Zurich, headed by Prof. Snedeker, focuses on three primary research areas: mechanical/biological based understanding of tendon disease and healing; micro-mechanical cell-biomaterial interactions and their implications for therapeutic success; and clinical biomechanics for improving existing orthopedic implant design and for the development of novel implants.
http://www.biomech.ethz.ch/research/jess-snedeker.html

ADVANCED GLYCATION ENDPRODUCTS – LINKING COLLAGEN PHYSICS TO A DERAILED TISSUE PHYSIOLOGY

Jess G. Snedeker[1,2], Amro Hussein[1,2], Fabian Passini[1,2], Alfonso Gautieri[1,2]

1. Dept. of Orthopaedics, University of Zurich, Switzerland; 2. ETH Zurich, Switzerland, 3. Politecnico di Milano, Italy

Advanced glycation end products (AGEs) form from oxidative chemical reactions between glucose and certain exposed amino acid protein residues. These oxidative products stochastically accumulate in normal ageing, but can be rapidly accelerated in diabetic individuals, or within an inflammatory tissue niche. Among the spectrum of potential AGEs that can form, intermolecular cross-links between low-turnover collagen structures have been posited to play a potentially central role in age-related connective tissue disorders [Snedeker and Gautieri, 2014]. In this talk we will review a range of in vitro experimental studies from our laboratory that have aimed at more precisely characterizing the physical effects of AGE cross-linking on multi-scale collagen mechanics [Li, 2013] [Fessel, 2014] [Gautieri, 2017]. We also present our recent work on how AGEs may act to re-regulate cellular response to matrix damage, with potentially deleterious effects on tissue homeostasis and repair [Snedeker and Foolen, 2017].

References

Gautieri and Snedeker, MLTJ 4:303-308, 2014.
Li Y et al, Matrix Biol, 32:169-177, 2013.
Fessel et al. PLoS One, 9:e110948, 2014.
Gautieri et al, Matrix Biol, 59:95-108, 2017.
Snedeker and Foolen, Acta Biomater, 63:18-36, 2017

Prof Karl Kadler

Karl Kadler obtained his PhD from the University of Manchester in 1984 for developing computer-based methods for studying collagen fibrils, which are the most abundant protein polymer in vertebrates and the structural basis of tissues. He then took up a postdoctoral position with Dr. Darwin J. Prockop (Rutgers Medical School, New Jersey) and showed how mutations in collagen-I that cause osteogenesis imperfecta (brittle bone disease) can introduce kinks into the collagen molecule and stop normal mineralization of bone. In 1989 he secured a Wellcome Trust for a Senior Research Fellowship in Basic Biomedical Sciences (University of Manchester) and in 2000 was appointed Professor of Biochemistry. He holds an honorary award of Professor in Matrix Biology at the University of Copenhagen, and is recipient of the Fell-Muir Award by the British Society for Matrix Biology in recognition of his service to matrix biology. Karl is currently a Wellcome Trust Investigator, Director of the Wellcome Trust Centre for Cell-Matrix Research, and Director of the Cellular and Developmental Systems Research Domain at the University of Manchester. He has served on grant awarding panels for the MRC, Wellcome Trust, the Academy of Finland Science Research and is currently a serving member of the Disease Panel at Arthritis Research UK. His research is focused on understanding how cells make mechanically strong tissues that are rich in collagen fibrils. He has recently shown that the circadian clock regulates the secretory pathway in fibroblasts. This research is aimed at understanding the reasons for circadian clock regulated secretion of collagen and how changes in the circadian clock (caused by mutations, injury or age) affect tissue performance and tissue homeostasis, which might be a prelude to tissue degeneration and fibrosis.
https://www.research.manchester.ac.uk/portal/karl.kadler.html

Thursday 12th April 2018

9-10.30am Session 4 Biomaterials and cell-matrix interactions

Professor Matt Dalby (Glasgow**)** research interests include how cell behaviour is regulated by the nanotopography of materials through mechanotranduction pathways. He also has significant expertise in metabolomics and how dynamic factors and growth factor organization impact cell fate. Professor Dalby's work has focused on stem cell and osteoblast response to biomaterials, but the nature and underlying mechanism of these interactions is translatable to the cells of diseased tendon. Professor Dalby has published widely on cell-biomaterial interactions, with recent publications in Nature Biomedical Engineering and Biomaterials.
http://www.gla.ac.uk/researchinstitutes/biology/staff/matthewdalby/

NANOSCALE CONTROL OF MESENCHYMAL STEM CELL DIFFERENTIATION

Matthew Dalby

Centre for Cell Engineering, University of Glasgow

Mesenchymal stem cells (MSCs) are sensitive to nanoscale cues. In this talk, MSC differentiation in response to nanoscale materials and mechanical cues will be considered. In particular, osteogenesis of MSCs in 2D and 3D cultures driven by nanoscale vibrations (nanokicking) alone where techniques have had to be borrowed from gravitational wave physics to design a new bioreactor will be discussed. As will polymers for ultra-low dose, high efficiency growth factor delivery. In a recent application of this technology, nanoscale films of the polymer polyethylacrylate were used to organise fibronectin as biological networks that could present BMP-2 in a highly physiological manner and at 500 fold lower dose that when used clinically in soluble format. This was delivered into a veterinary patient, a female Munsterlander, who was due for amputation due to a 2 cm non-union fracture. Complete healing was seen within 6 weeks.
Acknowledgements. We thank BBSRC, MRC, EPSRC and Find A Better Way for funding this research.

References

Llopis-Hernandez, V. et al. *Science Advances* 2, e1600188, 2016.
Tsimbouri, P.M. *et al.* Nature Biomedical Engineering, 1, 758-770, 2017.

Dr Sarah Snelling (Oxford**)** is a cell biologist with particular interest in biomaterial-directed immunomodulation to drive non-fibrotic repair of diseased tissues. Her work is focussed on modulating the activity of the full repertoire of cells present in diseased tendons. Dr Snelling is also keen to improve the translational pathway of biomaterials. Dr Snelling's previous work has focused on the pathobiology of osteoarthritis and tendon disease. This has established her expertise in the interaction of inflammatory and fibrotic pathways, and in the regulation of cell signaling in disease pathogenesis.
https://www.ndorms.ox.ac.uk/team/sarah-snelling

BIOMATERIALS FOR TENDON REPAIR – PAST, PRESENT AND FUTURE STRATEGIES

Sarah Snelling

NDORMS, University of Oxford

Despite advances and continued development in surgical techniques 40% of surgical repairs for rotator cuff tears fail. For ruptures of the achilles tendon, conservative treatment is generally recommended as surgical outcomes are equivalent. Augmentation of surgical repair of tendon tears is therefore necessary to improve patient outcomes. Implanted biomaterials are inherently bioactive and thus have the potential to provide mechanical as well as biological support for healing. We will briefly survey the biomaterials in current and past clinical use for *in situ* repair of tendon tears. Some of the key considerations necessary in the successful design and testing of biomaterials for tendon repair will then be discussed. Tendon repair should harness and exploit the endogenous response to biomaterials of the repertoire of cells present in torn tendons. This talk will emphasise the importance of considering the activity of biomaterials throughout their *in vivo* lifetime and the necessity to use well definied tissue endpoints when developing and testing new biomaterials for tendon repair.

11.15 – 12.45 Session 5 Bioreactors in Tendon Tissue Engineering

Prof David L. Butler is Emeritus and Adjunct Professor of Biomedical Engineering at the University of Cincinnati. He received his Ph.D. in Engineering Mechanics and Biomechanics from Michigan State University. His research has focused on soft tissue and joint biomechanics, measuring in vivo tissue forces and function, and developing the subdiscipline of functional tissue engineering at the interface between tissue engineering and developmental biology to improve tissue repair. He is the author of over 150 peer-reviewed publications. Dr. Butler is the recipient of two Kappa Delta Awards from the American Academy of Orthopaedic Surgeons and the Gustas Larson Award and the HR Lissner Award from ASME. He is a fellow of ASME and inaugural fellow of AIMBE. NIH and NSF have supported his research and training efforts. He has also recently served as chairs of the US National Committee on Biomechanics and Sigma Xi at the University of Cincinnati. He has lead efforts to develop functional tissue engineering and tendon bioreactors to simulate in vivo strain conditions. Dr. Butler has also sought to establish success criteria as universities, industry and government labs conduct basic research and develop novel tissue engineering therapies for damaged and diseased musculoskeletal tissues. He is immediate past chair of the Fellows of the Graduate School at the University of Cincinnati that mentor young faculty and graduate students and advise university administrators on issues related to research and graduate education. He has been working with the Dean of the Graduate School to promote a new Graduate Student Fellows program to educate PhD students about what it means to pursue an academic career.
http://research.uc.edu/sigma/profile.aspx?epersonID=butlerdl

HISTORY, RATIONALE AND PROSPECTS FOR TENDON BIOREACTORS

David L. Butler (1), Hani Awad (2), Nathaniel Dyment (3), Jennifer G. Barrett (4), Michelle Wall (5), Albert Banes (5)

1. University of Cincinnati, USA; 2. University of Rochester, USA; 3. University of Pennsylvania, USA; 4. Virginia Tech, USA; 5. Flexcell International, US

Given the frequency, severity and fibrotic healing of many tendon injuries and the failure of conventional treatments to offer reliably good outcomes, tissue engineering has emerged as a potential solution. However, the challenges in engineering a tendon replacement *ex vivo* include understanding and controlling unique molecular, topographical and mechanical environments to: 1) optimize cell phenotype, 2) assimilate into native tendon and interact with muscle, bone and nerve, 3) possess mechanical properties to resist expected in vivo forces [Juncosa, 2003], 4) minimize rejection and reaction in the host, and 5) be feasible, economical and deliverable as a regulatory-body approved commercial product [Ratcliffe, 2015]. This talk will briefly review the history of tendon tissue engineering using principles of functional tissue engineering [Butler, 2000], accounting for the challenges of a tissue structure primarily composed of extracellular matrix. Several commercial and custom bioreactors will be assessed for their success in replicating tendon structure and function, and their practicality as a therapeutic modality [Youngstrom and Barrett, 2016]. While such reactors have been invaluable for studying basic tendon mechanobiology, the prospects for the translation of tendon tissue engineering as a therapeutic option rely on successfully integrating the requirements of patients, surgeons, regulatory agencies, and commercial entities.

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Prof Hazel Screen is a Professor of Biomedical Engineering and Chair of Bioengineering and Biomaterials at Queen Mary, University of London. She graduated from UCL with degrees in Mechanical Engineering and Advanced Instrumentation Systems and has remained at QMUL since completing a PhD at the Interdisciplinary Research Centre in Biomedical Materials in 2003, in the field of tendon mechanobiology. She has published over 100 papers in the area of tissue mechanics, utilising multiscale imaging approaches to establish tissue strains from the nano- to macro-scale, translate findings towards clinical relevance in managing tendinopathy and characterising whole body biomechanics, as well as towards life science research in the areas of mechanobiology as part of regenerative medicine research.
https://www.sems.qmul.ac.uk/staff/h.r.c.screen

MECHANOBIOLOGY IN TENDON TiSSUE ENGINEERING: IDENTIFYING & RECAPITULATING CELLULAR STRAINS

Chavaunne T Thorpe (1,2), Dharmesh Patel (1), Peter D Clegg (3), Helen L Birch (4), Stephanie J Bryant (5), Hazel RC Screen (1)

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3. University of Liverpool, UK; 4. University College London, UK; 5. University of Colorado Boulder, USA

Understanding how strain transfer through a tissue impacts cell strains is important for directing mechanobiology research. Tendon is a highly aligned composite, in which collagen is arranged in hierarchical levels. We have shown that tendon extension relies on shearing of adjacent collagen-units throughout the hierarchy, meaning tendon cells experience combined tension and shear [Thorpe et al. 2014]. Further, collagen sliding throughout the hierarchy differs between functionally distinct tendons, indicating concomitant variations in cell strain environment [Thorpe et al. 2015].

In commonly injured tendons, shearing appears primarily localised to the matrix between fascicles; the interfascicular matrix. Of note, there is a more active, mechanoresponsive cell population in this region, suggesting a role in maintaining and repairing tendon in response to mechanical stimuli [Spiesz et al. 2015]. Further investigation of this cell population is warranted.

To achieve this, we have developed a PEG fibre-composite material enabling combined tensile and shear strains to be directly applied to cells seeded onto fibres, more closely recapitulating the physiological cell environment [Patel et al. 2017]. Tuning the PEG allows cell shear:tension ratios to be manipulated to investigate influence on metabolism, whilst varied peptides can be incorporated to manipulate cell attachment to fibres. Preliminary data collated using this system suggests the expression of several matrix genes is shear-ratio driven. Knowledge of tendon mechanobiology is a key aspect of successful regenerative medicine approaches.

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Prof Sarah Walters is a Professor of Applied Mathematics at the Mathematical Institute, University of Oxford and a Fellow in Applied Mathematics at St Anne's college, Oxford. After reading Mathematics at the University of Cambridge, Sarah did her PhD in Applied Mathematics at the University of Leeds on Coronary Artery Haemodynamics. She then held postdoctoral positions in the Biomedical Engineering Departments at Northwestern University and the University of Michigan, before returning to the Department of Applied Mathematics and Theoretical Physics at the University of Cambridge where she held the Sir Michael Sobell Research Fellowship. She joined the faculty of the School of Mathematical Sciences at the University of Nottingham in 2001, before taking up her current position at the Mathematical Institute in Oxford in 2007. Sarah's research is in the application of mathematics to medicine and biology, and she has made substantial contributions to the fields of physiological fluid mechanics, and cell and tissue biomechanics. Her research provides fundamental insights into genuine biomedical problems that complement those obtained by experimental methods, and involves close multidisciplinary collaboration with life scientists, clinicians, bioengineers, and theoreticians. In 2012, Sarah was a recipient of a prestigious London Mathematical Society Whitehead Prize for "contributions to physiological fluid mechanics and the biomechanics of artificially engineered tissues". In 2006 she was awarded an Advanced Research Fellowship from the UK Engineering and Physical Sciences Research Council (EPSRC) in which she developed new models for perfusion bioreactors in tissue engineering, and she is currently a Royal Society Leverhulme Trust Senior Research Fellow (2017-2018). She has facilitated and promoted interdisciplinary and multi-disciplinary research through the establishment of new initiatives such as the EPSRC-funded network in Physiological Flow Modelling, and has been a lead figure in the organisation of many EPSRC-funded Mathematics-in-Medicine study groups, conferences, workshops and summer schools.
https://people.maths.ox.ac.uk/waters/Waters/Dr_Sarah_Waters.html

MATHEMATICAL MODELLING FOR BIOREACTOR DESIGN

Sarah Waters

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We demonstrate how mathematical modelling, analysis and computation, in combination with experimental studies, can provide insight into how the many different underlying biological processes interact within a bioreactor to generate engineered tissue. We show how such modelling approaches can be utilised to determine how these interactions may be optimised (via experimentally controllable bioreactor operating conditions) to achieve the end goal of producing functional tissues for implantation. These theoretical approaches limit the need for numerous and expensive bioreactor experiments, therefore saving time and money.

We discuss two bioreactor systems: the High-Aspect Rotating Vessel (HARV) [Dalwadi, 2018] and hollow-fibre membrane systems [Pearson, 2016]. In both systems, a porous biomaterial scaffold, seeded with cells, is cultured in a nutrient-rich fluid. Fluid flow is exploited to improve mass transfer of nutrient and growth factors to, and removal of waste products from, the cells. Additionally, the fluid flow influences the cells' mechanical environment. We develop multiphase models, accounting for the fact that biological tissue is composed of a wide variety of interacting components, coupled with flow and transport equations for the nutrient-rich culture medium surrounding the bioactive scaffold in the bioreactor.

References

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2pm-3.30pm Session 6 Clinical Trials and Translating Science to the Clinic

Prof Jonathan Cook (Oxford**)** is an experienced medical statistician and clinical trials with a particular interest in randomised trials of surgical interventions. He is the Chief Investigator of the PARCS feasibility study looking at the feasibility of a randomised trial of patch augmented rotator cuff surgery.
https://www.ndorms.ox.ac.uk/team/jonathan-cook

SYSTEMATIC REVIEW OF CLINICAL STUDIES OF PATCH AUGMENTED ROTATOR CUFF SURGERY

Jonathan Cook[1], Navraj Nagra[2], Mathew Baldwin[2], Gemma Greenall[2], David Beard[2], Jonathan Rees[2], Amar Rangan[3], Naomi Merritt[2], Melina Dritsaki[2], Sally Hopewell[2], Andrew Carr[2],

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Rotator cuff conditions, relate to the tendons and muscles surrounding the shoulder joint. They account for up to 70% of shoulder pain problems and are the third most prevalent musculoskeletal disorder after lower back and neck pain[Linsell, 2006; Carr 2015]. Many patients require surgery to repair the tear; however there is a high failure rate. Patch augmented surgery for rotator cuff repairs has recently been developed and appears promising. A growing number of patches have been produced using different materials and processes. However, the extent of the clinical evidence on their use for rotator cuff surgery is unclear. A systematic review of the clinical evidence on patch augmented rotator cuff surgery was carried out to identify and summarise the available clinical evidence.[PARCS, 2018] Multiple electronic databases were searched for clinical studies of patch augmented rotator cuff surgery. Screening of titles and abstracts and full text assessment was done by two independent reviewers. Data on the study design, the type of participants, type of intervention and outcomes were extracted. The findings of the review will be presented, and the strengths and limitations of the evidence base considered.

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PARCS (Patch Augmented Rotator Cuff Surgery Study) – A Feasibility Study webpage, https://www.ndorms.ox.ac.uk/clinical-trials/current-trials-and-studies/parcs [accessed 5 Apr 2018]

Prof Andrew Carr is the Nuffield Professor of Orthopaedic Surgery at the University of Oxford. He is an inter-disciplinary researcher distinguished for evaluating and developing surgical implants and technologies and for his leadership in surgical and musculoskeletal research. He is the Chief Investigator of two National Institute for Health Research funded studies evaluating novel bioactive implants.
https://www.ndorms.ox.ac.uk/team/andrew-carr

FIRST IN MAN TRIALS OF BIOACTIVE IMPLANTS FOR TENDON REPAIR

Andrew Carr

NDORMS, University of Oxford, UK

The use of surgical implants in clinical practice has transformed effective care of many medical conditions. In the past, many surgical implants were introduced in the US by the so called 510 (k) route, which simply required substantial evidence of equivalence to a device already on the market. In Europe approval is through notified bodies, who review evidence presented by the manufacturer. If is satisfied it makes a declaration of conformity and affixes a CE mark, allowing the device to enter the market.

Recent changes to regulation have, in the US, increased the uses of pre-market approval, increased transparency and justification during the submission process, improved a system of device recall, modified the process of new applications to make them more stringent, applied new processes to the review of existing devices, fortified and reduced the use of the 510(k) system. In Europe, the new EU rules established in 2017 will continue to use notified bodies to grant CE marks, but with increased oversight by competent authorities and a new medical device co-ordination group provide extra scrutiny for high risk devices, the European Commission will now be responsible for surveillance of implants through Eudamed and high risk implants will undergo assessment by the European Medicines Agency (EMA) the regulator or pharmaceuticals.

Clinical research in the form of clinical trials is both lengthy and costly. This lecture will discuss the design of trials for novel surgical implants in the context of the new regulatory frameworks.

Thank you to the Company of Biologists for generously sponsoring this meeting.