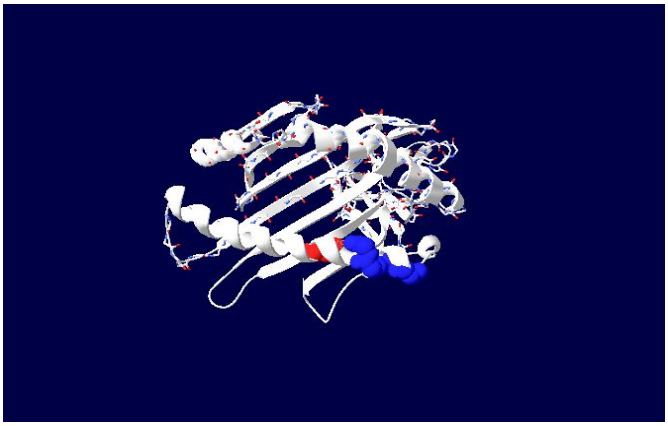
Oxford University Hospitals NHS Foundation Trust

NDORMS NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

UNIVERSITY OF OXFORD

OxKen: DPhil in Inflammatory and musculoskeletal disease

2026 Intake Project Book



OxKen: DPhil in inflammatory and musculoskeletal disease
2026 Intake Booklet

Introduction

The Kennedy Trust for Rheumatology Research-funded OxKen Programme offers fully funded DPhil places for up to 4 intercalating medical students per year in the Medical Sciences Division, focusing on musculoskeletal and inflammatory disease.

This booklet provides an overview for prospective students interested in pursuing a DPhil in Inflammation, Immunology and Musculoskeletal Disease, beginning in summer 2026.

Applications are invited from:

- Oxford medical students intercalating after Year 3 or 4 of the A100 standard entry course, or after Year 2 of the A101 graduate entry course.
- Students from other UK medical schools at a similar stage, subject to approval from their Director of Clinical Studies.

The cohort will commence on 1 July 2026, or 1 August for first-year clinical students.

The Programme offers research-based doctoral training for researchers from clinical and biological backgrounds. Participants will receive a world-leading research training experience that integrates: specialised, fundamental, subject-specific training tailored to individual research needs; education in translational research impact; and on- and post-programme mentorship. Students will have access to:

- a choice of interdisciplinary cutting-edge research projects
- the ability to gain a working in-depth knowledge of the fundamentals of inflammatory and musculoskeletal diseases and patient care through advanced level seminars.
- a world-renowned research environment that encourages the student's originality and creativity in their research.
- opportunities to develop skills in making and testing hypotheses, in developing new theories, and in planning and conducting experiments.
- an environment in which to develop skills in written work, oral presentation and publishing the results of their research in high-profile scientific journals, through constructive feedback of written work and oral presentations.

At the end of their DPhil course, students should:

- have a thorough knowledge of the basic principles of research into inflammatory disorders including the relevant literature and a comprehensive understanding of scientific methods and techniques applicable to their research.
- be able to demonstrate originality in the application of knowledge, together with a practical understanding of how research and enquiry are used to create and interpret knowledge in their field.
- have developed the ability to critically evaluate current research and research techniques and methodologies.
- be able to act autonomously in the planning and implementation of research.
- have the grounding for an influential researcher of inflammatory and musculoskeletal diseases in the future.

Research Themes

Our research themes relating to musculoskeletal disease are as follows:

1. Basic mechanisms of inflammation
2. Inflammatory and rheumatic disease
3. Patient-reported outcomes and, pain
4. Clinical trials and in vivo studies
5. Epidemiology, computational and data science
6. Tissue engineering and remodelling

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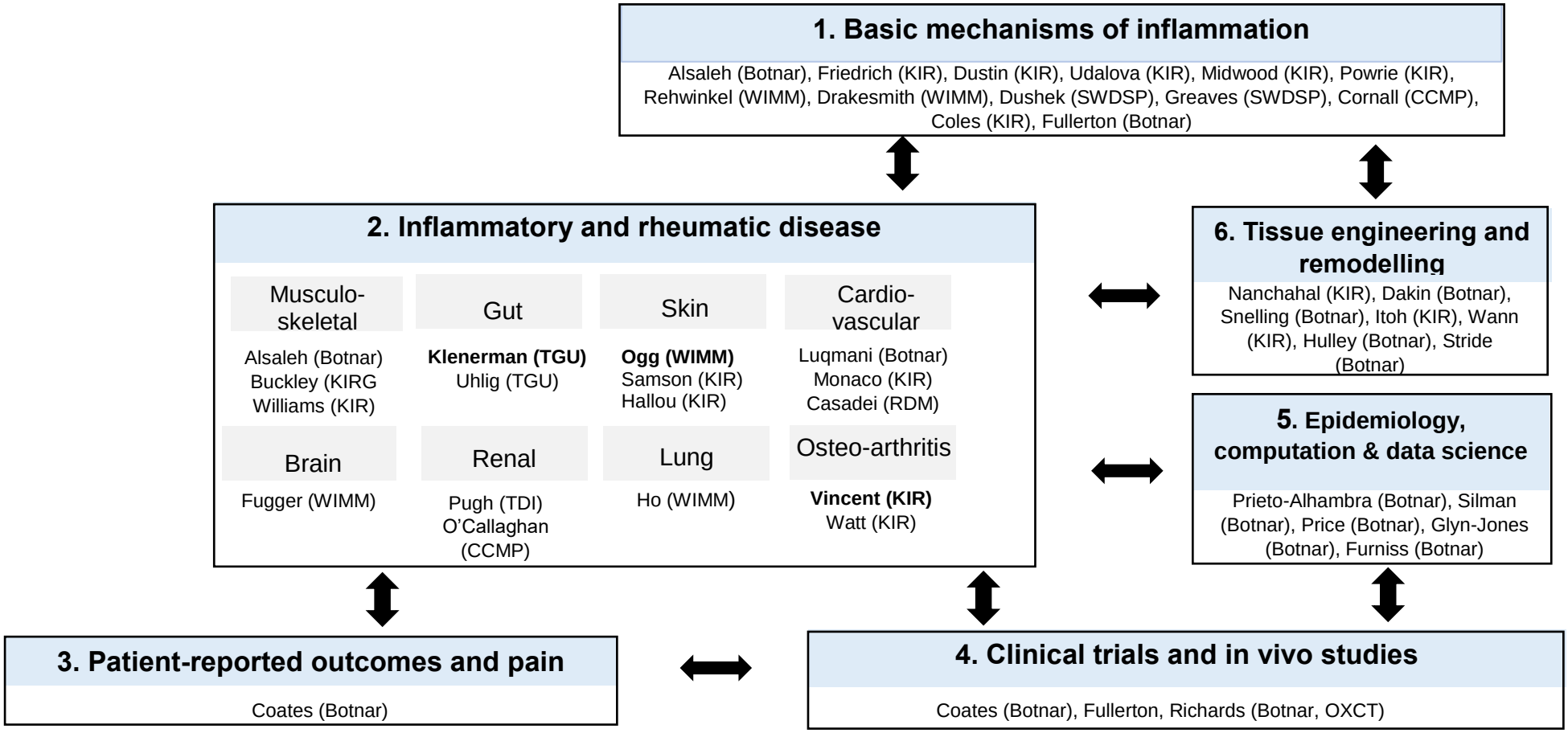
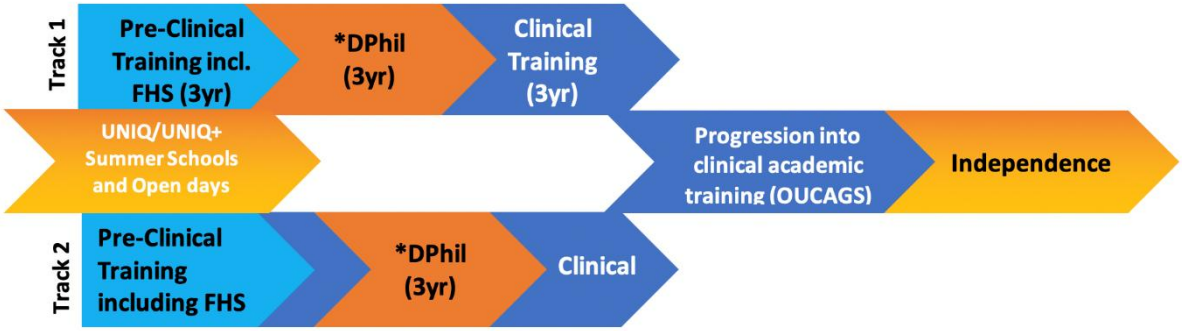
OxKen Research Themes



Abbreviations used: KIR: Kennedy Institute of Rheumatology. WIMM: Weatherall Institute of Molecular Medicine. SWDSP: Sir William Dunn School of Pathology. TGU: Translational Gastroenterology Unit. NDCN: Nuffield Department of Clinical Neurosciences. CCMP: Centre for Cellular and Molecular Physiology. RDM: Radcliffe Department of Medicine. TDI: Target Discovery Institute. OXCT: Oxford Centre for Clinical Therapeutics

Selection Criteria & Eligibility

Due to University requirements this program is only available to current medical students intercalating after year 3 or year 4 of the standard entry A100 course, and after year 2 of the graduate entry A101 course. There are two tracks for training as clinician scientists shown below.



Application Track 1 – Medical Undergraduates current 3rd year preclinical (Aug 2026)
Application Track 2 – 1st year clinical students (Jul 2026).

All applicants will be judged on the following:

- commitment and passion to a career in translational research in musculoskeletal /inflammatory disease
- evidence of motivation for and understanding of the proposed area of study
- commitment to the subject, beyond the requirements of the degree course
- preliminary knowledge of relevant research techniques
- capacity for sustained and intense work
- reasoning ability and academic curiosity.

Selection criteria will also include the project, the environment and relevance to the KTRR's mission statement.

Funding

All offered places are fully funded at the home rate. This includes stipend (currently £23,000 Y1, £24,759 Y2, £26,000 Y3), University and College fees, and a research consumables budget of £10,000 p.a.

How to Apply

We are holding an open day on 28th October at 4.30-6pm at the Kennedy institute of Rheumatology. Do come along and ask questions and meet students and directors. Prospective students should apply with a prioritised list of three projects selected from this booklet by **12:00 midday UK time on: Tuesday 2nd December 2025.**

It is strongly suggested that students contact supervisors of projects they are interested in applying for prior to application.

We will also accept student-generated projects in the fields of inflammatory and musculoskeletal diseases. Please note that your primary project supervisor should be within NDORMS.

Applications are invited from 15 September 2025 to 2 December 2025 (12.00). Please apply through MSD DTC (DPhil in inflammatory and musculoskeletal disease https://www.ox.ac.uk/admissions/graduate/courses/dphil-inflammatory-and-musculoskeletal-disease). Colleges currently accepting OxKen students are listed on the 'College Preference' tab.

Shortlisted students will be invited to interview (on Teams) on Tuesday 13th January 2026. Students can jointly apply to both OxCat and OxKen training programs. If successful, students will be allocated a project on the basis of their ranking during the review process.

Current Student Cohort

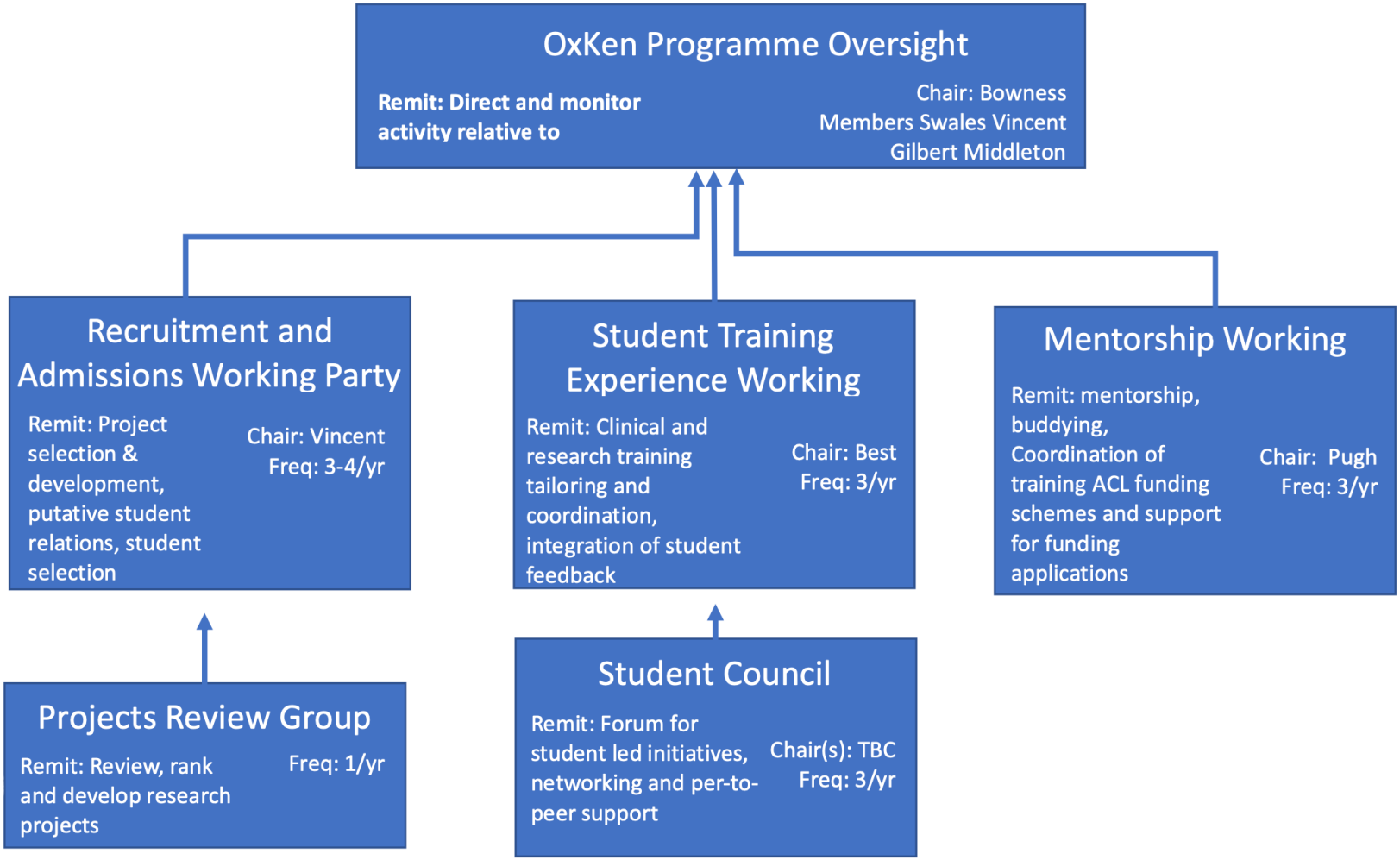
We have 11 current and 7 alumni students on the OxKen programme.

Projects at a Glance

Project ID	Title	Supervisor(s)	Themes
#OxKEN-2026/1	Preventing PsA – patient acceptability to design future trials	Supervisor 1: Laura Coates Co-Supervisor/s: Emma Dures, Marie Falahee, Jorien Veldwijk	4, 3
#OxKEN-2026/2	Immature neutrophils and the vasculature: friends or foes?	Supervisor 1: Irina Udalova Co-Supervisor/s: Professor Raashid Luqmani, Dr Kristina Zec	2, 1
#OxKEN-2026/3	Identifying therapeutic combinations for immune mediated inflammatory disease using computational modelling, artificial intelligence and experimentation	Supervisor 1: Prof. Mark Coles Co-Supervisor/s: Prof. Eamonn Gaffney, Prof. Christopher Buckley	5
#OxKEN-2026/4	Characterizing the ageing phenotype of synovial tissue subtypes (fibroblasts and macrophages) in RA and OA.	Co-Supervisor/s: Dr Ghada Alsaleh, Prof Tonia Vincent, Professor Christopher Buckley	2 ,1, 6
#OxKEN-2026/5	Autoantigen keratin-17 as a key driver of anterior uveitis	Supervisor 1: Prof Christopher Buckley Co-Supervisor/s: Dr Srilakshmi Sharma, Dr Lakshanie Wickramasinghe	1
#OxKEN-2026/6	Epigenetic targeting of fibroblasts as a novel therapeutic avenue for fibro-stenotic Crohn's disease	Supervisor 1: Dr Matthias Friedrich Co-Supervisor: Professor Simon Travis	1 (2)
#OxKEN-2026/7	Using large language models, genomics, and proteomics to phenotype immune-mediated disease	Supervisor 1: Prof Daniel Prieto-Alhambra Co-Supervisor/s: Dr Albert Prats-Uribe, Dr Junqing Xie	5

#OxKEN-2026/8	Elucidating the Mechanisms of RNA Splicing in the Regulation of Inflammatory Responses	Supervisor 1: Associate Prof Adam Cribbs Co-Supervisor/s: Associate Prof Sarah Snelling, Prof Dominic Furniss, Dr Mathew Baldwin	1
#OXKEN-2026/9	Harnessing human genomic, transcriptomic and proteomic data to identify novel therapeutic targets	Supervisor 1: Dr Yang Luo Co-Supervisor/s: Prof Tonia Vincent	1, 2, 5
#OXKEN-2025/10	How does metabolism program B cell immunity?	Lead Supervisor (1): Alex Clarke Supervisory team: Mike Dustin	1, 2
#OXKEN-2026/11	Elucidating the functional phenotypes of fibroblast sub-populations in tendinopathy	Supervisor: Prof Stephanie G Dakin Co-Supervisors: Dr Jessica E Ackerman, Mr Andrew Titchener	2
#OXKEN-2026/12	The molecular relationship between obesity and pain in osteoarthritis (OA)	Supervisor 1: Professor Tonia Vincent Co-Supervisor/s: Professor Zam Cader, Dr Thomas Perry	2
#OXKEN-2026/13	Promotion of intrinsic cartilage repair in osteoarthritis (OA)	Supervisor 1: Professor Tonia Vincent Co-Supervisor/s: Dr Adrien Hallou	2
#OXKEN-2026/14	Optimizing oral iron dosing for patients with chronic inflammatory disorders using plasma hepcidin profiles and stable iron isotopes: haemodialysis patients as an example	Supervisor 1: Dr. Nicole Stoffel Co-Supervisor/s: Prof. James Fullerton	1, 4
#OXKEN-2025/15	Mapping the tissue biology of inflammasome activation in inflamed arthritic joints	Supervisor 1: Jelena Bezbradica Mirkovic Co-Supervisor/s: Madelon de Jong, Chris Buckley	1

OxKen Governance Structure



Project Proposals

1. #OxKEN-2026/1 Preventing PsA – patient acceptability to design future trials

Supervisor 1: Laura Coates

Co-Supervisor/s: Emma Dures, Marie Falahee, Jorien Veldwijk

PROJECT OVERVIEW:

Around 30% of people with psoriasis will go on to develop a related inflammatory arthritis called psoriatic arthritis. This can cause inflammation in the peripheral joints, tendons, spine and other musculoskeletal tissues and significant impairment of quality of life. A large European consortium of researchers called HIPPOCRATES (https://www.hippocrates-imi.eu/) has been funded to further research into psoriatic arthritis. Within this, Professor Coates is leading a 5-year project examining how to predict and potentially prevent the onset of PsA. This DPhil has been co-designed with members of another large consortium (PREFER) which is examining patient preferences in research.

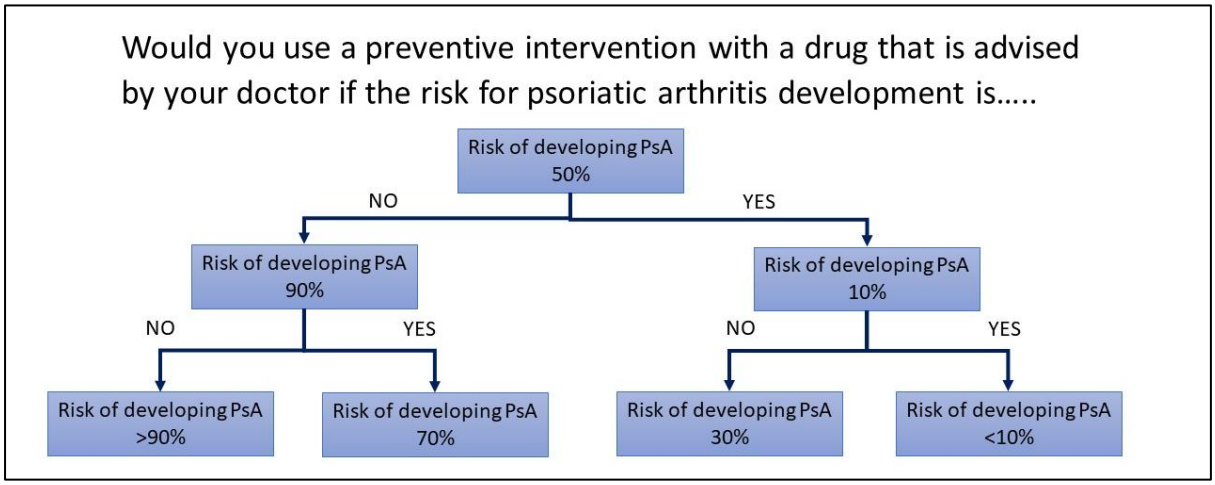
This DPhil project will establish the acceptability of preventative treatment for PsA amongst people with psoriasis. It will help us to design a future interventional study aiming to prevent the progression to psoriatic arthritis.

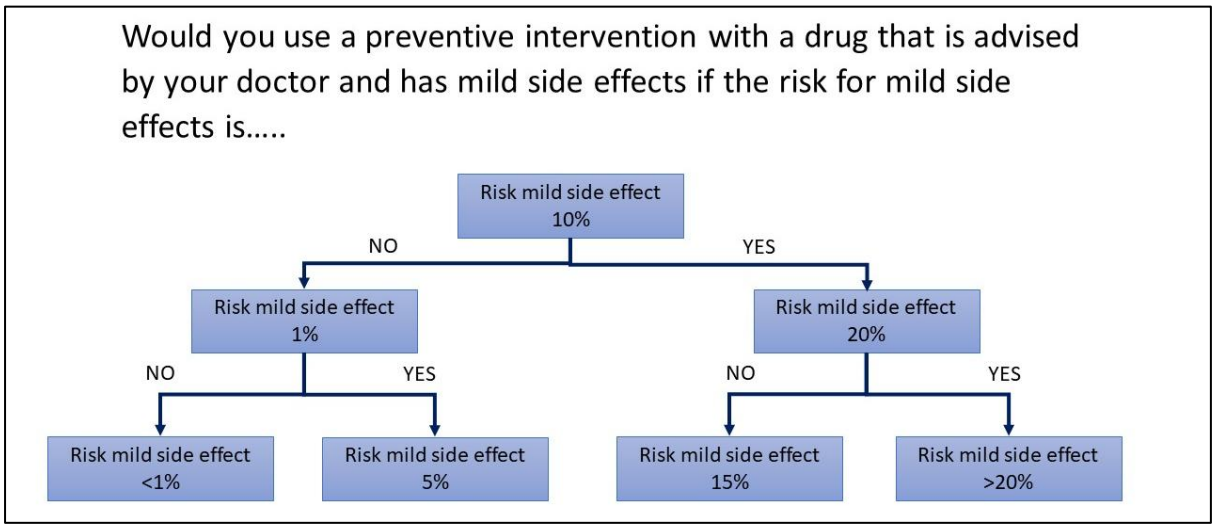
Whether people would be happy to join a preventative study is likely to depend on a lot of factors, Training will be provided in qualitative research techniques to lead focus groups of people with psoriasis. This qualitative work will explore the different factors that would influence their choice about enrolling in a preventative study such as:

- Risk of developing arthritis
- Side effects of any medication/intervention
- Whether the medication also improves psoriasis
- What previous treatments people have received for psoriasis

Additional work with patients will explore individual and socio-economic barriers and enablers for people to enrol in a future study and the outcomes important to patients that should be included in a preventative study.

Following this work, with expertise from Dr Falahee and Dr Veldwijk, you will co-design a discrete choice experiment to measure patient's preferences for preventative therapy. This will explore patient preferences for the attributes of preventative treatments and calculate the minimum benefit levels that patients require given different levels of side effects. This work will build on a threshold technique study that is currently being undertaken looking at these factors. For example, the current study asks:





In the discrete choice experiment we will build on these thresholds and give participants a choice between two different theoretical treatments to see which they would decide. They will then be given two different treatment options, each with different side effects and doses. People will also have an option to 'opt out' if they would not like to take either treatment.

For example:

"You have recently developed some pain in your joints. Tests have shown that your risk of developing psoriatic arthritis in the next 2 years is 50%. Your doctor has asked you to consider taking a treatment to reduce that risk for one year. Which of these treatments would you pick?".

	Drug A	Drug B	No Drug
Risk of developing PsA	10%	30%	50%
Mode of administration	Injection	Oral	-
Treatment frequency	Weekly	Daily	
Risk of mild side effects	5%	5%	-
Risk of serious side effects	3%	1%	-
I would choose			

This work will contribute directly to the design of a future trial aiming to test medications aiming to prevent the evolution from psoriasis to psoriatic arthritis. You will be a key member of the international HIPPOCRATES consortium supporting international networking opportunities.

KEYWORDS: qualitative, patient preferences, psoriatic disease, clinical, priorities

TRAINING OPPORTUNITIES:

This project represents an excellent opportunity for a keen scientist to develop skills in qualitative and patient-focused research. Training will be provided in

1. qualitative research and nominal group techniques
2. discrete choice experiments
3. biostatistics
4. patient involvement in research

The supervisors have significant experience in DPhil supervision and are world-leaders in different elements of this proposal. The study will have strong links to two large IMI-funded European research consortia (HIPPOCRATES - https://www.hippocrates-imi.eu/ and PREFER - https://www.imi-prefer.eu/) providing excellent networking with other researchers across Europe.

KEY PUBLICATIONS:

1. **Coates LC**, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, Meads DM, Emery P, Conaghan PG, Helliwell PS. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015 Dec 19;386(10012):2489-98.
2. Tucker L, Allen A, Chandler D, Ciurtin C, Dick A, Foulkes A, Gullick N, Helliwell P, Jadon D, Jones G, Kyle S, Madhok V, McHugh N, Parkinson A, Raine T, Siebert S, Smith C, Tillett W, **Coates LC**. The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs. Rheumatology (Oxford). 2022 Aug 30;61(9):e255-e266.
3. Simons G, Schölin Bywall K, Englbrecht M, Johansson EC, DiSantostefano RL, Radawski C, **Veldwijk J**, Raza K, **Falahee M**. Exploring preferences of at-risk individuals for preventive treatments for rheumatoid arthritis. Scand J Rheumatol. 2022 Sep 30:1-11. doi: 10.1080/03009742.2022.2116805. Online ahead of print. PMID: 36178461
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5. **Dures E**, Hewlett S, Lord J, Bowen C, McHugh N; PROMPT Study Group, Tillett W. Important Treatment Outcomes for Patients with Psoriatic Arthritis: A Multisite Qualitative Study. Patient. 2017 Aug;10(4):455-462. doi: 10.1007/s40271-017-0221-4.

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2. #OxKEN-2026/2: Immature neutrophils and the vasculature: friends or foes?

Lead Supervisor (1): Professor Irina Udalova

Supervisory team: Professor Alex Clarke, Prof Raashid Luqmani

Postdoc Supervisor(s): Dr Kristina Zec

PROJECT OVERVIEW:

Vascular pathologies underline devastating diseases ranging from auto-immune vasculitis to the recent COVID-19 pandemic (**1**). Neutrophils, as the most abundant immune cells, have been reported to intimately interact with the vascular system either via direct cell-cell contact or indirectly through release of inflammatory cytokines or cellular substances. Fully functional mature neutrophils patrol the circulation and tissues to exert anti-microbial activity through several mechanisms including release of cytotoxic products, reactive oxygen species (ROS), neutrophil extracellular traps (NETs) and pore-forming molecules. These activities can cause vascular tissue damage if poorly controlled.

Inflammatory responses trigger the release of functionally distinct immature neutrophils into the circulation and tissues in different diseases, including severe COVID-19, where we, and others, identify the presence of neutrophil progenitors (**2**). Our recent work on giant cell arteritis (GCA) has shown that immature neutrophils can interact with endothelium, generate ROS and cause vascular leakage and damage that may lead to systemic vascular pathology (**3**).

This project will experimentally test a **possible direct involvement of immature neutrophils in endothelial damage** in a mouse system for imaging of neutrophil subset interactions with vascular walls *in vivo* (**4**). We will exploit our recently unravelled cell-intrinsic molecular regulators of neutrophil maturation and function (**5**) to genetically manipulate neutrophil phenotypes (i.e. cells and mouse strains deficient in specific regulators). In parallel, we will expand our analysis of neutrophil- and oxidative tissue damage-associated biomarkers in human biopsies (biobanked and fresh) of large (GCA) and small (ANCA, Lupus) vessel vasculitis patients, using the state-of-the-art spatial biology approaches, such as multi-parameter confocal microscopy and single cell spatial transcriptomics. Correlations between molecular signatures of vascular damage associated with immature neutrophils, endpoints and treatment outcomes will be assessed in a clinically well-defined cohorts.

The outcome of this study is expected to contribute significantly to development of new targets for therapeutic interventions to prevent detrimental vascular damage that is implicated in many diseases such as auto-immune vasculitis.

KEYWORDS: Neutrophils, Vasculitis, Multiplex Imaging, Spatial transcriptomics, Vascular pathologies

TRAINING OPPORTUNITIES:

The Kennedy Institute is a world-renowned research centre and is housed in a brand new state-of-the-art research facility. Training will be provided in techniques in a wide range of immunological tool kits (cell isolation, FACS, ELISA, primary cell culture); imaging (immunofluorescence on tissue sections, confocal intravital microscopy) and genomic (single cell and spatial transcriptomics) approaches. Multiplex assays such as the Luminex assay will be used for patient plasma profiling to identify key signaling molecules that modulate neutrophil-vasculature interaction. The candidate can benefit from the hands-on experience with these techniques in the Udalova and Clarke labs, and from access to clinical samples in the Luqmani group.

A core curriculum of lectures will be taken in the first term to provide a solid foundation in a broad range of subjects including inflammation, genomics, epigenetics, translational immunology and data analysis. Students will attend weekly seminars within the department and those relevant in the wider University. Students will be expected to present data regularly to the department, the Genomics of Inflammation lab and to attend external conferences to present their research globally. Students will also have the opportunity to work closely with both internal and external collaborators on live imaging and spatial omic analyses.

KEY PUBLICATIONS:

(1) Wang L, Luqmani R, **Udalova IA**. The role of neutrophils in rheumatic disease-associated vascular inflammation. ***Nature Review Rheumatology***. 2022 Mar;18(3):158-170.

(2) Oxford Covid-19 Immunology Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. ***Cell.*** 2022 Mar 3;185(5):916-938.e58.

(3) **Wang L**, Ai Z, Khoyratty T, Zec K, Eames HL, van Grinsven E, Hudak A, Morris S, Ahern D, Monaco C, Eruslanov EB, **Luqmani R**, **Udalova IA**. ROS producing immature neutrophils are linked to GCA vascular pathologies. ***Journal of Clinical Investigations Insight***. 2020 Oct 15;5(20):e139163

(4) Finsterbusch M, Voisin MB, Beyrau M, Williams TJ, Nourshargh S. Neutrophils recruited by chemoattractants in vivo induce microvascular plasma protein leakage through secretion of TNF. ***J Exp Med***. 2014 Jun 30;211(7):1307-14.

(5) Khoyratty T*, Ai Z*, Ballesteros I, Mathie S, Eames HL, Martín-Salamanca S, **Wang L**, Hemmings A, Willemsen N, von Werz V, Zehrer A, Walzog B, van Grinsven E, Hidalgo A, **Udalova IA**. Distinct transcription factor networks control neutrophil-driven inflammation. ***Nature Immunology***, 2021 Sep;22(9):1093-1106.

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Dr Kristina Zec Kristina.zec@kennedy.ox.ac.uk

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3. #OxKEN-2026/3: Identifying therapeutic combinations for immune mediated inflammatory disease using computational modelling, artificial intelligence and experimentation

Supervisor 1: Prof. Mark Coles

Co-Supervisor/s: Prof. Eamonn Gaffney, Prof. Christopher Buckley

PROJECT OVERVIEW:

Background: Advances in gene sequencing and imaging technologies are transforming how scientists undertake research in rheumatoid arthritis (RA), permitting human data driven therapy development. Using blood and tissue biopsies, we have been developing gene expression maps in joint pathology. Although these datasets have provided key insights into disease, they lack temporal and spatial information limiting their impact on therapeutic discovery and development. Thus, the challenge is to develop and apply new technologies that can provide new insights into RA and identify a cure.

Project Objectives: Using a combination of data analytics, computer simulations and experimental validation to identify disease mechanisms and use artificial intelligence to determine if combinations of existing therapeutics developed to treat cancer or other autoimmune diseases could be a CURE for RA.

Approach: In this project the student will develop and utilise multi-scale computational models, to simulate cellular and molecular interactions in time and space; and apply machine learning-based approaches to identify optimal therapeutic intervention strategies. In this research program we will utilise primary human RA datasets to build computer models focusing on two key disease mechanisms, joint inflammation and cartilage and bone destruction. Using the power of high performance computing, millions of computer simulations can be run, and artificial intelligence applied to identify novel intervention strategies. This will involve screening existing therapeutics that could potentially be repurposed to treat RA. The outputs from these simulations will be validated using human cell culture and in animal models. Because all computer models will be designed using primary human datasets, the translation of predictions to human clinical medicine will be de-risked. This novel approach has the potential to significantly change how therapies for rheumatoid arthritis are identified.

Specific Project Aims
1: Develop a multi-scale temporal and spatial model of macrophage – sublining layer fibroblast (Thy1+) function in human synovium, built on single cell RNAseq, cytometry and immunohistochemistry datasets from early and chronic RA permitting simulation of receptor-ligand interactions and signaling processes in the formation, maintenance and potential resolution of the inflammatory pathology.

2: Generate a computational simulation of lining layer fibroblast (Thy1-PRG4+) migration and invasion of bone and cartilage to identify key regulators of fibroblast directed migration and destructive potential that can be selectively targeted.

Thus, the aim of this DPhil project will be to use a combination of modelling, machine learning and experimental validation to identify potential therapeutic targeting strategies for human inflammatory disease.

KEYWORDS: Computational modelling, systems biology

TRAINING OPPORTUNITIES: The student will be based in the Kennedy Institute of Rheumatology taking advantage of data from world leading technologies in the institute including confocal microscopy, high dimensional Cell Dive imaging and 3D light sheet microscopy. obtain training in key cutting-edge technologies including: 3D light sheet and multi-plex high dimensional imaging; Spatial genomics and big data analysis. They will have access to BMRC computing cluster and appropriate systems biology training and learning computational/mathematical skills including use of Matlab or higher level programming languages.

KEY PUBLICATIONS:

Cosgrove J, Novkovic M, Albrecht S, Pikor NB, Zhou Z , Onder L, Mörbe U, Cupovic J, Miller H, Alden K, Thuery A, O'Toole P, Pinter R, Jarrett S, Taylor E, Venetz D, Heller M, Uguccioni M, Legler DF, Lacey CJ, Coatesworth A, Polak WG, Cupedo T, Manoury B, Thelen M, Stein JV, Wolf M, Leake MC, Timmis J, Ludewig B, Coles MC, B-cell Zone Reticular Cell Microenvironments Shape CXCL13 Gradient Formation, Nature Communications, 2020, Jul 22;11(1):3677. doi: 10.1038/s41467-020-17135-2.

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4. #OxKEN-2026/4Characterizing the ageing phenotype of synovial tissue subtypes (fibroblasts and macrophages) in RA and OA.

SUPERVISORS: Dr Ghada Alsaleh**,** Prof Tonia Vincent, Professor Christopher Buckley.

PROJECT OVERVIEW:

Rheumatoid arthritis (RA) and osteoarthritis (OA) are the most common forms of arthritis in the UK and carry a substantial medico-economic burden. Targeted therapies have improved outcomes in RA, yet many patients continue to experience persistent inflammation and progressive disability. OA, in contrast, lacks effective disease-modifying treatments.

Resident stromal cells of the synovium, particularly synovial fibroblasts (SF, also called fibroblast-like synoviocytes, FLS), actively drive inflammation and tissue degradation in both RA and OA. Distinct SF populations contribute differently: RA synovium is enriched for sublining, proinflammatory fibroblasts, whereas OA synovium shows accumulation of lining layer, pro-destructive fibroblasts. The molecular mechanisms underlying these differential behaviours remain poorly understood.

Synovial tissue macrophages (STMs) are another major resident population. In RA, chronic inflammation promotes infiltration of blood-derived macrophages, amplifying cytokine production, immune cell recruitment, and joint destruction, while reparative $MERTK^{+}$ tissue-resident macrophages decline. A similar imbalance is observed in OA, where inflammatory macrophages release cytokines and degradative enzymes that drive cartilage breakdown, alongside a reduction in $MERTK^{+}$ macrophages that limits tissue repair.

Macrophages and fibroblasts exist in close spatial and functional niches, and their cross-talk is critical in regulating joint inflammation and destruction. Differences in RA and OA synovium may arise not only from fibroblast ageing but also from macrophage senescence. Cellular senescence contributes to tissue degeneration in OA, whereas in RA, therapeutic induction of fibroblast senescence may limit inflammation. How age- and senescence-related changes in macrophages interact with fibroblast subsets to shape inflammatory versus degenerative environments remains unknown.

This project will investigate the role of age-related cellular senescence in shaping synovial tissue structure and function, focusing on fibroblast subsets (lining vs. sublining) and resident macrophage populations. By integrating expertise in stromal biology, macrophage immunology, and ageing research, we aim to uncover mechanisms that drive inflammation and tissue degeneration in RA and OA and identify potential avenues for novel therapeutic strategies.

PROJECT AIMS: This PhD studentship has three aims:

Aim1: Molecular characterization of ageing hallmark markers across synovial cell subsets, using multi-omics approaches.

Aim 2: Establish the anatomical localization of ageing-associated synovial cell subsets in human OA and RA synovium compared to inflammatory (STIA) and degenerative (DMM) mouse models, using CellDive and RNAscope to assess transcript- and protein-level expression of ageing hallmarks.

Aim 3: Bioinformatic integration of ageing signatures across fibroblast and macrophage subsets in human synovium and their counterparts in STIA and DMM mouse models, to define conserved versus disease-specific ageing trajectories.

KEYWORDS: Osteoarthritis, autophagy, ageing, Arthritis, Immunology.

TRAINING

The Botnar Research Centre plays host to the University of Oxford's Institute of Musculoskeletal Sciences, which enables and encourages research and education into the causes of musculoskeletal disease and their treatment. Training will be provided in techniques including flow cytometry, histochemistry, confocal microscopy, RNAscope assays, drug screen design and *in vitro* cell cultures (2D and 3D) of human chondrocytes, fibroblasts, various cell lines as well as using preclinical *in vivo* models of OA.

A core curriculum of lectures will be taken in the first term to provide a solid foundation in a broad range of subjects including musculoskeletal biology, inflammation, epigenetics, translational immunology, data analysis and the microbiome. Students will also be required to attend regular seminars within the Department and those relevant in the wider University.

Students will be expected to present data regularly in Departmental seminars, Alsaleh's group and attend external conferences to present their research globally, with limited financial support from the Department.

Students will also have the opportunity to work closely with colleagues in The Centre for Osteoarthritis Pathogenesis Versus Arthritis (OA Centre, https://www.kennedy.ox.ac.uk/oacentre/oacentre), Oxford, DRFZ Institute (https://www.drfz.de/uber-uns/koepfe/prof-dr-max-loehning/), Berlin, TIGEM Institute (https://www.tigem.it/research/faculty/settembre), Naples, and The Buck Institute for ageing research (https://www.buckinstitute.org/lab/campisi-lab/), California.

Students will have access to various courses run by the Medical Sciences Division Skills Training Team and other Departments. All students are required to attend a 2-day Statistical and Experimental Design course at NDORMS (Nuffield Department of Orthopaedics) and run by the IT department (information will be provided once accepted to the programmer).

SUPERVISORS:

Dr Ghada Alsaleh**:** https://www.ndorms.ox.ac.uk/research/research-groups/alsaleh-group-aging-in-the-musculoskeletal-system.

Prof Tonia Vincent: https://www.kennedy.ox.ac.uk/research/molecular-pathogenesis-of-osteoarthritis.

Professor Christopher Buckley: https://www.ndorms.ox.ac.uk/research/research-groups/stromal-cell-biology.

KEY PUBLICATIONS:

1. Croft, A. P. *et al.* Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246-251, doi:10.1038/s41586-019-1263-7 (2019).
2. Alsaleh, G. *et al.* Autophagy in T cells from aged donors is maintained by spermidine and correlates with function and vaccine responses. *Elife* **9**, doi:10.7554/eLife.57950 (2020).
3. Zhang, H. *et al.* Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. *Mol Cell* **76**, 110-125 e119, doi:10.1016/j.molcel.2019.08.005 (2019).
4. Zheng, G. *et al.* TFEB, a potential therapeutic target for osteoarthritis via autophagy regulation. *Cell Death Dis* **9**, 858, doi:10.1038/s41419-018-0909-y (2018).
5. Wu, C. L., Harasymowicz, N. S., Klimak, M. A., Collins, K. H. & Guilak, F. The role of macrophages in osteoarthritis and cartilage repair. *Osteoarthritis Cartilage* **28**, 544-554 (2020). https://doi.org/10.1016/j.joca.2019.12.007.
6. Watanabe, S., Alexander, M., Misharin, A. V. & Budinger, G. R. S. The role of macrophages in the resolution of inflammation. *J Clin Invest* **129**, 2619-2628 (2019). https://doi.org/10.1172/JCI124615.

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5. #OxKEN-2026/5: Autoantigen keratin-17 as a key driver of anterior uveitis

Supervisor 1: Prof Christopher Buckley

Co-Supervisor/s: Dr Srilakshmi Sharma, Dr Lakshanie Wickramasinghe

PROJECT OVERVIEW:

The uvea is the vascular and pigmented layer of the eye, lying between the sclera and the retina. It consists of the iris, ciliary body and choroid. The components of the uveal tract have several supportive functions for vision. Inflammation in the uvea (uveitis) is a leading cause of blindness in people of working age, responsible for between 10% to 20% of blindness in the United States and Europe. Anterior uveitis is the most common form of uveitis, with a prevalence of 2 per 1000 population. It has a strong genetic association with the class I MHC allele HLA-B27 and is characterised by a build-up of leukocytes within the anterior chamber of the eye with symptoms including pain, photophobia and reduction in visual acuity.

In our laboratory, we have generated a single cell atlas of the human uveal tract, and demonstrated that the stromal cells of the uvea, in particular the fibroblasts, display marked heterogeneity between the three uveal sites (Figure 1). Iris fibroblasts express high levels of keratin-17 (KRT17), an intermediate filament protein which is also found in skin adnexa such as hair follicles and in the nail bed. Unlike in the iris, keratin-17 is not expressed in either the ciliary body or choroid fibroblasts (Figure 2A). This finding has been validated by RNA *in situ* hybridisation in human eye tissue (Figure 2B&C). Work by other groups has demonstrated that keratin-17 is an autoantigen in psoriasis. This is of relevance to anterior uveitis as patients with psoriasis are more likely to develop anterior uveitis and nail bed disease than the general population.

Our group has received ethical approval to sample aqueous humour and blood from patients with uveitis. This allows us to investigate the cellular basis of anterior uveitis in detail. The three aims for this project are:

1. Determine whether patients with anterior uveitis have circulating T-lymphocytes which are reactive to keratin-17.
2. Determine whether the aqueous humour of patients with anterior uveitis contains T-lymphocytes reactive to keratin-17.
3. Characterise the T-lymphocyte subsets of the aqueous inflammatory infiltrate from patients with anterior uveitis.

The techniques that will be used to investigate these three aims including spectral cytometry using the Cytek Aurora and single cell transcriptomic analysis on the 10X Chromium platform. Both techniques will allow for extensive phenotyping of the leukocyte populations within the aqueous inflammatory infiltrate. In addition, *in vitro* cellular assays will be used to test T-cell reactivity and proliferation in response to antigens, including keratin-17 peptides.

This project is an excellent opportunity for a DPhil student to develop skills in experimental and computational techniques, and to drive a project that will advance our knowledge of the pathogenesis of anterior uveitis, and its connection with psoriasis in an eye-skin-joint axis.

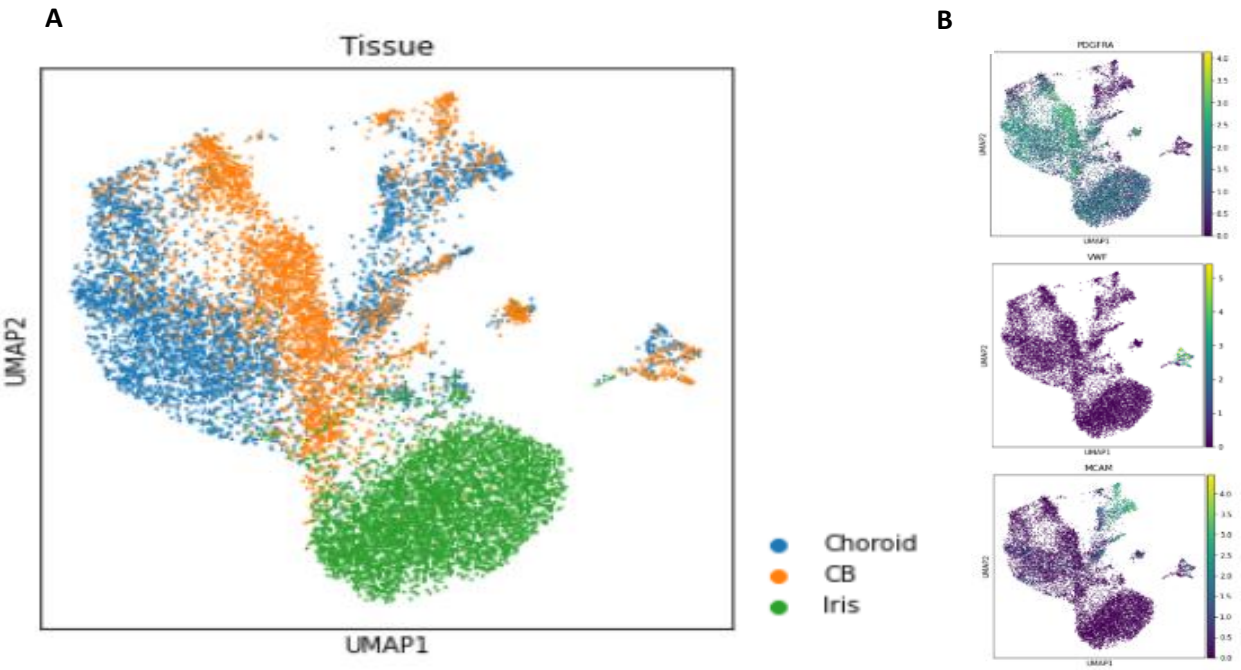

Figure 1. Single Cell RNA sequencing data demonstrates that fibroblasts of the iris (green) group separately to those of the ciliary body (orange) and choroid (blue) on single cell RNA sequencing.

A: UMAP of fibroblasts, pericytes and endothelial cells from the adult human uvea coloured by tissue of origin.

B: UMAPs of stromal cells coloured by canonical markers of fibroblasts (PDGFRA), pericytes (MCAM) and endothelial cells (VWF).

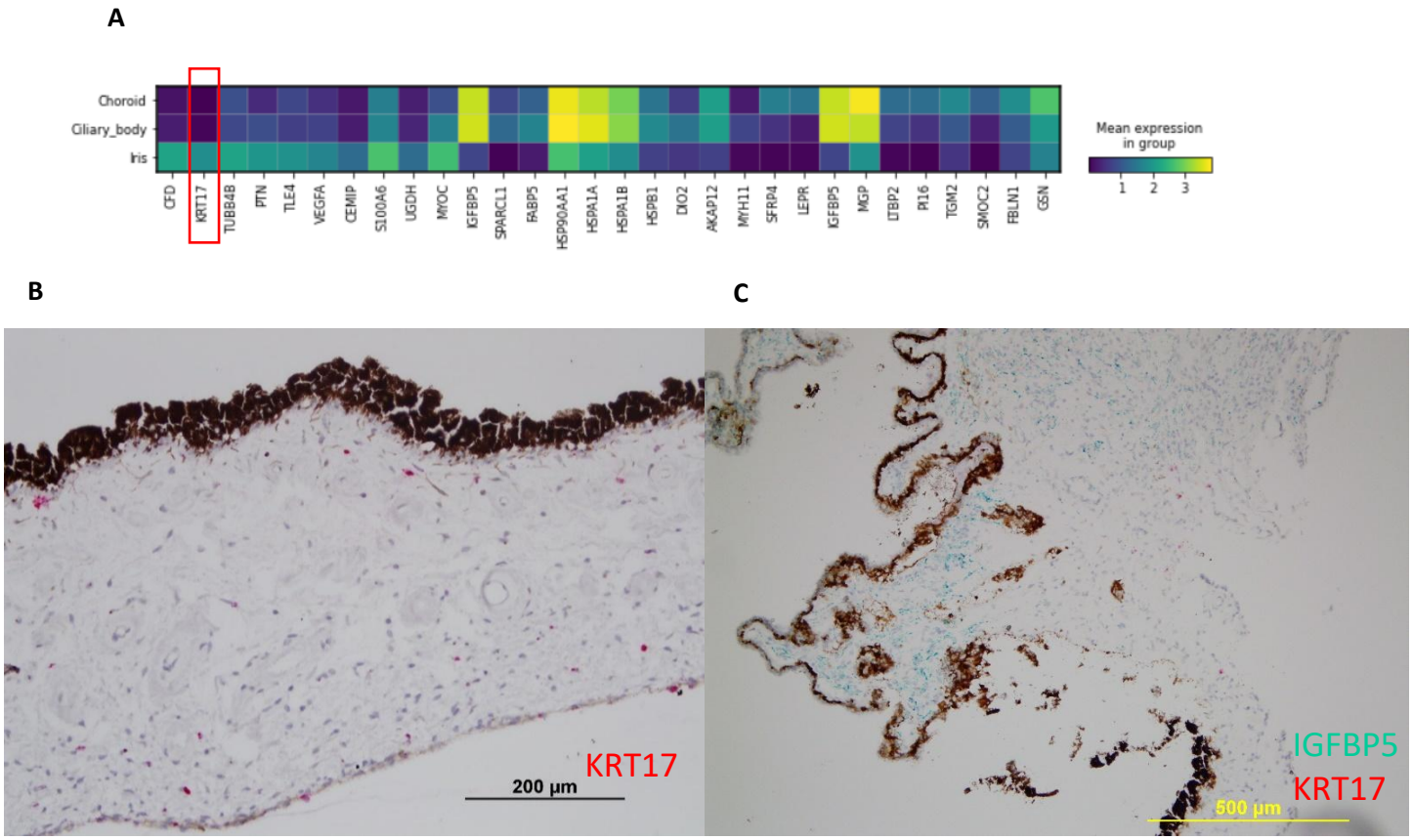

Figure 2. Kertain-17 expression is localised to the human iris.

A: Heatmap of top 10 significantly differentially upregulated genes in the fibroblasts of the iris, ciliary body and choroid compared to whole dataset. Keratin -17 marked by red box.

B and C: RNA Scope *in situ* hybridisation for KRT17 (B) and KRT17 and IGFBP5 (C) on human iris and ciliary body FFPE specimens, showing KRT17 expression specifically in the iris, and IGFBP5 expression specifically in the ciliary body.

KEYWORDS:

Anterior Uveitis, T-lymphocytes, Keratin-17, Psoriasis, Spondyloarthropathy

TRAINING OPPORTUNITIES:

The student will gain experience of leading a research project where patient samples are taken from bedside-to-bench. It will enable the student to learn a range of state-of-the-art techniques including spectral flow cytometry, bioinformatic single cell RNA sequencing analysis, *in vitro* culture, and functional cellular assays. The student will be a part of an established team of discovery scientists and clinicians within the Coles-Buckley group based at the Kennedy Institute, who have interest and experience in cross-organ comparison of inflammatory diseases.

The student will present regularly at laboratory and collaborator meetings as well as internal symposia, where they will develop skills in communicating their work to other researchers. They will also be encouraged to submit work to national and international conferences and be supported to write manuscripts for publication. Training is available in systematic literature search methods and the student will produce a literature review in the first part of their DPhil studies, with a view to publication.

KEY PUBLICATIONS:

1. Cunningham, ETE. and Zierhut M, Vision Loss in Uveitis. Ocul Immunol Inflamm, 2021. 29(6): p. 1037-1039.
2. Reekie, I.R., et al., The Cellular Composition of the Uveal Immune Environment. Front Med (Lausanne), 2021. 8: p. 721953.
3. Jin, L. and G. Wang, Keratin 17: a critical player in the pathogenesis of psoriasis. Med Res Rev, 2014. 34(2): p. 438-54.
4. Yunusbaeva, M., et al., Psoriasis patients demonstrate HLA-Cw*06:02 allele dosage-dependent T cell proliferation when treated with hair follicle-derived keratin 17 protein. Sci Rep, 2018. 8(1): p. 6098.
5. Denniston, A.K., et al., Aqueous humor suppression of dendritic cell function helps maintain immune regulation in the eye during human uveitis. Invest Ophthalmol Vis Sci, 2012. 53(2): p. 888-96.

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6. #OxKEN-2026/6: Epigenetic targeting of fibroblasts as a novel therapeutic avenue for fibro-stenotic Crohn's disease

Supervisor 1: Dr Matthias Friedrich

Co-Supervisor: Professor Simon Travis

PROJECT OVERVIEW:

An increasing number of people suffer from Crohn's disease (CD), not only in industrialised countries, but also in the Middle East, India, East Asia and Latin America. CD causes inflammation that spans all layers of the gastro-intestinal wall. In more than two-thirds of patients, the distal part of the small intestine (ileum) is affected. Up to 80% of these patients require surgery in their lifetime, because fibrosis – the excessive deposition of connective tissue – narrows the intestinal lumen. Rates of postoperative recurrence of fibrosis in CD are high (>80%), significantly reducing patients' quality of life and making the clinical management of CD challenging and costly. Commonly used medications to control inflammation in CD do not stop or reverse fibrosis, often rendering surgery the only option for intestinal obstruction. We therefore have to research the underlying causes of fibrosis progression, in order to provide better and alternative medical treatment options for patients.

Within this program, we will achieve this by:

- Focusing on the role of connective tissue fibroblasts, the dominant contributor to fibrosis in the tissue, and their interaction with immune and muscle cells;
- Using an animal model that mirrors fibroblast-driven progression of small intestinal fibrosis over time. This model also enables studying the effect on fibrosis progression when disrupting specific functions of fibroblasts;
- Studying the characteristics of pro-fibrotic fibroblasts, and specifically unexplored epigenetic changes that render it pro-fibrotic. In contrast to genetics, the 'code' (DNA) of the genome, epigenetics studies an additional layer of DNA modification ('histone code') which alters the accessibility of the genome for reading and writing;
- Assessing potential epigenetic modifiers to reverse pro-fibrotic fibroblasts back to normal fibroblasts.

Potential applications and benefits:

The overarching objective of this research is to generate fundamental insights into fibroblast-driven mechanisms of intestinal fibrosis, which can be leveraged for the rational design of anti-fibrotic drugs that are desperately needed. This is the translational interface between science and medicine.

As such, other researchers and clinicians will benefit from the generated insights into fibrosis pathogenesis, advancing our knowledge of this pathology and enabling the development of better advanced therapies. Within the proposed study, we will test the potential of targeting several fibroblast-specific pathways. In particular the epigenetic reversal of pro-fibrotic fibroblasts harbours great potential as a therapy once fibrosis is established. At the same time, the concept of an epigenetically-rewired pathologic fibroblast state is novel and will represent a major conceptual advance to the field. Furthermore, the study of fibrogenesis is pluripotential, since it applies to any organ in the body.

This study will lay the foundation for subsequent rational drug design in collaboration with pharmaceutical industry partners and bench-to-bedside translation initiatives. By doing this, we ensure that we are pursuing the most direct path to provide benefit for the patient in the clinic for this unmet need.

KEYWORDS: fibrosis, Crohn's, epigenetic, fibroblast, therapeutic

TRAINING OPPORTUNITIES:

Within this DPhil, you will have the opportunity to apply molecular and cellular *in situ* patient cohort phenotyping, pre-clinicial *in vivo* disease models, and *in vitro* screening and mechanistic assays, to study the role of epigenetics and fibroblasts in Crohn's disease. This will include cutting-edge techniques such as: spatial transcriptomics (Nanostring GeoMx or 10X Visium) and proteomics (laser dissection mass spec proteomics); RNAseq, ATACseq and ChIPseq; *in vivo* diseas models (mouse) based on Cre-loxP genetic modification; CRIPSR-Cas9 cellular manipulation; high-throughput therapeutic compound screens.

You will be working in a highly interdisciplinary team consisting of basic researchers, gastroenterologists, GI pathologists and computational biologists across Oxford and Cambridge univiersities, as well as the Cleveland Clinic in the U.S. There will be further opportunities to carry out specific sub-projects through established collaborations with pharmaceutical industry (Bristol Myers Squibb, Pfizer, Janssen, UCB, among others). You will receive clise supervision by both a basic scientist and a clinician – an ideal setting to carry out a DPhil that focusses on bench-to-bedside translation.

KEY PUBLICATIONS:

1. Friedrich M.*, Pohin M.*, Jackson M.A.*, Korsunsky I., Bullers S., Rue-Albrecht K., Christoforidou Z., Sathananthan D., Ravindran R., Peres R.S., Sharpe H., Wei K., Watts G.F.M., Mann E.H., Geremia A., Thomas T., Attar M., Oxford IBD Cohort Cohort Investigators, Roche Fibroblast Network Consortium, McCuaig S., Thomas L., Collantes E., Uhlig H.H., Sansom S., Easton A., Raychaudhuri S., Travis S.P., Powrie F.M. IL-1-driven stromal-neutrophil interaction in deep ulcers defines a pathotype of therapy non-responsive inflammatory bowel disease. ***Nature Medicine*** 2021; 27:1970. DOI: https://doi.org/10.1038/s41591-021-01520-5

2. Friedrich M.*, Pohin M.*, Powrie F. Cytokine Networks in the Pathophysiology of Inflammatory Bowel Disease. ***Immunity*** 2019; 50:992. DOI: 10.1016/j.immuni.2019.03.017

3. West N *, Hegazy A *, Owens B, Bullers S, Linggi B, Buonocore S, Coccia M, Görtz D, This S, Stockenhuber K, Pott J, Friedrich M, Ryzhakov G, Baribaud F, Brodmerkel C, Cieluch C, Rahman N, Müller-Newen G, Owens R, Kühl A, Maloy K, Plevy S, Keshav S, Travis S, Powrie F. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor–neutralizing therapy in patients with inflammatory bowel disease. ***Nature Medicine*** 2017; 23:579. DOI: 10.1038/nm.4307

4. Korsunsky I.*, Wei K.*, Pohin M.*, Kim E.Y.*, Barone F.*, Kang J.B., Friedrich M., Turner J., Nayar S., Fisher B.A., Raza K., Marshall J.L., Croft A.P., Sholl L.M., Vivero M., Rosas I.O., Bowman S.J., Coles M., Frei A.P., Lassen K., Filer A., Powrie F., Buckley C.D., Brenner M.B., Raychaudhuri S. Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases. ***Med*** *2022*; DOI: 10.1016/j.medj.2022.05.002

5. Landerholm K., Reali C, Mortensen N.J., Travis S.P.L., Guy R.J., George B.D. Short- and long-term outcomes of strictureplasty for obstructive Crohn's disease. *Colorectal Disease* 2020. DOI: 10.1111/codi.15013

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7. #OxKEN-2026/7: Using large language models, genomics, and proteomics to phenotype immune-mediated disease

Supervisor 1: Prof Daniel Prieto-Alhambra

Co-Supervisor/s: Dr Albert Prats-Uribe, Dr Junqing Xie,

PROJECT OVERVIEW:

Background and aims

Most of the current knowledge of the aetiology and natural history of immune-mediated diseases (IMID) was obtained using survey or primary collection cohort data, prone to selection bias and focussed on relatively small geographic areas. Our first objective will be to use international routinely collected health data (real world data) to generate up-to-date knowledge on the presentation and clinical phenotypes of IMIDs from across Europe and North America.

Secondly, we will utilise rich biobanks and novel mendelian randomisation methods to investigate the association between pre-specified determinants of health and disease including comorbidities and lifestyle (diet, smoking, etc) and their role as risk factors of each of the studied IMIDs.

Finally, we will use genomic and proteomic data to identify potential new therapeutic targets, to be validated using target trial emulation studies.

Data sources: we will analyse electronic health records and health claims data mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) from the UK, USA, and multiple European regions for Objective 1. Additionally, we will analyse UK Biobank and Latest Our Future Health biomedical data for Objectives 2 and 3.

Variables of interest:

- Conditions of interest will be IMIDs including rheumatoid arthritis, ankylosing spondylitis, psoriasic arthritis, systemic lupus erythematous, mixed connective tissue disorder, dermatomyositis, polymyositis, scleroderma, ulcerative colitis, and Chron's disease

- Covariates: we will conduct a literature review to identify all potentially modifiable risk factors for analysis in biobank data, e.g. overweight/obesity, lifestyle (smoking, alcohol drinking), glucose metabolism (diabetes, glucose, HbA1c), lipids metabolism (total and HDL/LCL cholesterol, tryglycerides, apolipoproteins), proteomics, and genomics

- Health outcomes of interest will include newly diagnosed cancer, cardiovascular disease, orthopaedic surgery, and dementia, disease-specific and overall mortality.

Analysis:
First, we will use large language models to generate and validate OMOP-based disease phenotypes for IMID nationally and internationally.
Secondly, we will use data-driven methods to characterise patients with IMID in terms of pre-existing comorbidity, socio-demographics, overlap, and medicine/s use. We will then investigate medicines use after diagnosis, and estimate the risk of key health outcomes.
Third, we will study the association between pre-specified risk factors and the probability of developing each of the IMIDs. For those conditions we confirm in the available data, we will use Mendelian Randomisation methods to triangulate the evidence and confirm or reject the identified association/s.
Finally, we will use proteomics and genomic data to identify medicines with potential benefits in terms of health outcome/s prevention for people with IMID.

KEYWORDS: artificial intelligence; epidemiology; immune-mediated disease; real world evidence; genomics

TRAINING OPPORTUNITIES: As part of your participation in the NDORMS DPhil programme you will have multiple opportunities for relevant training in immunology, epidemiology, clinical research, and real world evidence, all provided as stand-alone modules for our DPhil students. Additionally, successful candidates will be invited to join a weekly residential Oxford Summer School in Real World Evidence during June 2025. Additional training will be discussed formally with supervisors in the form of training need analyses, and planned accordingly.

KEY PUBLICATIONS:
Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis. Li X, Raventós B, Roel E, Pistillo A, Martinez-Hernandez E, Delmestri A, Reyes C, Strauss V, Prieto-Alhambra D, Burn E, Duarte-Salles T.BMJ. 2022 Mar 16;376:e068373. doi: 10.1136/bmj-2021-068373.PMID: 35296468

Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US. Li X, Burn E, Duarte-Salles T, Yin C, Reich C, Delmestri A, Verhamme K, Rijnbeek P, Suchard MA, Li K, Mosseveld M, John LH, Mayer MA, Ramirez-Anguita JM, Cohet C, Strauss V, Prieto-Alhambra D.BMJ. 2022 Oct 26;379:e071594

Clinical and Genetic Risk Factors for Acute Incident Venous Thromboembolism in Ambulatory Patients With COVID-19. Xie J, Prats-Uribe A, Feng Q, Wang Y, Gill D, Paredes R, Prieto-Alhambra D.JAMA Intern Med. 2022 Oct 1;182(10):1063-1070. doi: 10.1001/jamainternmed.2022.3858.PMID: 35980616

Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, Martinez-Hernandez E, Delmestri A, Verhamme K, Rijnbeek PR, Duarte-Salles T, Suchard MA, Ryan PB, Hripcsak G, Prieto-Alhambra D.BMJ. 2021 Jun 14;373:n1435. doi: 10.1136/bmj.n1435.PMID: 35727911

Venous or arterial thrombosis and deaths among COVID-19 cases: a European network cohort study. Burn E, Duarte-Salles T, Fernandez-Bertolin S, Reyes C, Kostka K, Delmestri A, Rijnbeek P, Verhamme K, Prieto-Alhambra D.Lancet Infect Dis. 2022 Aug;22(8):1142-1152. doi: 10.1016/S1473-3099(22)00223-7. Epub 2022 May 13.PMID: 35576963

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8. #OxKEN-2026/8: Elucidating the Mechanisms of RNA Splicing in the Regulation of Inflammatory Responses

Supervisor 1: Associate Prof Adam Cribbs

Co-Supervisor/s: Associate Prof Sarah Snelling, Prof Dominic Furniss, Dr Mathew Baldwin

PROJECT OVERVIEW:

Our immune system serves as a critical defense mechanism against diseases and operates under fine-tuned regulation to ward off infections. Alternative splicing (AS) is emerging as an integral component of this regulatory framework, particularly in modulating inflammatory responses. To comprehensively investigate the role of AS in disease states, it is imperative to establish a reference map of splicing events in healthy cells, with a focus on cell-type specificity. Utilising state-of-the-art single-cell and computational methodologies, such as scCOLOR-seq (refer to cited literature below), this research aims to construct a high-resolution spliceosome atlas for the healthy immune system. Concurrently, we will develop an open-source computational toolkit to facilitate the exploration of AS in immune-related diseases.

Motivation: The human genome comprises approximately 20,000 protein-coding genes, which are postulated to encode in excess of 100,000 distinct proteins. When accounting for the diversity introduced by T cell receptors, B cell receptors, and antibodies, the number of unique proteins potentially escalates into the millions. This proteomic diversity surpasses genomic diversity, partly due to alternative splicing and recombination events. Notably, splicing aberrations are prevalent in hematological malignancies and often correlate with mutations in the splicing machinery. To elucidate the mechanisms underlying such diseases, it is crucial to develop a reference spliceosome map for both healthy and inflamed cells.

Research Gap: A comprehensive understanding of the mechanisms by which alternative splicing influences inflammation in the immune system necessitates a baseline reference map of spliceosome activity in healthy immune cells. This map should also extend to various inflammatory states. Given the complexity of the human immune system, this endeavor requires single-cell resolution.

Anticipated Outcomes: The cornerstone achievement of this research will be the establishment of a spliceosome atlas for the healthy immune system. This atlas is poised to serve as an indispensable reference framework for elucidating the role of alternative splicing in various pathological conditions. Specifically, it will be instrumental for investigating chronic inflammatory diseases like rheumatoid arthritis, as well as in the field of oncology where inflammation is increasingly recognised as a significant factor in tumor progression.

KEYWORDS:

Splicing, single-cell sequencing, long-read sequencing, Omics, Computational biology

TRAINING OPPORTUNITIES:

You will acquire specialised proficiency in in vitro models pertinent to inflammation research. Additionally, you will gain hands-on experience in constructing sequencing libraries compatible with both Illumina (short-read) and Oxford Nanopore Sequencing (long-read) platforms. To supplement your experimental techniques, you will receive training in advanced computational biology methodologies for rigorous data analysis and the production of publication-quality figures.

KEY PUBLICATIONS:

- Cribbs et al. Histone H3K27me3 demethylases regulate human Th17 cell development and effector functions by impacting on metabolism. *PNAS* (2019). https://doi.org/10.1073/pnas.1919893117
- Philpott M et al. Nanopore sequencing of single-cell transcriptomes with scCOLOR-seq. *Nature Biotechnology* (2021). 10.1038/s41587-021-00965-w
- Baldwin, M.J., Cribbs, A.P., Guilak, F. *et al.* Mapping the musculoskeletal system one cell at a time. *Nat Rev Rheumatol* (2021). https://doi.org/10.1038/s41584-021-00600-7
- COvid-19 Multi-omics Blood ATlas (COMBAT) Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. *Cell* (2022). 10.1016/j.cell.2022.01.012

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9. #OXKEN-2026/9: Harnessing human genomic, transcriptomic and proteomic data to identify novel therapeutic targets

Supervisor 1: Dr Yang Luo

Co-Supervisor/s: Professor Jagdeep Nanchahal

PROJECT OVERVIEW:

Supporting human genetic data for novel therapeutic targets has been shown to double the success rate for subsequent clinical translation. We have used this approach for Dupuytren's disease, a common fibrotic disease of the hand. Multiple genome-wide association studies (GWAS) have shown the importance of Wnt signaling in this disorder. We identified TNF as a therapeutic target using diseased and control human tissue and showed that only myofibroblasts from Dupuytren's patients signalled via the canonical Wnt pathway. We went on to complete successful phase 2 clinical trials, meeting both the primary and a key secondary endpoint in the phase 2b.

This project will focus on discovering novel therapeutic targets for diseases by integrating human multi-omics data with laboratory data based on human tissue, cells, and preclinical models.

We will develop novel statistical methods to harness the wealth of omic-data in multi-ancestry large-scale biobank and consortium data. Through integrative analyses of genetic, transcriptome, proteomic, and clinical data, this approach promises an improved understanding of disease aetiology in a context-specific framework.

KEYWORDS:

Translational research, OMICs, immune-mediated diseases, biobanks, QTLs

TRAINING OPPORTUNITIES:

The successful candidate will benefit from dual supervision by an expert in genomics and computational biology, and a surgeon scientist with a focus on translational medicine. You will be based in the purpose-built labs at The Kennedy Institute of Rheumatology, a world-leading centre in the fields of cytokine biology and inflammation, with a strong emphasis on clinical translation.

This project is ideally suited for students with a background in statistical genetics who wish to expand their applied knowledge in the biological sciences, as well as those with a background in biology or clinical science who are interested in integrating biology with data science.

Comprehensive training will be provided in data science techniques, including statistical data analysis and visualization with R, developing computational pipelines with Python/NextFlow, and utilizing high-performance computing clusters. The student will gain expertise in analyzing advanced sequencing datasets, such as whole genome, RNA, and proteomic sequencing.

The Kennedy Institute offers a vibrant PhD program, featuring a weekly journal club, seminars, student symposia, and regular internal presentations and training sessions. A core curriculum of lectures will provide a solid foundation in diverse subjects, including data analysis, statistical methods, and immunology summer school. In addition to institutional support, the successful applicant will benefit from the University of Oxford's college system. Students will also have the opportunity to collaborate closely with both computational and experimental scientists.

KEY PUBLICATIONS:

Nanchahal J, Ball C, Rombach I, Williams L, Kenealy N, Dakin H, O'Connor H, Davidson D, Werker P, Dutton SJ, Feldmann M, Lamb SE. (2022)
Anti-Tumour Necrosis Factor Therapy for Early Stage Dupuytren's Disease (RIDD): a phase 2b randomised double blind, placebo-controlled trial.
Lancet Rheumatology. 4(6): e407-16

Luo, Y. et al. A high-resolution HLA reference panel capturing global population diversity enables multi-ethnic fine-mapping in HIV host response. Nature Genetics (2021)

Ishigaki, K., Sakaue, S., Terao, C. **Luo, Y**. et al. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. Nat Genet 54, 1640–1651 (2022). https://doi.org/10.1038/s41588-022-01213-w

Riesmeijer S, Kamali Z, Ng M, Drichel D, Piersma B, Becker K, Layton T, **Nanchahal J**, Nothnagel M, Vaez A, Hennies H, Werker P, Furniss D, Nolte I. A genome-wide association meta-analysis implicates Hedgehog and Notch signaling in Dupuytren's disease (2024). Nature Communications 15(1): 199

Verjee LS, Verhoekx J, Chan J, Krausgruber T, Nicolaidou V, Izadi D, Davidson D, Feldmann M, Midwood KS, **Nanchahal J** (2013)**.** Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a novel therapeutic target*. Proceedings of the National Academy of Sciences, USA.* 110: E928-937

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10. #OXKEN-2026/10: How does metabolism program B cell immunity?

Lead Supervisor (1): Alex Clarke

Supervisory team: Mike Dustin

Postdoc Supervisor(s):

PROJECT OVERVIEW:

The systems and pathways of cellular metabolism, modified either by the microbiome or cell-intrinsic programs, are critical to almost all aspects of the immune response. An essential function of metabolism is to dynamically respond to the needs of the cell, typically as it encounters a new microenvironment, or is required to rapidly divide, secrete cytokines, or produce antibodies.

One of the most important outstanding questions in the field is how immune cell metabolism actually operates within tissues in life, and how this is altered in disease.

The germinal centre reaction is a tightly choreographed process occurring in secondary lymphoid tissue, as B cells refine their antigen specificity through interaction with T follicular helper cells. The GC reaction is essential for the production of high affinity antibodies and humoral immunity.

GC B cells have the highest proliferation rate of any cell in the body, and yet which metabolic programs are activated and are essential for this process is poorly understood. Importantly, events occurring in the GC reaction lead to the majority of non-Hodgkin's lymphomas, and are dysfunctional in autoimmune disease. This project aims to identify and understand metabolic programs active in GC B cells, to modify them experimentally using conditional knockout approaches in mouse models, and to target them therapeutically in pre-clinical models.

In this project, you will study the metabolic pathways activated during the germinal centre (GC) reaction in health and in autoimmune disease, using cutting edge technologies and methods which allow measurement of metabolism with high *in vivo* fidelity. You will have the opportunity to attend the outstanding educational programme provided at the KIR, and to also regularly present your own data in group meetings, seminars, and at international conferences.

KEYWORDS: Metabolism, B cell immunity, Autoimmunity, Lymphoma, Vaccines

TRAINING OPPORTUNITIES:

This project provides a broad training in immunology, with comprehensive coverage of standard and advanced techniques including disease models, advanced flow cytometry, confocal imaging, and single cell RNA sequencing. For study of metabolism, you will develop expertise in stable isotope resolved metabolomics, and extracellular flux measurement using the Seahorse platform, and the bioinformatic analysis of these data. Computational biology training will be provided, both within the group and in formal courses.

KEY PUBLICATIONS:

Johnstone J, Yazicioglu Y, Clarke AJ. Fuelling B cells: dynamic regulation of B cell metabolism. *Current Opinion in Immunology. 2024, 91, 102484*

Yazicioglu Y*, Marin E*, Bentkowska K, Andrew H, Johnstone J, Mitchell R, Wong Z, Zec K, Fergusson J, Borsa M, Raza IG, Attar M, Ali M, Kronsteiner B, Furlani I, MacRae J, Devine MJ, Coles M, Buckley C, Dunachie S, Clarke AJ. Asparagine availability controls germinal centre B cell homeostasis. *Science Immunology.* 2024. 9(102), pp. eadl4613 *Equal authorship.

Yazicioglu Y, Marin E, , Sandhu C, Galiani S, Raza I, Ali M, Kronsteiner B, Compeer E, Attar M, Dunachie S, Dustin ML, Clarke AJ. Dynamic mitochondrial transcription and translation in B cells control germinal center entry and lymphomagenesis. *Nature Immunology.* 2023. 24(6):991-1006

Psarras A, Clarke AJ. A cellular overview of immunometabolism in systemic lupus erythematosus. *Oxford Open Immunology*. 2023. 4(1): iqad005

Müschen, M. (2019). Metabolic gatekeepers to safeguard against autoimmunity and oncogenic B cell transformation. *Nat Rev Immunol*, DOI: 10.1038/s41577-019-0154-3

THEMES:

Immunology

Molecular, Cell and Systems Biology

Translational Medicine and Medical Technology

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11. #OXKEN-2026/11: Elucidating the functional phenotypes of fibroblast sub-populations in tendinopathy

Supervisor: Prof Stephanie G Dakin

Co-Supervisors:, Mr Andrew Titchener

BACKGROUND: Tendon injuries including tendinopathy and rupture are a significant cause of pain and disability. These injuries are challenging to treat, require prolonged rehabilitation and frequently recur. Currently no therapeutic treatment exists to improve resolution of tendon injury, and this is largely due to a lack of knowledge of the cellular and molecular processes underpinning tendon disease and fibrotic healing. We have developed access to joint soft tissues from well-phenotyped patient cohorts, providing a platform to investigate the cellular basis of tendon disease. Our discoveries have catalysed a step change in understanding of how inflammation contributes to the development of chronic tendon disease, highlighting:

1. Macrophages show complex activation states that change with disease stage
2. Diseased tendon fibroblasts show an activated pro-inflammatory phenotype (expressing pathogenic markers including CD90), showing capacity for inflammation memory
3. Diseased tendon fibroblasts show dysregulated resolution responses

Our studies reveal that tissue-resident stromal cells including tendon cells (fibroblasts) are pivotal populations sustaining chronic tendon inflammation. These cells represent untapped therapeutic targets in the treatment of tendinopathy. Recent work studying tendinopathic patient tissues and cells has identified multiple populations of tendon fibroblasts, however their distinct biological functions are not known, hampering efforts to precisely therapeutically target tendon populations driving inflammation and fibrosis.

PROJECT OVERVIEW: This project will identify tendon fibroblast sub-populations causal to tendon homeostasis, inflammation, and fibrosis. We recently identified a population of DKK3+ pro-resolving fibroblasts in frozen shoulder capsule (ligament) patient tissues where fibrosis is self-limiting (Figure 1 & Ng *et al.* 2024). Whilst DKK3+ fibroblasts are also found in tendon tissues (Figure 1) we hypothesize that the resolving circuit we identified in frozen shoulder becomes dysregulated in tendinopathy. We also hypothesize that a sub-population of pathogenic CD90+ tendon fibroblasts (Figure 2) provide a continued inflammatory stimulus, further interrupting resolution by driving chronic inflammation and fibrosis during tendinopathy. This project will utilize patient tendon tissues and cells to:

1) Identify the transcriptional signatures of resolving, inflammatory and fibrotic tendon cell populations
2) Spatially map distinct resolving, inflammatory and fibrotic tendon cell populations within patient tissue sections

3) Advance the development of 3D models comprised of patient-derived cells to study distinct tendon cell populations *in vitro*
4) Test candidate small molecules to target resolving and pathogenic tendon sub-populations *in vitro*

PROJECT IMPACT: The findings from this project will advance understanding of the cellular basis of chronic inflammation and fibrosis in tendon disorders, informing new therapeutic approaches to moderate the pathogenic phenotype of CD90+ tendon cells whilst potentiating the protective actions of resolving DKK3+ tendon cells.

KEYWORDS: tendon, tendinopathy, inflammation, fibrosis, fibroblast

Figure 1

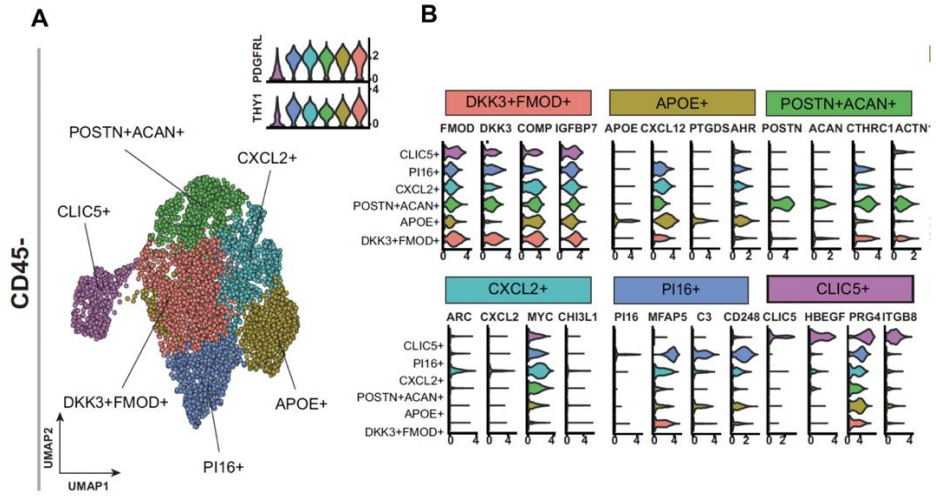

Figure 1. Resolving fibroblasts populate a resolving fibrotic niche during self-limiting frozen shoulder. (A) scRNA-seq analysis of adult shoulder capsule from tissue biopsy samples collected from comparator (n=6) and frozen shoulder (n=4) patient donors. UMAP shows the 6 identified fibroblast clusters, including a resolving population of DKK3+ fibroblasts. (B) Selected fibroblast cluster marker genes.

Figure 2.

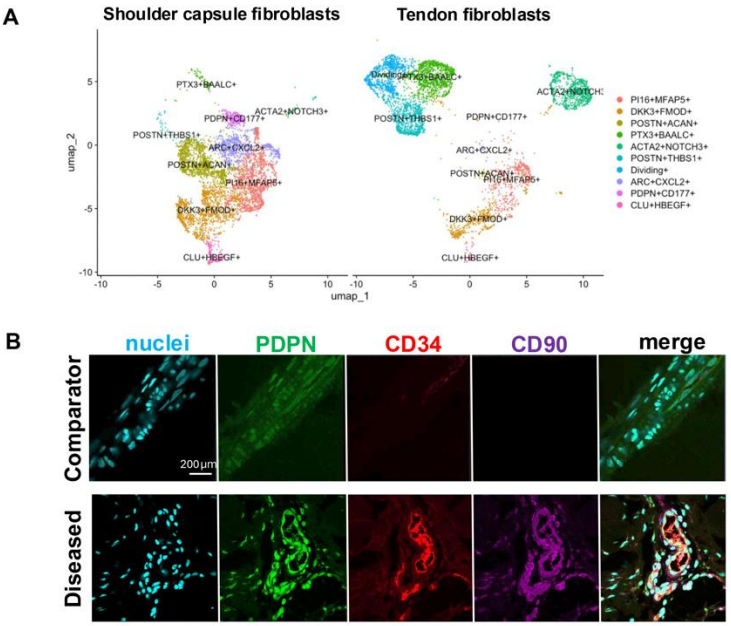

Figure 2. Fibroblast sub-populations across resolving and persistent fibrotic niches. (A) UMAPs show integrated dataset of fibroblasts isolated from shoulder capsule and tendon patient tissues, identifying distinct fibroblast sub-populations. Fibroblasts isolated from shoulder capsule patient tissues are enriched for the resolving DKK3+ fibroblast population relative to tendon tissues. (B) Spatial topography of tendon cell niches. Representative confocal images of comparator and diseased patient tendon tissues illustrating immunostaining markers of activated fibroblasts. CD90 (violet), a marker of pathogenic fibroblasts is highly expressed in diseased tendon tissues, which show increased cellularity and distorted structure relative to comparator tendons.

TRAINING OPPORTUNITIES:

This project represents an excellent training opportunity for a young scientist with an interest in biology and bioinformatics. Training will be provided in the following aspects:

1) Analysing Next Generation Sequencing (NGS) data sets for mechanistic study of tendon fibroblast functions
2) Bioinformatic modelling of tendon-immune cell interactions
3) Preparing patient tissues for multiplex immunostaining and utilising advanced imaging techniques
4) Developing 3D organoids to model tendinopathy
5) Testing candidate small molecules to resolve inflammation and fibrosis in tendinopathy 3D models

KEY PUBLICATIONS:

Ng M, B.R., Gacaferi H, Davidson S, Machado CC, Reekie I, Attar M, Windell D, Kurowska-Stolarska M, MacDonald L, Alivernini S, Garvilles M, Jansen, Bhalla A, Lee A, K, Charlesworth J, Chowdhury R, Klenerman P, Powell K, Hackstein CP, ICECAP study group, Furniss D, Rees J, Gilroy D, Coles M, Carr AJ, Sansom S, Buckley CD, Dakin SG. A single cell atlas of frozen shoulder capsule identifies features associated with inflammatory fibrosis resolution. **Nat Commun** 15, 1394 (2024). https://doi.org/10.1038/s41467-024-45341-9. PMID:38374174.

Johnson PA, Ackerman JE, Kurowska-Stolarska M, Coles M, Buckley CD, Dakin SG (2023) Three-dimensional, in-vitro approaches for modelling soft-tissue joint diseases. **Lancet Rheumatol.** Sep;5(9):e553-e563. doi: 10.1016/S2665-9913(23)00190-X. PMID: 38251499.

Ackerman JE, Best KT, Muscat SN, et al. Defining the spatial-molecular map of fibrotic tendon healing and the drivers of Scleraxis-lineage cell fate and function. *Cell Rep* 2022; **41:** 111706.

Dakin SG, Coles M, Sherlock JP, Powrie F, Carr AJ, Buckley CD (2018). Pathogenic stromal cells as therapeutic targets in joint inflammation. **Nat Rev Rheumatol**. Dec;14(12):714-726. doi: 10.1038/s41584-018-0112-7. PMID: 30420750

Dakin SG, Martinez FO, Yapp C, Wells G, Oppermann U, Dean BJF, Smith RDJ, Wheway K, Watkins B, Roche L, Carr AJ. (2015) Inflammation activation and resolution in human tendon disease. **Sci. Transl. Med**. Oct 28;7(311):311ra173. doi: 10.1126/scitranslmed.aac4269 PMID: 26511510

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12. #OXKEN-2026/12: The molecular relationship between obesity and pain in osteoarthritis (OA)

Supervisor 1: Professor Tonia Vincent

Co-Supervisor/s: Professor Zam Cader, Dr Thomas Perry

PROJECT OVERVIEW:

Pain is the most common symptom of osteoarthritis (OA); a disease that has huge societal impact and which is increasing with population obesity and age. Surprisingly, it is still unclear where pain originates from and how best to manage it[1]. Many patients with OA pain will have evidence of central sensitisation (leading to chronic pain syndromes) but in most patients, pain improves with joint replacement indicating that the primary driver of pain in OA originates in the joint. Vincent's group was the first to show in mice with OA, that pain is dependent upon pain fibre sensitisation by nerve growth factor (NGF)[2,3]. This work revealed that pain could be inhibited by blocking NGF, a target that was subsequently confirmed in clinical trials using anti-NGF neutralising antibodies[4]. Unfortunately, a new licence for this as a treatment for OA pain was declined by the FDA due to an unacceptable risk:benefit ratio (around 8% of individuals taking the drug developed rapidly progressive OA). The other recent treatment which has been shown to be successful in reducing knee OA pain is weight loss. This was shown recently in Novo Nordisk's STEP 9 trial in which Semaglutide, a GLP-1 receptor agonist, delivered over 1 year, was associated with significant weight loss and reduction in pain (https://www.medscape.com/viewarticle/semaglutide-improves-knee-osteoarthritis-pain-physical-2024a10007s0?form=fpf). Together these data suggest that there are neuronal sensitisers in the joint that are modulated by obesity and/or GLP-1 pathway activity.

Our group have also recently completed the largest proteomic analysis of synovial fluid of OA patients in which over 1400 samples were analysed using the SomaScan platform (>7000 proteins) (STEpUP OA). As each sample was associated with matched pain, radiographic scores and other patient demographic data (including body mass index, BMI), we have been able to explore proteins in the joint that are associated with pain severity[5]. In addition, in collaboration with Cader, we have also shown that OA synovial fluid is able to activate human pain fibres in vitro (derived from induced pluripotent stem cells, iPSCs). These data suggest that there are sensitisers other than NGF in the fluid capable of doing this. We therefore have a unique resource and powerful tools to investigate the influence of obesity on OA pain.

The aims of this project are:

1. To use STEpUP OA data to explore molecules that are associated with pain when patients are stratified by BMI into "obese" and "non-obese" groups, or when using BMI as a continuous variable.
2. Test candidate molecules/pathways on human iPSC-derived pain fibre activity in vitro.

3. Use in vitro (porcine) and in vivo (mouse) OA models to measure the influence of GLP1-R agonists on NGF regulation, and other molecules identified from aims 1 and 2.

KEYWORDS: osteoarthritis (OA), pain, iPSCs, proteomics, obesity

TRAINING OPPORTUNITIES:

The Kennedy Institute is a world-renowned research centre and is housed in a state-of-the-art research facility. Full training will be provided in a range of cell and molecular biology techniques. A core curriculum of 20 lectures will be taken in the first term of year 1 to provide a solid foundation in musculoskeletal sciences, immunology and data analysis. Students will attend weekly departmental meetings and will be expected to attend seminars within the department and those relevant in the wider University. Subject-specific training will be received through our group's weekly supervision meetings and at least termly meetings with co-supervisors. Students will also attend external scientific conferences where they will be expected to present the research findings. Specific to this project, the student will gain an in-depth training in data analysis using the STEpUP OA dataset and will learn basic principles of coding using R. Human nociceptor work will be carried out with Cader with appropriate training in differentiation protocols and quantitative activation outputs. In addition, the student will gain experience in a wide range of standard laboratory procedures including western blotting, qPCR and in vivo injury models (including surgical models of OA).

KEY PUBLICATIONS:

1 Vincent, T. L. Peripheral Pain Mechanisms in Osteoarthritis. *Pain* **161** (2020). https://doi.org:doi.org/10.1097/j.pain.0000000000001923

2 Driscoll, C. *et al.* Nociceptive Sensitizers Are Regulated in Damaged Joint Tissues, Including Articular Cartilage, When Osteoarthritic Mice Display Pain Behavior. *Arthritis & rheumatology (Hoboken, N.J.)* **68**, 857-867 (2016). https://doi.org:10.1002/art.39523

3 McNamee, K. E. *et al.* Treatment of murine osteoarthritis with TrkAd5 reveals a pivotal role for nerve growth factor in non-inflammatory joint pain. *Pain* **149**, 386-392 (2010). https://doi.org:10.1016/j.pain.2010.03.002

4 Tive, L. *et al.* Pooled analysis of tanezumab efficacy and safety with subgroup analyses of phase III clinical trials in patients with osteoarthritis pain of the knee or hip. *Journal of pain research* **12**, 975-995 (2019). https://doi.org:10.2147/JPR.S191297

5 Perry, T. A. *et al.* Deconvoluting synovial fluid molecular endotypes in knee osteoarthritis: primary results from the STEpUP OA Consortium. (2024). https://doi.org:https://www.medrxiv.org/content/10.1101/2024.06.05.24308485v2.full.pdf

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13. #OXKEN-2026/13: Promotion of intrinsic cartilage repair in osteoarthritis (OA)

Supervisor 1: Professor Tonia Vincent

Co-Supervisor/s: Dr Adrien Hallou

PROJECT OVERVIEW:

For a long time there has been a falsely held belief that articular cartilage does not repair itself, and that this contributed to the very high prevalence of osteoarthritis (OA), the most common form of arthritis. Cartilage does repair, even in a severely damaged joint, so long as the mechanical environment of the joint has been corrected. Indeed, a procedure call surgical joint distraction, in which the two surfaces of the joint are pulled apart by an external metal frame, is associated with regrowth of articular cartilage (assessed on MRI) and significant improvement in pain and function[1]. Through a combination of careful in vitro mechanistic work exploring how cartilage responds to injury, through in vivo models and through large scale proteomic analysis of human synovial fluid from OA patients, including before and after joint distraction, we have uncovered the primary mechanism by which cartilage repairs[2,3]. This involves the release of growth factors from cartilage which activate repair cells, followed by switching off of the pathways to enable repair cells to form cartilage cells again. This project will investigate the function of specific growth factors in this response – identified by us by proteomics but largely uncharacterised thus far. The project will involve working with novel genetically modified mice, human data sets and in vitro assays where both the biochemical and mechanical environment of the cartilage cells can be controlled. Parallels will be drawn with skin wound healing, one of the best characterised regenerative systems[4], using the same genetically modified animals as these are more accessible and faster models, and all of the growth factors identified by us thus far are also expressed in the skin.

Ultimately, we wish to establish whether it is possible to identify patients whose repair pathways can be modified to improve their clinical outcome. As pharma companies are now moving from anti-inflammatory to pro-regenerative therapies for OA, this project is timely and likely to be highly informative for academia and industry alike.

KEYWORDS:

Osteoarthritis (OA); cartilage; regeneration; skin wound healing; growth factors; mechanobiology

TRAINING OPPORTUNITIES:

The Kennedy Institute is a world-renowned research centre and is housed in a state-of-the-art research facility. Full training will be provided in a range of cell and molecular biology techniques. A core curriculum of 20 lectures will be taken in the first term of year 1 to provide a solid foundation in musculoskeletal sciences, immunology and data analysis. Students will

attend weekly departmental meetings and will be expected to attend seminars within the department and those relevant in the wider University. Subject-specific training will be received through our group's weekly supervision meetings. Students will also attend external scientific conferences where they will be expected to present the research findings. Specific to this project, the student will gain an in-depth training in cell biology, with a wide range of laboratory procedures including western blotting, qPCR, bulk tissue sequencing, immunohistochemistry, advanced microscopy, single-cell RNA sequencing, spatial transcriptomics, and computational image and data analysis[5] as well as in vivo model experience (OA and focal cartilage repair models). They will learn how to interrogate large human molecular datasets with coding experience in R and/or Python as required for the project.

KEY PUBLICATIONS:

1. Wiegant K, van Roermund PM, Intema F, Cotofana S, Eckstein F, Mastbergen SC, et al. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013;21(11):1660-7.
2. Watt FE, Hamid B, Garriga C, Judge A, Hrusecka R, Custers RJH, et al. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis Cartilage. 2020;28(3):324-33.
3. Keppie SJ, Mansfield JC, Tang X, Philp CJ, Graham HK, Onnerfjord P, et al. Matrix-Bound Growth Factors are Released upon Cartilage Compression by an Aggrecan-Dependent Sodium Flux that is Lost in Osteoarthritis. Function (Oxf). 2021;2(5):zqab037.
4. Sarate RM, Hochstetter J, Valet M, Hallou A, Song Y, Bansaccal N, Ligare M, Aragona M, Engelman D, Bauduin A, Campàs O, Simons BD and Blanpain C. Dynamic regulation of tissue fluidity controls skin repair during wound healing. Cell, In press 2024.
5. Hallou A, He R, Simons BD and Dumitrascu B. A computational pipeline for spatial mechano-transcriptomics. Nature Methods, In press 2024. Preprint: bioRxiv 2023.08.03.551894

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14. #OXKEN-2026/14: Optimizing oral iron dosing for patients with chronic inflammatory disorders using plasma hepcidin profiles and stable iron isotopes: haemodialysis patients as an example

Supervisor 1: Dr. Nicole Stoffel
Co-Supervisor/s: Prof. James Fullerton

PROJECT OVERVIEW:
In chronic inflammatory disorders, elevated hepcidin reduces iron absorption and increases the risk of iron deficiency anaemia, making oral iron supplementation challenging. Chronic kidney disease (CKD) patients, who have plasma hepcidin levels up to 10 times higher than healthy adults, will be used as an example for these conditions.
Iron deficiency anaemia (IDA) is a common complication in patients with CKD. High plasma hepcidin (PH) in CKD due to chronic inflammation and decreased renal clearance decreases iron absorption from oral iron supplements. PH is a small molecule that is partially cleared from the circulation during haemodialysis (HD). We speculate that the ideal time for the intake of oral iron would be at the conclusion of HD, when PH is low, and would result in higher absorption than at other times.

Phase 1: In CKD patients (n=12) on HD, we will define the profile of PH during and after HD, to establish the optimal timing for dosing of oral iron. During a 4-h session of HD, we will measure PH at the beginning of HD, during HD at 60-, 120-, 180-, 210- and 240-minutes (conclusion) and post-HD at 30-, 60- and 90-minutes. We will also measure PH at time of the usual evening dose of oral iron, as a comparator.

Phase 2: Based on the results of Study 1, we will compare fractional and total iron absorption from 200 mg doses of oral iron as ferrous sulfate given according to the current dosing regimen for CKD patients to iron absorption from doses given just before the onset of HD (peak of PH) and at the conclusion of HD (nadir of PH). We hypothesize that iron absorption will be significantly greater from the dose given at the conclusion of HD, when PH is low, than from the other two doses, when PH is high. We will recruit CKD patients undergoing maintenance HD (n= 12) into a 19-day study.

The **general objectives of this project** in patients with chronic kidney disease (CKD) receiving HD thrice weekly will be to: 1) confirm the decrease in plasma hepcidin (PH) during haemodialysis (HD) and determine the concentration and duration of the period of nadir PH at the end of an HD session; 2) use stable iron isotopes to quantify fractional iron absorption from oral iron doses using the current standard of care at (evening dosing) compared to an optimized dosing regimen where an oral dose of ferrous iron is given at the PH nadir at end of an HD session.

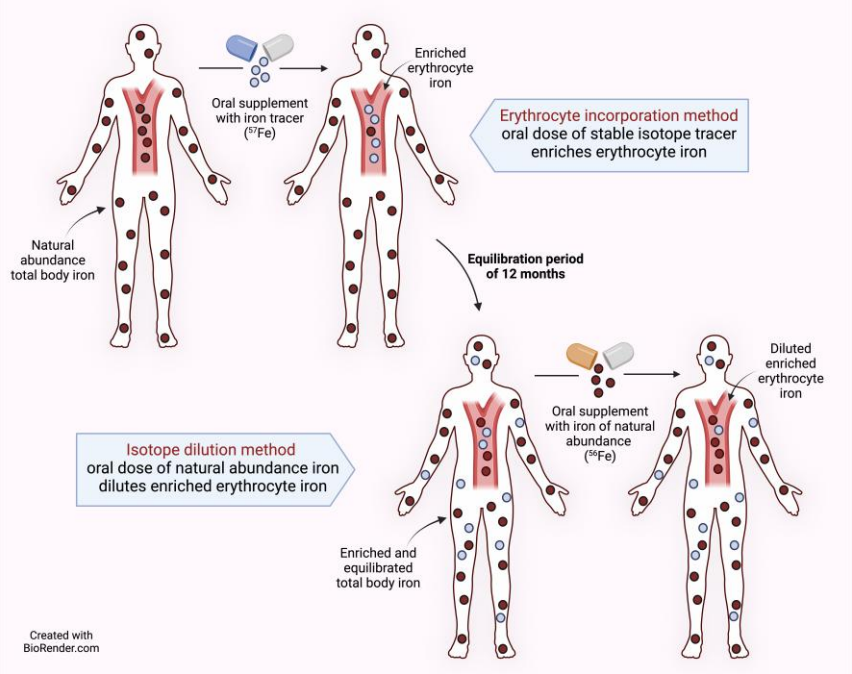

Figure 1. Overview of two stable iron isotope methods: erythrocyte iron incorporation and isotope dilution.

KEYWORDS:
Iron deficiency anaemia, chronic inflammatory disease, chronic kidney disease, oral iron treatment, iron absorption,

TRAINING OPPORTUNITIES:
You will gain hands-on experience in a variety of cutting-edge techniques and clinical trials, including:

- **Conducting Clinical Trials**: You'll be involved in running an experimental studies using stable iron isotopes. This provides a unique opportunity to see how trials are designed, executed, and analyzed.
- **Mastering Stable Iron Isotope Techniques (Phase 1**): Learn the traditional stable iron isotope method, where you'll measure iron isotope concentrations after tracer administration to determine fractional iron absorption from a single supplement. This precise technique is essential for understanding nutrient absorption at the molecular level.
- **Performing Isotopic Measurements via ICP-MS**: You'll work with cutting-edge technology like Inductively Coupled Plasma Mass Spectrometry (ICP-MS) to measure shifts in iron isotopic ratios in red blood cells. This hands-on lab experience will deepen your understanding of advanced analytical techniques.
- **Conducting Immunoassays:** You'll perform assays to measure important predictors of iron metabolism, including iron status and inflammation markers. This training will enhance your skills in biomarker analysis and interpretation.

KEY PUBLICATIONS:

Weiss, G., et al., *Serum hepcidin concentration in chronic haemodialysis patients: associations and effects of dialysis, iron and erythropoietin therapy.* Eur J Clin Invest, 2009. **39**(10): p. 883-90.
Zaritsky, J., et al., *Reduction of serum hepcidin by hemodialysis in pediatric and adult patients.* Clin J Am Soc Nephrol, 2010. **5**(6): p. 1010-4.
Peslova, G., et al., *Hepcidin, the hormone of iron metabolism, is bound specifically to alpha-2-macroglobulin in blood.* Blood, 2009. **113**(24): p. 6225-36.
Hotz, K., P.A. Krayenbuehl, and T. Walczyk, *Mobilization of storage iron is reflected in the iron isotopic composition of blood in humans.* Journal of Biological Inorganic Chemistry, 2012. **17**(2): p. 301-309.

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Prof. James Fullerton: james.fullerton@ndorms.ox.ac.uk

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15. #OXKEN-2025/15: Mapping the tissue biology of inflammasome activation in inflamed arthritic joints

Supervisor 1: Jelena Bezbradica Mirkovic,

Co-Supervisor/s: Madelon de Jong, Chris Buckley

PROJECT OVERVIEW:

Inflammasomes are infection- and tissue damage-sensing pathways expressed largely in macrophages. When overactivated, they perpetuate disease pathology in many chronic inflammatory diseases. Inflammasome activation results in the secretion of pro-inflammatory cytokines IL-1b and IL-18, and lytic cell death, resulting in the local release of alarmins. We, as a field, have typically studied inflammasomes in vitro, which allowed us to map the basic pathway biology. New imaging tools, animal models and spatial technologies allow us now to move inflammasome signalling studies into the tissue and begin to understand the spatial context driving inflammasome activation.

In this project, we will combine in vitro experiments with in vivo analyses of mouse and human inflamed joint synovium as a model to map the tissue biology of inflammasome activation in sterile inflammation.

The objectives of this work are to

1. Perform spatial profiling of inflammasome activation over the course of disease, to understand when and where the inflammasome pathway becomes activated in the inflamed tissue, using inflammasome-reporter mice
2. Map the main cells responding to inflammasome-derived signals and define the functional programmes elicited by these signals, using spatial profiling of an animal disease model, followed by validation in human data sets.

The project will benefit from expertise in inflammasomes in sterile inflammation (Jelena Bezbradica Mirkovic), the biology of arthritis (Chris Buckley), and the biology of macrophage-fibroblast crosstalk in inflammation (Madelon de Jong)

KEYWORDS: Macrophages, Cell-cell communications, Inflammation, Inflammasomes

TRAINING OPPORTUNITIES: Tissue imaging, biochemistry, spatial analysis of cell-cell interactions, disease model of arthritis

KEY PUBLICATIONS:

Croft, A. P. *et al …*Chris Buckley. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246-251 (2019). https://doi.org:10.1038/s41586-019-1263-7

de Jong M *et al.* An IL-1β-driven neutrophil–stromal cell axis fosters a BAFF-rich protumor microenvironment in individuals with multiple myeloma. *Nature Immunology* 25, (2024) https://www.nature.com/articles/s41590-024-01808-x

Bezbradica JS and Bryant C Inflammasomes as regulators of mechano-immunity. *EMBO Reports* 25, (2023) https://www.embopress.org/doi/full/10.1038/s44319-023-00008-2

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FAQs for prospective students regarding the OxKen (and Oxcat) MB DPhil training programs

Clinical skills and training:

Financing post PhD – how do I pay for clinical school?

If you start the DPhil after year 4/GE2, when NHS Bursaries cover course fees, we will notify them to 'stop the clock' and your bursary will simply restart to cover fees for the rest of the clinical course once you rejoin medicine.

If you start the DPhil after FHS/GE1 in order to qualify for an NHS Bursary to cover the initial clinical year you will need to defer taking your DPhil (you can and should complete the thesis submission and viva); since Student Finance England use the ELQ (Equivalent or Lower Qualification rule) and do not offer support for students returning to medicine from an MSc or (completed) DPhil.

How do I keeping up my clinical skills, keep in touch with clinical medicine and Integrate my long-term clinical training into my DPhil?

We will make sure you are ready to enter your clinical course at the end of your three years of research (and not feeling too rusty!) by scheduling in your third-year regular dedicated clinical teaching sessions, including refresher courses for themes relevant to clinical medicine, and clinical refresher teaching from clinical academics.

How will I reintegrate into clinical school?

During your research you will have regular contact with Dr Swales. Catherine is both Director of Clinical Studies and a member of both the OxKen and OxCat management committees; she is your primary point of contact when you

commence clinical training. Prior to returning to the clinical course there will be refresher sessions to support the transition back into clinical school.

If you start the DPhil during clinical (ie after year4/GE2), you will also have your Educational Supervisor to support you throughout the DPhil, alongside college supervisors.

Research

This is a 3-year program; many DPhils are 4-year programs. Do you have advice on doing a PhD in 3 years instead of 4?

We do our upmost to help you finish in 3 years. We vet all projects and do not support those that we view as high risk or overambitious – for example those involving setting up a new disease model or studying patients or patient samples where the study has not already commenced. Thus, whilst all original scientific research entails some risk in terms of outcomes, we do everything possible to "de-risk" projects.

We ensure that all projects have a clinical supervisor or co-supervisor who we expect to have an eye on your long term clinical training and career.

We will meet with you regularly throughout your research to check that you are on track and assist/advise if we think there may be issues so as to maintain this.

Will we get talks on academic careers in medicine?

Yes, this is an area we will have talks on, usually hosted by the OUCAGS (Oxford University Clinical Academic School). All Oxken/Oxcat students have access to OUCAGS talks and become part of the community of oxford clinical academics at different career stages.

Professor Paul Bowness
NDORMS

Oxford University Hospitals NHS Foundation Trust

NDORMS NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

UNIVERSITY OF OXFORD

Want to find out more?

Come along to the OxKen Open day on 28th October, 16:30 to 18:00,
Venue: Kennedy Institute, Old Road Campus, Roosevelt Drive, Headington, Oxford, OX3 7FY. (map)

The Kennedy Trust for Rheumatology is pleased to invite you to our joint Open Day for any medical students interested in pursuing a DPhil in the fields of Cancer Science or Musculoskeletal Disease, Inflammation and Immunology respectively. **This is only open to medical students intercalating after year 3 or year 4 of the standard entry A100 course, and after year 2 of the graduate entry A101 course.**.

Agenda

- Catherine Swales: welcome and introduction – why should I do research now?
- Paul Bowness: outline of OxKen scheme, research areas and projects available
- Julian Knight: funding DTC training and practicalities
- Panel Q and A

Colleges Accepting OxKEN Applications

Full list also available on the 'College Preference' tab on https://www.ox.ac.uk/admissions/graduate/courses/dphil-inflammatory-and-musculoskeletal-disease

College	Contact
Balliol	Adam Caulton Tutor for Graduate Admissions Balliol College Broad St Oxford OX1 3BJ Email: graduate@balliol.ox.ac.uk
Brasenose	Dr Felicity Shelley Admissions Officer Brasenose College Radcliffe Square Oxford OX1 4AJ Email: admissions@bnc.ox.ac.uk
Corpus Christi	Rachel Clifford Academic Registrar Corpus Christi College Merton St, Oxford OX1 4JF Email: rachel.clifford@ccc.ox.ac.uk
Exeter	Dr Chris. Ballinger Senior Tutor & Official Fellow Exeter College Oxford OX1 3DP Email: admissions@exeter.ox.ac.uk *Do not take for the graduate entry medicine programme
Green Templeton	Dr Alison Stenton Senior Tutor Green Templeton College, 43 Woodstock Rd Oxford OX2 6HG Email: admissions@gtc.ox.ac.uk; alison.stenton@gtc.ox.ac.uk

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Harris Manchester	Professor Bee Associate Professor and Fellow of Harris Manchester College, Oxford University Email: bee.wee@ouh.nhs.uk Dr Gina Hadley Official Fellow (John Henry Felix Fellow) and Associate Tutor in Medicine, Email: gina.hadley@hmc.ox.ac.uk. Professor Mark Harris, Tutor for Graduates: Email: mark.harris@theology.ox.ac.uk Victoria Lill, Tutor for Admissions: Email: victoria.lill@hmc.ox.ac.uk
Hertford	Bjarke Frellesvig, Tutor for Graduates Megan Roper, Registrar & Director for Admissions Alfie Deere-Hall, Admissions Officer Hertford College, Catte St, Oxford OX1 3BW Email: graduate.admissions@hertford.ox.ac.uk
Jesus	Dr Alexandra Lumbers Academic Director Jesus College, Turl Street, Oxford, OX1 3DW Email: alexandra.lumbers@jesus.ox.ac.uk
Lady Margaret Hall	Dr Ben Higgins Fellow in English and Tutor for Graduates Lady Margaret Hall Norham Gardens Oxford OX2 6QA Email: tutor.graduates@lmh.ox.ac.uk
Linacre	
Lincoln College	Richard Little Admissions Officer Lincoln College Email: richard.little@lincoln.ox.ac.uk
New College	Dr. Beth Psaila CRUK Advanced Clinician Scientist & Group Leader, MRC Weatherall Institute of Molecular Medicine. Haematology Consultant, Oxford University Hospital NHS Trust Senior Fellow of New College Oxford Email: bethan.psaila@ndcls.ox.ac.uk
Pembroke	Miss Caroline Barnes MA Oxf Academic Registrar & Director of Admissions Pembroke College Pembroke Square Oxford OX1 1DW Email: caroline.barnes@pmb.ox.ac.uk Email: admissions@pmb.ox.ac.uk

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Reuben	Dr Caroline Mawson Senior Tutor Reuben College University of Oxford Email: senior.tutor@reuben.ox.ac.uk Avalon Floyd, Graduate and Admissions Administrator, Reuben College University of Oxford Email: admissions@reuben.ox.ac.uk
St Catherine's	Cressida Chappell Academic Registrar St Catherine's College Manor Road, Oxford OX1 3UJ Email: college.office@stcatz.ox.ac.uk
St Cross	
St Hilda's	Dr Sarah Norman Senior Tutor & Tutor for Admissions St Hilda's College University of Oxford Oxford OX4 1DY Email: sarah.norman@st-hildas.ox.ac.uk
St Hugh's	
St John's	Professor Jaideep J Pandit Professor of Anaesthesia University of Oxford St John's College Oxford OX1 3JP Email: jaideep.pandit@sjc.ox.ac.uk
Somerville	Steve Rayner Senior Tutor, Somerville College Oxford OX2 6HD Email: senior.tutor@some.ox.ac.uk
The Queen's College	Professor Rebecca Beasley Tutor for Graduates The Queen's College tutor.postgraduates@queens.ox.ac.uk admissions@queens.ox.ac.uk

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Trinity	Mrs Ashley Maguire Academic Administrator, Trinity College Broad Street Oxford OX1 3BH Email: academic.administrator@trinity.ox.ac.uk Tel: 01865 279910.
Wadham	Ms Lynn Featherstone Tutor for Admissions Wadham College Oxford OX1 3PN Email: lynn.featherstone@wadham.ox.ac.uk
Wolfson	Emily-Beth (EB) Hill Admissions & Academic Officer Wolfson College, Oxford Email: admissions@wolfson.ox.ac.uk
Worcester	Dr Robert Smith Tutor for Graduates Worcester College Oxford OX1 2HB Email: graduate.enquiries@worc.ox.ac.uk;
Wycliffe Hall	

OXKEN Co-applicants

Paul Bowness, Co-Director: Professor of Experimental Rheumatology & Consultant Rheumatologist

Tonia Vincent, Co-Director: Prof Musculoskeletal Biology & Consultant Rheumatologist; Director, Centre for OA Pathogenesis Versus Arthritis

Catherine Swales: Director of Clinical Studies University of Oxford Medical School, Consultant Rheumatologist

Prof J Knight : Director, Medical Sciences Division Graduate School

Chris Pugh:* (now Prof D Furnis) Director of Oxford University Clinical Academic Graduate School

Paul Klenerman: Sidney Truelove Professor of Gastroenterology; Head Translational Gastroenterology Unit

Jane Dale: Head of Education Policy and Planning, Medical Sciences Division

David Vaux: Deputy Head of Medical Sciences Division (Education)

Denise Best: (now retired) Associate Director, Oxford University Academic Graduate School

Graham Ogg: Professor of Dermatology; Interim director MRC Human Immunology Unit, WIMM

Robert Wilkins: Director of Preclinical Studies