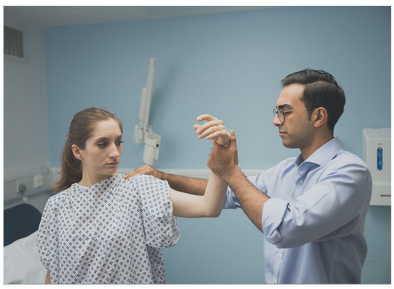
2018







BOTNAR RESEARCH CENTRE

RESEARCH STRATEGY REVIEW

NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

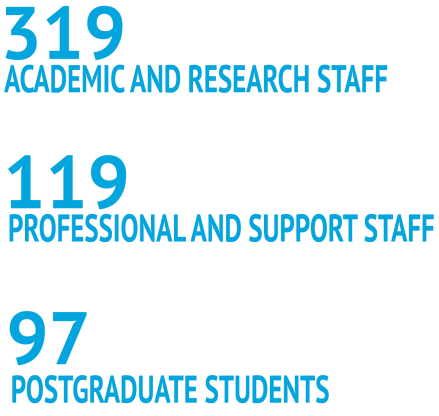
BOTNAR
RESEARCH CENTRE | NDORMS

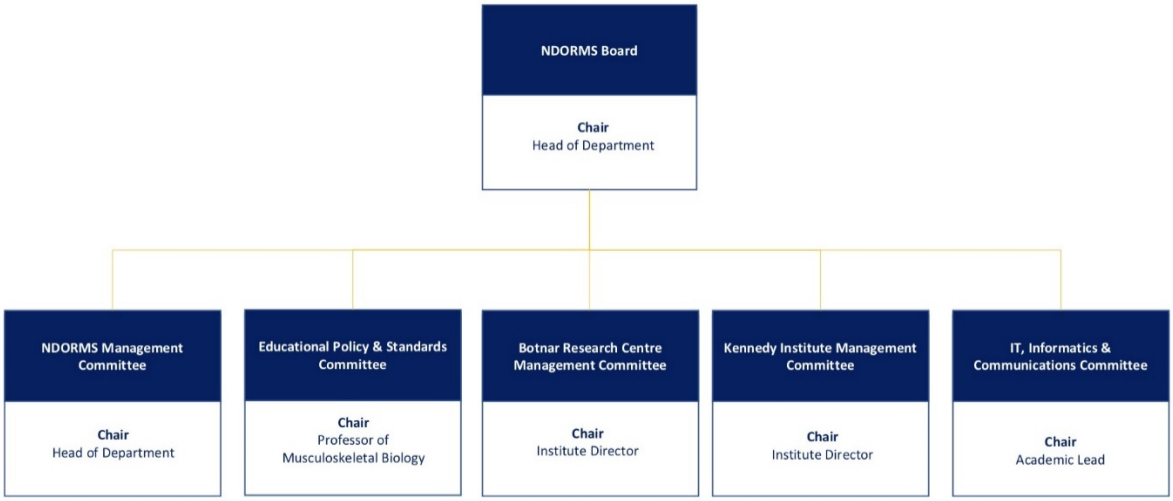
UNIVERSITY OF OXFORD

The Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) is part of the University of Oxford's Medical Sciences Division (MSD). It consists principally of two research institutes: the Botnar Research Centre and the Kennedy Institute of Rheumatology, as well as a Core Administration Team supporting both institutes, based in the Nuffield Orthopaedic Centre (NOC). NDORMS also has teaching and research space in the NOC and the John Radcliffe Hospital (JR).

The co-location with NHS services puts the department in an excellent position, with basic science researchers working alongside clinician scientists. This substantially improves research capability, enables access to patients, and facilitates the interaction between clinical and basic science researchers, which is essential for successful translational research.

The department is governed by a number of committees, which report to the NDORMS Board. Membership of these committees is open to all departmental staff and students through advertisement and selection by a gender-balanced panel.

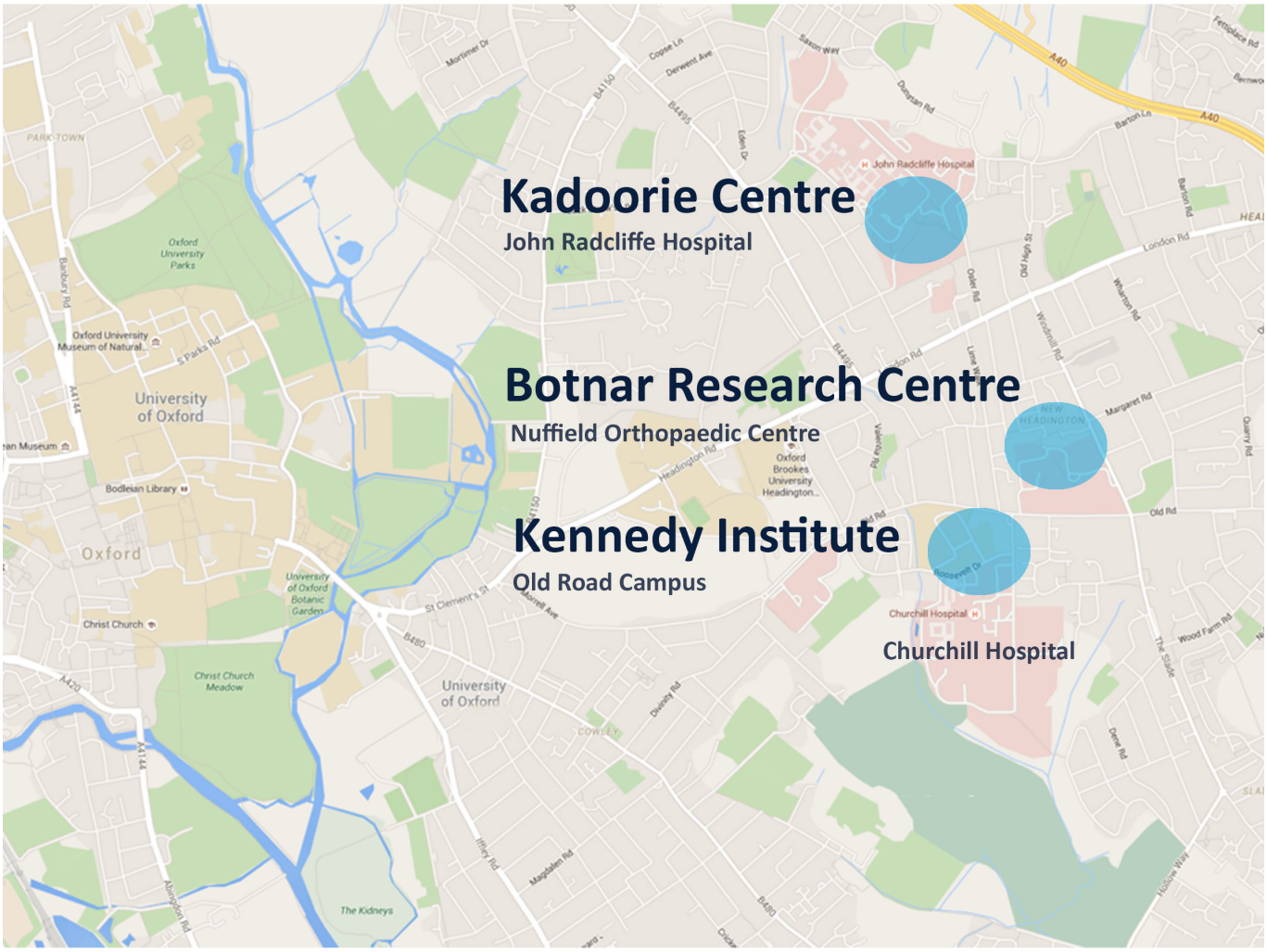




NDORMS Board and committees

The department teaches orthopaedics, trauma, emergency medicine and rheumatology to all undergraduate clinical students (168 students/year), who are recruited centrally to the University's Medical School. We also offer a part-time taught MSc in Musculoskeletal Sciences for 15 clinical trainees.

NDORMS has two Directors of Graduate Studies (DGS), one based in the Botnar Research Centre and one based in the Kennedy Institute of Rheumatology.



Map of the Headington region of Oxford showing the location of the NOC, the Botnar Research Centre and the Kennedy Institute of Rheumatology.

Equality and Diversity and the Athena Swan Charter

NDORMS has held an Athena SWAN Silver award since 2015, which was successfully renewed in November 2018.

In NDORMS, we actively encourage a culture that supports work-life balance and a family-friendly work ethic, where both men and women appreciate and value a flexible workplace. We aim to enable all staff to lead a balanced and fulfilling life.

The department operates a family-friendly policy, including arrangements for part-time working, job shares and flexi-time. We have part-time staff across all grades and the department's management is strongly committed to providing equal opportunities for all.

We are proud to say that **98% of our students, 88% of our academics and 96% of our professional and support staff would recommend working at NDORMS.**

We organise regular academic and social events that bring together students, early-career researchers and staff from across the department. We create a working environment that promotes honesty, equality and fairness and we pride ourselves on the good working relationship we are able to build with all our staff. As a growing department, we frequently offer a range of new posts to join our dynamic, friendly team. We are committed to recruiting on merit after fair and open selection, and we welcome applications from a diverse range of candidates.

We aim to provide positive development and an open, supportive and family-friendly research environment. To achieve this, NDORMS has a dedicated Equality and Diversity Advisor, who coordinates the Athena SWAN self-assessment team. This team meets on a termly basis and ensures progress with the Athena SWAN Silver action plan, covering the following:

- Welcome and support for new staff
- Mentoring and Personal Development Review (PDR) schemes
- Support for students and postdocs on their career progression
- Support for researchers and academics when applying for grants and fellowships
- Improving staff awareness of promotion opportunities
- Raise staff awareness on reporting systems on bullying and harassment
- Support outreach activities

Athena SWAN self-assessment team (from top left): Andrew Carr, Kim Midwood, Wulf Forrester-Barker, Maria Granell-Moreno, Natasha Whibley, Clare Jarvis, Jim Dunford, Jodie Ririe, Catherine Swales, Patrick Garfjeld, Grace Le, Daniel Prieto-Alhambra, Dominic Furniss and Roxanna Abhari

Core Administration Management Team

Left: Angela Truesdale, Head of Administration; right: Helen Heyworth, Head of Finance

The overall management of the core administration teams comes under the Head of Administration, Angela Truesdale, and the Head of Finance, Helen Heyworth. The core teams consist of the Communications Team, the Human Resources Team, the Finance Team and Information Governance.

We work with the Head of Department on all aspects of policy, strategic planning, development, growth and sustainability whilst enabling the administrative team to provide the services, resources, advice and information required for the Department's effective operation and growth.

The Head of Administration is responsible for the non-academic management and administration of the department, which enables the academic and research staff to successfully focus on their teaching, research, clinical and general academic responsibilities.

The Head of Finance is responsible for managing the department's growing annual budget and contributing to its long-term strategic planning through costing and scenario modelling for new initiatives. Detailed management information and specialist financial expertise is provided to both the Head of Department and the Director of the Kennedy. In addition, the Head of Finance has overall responsibility for the department's finance delivery to MSD.

We both work closely with the Institute Administrator of the Botnar Research Centre and the Head of Operations of the Kennedy Institute of Rheumatology.

We also interact with the staff in the MSD office; senior administrative staff in the University; other departmental administrators, the Oxford Universities Hospital Trust; external sponsors; and with other institutions.

Communications and Engagement

Communications Team (from left to right): Natalie Ford, Jo Silva, Katy Riggs and Tiya Muluzi

The Communications Team at NDORMS delivers an exciting and busy communications and public engagement programme, around three key areas: internal communications; external communications; and outreach and engagement.

The team have a wealth of experience in strategic communications, outreach and engagement, grant application, video, photography, social media, writing, media relations, message crafting, internal communications, and creative problem solving that enables them to deliver well-crafted and audience-focused messages in line with key aspects of the communication strategy such as:

The development and delivery of strategic communications for high-profile projects and research groups (e.g. Athena SWAN, Act on Acceptance); alignment with funder priorities; production of the bulletin; preparation of news, feature articles and research pages for the websites as well as press releases for key outputs; management and production of high-quality digital content to support a variety of projects, from videos to infographics; support for researchers with research and public engagement grant applications; development of activities for upcoming science festivals; production of content for our social media platforms; delivery of inductions, as well as communications, media and engagement training, briefings and coaching to staff and students.

Human Resources

Human Resources Team (from left to right): Jodie Ririe, Shabnam Mukairshoeva, Clare Jarvis, Beata Giglio, Jessica Heath, Lucy Hilsdon, Morwenna Purves

The Human Resources Team (HR) is based in the NOC, supporting both institutes. NDORMS employs professionally qualified (CIPD trained) HR staff to ensure that all HR processes within the department meet current equality legislation.

In addition to looking after all staff on payroll, the team manages 95+ recruitment exercises a year and the department's honorary contracts, casual workers and visitors. They also work closely with MSD for academic and clinical recruitment exercises.

For up-to-date information on the opportunities available, see the *Working with us* section on the NDORMS website https://www.ndorms.ox.ac.uk/about/working-with-us

The HR team offers support in a variety of topics, namely: visa applications; maternity or paternity leave; flexible working; transition back to full-time work from part-time or career breaks. They also support our commitment to career development for professional and support staff through the PDR process, training and regrading.

If you have any HR query, big or small, please feel free to contact the HR team. They have a variety of HR backgrounds, and are ready to help, advise you, or just listen. The team is available on hr@ndorms.ox.ac.uk and one of the team will get back to you as soon as possible.

Finance

Finance Team (from left to right): Simon Emmanuel, Ivana Ilic, Hannah Dade, Helen Dyson, Rosie Glenn, Margaret Roberts

The NDORMS Core Finance Team supports both the Kennedy Institute of Rheumatology and the Botnar Research Centre, working closely with the Grants and Purchasing teams together with the Institute Administrators.

The Finance team offers day-to-day support and advice on finance-related matters to all NDORMS staff. They process invoices for both institutes, communicate with suppliers, raise Accounts Receivable Invoices, process departmental cross charges and administer the department credit card and petty cash float. They also bank cash and cheques into NDORMS accounts and produce reports and analysis for General Ledger cost centres.

The Botnar Research Centre

The Botnar Research Centre provides world-class facilities for scientists in the field of musculoskeletal research. The Centre takes a multidisciplinary approach to medical research, encompassing orthopaedic, rehabilitation and rheumatology clinical scientists, bone oncologists, laboratory scientists, epidemiologists, engineers and statisticians. The Botnar also hosts the Oxford Clinical Trials Research Unit (OCTRU) and the Centre of Statistics in Medicine (CSM), providing excellent statistical support to all aspects of clinical research.

The Botnar Research Centre opened in 2002, with a large annexe completed in early 2013. To accommodate its rapid growth, the Centre will open another wing in 2019/20. The Botnar is now home to around 300 staff and postgraduate students, who enjoy the international and friendly atmosphere of this workplace and benefit from the vast knowledge of leading experts in the field of musculoskeletal research.

The Institute's research is funded by a grants portfolio worth over £54m.

Major supporters include the National Institute for Health Research (NIHR), the Medical Research Council (MRC), the Wellcome Trust, Arthritis Research UK, Cancer Research UK (CRUK) and the European Commission.

Sharing the site of the NOC – the largest specialist academic musculoskeletal hospital in the UK – puts the Botnar in a unique position to foster collaborations between basic scientists and clinicians, which is essential to success in medical research.

CSM provides in-house support in: applied statistical research, statistics support and collaboration on specific healthcare projects, development of reporting guidelines and monitoring of their uptake and education and training for internal and external researchers. OCTRU complements this by supporting the design, conduct and reporting in both early and later phase clinical trials.

The Botnar Research Centre is also home to staff from the Nuffield Department of Surgical Sciences (NDS) and the Department of Engineering Science, representing the breadth of scientific collaboration.

Botnar Research Centre Administrative Support and Facilities

Dr Sonja Pawelczyk, Institute Administrator

The Botnar Research Centre Administrative and Facilities teams offer support to all staff and students based in the building. The teams are headed by the Institute Administrator, Dr Sonja Pawelczyk, who provides support to Botnar researchers and ensures the smooth running of the Institute and its facilities.

The Institute Administrator also liaises with the Core Administration teams in NDORMS and works closely with the Director of the Botnar Research Centre and senior staff on the strategic plan of the Institute. This includes the Botnar's upcoming expansion, with the development of Botnar phase 3, planned to open in early 2020.

Botnar 3 will host the new chair of Biomedical Engineering, a cross-divisional appointment between MSD and the Mathematics, Physics and Life Science Division (MPLS). The Institute Administrator is working closely with the Department of Engineering to facilitate this joint venture.

The Botnar Research Centre Admin Team

Left: Isuara Thomas, Receptionist; right: Robert Grayson, Administrative Assistant

The Botnar is well supported by the Botnar Receptionist who welcomes visitors to the building and acts as first point of contact for contractors and engineers, and the Administrative Assistant, who provides general support to the Botnar Research Centre Admin Team.

Building and Facilities Team

Building and Facilities team (from eft to right): Fryad Karim, Dave Banfield, Alan Bateman, Nick Gee, Jack Stockford

The role of the Botnar Buildings and Facilities Team, led by the Technical Services Manager, Dave Banfield, is to ensure the care, maintenance and upkeep of the Botnar Research Centre and associated buildings, and the provision of safe, efficient and cost-effective technical facilities and working environments for the building's occupants in both office and laboratory areas.

The Botnar Orders Team

Sasha Dahl, Purchasing Officer

Headed by the Purchasing Officer, The Botnar Orders team ensures that all purchasing transactions across the department are carried out in best practice and in accordance with the University and external financial regulations. They are the first contact for gaining Oracle access and can provide assistance in using the database.

The Human Tissue Authority Team

Martin Taylor, Human Tissue Manager

The Human Tissue Manager is responsible for the maintenance of the human tissue collection of the Botnar Research Centre. He ensures good clinical practice and legal compliance by implementing and maintaining a quality management system within a Human Tissue Authority (HTA) licensed facility with research ethics approval. He is also responsible for the collection, processing, storing, archiving and administration of human tissue and blood stored within the Botnar Research Centre and the University of Oxford's tissue laboratory in the NOC.

The IT Team

Left: Pete Salmond, IT Support Manager; right: Jim Busby, IT Support Officer

The IT Manager, supported by the IT Officer, takes care of the day-to-day aspects of IT within the Institute, manages IT projects and advises on the strategic direction of IT and IT support at the Botnar Research Centre. Working with senior academics and support staff, they identify and manage IT infrastructure projects to ensure that the Botnar Research Centre continues to be a world-leading research organisation.

Post-Graduate Research Students

NDORMS provides excellent opportunities for high quality research training in leading areas of musculoskeletal and inflammatory sciences and offers an outstanding environment for undertaking a DPhil (Oxford's equivalent to a PhD).

The Department delivers a comprehensive training programme for students, which includes relevant scientific subjects, a formal taught component, seminars and access to training in transferable skills.

We welcome both clinical and non-clinical postgraduates and have several full-time student opportunities funded by the Department and various national bodies.

Our **vision** is for our graduate students to develop into scientists of the highest calibre with excellent future career prospects.

All graduate students are guided by a specialised team that includes the academic supervisor(s), a Director of Graduate Studies (Associate Professor Afsie Sabokbar for the Botnar) and a Graduate Studies Officer (Samuel Burnell).

The DGS oversees the graduate students' studies, including facilitating and monitoring academic progress as well as advising on the specific milestones required for completion of a post-graduate degree at Oxford. The DGS provides individual and confidential support for students whenever necessary and will also convey any feedback from the student relating to their studies to the Departmental Graduate Studies Committee where necessary. The Graduate Studies Officer (GSO) provides administrative support for students.

Left: Associate Professor Afsie Sabokbar, DGS Botnar; right: Samuel Burnell, Graduate Studies Officer

Taught MSc in Musculoskeletal Sciences

The Taught MSc in Musculoskeletal Sciences, a part-time two-year course integrating orthopaedics and rheumatology, delivers an internationally renowned programme.

The course provides graduate students with academic training in the principles and scientific aspects of common musculoskeletal diseases and statistical and epidemiological tools used in the research of musculoskeletal diseases. The course also comprises advanced modules on rheumatology, trauma and orthopaedics.

This multidisciplinary programme is delivered by academics spanning multiple departments from within the University of Oxford, with guest lectures from internationally renowned experts in this field.

Our **vision** is to train future leaders in musculoskeletal sciences to enable scientific and clinical excellence that changes the research and treatment of musculoskeletal diseases.

Students receive comprehensive training in scientific writing skills and course assessment on literature review and grant writing assignments. Opportunities are also available to experience involvement in established research projects within NDORMS.

The Taught MSc programme prepares students for an academic career in musculoskeletal sciences to facilitate the delivery of transformational research from bench to bedside.

Left: Associate Professor Stephanie Dakin, Director of the Taught MSc in Musculoskeletal Sciences; right: Lydia Underdown, Taught MSc Course Administrator

Taught MSc Organising Committee members:
Professor Paul Bowness
Andrew Wainwright
Ben Kendrick
Dr Catherine Swales
Professor Alan Silman
Associate Professor Daniel Prieto-Alhambra

Grants Support

Grants Team (from left to right): Martin Holt, Jessica Ryan-Phillips, Sarah Keenan, Edward Bond

The Botnar Research Centre offers substantial assistance to those academics interested in applying to both internal and external funding bodies. The Botnar Research Centre has an experienced grants team of five (one on maternity leave), with a collective experience in excess of 20 years in grant management. The team has a mixed background in Immunology, Statistics and Business Management.

Team members are allocated to roles in:

- finding and promoting opportunities and sharing with the relevant teams within the Institute
- assisting with applications – reading, editing and providing direction on how to present
- budgeting research costs
- reporting and maintaining successful awards

As the Department crosses multi-disciplinary areas, including Rheumatology, Orthopaedic and Plastic Surgery, Musculoskeletal Trauma, Rehabilitation, Statistics and Clinical Trials, Laboratory Sciences and Biomaterials themes, the team has experience in funding from a large variety of funding bodies including UK charities, European Union, Research Councils, Department of Health and industrial collaborators.

Funder Type	Portfolio Value
Charity QR	£10,755K
Research Councils	£750K
UK Government	£26,842K
EU Government	£1,837K
Industry	£13,355K
Other	£687K
Total	**£54,227K**

Applicants are encouraged to discuss applications with the Grants Team and their academic section head before submission to identify potential areas which may require strengthening. Where possible, the previous successful applicants will also advise on what was considered favourable.

If an applicant is applying for a fellowship, the Grants Team and the Institute Management will offer 'mock interviews' with an interdisciplinary panel selected within the Institute to ensure all applicants are fully prepared. Where possible we will ensure that the interview panel is filled by either previous successful applicants or staff members who have previously advised the funding panels. This has proved invaluable to a number of the junior academics.

Future Plans

In the last 12 months, the Botnar has aligned itself with two new research areas, Myeloma and Engineering.

Professor Udo Oppermann is leading a myeloma centre with colleagues from the Radcliffe Department of Medicine (RDM) and the Department of Oncology. To support this venture's success, in the next two years we will work to get the appropriate funders on board, as well as recruit key staff on long-term fellowships or programmes from CRUK and Myeloma UK.

In May 2018, Professor Eleanor Stride started a joint appointment with Engineering Science. To ensure this theme is successful the Institute is looking at increased opportunities with the Engineering and Physical Sciences Research Council (EPSRC), Royal Academy of Engineering and related industrial partners amongst others.

Academic Sections

Experimental Rheumatology

Experimental Rheumatology (from top left to right): Peter Taylor; Paul Bowness; Hussein Al-Mossawi; Laura Coates; Nigel Arden; Kassim Javaid; Raashid Luqmani

Overview and scope

The group's five-year work plan and strategic vision involves the work of the following Principal Investigators (PIs) based at the Botnar Research Centre: Professor Peter Taylor, Professor Paul Bowness, Dr Hussein Al-Mossawi, Dr Laura Coates, Professor Nigel Arden, Dr Kassim Javaid and Professor Raashid Luqmani.

Working across NDORMS and based primarily at the Kennedy Institute, are Dr Fiona Watt, Dr Jonathan Sherlock and Professor Chris Buckley.

The specialty areas covered include the following sub-themes:

Rheumatoid arthritis (Taylor), Psoriatic arthritis (Coates, Bowness, Al-Mossawi, Taylor, Ankylosing spondylitis (Bowness, Al-Mossawi, Taylor), Osteoarthritis (Watt, Arden), Bone pathology (Javaid), Vasculitis (Luqmani), Entheseal and rheumatic eye disease (Sherlock, Taylor, Buckley).

Rheumatoid arthritis – aims
(Taylor)

- The overarching research goal is to determine new therapeutic targets that address existing unmet needs in rheumatoid arthritis (RA) and to translate this understanding into new patient therapies
- Employ CyTOF technology to probe blood and synovial tissue immune cells to understand the molecular and cellular correlates of differences between low and high disease activity in parallel cohorts of RA patients treated with targeted therapies and conventional synthetic Disease-modifying antirheumatic drugs (DMARDs) and to generate a unique archive of immune cell biomarker profiling

- Investigate the expression of novel kinase isoforms *ex vivo* in RA synovial derived cells, and the effect of selective inhibitors in the expression of pro- and anti-inflammatory cytokines by those cells
- Investigate the expression of Salt inducible kinase (SIK) isoforms *ex vivo* in RA synovial derived cells, and the effect of novel SIK inhibitors in the expression of pro- and anti- inflammatory cytokines by those cells
- Test the hypothesis that citrullinated HLA class I histocompatibility antigen, alpha chain E (HLA-E) peptide ligands can be exploited for future therapies aimed at curing RA
- Lead a phase II, randomised, double blind, placebo-controlled, dose response, multicentre trial to evaluate the efficacy, safety and pharmacokinetics of EP4 inhibition in combination with methotrexate, in DMARD-naïve early RA

Psoriatic arthritis – aims

(Coates, Taylor, Bowness, Al-Mossawi)

- The overarching research goal is to determine the optimum treatment paradigm for psoriatic arthritis (PsA) using existing csDMARDs and bDMARDs and determine precision medicine correlates
- Establish the MONITOR cohort of early PsA establishing real-life outcomes for T2T approach with matched biological samples to examine the biological phenotype of disease
- Use RNA sequencing and other multi-parameter approaches to predict treatment response in the MONITOR cohort
- Establish optimal therapy for moderate/severe PsA using SPEED RCT
- Develop a new interventional study to embed in the cohort examining treatment according to tissue involvement in PsA
- Establish a national study examining early diagnosis of PsA in dermatology to develop a diagnostic algorithm (aiming for NIHR funding)
- Use single-cell sequencing techniques to interrogate synovial fluid in PsA to high resolution and identify novel therapeutic targets
- Optimise and personalise the approach to management in PsA using translational approach within a large multicentre cohort
- Develop, test and implement strategies for early diagnosis and optimal management of PsA for roll out nationally

Ankylosing Spondylitis – aims

(Bowness, Al-Mossawi, in collaboration with Taylor in clinical trials)

- The overarching research goal is to understand the molecular mechanisms causing inflammation in Ankylosing Spondylitis and to translate this understanding into new patient therapy
- Investigate the functional basis of known disease-associated genes
- Based on our discoveries in pathobiology and genetic associations, to explore novel approaches to stratification of patients for targeted therapies
- Investigate novel molecular targets and test new potential therapeutic compounds in preclinical studies using primary patient-derived cells
- Lead a national, early phase II experimental medicine clinical trials investigating the effect of GM-CSF ligand blockade in ankylosing spondylitis

Osteoarthritis – aims
(Arden)

- The overarching goal is to lead a consortium of osteoarthritis (OA), rheumatology and orthopaedic societies and researchers, working with regulators and industry, to produce and validate a formal definition and set of outcomes of early knee OA
- Produce an internet based prediction tool for the development of knee OA with a tailored secondary prevention app that will be trialled in a formal randomised clinical trial
- Work with large international consortia exploring the role of omics in predicting and assessing treatment response in OA
- Produce novel means to assess and disseminate the evidence-based results for the treatment of OA. Working with Osteoarthritis Research Society International (OARSI), we will produce an app for patients to access the data
- Investigate the association of physical activity with the long-term risk of knee and hip OA using an international IPD meta-analysis to generate physical activity guidelines
- Assess the cost effectiveness of long-term follow-up of knee replacement

Bone pathology – aims
(Javaid)

- The overarching goal is to develop centres of excellence for research and service in fracture prevention and adult rare bone disease
- Investigate the epidemiology and predictors of effective service delivery fracture prevention at the national and international level and develop, implement and evaluate quality improvement for effective, efficient secondary fracture prevention in the NHS and other health care settings across the globe
- Develop a national/international centre of clinical and research excellence for adults with rare bone diseases, from which to lead multicentre trials of new therapeutics

Vasculitis – aims
(Luqmani and collaborations)

- The overarching research goal is to investigate novel biomarkers in vasculitic disorders and to determine the efficacy of repurposed and new therapeutics
- Define the role of neutrophils and their products in systemic vasculitis including giant cell arteritis and anti-neutrophil cytoplasm associated vasculitis. We aim to define subsets of neutrophils or functional subsets to target for therapy or protect to prevent complications of therapy
- Investigate and develop imaging and circulating biomarkers to define subgroups of giant cell arteritis for prognosis, therapy selection and improvement in outcomes
- We have recently completed data collection for over 6800 new cases of vasculitis or controls for a classification criteria project in vasculitis (DCVAS) funded by ACR, EULAR and Vasculitis Foundation. Following the classification criteria projects (nearing completion), we plan to analyse the data and produce diagnostic criteria in the next two to three years
- The UKIVAS registry (chief investigator Luqmani) contains over 4000 patients in the UK and Ireland; we plan long term outcome studies of different forms of vasculitis. The PROTEA project will collect data on 1000 patients with GCA over the next five to seven years. We will evaluate biomarkers in the cohort and explore novel therapies in this group
- Plan trials to define the effectiveness of different therapies in systemic vasculitis, including ANCA associated vasculitis (current collaboration with Todd group – ANVIL, and recently

funded MRC clinical trial of hydroxychloroquine in moderately active diseases – led by D'Cruz, Luqmani et al), and taking part in commercial studies of AAV

- Therapies in large vessel vasculitis including IL6R inhibitor therapy in GCA, making use of the ultrasound training programme we have developed

Entheseal and rheumatic eye disease – aims

(Sherlock, Taylor, Buckley collaboration)

- The overarching goal is to characterise the T cell and stromal populations of the eye and assessment of their role in anterior uveitis
- We have established an extensive ophthalmology network from which we will obtain tissue for deep immunopathological analysis and undertake single cell molecular profiling of uveitis pathogenic cells
- Investigate the IL23 responsive T cells in human ocular tissue using specialist imaging, FACS and CyTOF. We will explore the use novel compounds to modulate IL23 pathways in these cells

Orthopaedic and Plastic Surgery

Orthopaedic and plastic surgery (from top left to right): Professor Andrew Carr, Professor Jonathan Rees, Professor David Beard, Associate Professor Sarah Snelling, Professor Siôn Glyn-Jones, Professor Andrew Price, Associate Professor Dominic Furniss, Dr Tim Theologis, Professor David Murray, Professor Chris Lavy, Professor Amar Rangan

We aim to achieve global impacts in the surgical care of patients with major improvements in health provision, evidence for treatment and patient outcomes, through the leadership, research and innovations of the section's academics.

Our research in orthopaedics and plastics is changing medical care and transforming the lives of patients worldwide.

Research leading to changes in national guidelines and policies

- **Shoulder surgery**
  CSAW (Carr, Rees, Beard) – The CSAW placebo controlled trial of arthroscopic subacromial decompression (Lancet 2017) has resulted in significant global changes in the use of the most commonly performed shoulder operation. Professional guidelines have been modified and commissioners of care have altered their policies. In July 2018, the NHS significantly restricted the use of subacromial decompression surgery in all UK hospitals
- **Hip replacement**
  Metal-on-metal total hip replacement (Murray, Glyn-Jones) – Major health risk problems with this type of joint replacement were identified by researchers from NDORMS leading to new NICE guidance published in 2014. Now these replacements are almost never used.
- **Shoulder fractures**
  PROFHER (Rangan) – This trial influenced NICE guidance on proximal humeral fractures published in February 2016. Adoption of the findings recommends consideration of non-surgical management for low energy displaced proximal humeral fractures. This is leading to cost savings to the NHS of £2.5 million annually by reducing surgical interventions for proximal humeral fractures by 50%.

NIHR NHS Tools developed

- ACHE Tool (Beard and Price) – This influential HTA study demonstrates a patient's capacity to benefit from total hip replacement and total knee replacement.

Patents filed

- 8573 BioPatch: priority date 04/10/2013, now in national phase in EU, US, China (Carr)
- 10169 BioYarn: Priority date 18/09/2013, now in national phase in EU, US, China (Carr)
- WO2017085479 Proximal Tibial Osteotomy System (Price)
- PCT: PCT/GB2017/053107 Filed 13/10/2017: Wireless Assessment of Surgical Skills Tool (Rees)
- UK: GB1617389.0 Filed 13/10/17: Wireless Assessment of Surgical Skills Tool (Rees)

University Spin out companies

- ProMapp Ltd – Health Outcomes, Pathway Planning and Surveillance Solutions (Beard, Rees, Price)

James Lind Alliance (JLA)

- Since 2014, we have raised funding for and lead six JLA Priority Setting Partnerships (PSPs) to inform national research priorities (Price, Rees, Furniss, Theologis)

The Oxford Knee

- Returned as an Impact in REF 2014, further developments include an atlas based decision aid to help surgeons identify appropriate patients. This validated atlas has high sensitivity and specificity and has been copyrighted by the University and made internationally available (Murray)
- We have developed and patented a device to assist with stress x-ray assessment and surgical decision making, which is now being commercialised (Murray)

Patient Reported Outcome Measures (PROMs)

- The Oxford Scores have been translated into 20 languages and are being used worldwide in clinical trials and in national joint replacement registries. They have been adopted by many health providers and regulators globally, providing outcome data that leads to policy and treatment guideline changes (Carr, Murray)
- In collaboration with the Department of Public Health and Keele University, we have now also developed a new generic NHS Digital supported MSK PROM – the MSK-HQ – for use in primary and intermediate care in the NHS (Beard, Rees, Price)

The Oxford Scores are translated in 20 languages and are used worldwide by health professionals and in policy and healthcare guidelines.

Global Surgery

- Publication of the Lancet Commission on Global Surgery has led to a large number of global initiatives in surgery around the world (Lavy)
- Setting up of a Lancet Commission on Global surgery website http://www.lancetglobalsurgery.org/
- The World Bank now collects surgical data: https://data.worldbank.org/indicator
- The World Health Assembly recording its first ever resolution involving surgery: "Strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage" http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R15-en.pdf
- Many Low and Middle Income countries are now developing national Surgical Action Plans

The Future at the Botnar

Research Themes

Our PIs are always expanding our research into key areas and are currently considering the 2017 NIHR Oxford Biomedical Research Centre Musculoskeletal Theme and the newly published National Objectives of the Royal College of Surgeons of England (Minimally invasive surgery, Robot-assisted surgery, Nanotechnology, Imaging, Artificial intelligence, Virtual reality, Augmented reality, Genetics and genomics, Regenerative medicine, Tissue engineering, Transplantation, 3D printing and planning, Implants and prosthetics, Stem cells, Pharmacology).

Clinical trials of surgical implants and technologies (Carr)

- Ensure the findings of the CSAW trial are translated into changes in health care policy and practice
- Continue the development and evaluation of surgical implants and technologies for the treatment of tendon disease and tear: conduct and report the Wellcome Trust and NIHR i4i funded Biopatch and Bioyarn Trials (2016-2022)
- Further investigate the co-application of novel biomimetic scaffolds (BioPatch and BioYarn) with growth factors and endogenous cells
- Translate these novel scaffolds into other areas of surgery and medicine
- Explore commercial opportunities for Biopatch and Bioyarn

Surgical Technology, Surgical Learning and Delivery of Orthopaedic Treatments (Rees)

- Improving Treatment Delivery to patients through technology innovations, trials and epidemiology
- Sensor technology for patient rehabilitation – Preventing surgery with enhanced rehabilitation (Industry collaboration – McLaren Applied Technologies*)*
- Decision Making and Implant Performance in shoulder replacement surgery – research with the Royal College of Surgeons (RCS) and National Joint Registry – disseminated through national leadership roles with BESS/NJR/NICE/ODEP
- Innovations in Biomedical 3D Printing – increasing collaboration with Engineering Science
- Improving shoulder surgery through imaging innovations and minimally invasive surgery – increasing collaboration with Engineering Science and Industry Partners
- Sensor technology to optimise surgical skills and outcomes (Industry collaboration – McLaren*)*
- Stratifying primary care pathways for shoulder patients *(*PANDA-S Programme with Keele*)*

Surgical Interventions Trials Unit – SITU (Beard)

SITU is one of seven dedicated RCS trials units dedicated to evaluation of surgical procedures. The unit is linked to OCTRU and CSM, also based in the Botnar.

- SITU promotes and is at the forefront of surgical evaluation both in the UK and internationally
- SITU aims to maintain a minimum of 10 current and substantial portfolio trials and remain financially independent using grant income from NIHR, MRC, Charity and Industry (for core team funding)
- Each trial addresses a valuable question for surgical intervention and will change clinical practice
- The unit's objectives are linked to those of the RCS STC initiative and include the promotion of new chief investigators on trials, education of trainees on trial methodology and inter disciplinary collaboration

- New trials and studies funded include NINJA, SPAARK, MANTIS, PARCS, ALLIKAT, SARCR, MACRO, BIOYARN, SUCCESS, PANDA S, STIFF-F. Existing areas of research have been further developed (design of surgical trials, placebo control, outcome for arthroplasty, qualitative aspects of trial design and delivery)

Genetics, Epidemiology and Treatment of Hand Conditions (Furniss)

- Establishment of new therapeutic targets in fibrosis (Evotec/Lab282). Pursue the development of DDR2 and MMP14 – therapeutic targets in fibrosis. Explore the viability of each target in fibrosis, inflammatory arthritis, and cancer
- Single Cell Biology of fibrosis and connective tissue (European Research Council/Wellcome) – study the single cell biology of fibrosis and connective tissues to look for functional subsets that can be targeted in fibrotic diseases
- From Genotype to Phenotype (3C and derivatives, ATACseq) – to link genotype (from GWAS) to affected genes, in relevant connective tissues harvested at surgery. Other groups have only used blood
- Bench to Bedside to Bench in Hand OA (Furness/Watt/Vincent). The establishment of a phase 1 trial of retinoic acid breakdown inhibitor (eg Talarazole) in patients with Hand OA awaiting trapeziumectomy. Subsequent inhibitor testing on the biochemistry of RetA in harvested trapezium samples

Global Orthopaedic Surgery (Lavy)

- Development of Oxford Global Surgery Group – interdisciplinary team involving, NDORMS, NDS, Nuffield Department of Clinical Neurosciences and Nuffield Department of Women's Reproductive Health
- Become the UK's leading global surgery centre
- Consider the global components to each NDORMS research project
- Develop a network based in Oxford as the advisory centre for global surgery research and education
- Seek funding for Oxford based surgeons to have one PA per surgeon to become involved with global surgery research/training
- Obtain funding and run a multi-centre trial of retinoic acid beta agonist in spinal cord contusion

Imaging and Evaluation of Treatment Innovations for the Hip (Glyn-Jones)

- Hip imaging technology development to enable stratification methods, operative planning, dynamic sequences and segmentation and 3D construction to STL/other printing formats
- Research in 3D printing of plastics and additive layer manufacturing for pre-operative planning templates, patient education, non-operative treatment and intraoperative guidance for arthroscopic and arthroplasty surgery
- 3D printing of bio-materials for use in the hip including bio-absorbable metals in joint preservation/replacement, collagen scaffolds and combined metal/organic scaffolds

Outcome Scores, Enhancing Patient Pathways and Implant Surveillance (Price)

- Continue with the knee research programme
- Develop a programme of research in revision lower limb arthroplasty
- Run a national surgical trial on meniscectomy

- Focus on peri-operative management and enhanced recovery after knee surgery. Translate and investigate such principals to the peri-operative management of patients in orthopaedic surgery as a whole
- Develop a theme of research looking at infection after implantation of devices in orthopaedic surgery

Orthopaedic Engineering (Murray)

- Continue to improve the Oxford partial knee replacement leading to appreciable health cost savings, with day case surgery, improved patient outcomes and decreased risks
- Improve outcomes for total knee replacements, using experience with partial replacements to substantially improve the results of total replacements
- Continue to develop a new system of functional joint assessment based on ultrasound and motion analysis that will display the information in realistic manner that is simple to interpret
- Explore the relationship of mechanical factors in the initiation and development of osteoarthritis, and its subsequent biological processes
- Explore new materials for joint replacement, as current materials are rigid and not representative of human tissues. Consider implanting biomaterials that may stimulate formation of new bone and cartilage
- Explore the use of 3D printed patient matched instrumentation and implants to improve outcomes

Hand and Plastic Surgery (Jain)

- Lead the national research agenda by taking forward ideas generated by the JLA in hand surgery and British Association of Plastic, Reconstruction and Aesthetic Surgeons (BAPRAS) Delphi exercise and linking to the British Society for Surgery of the Hand and BAPRAS research agenda
- Deliver large national clinical trials. One NIHR funded trial is underway and three further trials are in set up
- As the world leaders in multicentre clinical research via the Reconstructive Surgery Trials Network, develop international collaborations with Europe and Australia who want to follow this model with Oxford as a hub

Childrens Orthopaedics (Theologis)

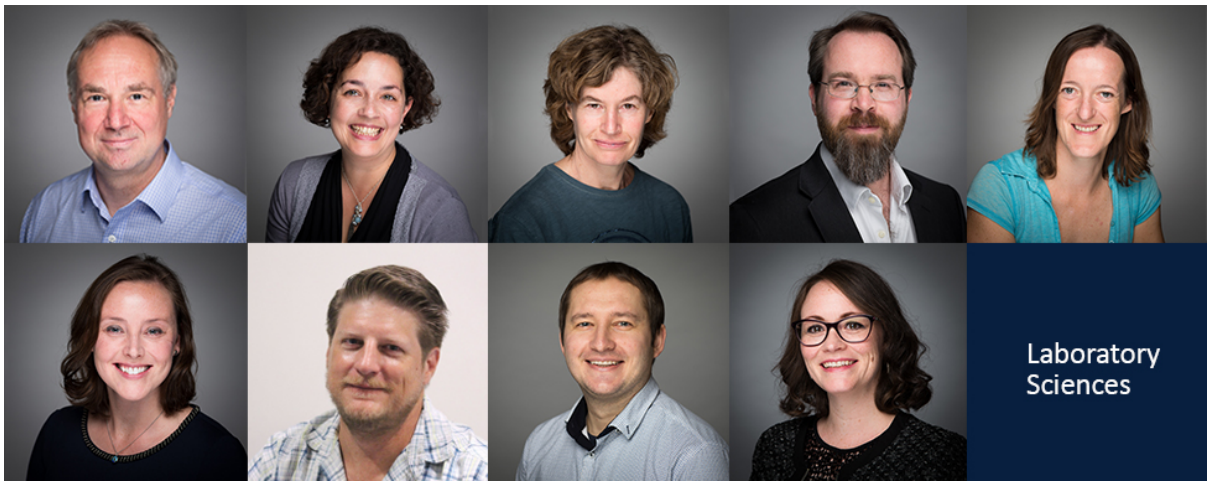
- Lower limb paediatrics – Complete the JLA PSP
- Lower limb paediatrics – Conduct a project on prediction of mild hip dysplasia based on neonatal Cranial Ultrasound Scan (USS)
- Lower limb paediatrics – Flat Feet Clinical Trial (commissioned HTA call)
- Lower limb paediatrics – Biomechanics and Epidemiology programme for paediatric foot deformity and risk of OA. Flat feet, genu varum/valgus, torsional deviations and relationship to the development of osteoarthritis
- Cerebral palsy (CP) – Develop a set of core outcomes for lower limb orthopaedic surgery in CP to inform the clinical trial comparing multi-level surgery vs natural history vs minimally invasive surgery

Spine (Rothenfluh)

- Continue with Spinal fusion indications and outcomes randomised trial (SpInOuT) – Funding NIHR Research for Patient Benefit (RfPB) Programme
- Outcome measurement in adult spinal deformity

- Adult spinal deformity surgery indications and outcomes. This programme aims to establish best-evidence treatment pathways for adult spinal deformity based on reproducible indications for non-operative or operative treatment accounting for resource utilisation, cost-effectiveness and value. A multi-centre observational cohort study with nested case-control studies are required to compare outcomes in specific subgroups of patients and allow risk-stratification

Laboratory Sciences



Laboratory Sciences (from top left to right): Professor Udo Oppermann, Professor Claire Edwards, Associate Professor Philippa Hulley, Associate Professor James Edwards, Dr Helen Knowles, Associate Professor Stephanie Dakin, Associate Professor John Christianson, Dr Siim Pauklin, Dr Gillian Farnie

Context

Over the past decade, the Laboratory Sciences section at the Botnar Research Centre has seen a considerable evolution from investigator teams studying largely genetic associations to musculoskeletal diseases (MSKD) to a wider range of areas, including target discovery and understanding of disease mechanisms.

These research activities currently comprise primary and secondary bone cancer, inflammatory diseases/autoimmunity as well as investigations into mechanisms of skeletal cell biology, stem cell ageing, epigenetics and signalling mechanisms, focused on regenerative medicine approaches. The laboratory research facilities are utilised by PIs forming the core of the section, including molecular and cell biologists besides clinical as well as engineering colleagues, thus fostering significant interactions and collaborations between basic and applied sciences research teams.

The investigator teams of the Laboratory Sciences section consist of eight senior academic posts (Oppermann, Chair in Musculoskeletal Sciences and seven Professors at Assistant (URL) or Associate Professor level (C Edwards, Hulley, Knowles, J Edwards, Dakin, Christianson and Farnie), in addition to two junior principal investigators (Pauklin, Vecellio).

Non-basic (i.e. clinical) researchers who have significant basic research activities include teams from the orthopaedics (Carr, Athanasou, Furniss) and rheumatology (Bowness, Taylor) sections of NDORMS, as well as engineering (Thompson) from MPLS.

Strategic recruitment of early career academics is ongoing to strengthen computational and systems biology approaches.

Training and student supervision

Postgraduate training and education are important components of the Laboratory Sciences section. At any given time, 25-30+ students are pursuing their DPhil linked to experimental laboratory science research, generating a vibrant research environment.

Research environment

Significant investments into research technologies have occurred within the last eight years, and accessible platforms open to all researchers currently comprise single-cell proteomic (mass cytometry (Cytof), flow cytometry) and transcriptomic (cell sorting, encapsulator, Illumina Next-seq) instrumentation, as well as imaging platforms including multi-photon and confocal setups.

We have currently organised these platforms into four small research facilities (SRFs; SRF biomarker, histology, imaging and next-generation sequencing) which are available to researchers in the wider university.

Strategic goals 2018-2021

The primary strategic goal for the Laboratory Sciences section is to increase its international reputation as a research centre of excellence in basic and applied musculoskeletal sciences.

The existing team of basic research and clinical PIs can efficiently progress translational research along the two major lines as outlined below. Although seemingly different, the skills and tools developed in the thematic areas offer ample opportunities to interact between different NDORMS teams, for example working in immuno-oncology, drug discovery, computational biology, clinical trials and regenerative medicine.

- **Primary and secondary bone cancer**
  A significant fraction of Botnar laboratory and clinical investigators (Athanasou, Hassan, Javaid, C Edwards, J Edwards, Oppermann, Pauklin, Christianson, Knowles) are involved in bone cancer research. The BRC-supported sarcoma theme (led by Hassan, Athanasou) is a nucleation point in translational primary bone cancer research, whereas the recent formation of the Oxford Translational Centre for Myeloma Research (Oppermann, Edwards, Christianson, Javaid) provides a translational hub for plasma cell malignancies. In addition, the breadth provided by basic research investigators in cancer and bone biology (Pauklin, Knowles, Edwards) enables Botnar researchers to further interact within the Oxford community, foster international collaborations and public -private partnerships

- **Inflammatory diseases, regenerative medicine, functional genomics and drug discovery**
  (Taylor, Bowness, Furniss, Carr, Oppermann, Knowles, Farnie, Hulley, Vecellio, Dakin) Research into inflammatory, age-related, fibrotic, metabolic and benign proliferative conditions constitutes the second arm of Botnar laboratory activities. These are largely comprised of MSKD areas, such as autoimmune, inflammatory or fibrotic conditions (Taylor, Bowness, Furniss, McCann/Nanchahal, Edwards, Hulley, Vecellio, Dakin), regenerative medicine (Carr) and women's health (Oppermann). The latter activities constitute an element in the Oxford-Bayer Alliance in Women's Health, a public-private partnership between several Oxford departments (NDORMS, NDM, NWRH) with the aim to validate and develop clinical candidates in areas of unmet need including endometriosis, uterine fibroids and polycystic ovary syndrome (Oppermann). The research activities underpin various stages of drug discovery including pre-clinical target validation and cell assay development (Oppermann, Farnie, Knowles, Hulley)

Trauma

Trauma (from top left to right): Matt Costa, Xavier Griffin, Dan Perry, Steve Gwilym, Keith Willett, Liz Tutton, David Metcalfe, James Masters, Miguel Fernandez, David Keene

Chief Investigators

Matt Costa, Xavier Griffin, Dan Perry, Steve Gwilym, Keith Willett, Liz Tutton. Plus, academic trainee Chief Investigators (CIs): David Metcalfe, James Masters, Miguel Fernandez, David Keene.

Overarching strategy

To improve the care of patients with musculoskeletal trauma by creating the evidence-base for clinical and cost effective interventions.

Methodological Focus

Efficient Clinical Research Design: embedding multicentre randomised trials in routine data and cohort studies to enhance recruitment and reduce cost.

Development Plan

To create an Institute of Musculoskeletal Trauma at the University of Oxford.

Five-year plan – key areas:

1. Efficient recruitment: embedding trials within cohorts

WHiTE – Hip Fracture Studies

Hip fracture affects 70,000 patients in the UK each year. Our work has demonstrated that it leads to a permanent 20% reduction in health-related quality of life for patients. Caring for patients with hip fracture costs the NHS and Social Services in the UK over £2 billion annually.

Led by the Oxford Trauma group, the World Hip Trauma Evaluation (WHiTE) is a comprehensive cohort of UK patients who have sustained a hip fracture. This study is a flagship project for UK trauma as hip fracture is a marker condition for fragility fractures more broadly.

We plan to:

- Extend WHiTE cohort as the framework for embedded trials as well as an independent observational study; recruited 14,000 patients to date (Griffin, Costa)
- Complete current embedded trials: WHiTE4: X-Bolt (Griffin), WHiTE5 (Frnandez), WHiTE7: WHISH (Masters), WHiTE8: Copal (Costa), WHITE9: Transfusion (Griffin)
- Develop further WHiTE trials in: surgery (Costa, Griffin, Fernandez) peri-operative pain (Costa), rehabilitation (Keene) + External co-CI collaborators
- Develop evidence syntheses around the WHiTE studies (Griffin)

BOSS: Paediatric cohort studies (Perry)

There are very few high-quality studies ever completed in children's orthopaedic surgery, with a key driver being that diseases are rare and even specialist surgeons often see only a handful of any disease. The British Orthopaedic Surgery Surveillance Study (BOSS) is an efficient mechanism designed to collect anonymised case details of rare orthopaedic diseases throughout the UK, linked to Hospital Episode Statistics (HES) data to maximise case finding. Embedding nested trials within this network could revolutionise clinical care for these rare diseases.

- Complete follow-up for BOSS SCFE and Perthes Cohorts: recruitment closed with 857participants and 90% SCFE data capture
- Develop BOSS network as vehicle for embedded trials – particularly NIHR Health Technology Assessment (NIHR-HTA) SCIENCE and FORCE trials
- Develop new trials in paediatric forearm fractures (CRAFFT)
- Extend embedded trials within BOSS to elective diseases, following the British Society for Children's Orthopaedic Surgery (BSCOS) research agenda

DRAFT: Distal radius studies

Over 100,000 patients break their wrist (distal radius) each year in the UK. Many Of these patients can be treated in a simple plaster cast or brace and return to normal activities after their injury. However, some patients have more severe fractures that are associated with long-term loss of function. Deciding which patients benefit from which interventions is a key challenge for patients and the NHS.

- Complete long-term follow-up of NIHR-HTA DRAFFT cohort (Costa)
- Complete NIHR-HTA DRAFFT-2 embedded trial (Costa)
- Complete WOODCAST trial (Gwilym)

- Develop DRAFT Rehab trial (Keene)
- Develop evidence syntheses around the DRAFFT studies (Costa)

Major trauma: studies involving complex multi-system injuries

'Major trauma' is the term used to describe the most severe injuries which patients can suffer. Patients with major trauma are often involved in serious road traffic accidents and falls from height. Their injuries may affect many parts of the body, including the head and chest as well as arms and legs. Major Trauma is the leading cause of death in patients under the age of 45 in the UK and a huge problem around the world. Investigating this area is central to any trauma research strategy.

- Complete WOLLF trial (Costa)
- Complete WHIST trial (Costa)
- Develop Open Fracture cohort linked to TARN (Griffin, Tutton)

AIM: ankle fracture studies

Fractures of the ankle are common and debilitating injuries. They can occur in young patients playing sport and other high-energy activities but are increasingly common in older patients with fragile bones. Allowing patients to move and to put weight through their healing ankle as soon as possible is important for all patients, but particularly for older patients whose quality of life may be greatly restricted by prolonged periods of immobilisation.

- Complete AIM long-term follow-up (Willett, Lamb, Tutton, Keene)
- Complete SPRAINED study (Lamb, Keene, Gwilym)
- Develop op vs non-op ankle fracture trial (Griffin)

Shoulder and elbow fracture studies

Fractures of the shoulder (proximal humerus) are the fourth most common fracture of a major bone in the UK. Patients often suffer a permanent restriction in movement in their joints after such injuries. Despite recent large-scale studies, it is still not clear which patients may benefit from surgery for their fracture, nor how best to enable their rehabilitation.

- Complete NIHR- HTA ProFHER2 trial (Gwilym with Amar Rangan)
- Develop humeral fracture trial (Gwilym)

Achilles tendon studies

The Achilles tendon is the largest tendon in the human body and transmits the huge forces from the calf muscles to the foot to enable walking running and jumping. When the tendon ruptures, it is a very disabling injury. On average, it takes patients nine months to return to normal activities and for sportsmen and women it can be a career ending injury. Around 30 per 100,000 patients rupture this tendon each year.

- Complete STAR (Costa)
- Complete PATH-2 (KM)
- Develop TA Rehabilitation trial (MC)

2. Efficient data collection: linking routine datasets to trial data

The collection of outcome data in clinical trials is time-consuming, expensive and often incomplete. If we can use routinely collected data to provide clinically important outcomes for patients, we can save time and money, and reduce the burden of questionnaires for patients.

We will develop the infrastructure to support large scale trials based in/linked to routine NHS and Social Care datasets in the UK, and collaborate internationally to compare and contrast UK data with other national datasets. These work streams will be supported by key appointments in research information management, governance and programming. Ongoing research plans:

- Complete WHiTE data linkage to the National Hip Fracture Database (NHFD) +/- HES, the Office for National Statistics (ONS) and the Clinical Practice Research Datalink (CPRD) (Metcalfe)
- Complete BOSS data linkage to HES (Perry)
- Develop Open Fracture cohort data linkage to TARN (Griffin)
- Develop international data collection platforms using the Global Fragility Fracture Network
- Develop health services research collaborations to model UK and international hip fracture care pathways (Costa)

3. Efficient outcome collection: embedding core outcome sets in routine treatment pathways

Bringing research information together from different sources (evidence synthesis) is a potentially powerful way to answer questions that are important to patients and the NHS. However, evidence in musculoskeletal trauma is usually hampered by the fact that different researchers use different ways to measure the success or failure of their treatments.

By developing 'Core Outcome Sets' (COS) – outcomes which are collected in all studies in a particular area – we can enable evidence synthesis. It is important that the core outcomes we measure are the most important outcomes for patients.

- WHiTE core outcome set now well-established in the UK. Extend internationally (Costa)
- Complete development of COS for open fractures (Griffin)
- Complete development of COS for Perthes' disease (Perry)
- Complete development of COS for paediatric elbow fracture (Perry)
- Develop population wide normative values for trauma-relevant PROMIS (Gwilym)

Development Plan - Increasing capacity to support strategic growth

One year rolling plan

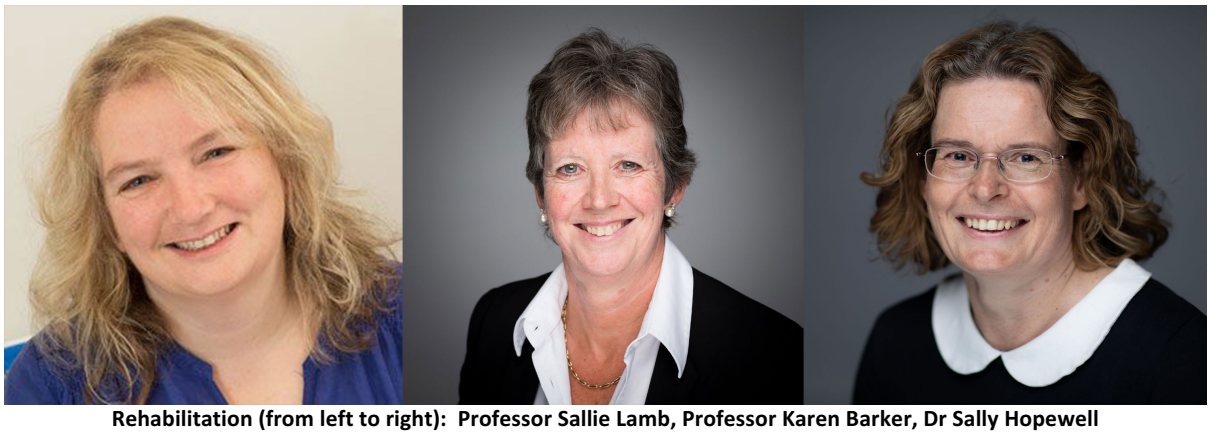
- Develop big data and research information technology infrastructure in the Kadoorie Centre
- Integrate the Oxford Trauma research staff at the Botnar site
- Extend methodological integration with OCTRU and CSM
- Extend collaborations with translational research relevant to musculoskeletal trauma at Botnar and Kennedy Institutes, and the University more widely
- Develop existing partnership with academic Emergency Medicine at the John Radcliffe site, and around the UK
- Consolidate and support the UK Musculoskeletal Trauma Research Network

- Develop and enhance international collaborations in trials and health services research in musculoskeletal trauma

Five-year plan: creation of Institute of Musculoskeletal Trauma

- Secure room for expansion of the Oxford Trauma team on the John Radcliffe site
- Consolidate key international collaborations in musculoskeletal trauma

Rehabilitation



Rehabilitation (from left to right): Professor Sallie Lamb, Professor Karen Barker, Dr Sally Hopewell

Overview

NDORMS, the NOC and the JR have a long history of supporting rehabilitation research. This capacity has been important in underpinning the development of related clinical disciplines and practice, and supporting research in other areas that are important to NDORMS including measurement of human performance, development of outcome measures and interventions, and expertise in patient-facing aspects of clinical research.

We have committed to developing and evaluating research-driven, accessible, high-quality, low-cost interventions for musculoskeletal health conditions. We do this through large pragmatic trials in everyday practice settings which include economic evaluation. Our work includes a suite of impact studies to quantify the numbers of clinicians trained in these interventions, the quality of training and data to understand implementation and show that research findings can be replicated in everyday clinical practice.

Context

The NHS, other health systems and countries without established health systems are facing the challenge of an ageing population and a high volume of disabling musculoskeletal conditions at all stages of life. In the NHS, the squeeze on bed-days means that rehabilitation is facing the challenge of delivery in remote settings with low staff numbers. Low-cost, effective interventions are needed.

Grant Income/publications

The 2018 current active grant portfolio for Rehabilitation Research is about £15 million (including grants currently held by Professor Sallie Lamb at Warwick University). Our group has been involved in over 14 publications in BMJ/Lancet/JAMA since 2015.

PIs: Lamb, Barker, Beard, Smith, Williamson, Hopewell, Rangan, Keene, Willett, Costa, Javaid, Cooper, Silman, Toye.

Research leading to changes in national guidelines and impact on clinical practice

- **Exercise for rheumatoid arthritis in the hands**
  Inflammation and pain of the small joints of hands are the most common presentation of Rheumatoid Arthritis, and one of the most disabling. Our trials in this area, published in the Lancet, precipitated an update of the NICE clinical guideline. We have subsequently published a range of secondary and qualitative analyses to aid implementation, and have developed a web-based platform to disseminate training to clinicians across the NHS and undertaken an NHS based implementation study. We have trained over 400 clinicians, and have tracked implementation in 36 NHS Trusts. We plan to scale the implementation further, including evaluation of a direct to patient package, and international dissemination

- **Back pain is the leading cause of global disability**
  Our group has a long history of research in this challenging condition. We have been at the forefront of developing novel rehabilitation solutions over the last 30 years. We have demonstrated a novel multi-modal rehabilitation package to be as least as effective as surgery for chronic low back pain, and that cognitive therapies offer highly cost-effective intervention. Our work has supported many of the recommendations of the NICE and other international guidance on LBP. We have launched accredited training modules via the web, and trained over 600 registered health care professionals in a first phase release of the training in the NHS. In addition, we have measured impact at the patient level, demonstrating it is possible to replicate the findings of research in clinical practice. The BeST intervention was chosen by the NIHR as one of it is ten interventions to demonstrate the power of research in the NHS

Not for profit and social enterprises

For the majority of our interventions, not-for-profit/social enterprise models are the most appropriate.

Our target is to develop societal and health wealth. This will enable us to develop effective partnerships with other Universities and charities, and one in which we can minimise the tensions of commercial profit. We are working with a series of governmental agencies and charities including Arthritis Research UK, Public Health England and Open University to achieve these aims.

Future Research Themes

Frailty, falls and injury

- Generate highest-quality evidence to inform international guidance on falls prevention including the National Institute of Clinical Excellence (NICE). [Complete a suite of three Cochrane systematic reviews of community-based fall prevention interventions, co-funded by NICE to inform the update of clinical guidance in this area]
- Generate evidence from large scale real-world clinical trials, to inform the development of health policy to reduce injury, frailty and disability in the ageing population in the UK and beyond. [Publication and secondary analysis of the Prevention of Fall Injury Trial of 10,000 people in England]
- Publish work on the external and second stage validation of a simple screening tool for predicting falls
- Work with international partners in completing and sharing the results of pragmatic clinical trials to inform global policy [Collaboration with UCLA, Yale and other North American institutions]

- Develop a new programme of work on adherence to exercise in older populations, especially those who are frail or suffering from cognitive impairment
- Develop new high-potency, low-intensity exercise training programmes for frail older people
- Submit new trial applications for pragmatic trials of systematic bone health intervention in primary care, alternative exercise interventions for falls prevention in the community and prediction tools for frailty, falls and injury

Ageing musculoskeletal and body systems

- Develop new paradigms and test interventions to target movement disability in a range of chronic musculoskeletal conditions of older age [work funded by NIHR Programme grant, NIHR HTA trial grants]
- Characterise common presentations of musculoskeletal disease and disability in older people [work funded by NIHR Programme grant], to explore multi-morbidity and identify challenging complexes of diseases
- Develop new collaborations to explore cellular, molecular and genetic mechanisms of ageing in the musculoskeletal system, utilising cohorts we have established, and the utility of various markers (including imaging markers)

Improving the efficiency, quality, accessibility and impact of research in rehabilitation.

- Explore methods of improving quality of non-Clinical Trial of an Investigational Medicinal Product (CTIMP) trials, particularly where registration and oversight of a recognised regulatory authority is not mandated
- Disseminate through collaboration, teaching and scholarship the principles of good quality research design, and the need for well-designed and reported studies, at the point of study design and launch
- Implement and report on the use of adaptive designs for complex interventions studies, and to evaluate the design characteristics. [funded by MRC Methodology grant]

Increasing the global reach of our research and interventions

- To expand the dissemination of our interventions to low and middle income countries [seek funding through the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford (CLAHRC) global mechanism]
- To expand the dissemination of high-quality musculoskeletal research to low and middle income countries
- To assist and host international research fellows who are involved in developing and evaluating rehabilitation interventions in low and middle income countries [three planned and funded visits and a possible fourth]

Fracture and operative management of musculoskeletal conditions in older people – providing effective rehabilitation across the NHS/social/community interface

- Develop novel service delivery models and interventions that can respond to prevailing pressures to reduce hospital length of stay but maintain engagement and improve outcome of common surgical procedures in frail older people [funded by several NIHR-HTA trials in knee replacement, hip fracture, and Ankle fracture]

- Complete a series of definitive trials to estimate the effectiveness and cost-effectiveness of different models of rehabilitation care, in comparison to, supplementary to, or to prevent the need for surgery. [funded by NIHR-HTA]
- To undertake feasibility and proof of concept studies [funded by NIHR post-doctoral fellowship]

Non-operative management of musculoskeletal conditions, with a focus on scalability, ease of access and maximising effectiveness. We will complete programmes in the following areas and plan appropriate implementation activity

- Shoulder conditions. We have active grants in frozen shoulder, sub-acromial impingement, and shoulder dislocation [funded by NIHR-HTA grants]
- Primary, community and supported self-management of common musculoskeletal conditions including back pain, shoulder pain, neck pain
- Early intervention and self-management
- To continue and extend joint work with the surgical/plastics theme on fibrosis as a therapeutic target
- Complete a series of studies on management of Achilles Tendinopathy. This includes the PATH-2 study where we are examining efficacy and mechanisms of action of platelet therapy. With Costa et al, we are investigating different rehabilitation interventions in comparison to surgery for acute rupture of the TA

Children's orthopaedics/skeletal deformity

- Provide expertise for grant applications for orthotic devices in orthopaedic flat feet and other skeletal deformity
- Complete the write-up of feasibility work and intervention development for idiopathic adolescent scoliosis
- Publish novel insights into the epidemiology of idiopathic adolescent scoliosis

Broader effects of muscle and joint training

- Understand how and if intervention on the musculoskeletal system (for example through exercise training of large muscles) is a mechanistically plausible route to slowing ageing in a range of body systems, including cognition and cognitive impairment, and frailty driven by low grade inflammation. [NIHR-HTA funded, CLAHRC supported, published in BMJ]
- Bring knowledge of training the damaged neuromuscular skeletal system to the clinical management of other conditions, including rehabilitation programmes for breast cancer and head and neck cancer

Maximising patient perspective and involvement

- Develop computer adaptive testing and outcome measures for rapid evaluation of shoulder and upper limb impairment
- Encourage an active and high-quality programme of qualitative work to capture patient experience, improve process evaluation, and ultimately implement interventions and concepts
- Work with local groups in the CLAHRC, BRC and AHSN to share and develop good practice

Developing profile and influence

The Centre for Rehabilitation Research was established five years ago to focus activity in this area, and to provide visibility to the research being undertaken. We have developed a number of strategic collaborations, and will continue to do so over the next five years, namely with the charity Arthritis Research UK (which has now expanded its role for advocating for best practice in the clinical care of people with arthritis), Public Health England (which has identified both musculoskeletal conditions and falls prevention as national strategic goals), and a wide variety of researchers and research networks across the globe.

We engage positively with opportunities for public engagement and various media to promote and disseminate our work. Nearly all of our trials are multicenter, and hence we have built important national and international networks. Locally we are theme leaders and active partners in both the CLAHRC and BRC.

Providing a unique training and development environment and supporting early career researchers

We have the great benefit of working closely with OCTRU and CSM. We have supported early-career researchers and academics from across the world to work with us, and to benefit from the environment we offer.

We have supported Maddox (Kings College) to success in an NIHR Career Development Award, Stubbs (Royal Holloway) and Comer (Leeds Musculoskeletal) to NIHR Clinical Lectureships, Lee (University of New South Wales) to an NHMRC Career Development Fellowship, Cury Ribeiro to a Hercules Fellowship and internally, Keene to an NIHR Post-Doctoral Research Fellowship and PJ to a Harkness Fellowship. We will continue to work with early-career researchers to maximise the success in fellowship competitions.

Several of our researchers have won awards for their work. We have also supported investigators to success in national competitions including Smith (Research for Patient Benefit), Fordham (NIHR HTA/CLAHRC), Hopewell (to her first Chief Investigator position in an NIHR HTA trial), and Williamson (as lead investigator in the NIHR Oxford CLAHRC).

Centre for Statistics in Medicine

Centre for Statistics in Medicine (from top left to right): Professor Sallie Lamb, Professor Jonathan Cook, Professor Daniel Prieto-Alhambra, Professor Gary Collins, Dr Sally Hopewell, Associate Professor Sue Dutton, Dr Rafael Pinedo-Villanueva, Jacqueline Birks, Dr Marialena Trivella

Aims

- Provide leadership and excellence in the discipline of medical statistics at a local, national and international level to improve the quality, transparency and value of medical research
- Collaborate with a range of disciplines to ensure excellence in the application of statistical methods in medical research projects within the Medical Sciences Division of the University of Oxford, and national and international collaborations/projects
- Develop and extend methodology in medical statistics and reporting of medical research

Themes

- Clinical trials
- Observational research and routinely collected data
- Research quality and reporting (incorporating EQUATOR)

Impact

The activities and research undertaken in CSM contribute to improving the design, conduct and quality of medical research in a number of ways. These include:

- Reporting of clinical trials, prognostic and diagnostic studies. Members of CSM have been instrumental in leading and contributing to developing international consensus on reporting and methodological conduct of health research. (Case study 1: CONSORT and other methodological guidelines and EQUATOR.
- Facilitating excellence, speed and volume of clinical trials within the NHS, University and industry. Our work in clinical trials involves supporting chief investigators, training for the many disciplines involved, pushing up standards to ensure compliance with statutory regulation, enabling academic sponsors to host trials that are breaking new ground in discovery science and appraisal of safety, efficacy and cost effectiveness of existing health services. (Case study 2: UKCRC registration, numbers of trials across a broad range of disciplines, key discoveries)

- Extending the use of routinely collected health data to interrogate the safety and effectiveness of a range of health interventions including surgery and medicines. (Case study 3: Pharmaco- and device post-marketing surveillance)

Expansion and adaptability

The pace of medical research is moving quickly, and the expectations of society and funders is high. We have a duty of care to conduct high quality research as quickly as we can.

We anticipate some expansion in the numbers of people who are employed through CSM in the next five years. This will be driven by success in grant applications but also planned investments by NDORMS and potentially other departments.

Due to the appointment of the new Climax chair in Clinical Therapeutics and the consolidation of the Kennedy programme (ATAP), we anticipate seeing an increasing emphasis on early phase clinical trials and those using adaptive designs. CSM will provide a focus for this activity across the MSD, as we are currently the only group of statisticians supporting early phase clinical trials.

Developing people and attracting talent

Like many universities, Oxford has a challenge to attract sufficient numbers of statisticians. We are developing a strategy to attract people, including the following: [1] Much closer link up to the Oxford University MSc in Statistics and Medical Statistics; [2] Providing funded internships for the Oxford/Warwick DPhil in Statistics – and in particular targeting statisticians who have interest in academic medical statistics; [3] Working more closely with industry to explore whether exchange of statisticians between the academic and industry environment is possible; and [4] Hosting the Young Statisticians Conference in 2018.

There has been a significant expansion in the funded opportunities available to help junior statisticians gain their doctorate and to move into working in either applied or more methodological statistics. We are reviewing our job descriptions, being more explicit about training positions and formalising our training programmes, encouraging motivated and talented statisticians to undertake a doctorate, and reviewing our expectations for internal promotion and regrading.

Internal and external collaborations

We have a number of formal collaborations with other departments in the MSD, and the possibility of bringing more groups into the OCTRU collaboration. In the last year, we have made excellent progress in developing links with the Statistics Department (through Professor Chris Holmes).

International collaborations include CONSORT (Consolidated Standards for Reporting Randomised Trials) Executive – as a member of the CONSORT Executive producing international guidelines for the conduct and reporting of clinical trials. Université Paris Descartes on “Research on Research” – leading research into the methodology and design of randomised trials and systematic reviews. Trial Forge – which aims to improve efficiency of clinical trials. Aarhus University Clinical Epidemiology (Denmark), Karolinska Research Institute – Geriatric Pharmacoepidemiology (Sweden), and strengthened links with partners from Medical Informatics at Erasmus Medical Centre Rotterdam (Netherlands) amongst others. Prognosis (UMC Utrecht, Keele University, KU Leuven University of Freiburg, and others), Propensity scores (McMaster University, University of Montpellier).

Biomaterials and Biomedical Engineering

Biomaterials and Biomedical Engineering (from top left to right): Professor Eleanor Stride, Mark Thompson, Professor Andrew Carr, Pierre-Alexis Mouthuy, Amy Zavatsky, Constantin Coussios, Robin Cleveland, Robert Carlisle

The Biomaterials and Biomedical Engineering team will be housed in the new section of the Botnar, The Marcella Botnar Wing, that is currently under construction and is due to be occupied in early 2020.

Biomodulation

Overview and Scope

The new Biomodulation theme will exploit the synergies between the research on drug delivery and biomechanics being carried out within the Institute of Biomedical Engineering (IBME) and on musculoskeletal and inflammatory conditions in the Botnar Research Centre and Kennedy Institute. Its focus will be developing and utilising biomaterials that actively modify the tissue environment to promote therapy.

The team will be housed in the Marcella Botnar Building, opening in early 2020, and will bring together existing investigators from the Oxford Institute of Biomedical Engineering (IBME) and NDORMS with new academics specialising in biophysics and pharmacological engineering who will be recruited over the next 18 months.

The team will also seek to strengthen existing collaborations with the Departments of Mathematics, Materials Science, Chemistry and The Weatherall Institute for Molecular Medicine (WIMM), through co-supervision of researchers.

Central to the team's activities will be engagement with clinical colleagues, regulators and industrial collaborators to facilitate translation of the research into clinical practice.

Key Themes

Tissue and cellular biophysics

- Understanding the pathways underpinning mechanostimulation for therapeutic delivery and tissue regeneration
- Investigating the relationship between mechanical stimuli and immunomodulation
- Development of novel microscopy techniques, including ultra-high speed imaging for studying tissue and cellular response.
- Movement as medicine – monitoring and devices for mechano-modulation in recovery and rehabilitation

Stimuli responsive drug delivery systems

- Designing agents for encapsulation and triggered release
- Exploiting physical stimuli (ultrasound, light, magnetic fields) for targeted delivery of therapy to improve therapeutic ratio
- Combining pharmaceutical and mechanostimulatory approaches to promote tissue repair
- Developing real-time treatment monitoring techniques
- Theranostic device development for combined therapeutic delivery and monitoring

Scaleable bio-manufacturing

- Development of novel fabrication processes for micro and nanoencapsulation that are amenable to scale up and compliant with good laboratory/manufacturing practice
- High precision additive manufacturing of patient-specific models and implants

Next generation models for pre-clinical testing

- Developing clinically relevant tissue models for pre-clinical testing including: computational modelling, organoids, instrumented microfluidic systems and perfused organs.
- Consultation with regulatory bodies on integration of models into the approval process for novel therapies.

Current Funding & Key Projects

Bone fracture healing with targeted nanobubbles (EPSRC)

Bone fractures are a major societal problem costing the UK economy more than £2 billion a year. A significant portion of this cost can be attributed to the 5-10% of bone fractures that fail to heal appropriately with current clinical interventions.

The aim of this project is to develop a system for targeted delivery of drugs that promote bone healing using a combination of focused ultrasound applied externally to the body and drug-loaded nanodroplets (NDs) delivered by intravenous injection. The project is a collaboration between the IBME (Stride), NDORMS (Carr) and Southampton University (Nick Evans, Dario Carugo, Richard Oreffo).

Ultra-high speed imaging system (Rosalind Franklin Institute – RFI)

A key challenge in developing stimuli responsive drug delivery systems is characterising tissue response at high frequencies. This project seeks to develop the first camera in the world able to capture up to 100 million individual frames per second at one megapixel resolution and operate across a wide optical spectrum from ultraviolet to infrared.

The new instrument will be a key part of the core capability of the RFI's INSIGHT (imaging with light and sound) theme, which will be devoted to developing technology for imaging and therapy at the intersection of light and sound.

https://www.rfi.ac.uk/worlds-best-video-camera-to-develop-cures-for-deadliest-cancers/

Engineering Systems for Modulating Tissue Hypoxia (CRUK and PCRF)

Hypoxia, i.e. a reduction in dissolved oxygen concentration below physiologically normal levels, has been identified as playing a critical role in the progression of several diseases, including many types of cancer. Once a hypoxic environment develops within a solid tumour, cell populations become resistant to multiple forms of treatment, including radiotherapy, several types of chemotherapy and immunotherapy.

In collaboration with the University of Ulster, Professor Stride's team have oxygen filled microbubbles as delivery vehicles for the treatment of severely hypoxic tumours such as those seen in pancreatic cancer. They are now working with oncologists in Oxford (Professor Katherine Vallis) and Belfast (Mark Love, Mark Taylor) to translate the approach into clinical use.

Oxford Centre for Drug Delivery Devices (EPSRC)

The Oxford Centre for Drug Delivery Devices (OxCD3) is a £10.1m multi-disciplinary research centre supported by a five-year EPSRC Programme Grant in partnership with 12 industrial partners from across the medical device and pharmaceutical sectors.

The Centre aims to develop engineering approaches, from inception to manufacture, for device-based delivery of novel classes of anti-cancer therapeutics including siRNA, radiopharmaceuticals, viruses and antibodies. A key focus of OxCD3 is the exploitation of physical mechanisms triggered by ultrasound, magnetic fields or shock waves, to improve the delivery and penetration of drugs into tumours (www.drugdelivery.org).

Future plans

Recruitment

- Two new Associate Professors will be recruited in the areas of biophysics and pharmacological engineering
- Business cases for additional team members in immunology and mathematical modelling will be developed

New projects

Successful bids for projects on targeted delivery for bone fracture repair and ultra-high speed imaging have been made as detailed above. Over the next five years, funding will also be sought in the following areas:

- Drug-loaded electrospun fibres for tissue repair (2018-19)
- Investigating the role of hypoxia in the development of bone metastases (2018-19) leading to a larger application on modulating hypoxia for a range of diseases (2021-22)
- Renewal of OXCD3 with extension to antimicrobial and regenerative applications (2019-20)
- Programme grant on stimuli responsive drug delivery and immunomodulation (2020-21)
- Mechanobiology at high strain rates: tissue trauma and damage control (2019-21)
- Elective surgery wound healing – monitoring and optimising mechano-modulation (2020-21)
- Development of an electron microscopy suite (2022-23)
- Biomimesis for pre-clinical testing (2021-22)

Proposed clinical trials

- Oxygen loaded microbubbles for pancreatic cancer (FIH 2020 – funding applied for)
- Modulating hypoxia in post-surgical recovery (FIH 2020 – funding applied for)

Facilities and resources

- Clean room for biomanufacturing
- 3D printing hub (Engineering Science, NDORMS)
- Integrated quantitative microscopy hub (NDORMs, WIMM)
- High speed imaging hub (Engineering Science, Materials, Zoology)

Training

- Engagement with doctoral training centres in quantitative biology, systems biology and medical imaging
- Development of training in research translation (GMP, CE Marking etc.) for researchers
- Development of training in statistics and ethics in clinical trial design for researchers

Public engagement

- Continue and extend outreach activities in local schools through Royal Academy of Engineering funding (including Lab Open Day)
- Royal Society Summer Exhibition and Big Bang Fair
- Development of new team website and social media

For more information about the **Botnar Research Centre** visit our website at **www.ndorms.ox.ac.uk**

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