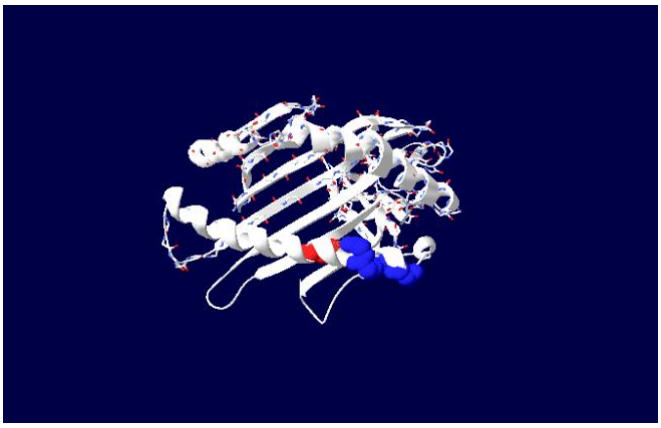
Oxford University Hospitals NHS Foundation Trust

NDORMS NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

UNIVERSITY OF OXFORD

OxKen: DPhil in inflammatory and musculoskeletal disease

2023 Intake Project Book



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Introduction

The Kennedy Trust for Rheumatology Research-funded OxKen programme will fully fund 4 Oxford University medical students each year from 2021-5 to undertake DPhils in the Medical Sciences Division in the fields of musculoskeletal disease, inflammation and immunology.

This booklet provides an overview for prospective students looking to study for a DPhil in Inflammation, Immunology and Musculoskeletal Sciences at Oxford University, starting in 2023. Applications from current Oxford medical students are welcomed to start directly after preclinical training (Final Honours School) or after the first clinical year. The cohort will start on 1 September (or 1 August for first year clinical students) 2023.

The Programme provides research based doctoral training for researchers from clinical and biological backgrounds. clinical training. In the programme students will receive a world-leading research training experience that integrates an education initiative spanning patient care, and research impact; on- and post-programme mentorship; and a specialised, fundamental, subject-specific training tailored to individual research needs. Students participating in the scheme will be offered:

- 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 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
4. Clinical trials and in vivo studies
5. Epidemiology, computational and data science
6. Tissue engineering and remodelling

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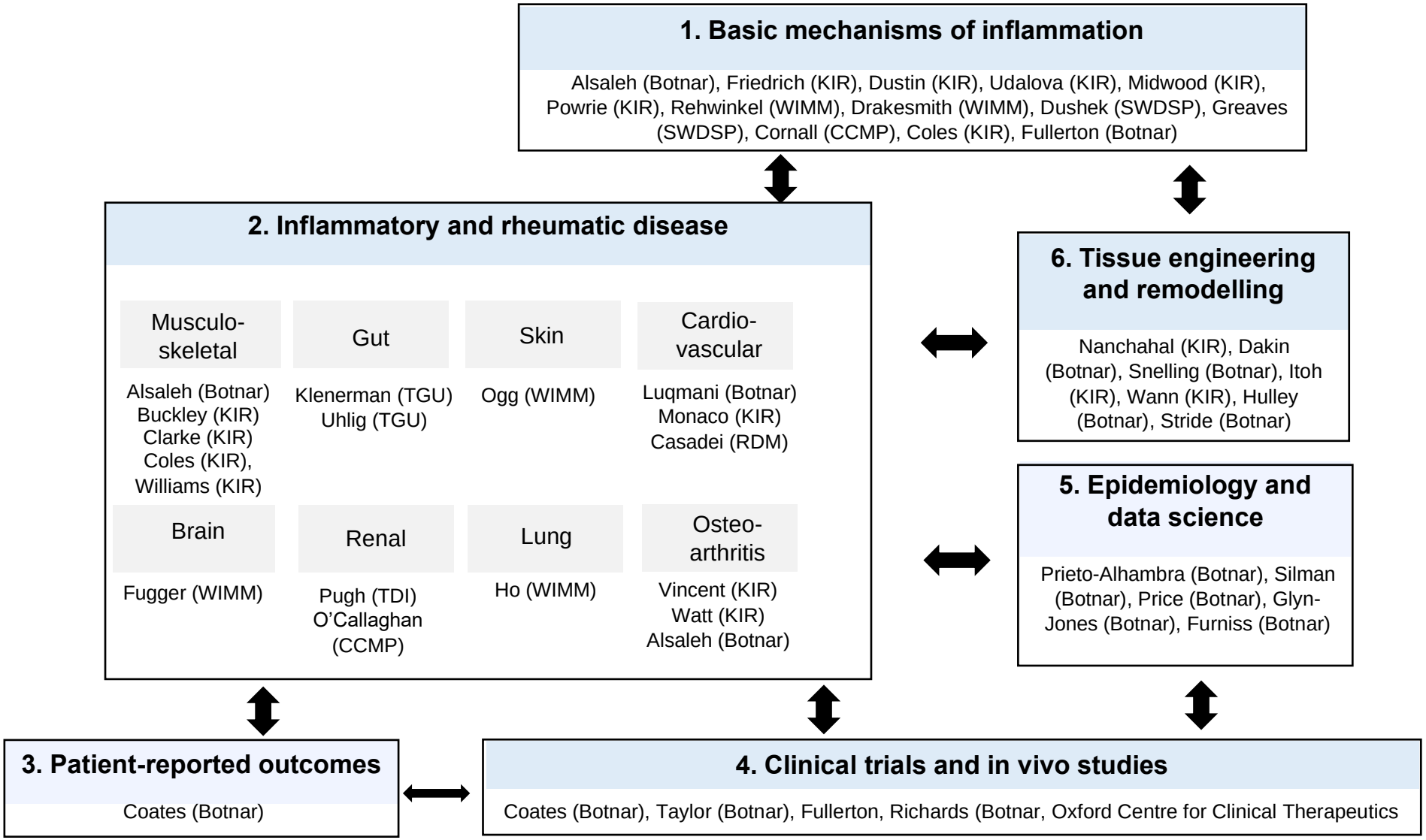
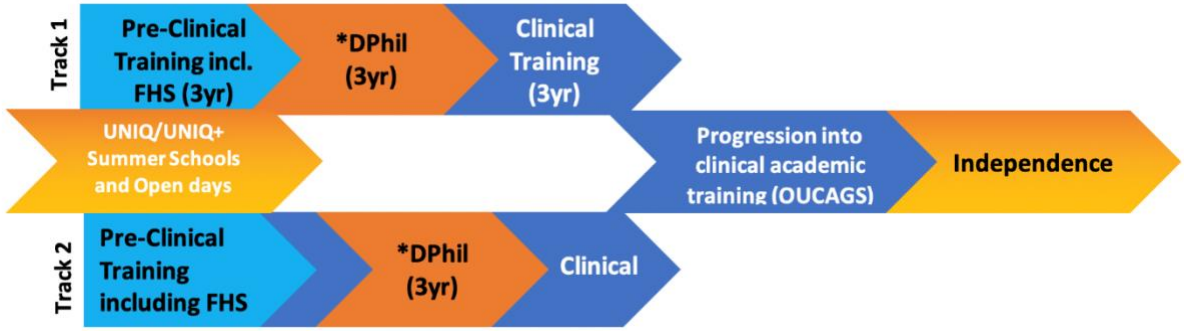
OxKEN Research Themes



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

Selection Criteria & Eligibility

Due to University requirements this program is only available to Oxford University students studying Medicine currently in their third (FHS) or 4th (first clinical) years. There are two tracks for training as clinician scientists shown below.



Application Track 1 – Medical Undergraduates current 3rd year preclinical (to start 01 Sept 2023)
Application Track 2 – 1st year clinical students (to start 01 Aug 2023).

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 salary/stipend (currently £21,586 PA), University and College fees, and a research consumables budget of £10,000 p.a. Top up fees for one overseas student may be available on a competitive basis. Also, on a competitive basis, we will pay clinical fees for one year for up to two students in track 1 if they do not qualify for funding due to ELQ.

How to Apply

Prospective students should apply with a prioritised list of three projects selected from this booklet by **12:00 midday UK time on: Friday 9 December 2022.**

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 inflammation and musculoskeletal diseases - although you will need to find projects supervisors.

Applications are invited from 31 Oct 2022 to 9 Dec 2022 (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 at the end of this booklet.

Shortlisted students to interview (on Teams) on Tuesday 24th January. Students are welcome to jointly apply for the OxCat and OxKen training programs which will be interviewed together. If successful, students will be allocated a project on the basis of their ranking during the review process.

Projects at a Glance

Project ID	Title	Supervisor(s)	Themes
#OxKEN-2023/1	Influence of Modifiable factors in PsA contributing to treat to target success (the IMPACT study)	Supervisor 1: Laura Coates Co-Supervisor/s: Emma Dures, Marie Falahee, Jorien Veldwijk	4, 3
#OxKEN-2023/2	Elucidating T cell phenotype and function in frozen shoulder	Supervisor 1: Stephanie G Dakin, Co-Supervisor/s: Christopher Buckley, Mark Coles	2 (5)
#OxKEN-2023/3	Co-prevalence of liver disease in psoriatic disease (COLIPSO)	Supervisor 1: Laura Coates Co-Supervisor/s: Paul Klenerman, Hussein Al-Mossawi	2 (4)
#OxKEN-2023/4	Understanding and exploiting antigen discrimination by T cells	Supervisor 1: Omer Dushek Co-Supervisor/s: P. Anton van der Merwe	1
#OxKEN-2023/5	Gamma-delta intra-epithelial lymphocytes in coeliac disease	Supervisor 1 Paul Klenerman, Co-Supervisor/s: Michael FitzPatrick, Holm Uhlig	2
#OxKEN-2023/6	Investigating the role of neutrophil subsets in vascular inflammation	Supervisor 1: Irina Udalova Co-Supervisor/s: Professor Raashid Luqmani, Dr Kristina Zec (Versus Arthritis Fellow)	2 (1)
#OxKEN-2023/7	Investigating interactions between oxygen-sensing pathways and autoimmunity	Supervisor 1: Fadi Issa Co-Supervisor/s: Katherine Bull; Joanna Hester; Chris Pugh	1
#OxKEN-2023/8	Form meets function in synovium: Did the evolution of power and precision grip	Supervisor 1: Prof. Mark Coles Co-Supervisor/s: Prof. Christopher Buckley	2 (5)

	drive development of rheumatoid arthritis?		
#OxKEN-2023/9	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	5
#OxKEN-2023/10	'Towards equity in medicine with big health data, epidemiology, and Artificial intelligence'	Supervisor 1: Daniel Prieto-Alhambra Co-Supervisor/s: Sara Khalid, Laura Coates, Gary Collins, Antonella Delmestri	5
#OxKEN-2023/11	Developing and testing a humanised mouse model of fibrosis	Supervisor 1: Prof Dominic Furniss, NDORMS Co-Supervisor/s: Prof. Fadi Issa, NDS	6 (1)
#OxKEN-2023/12	Investigation of DDR2 signalling that promotes synovial cell invasion into cartilage in rheumatoid arthritis	Supervisor 1: Prof Yoshifumi Itoh Co-Supervisor/s: Prof Chris Buckley; Prof Richard Williams	2 (1)
#OxKEN-2023/13	Characterizing the ageing phenotype of fibroblast populations in the synovium of RA and OA patients.	Dr Ghada Alsaleh**,** Prof Tonia Vincent, Professor Christopher Buckley	2 (1, 6)
#OxKEN-2023/14	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-2023/15	A cellular atlas of the human hip to understand the relationship between femeroacetabular impingement and hip osteoarthritis	Supervisors: Associate Professor Sarah Snelling, Associate Professor Adam Cribbs, Associate Professor Philippa Hulley, Dr Mat Baldwin. External Supervisor Mr Vikas Khanduja (Cambridge)	2 (6)
#OxKEN-2023/16	Spatial exploration of hypoxic signalling and inflammation in chronic hepatitis B.	Supervisor: Jane McKeating and Co-Supervisor: Fadi Issa	1
#OxKEN-2023/17	Establishing the Insulin-like growth factor 1 (IGF-1) axis as a therapeutic target in carpal tunnel syndrome and trigger finger	Supervisor 1: Prof Dominic Furniss, NDORMS Co-Supervisor/s: Prof Tonia Vincent, NDORMS; Prof Valentine Macaulay, NDS; Mr Akira Wiberg, NDORMS	2 (1)
#OxKEN-2023/18	Matrix architecture in the perivascular niche: a master regulator of lymphocyte infiltration in inflammatory disease?	Supervisor 1: Prof Kim Midwood Co-supervisors: Prof Dame Fiona Powrie, Dr Shirish Dubey, Mr. Jean-Baptiste Richard	1 (2,6)
#OxKEN-2023/19	The dark side of hypoferremia: does iron deficiency disable innate immunity in humans?	Supervisor 1: Associate Prof James Fullerton Co-Supervisor/s: Prof Hal Drakesmith	1
#OxKEN-2023/20	A clinically-relevant musculoskeletal humanoid shoulder for studying joint instabilities and diseases	Supervisor 1: Co-Supervisor/s: Pierre-Alexis Mouthuy, Julie Stebbins, Steve Gwilym	6 (2)
#OxKEN-2023/21	Epigenetic targeting of fibroblasts as a novel	Dr Matthias Friedrich Co-Supervisor: Professor Simon Travis	1 (2)

	therapeutic avenue for fibro-stenotic Crohn's disease		
#OxKEN-2023/22	Interrogating immune-mediated inflammatory disease via cutaneous human immune challenge	Supervisor 1: Assoc Prof James Fullerton Co-Supervisor/s: Prof Chris Buckley	1 (2)
#OxKEN-2023/23	Developmental engineering models of skeletal ciliopathies	Supervisor: Dr Angus Wann Co-Supervisor 1: Professor Tonia Vincent	6

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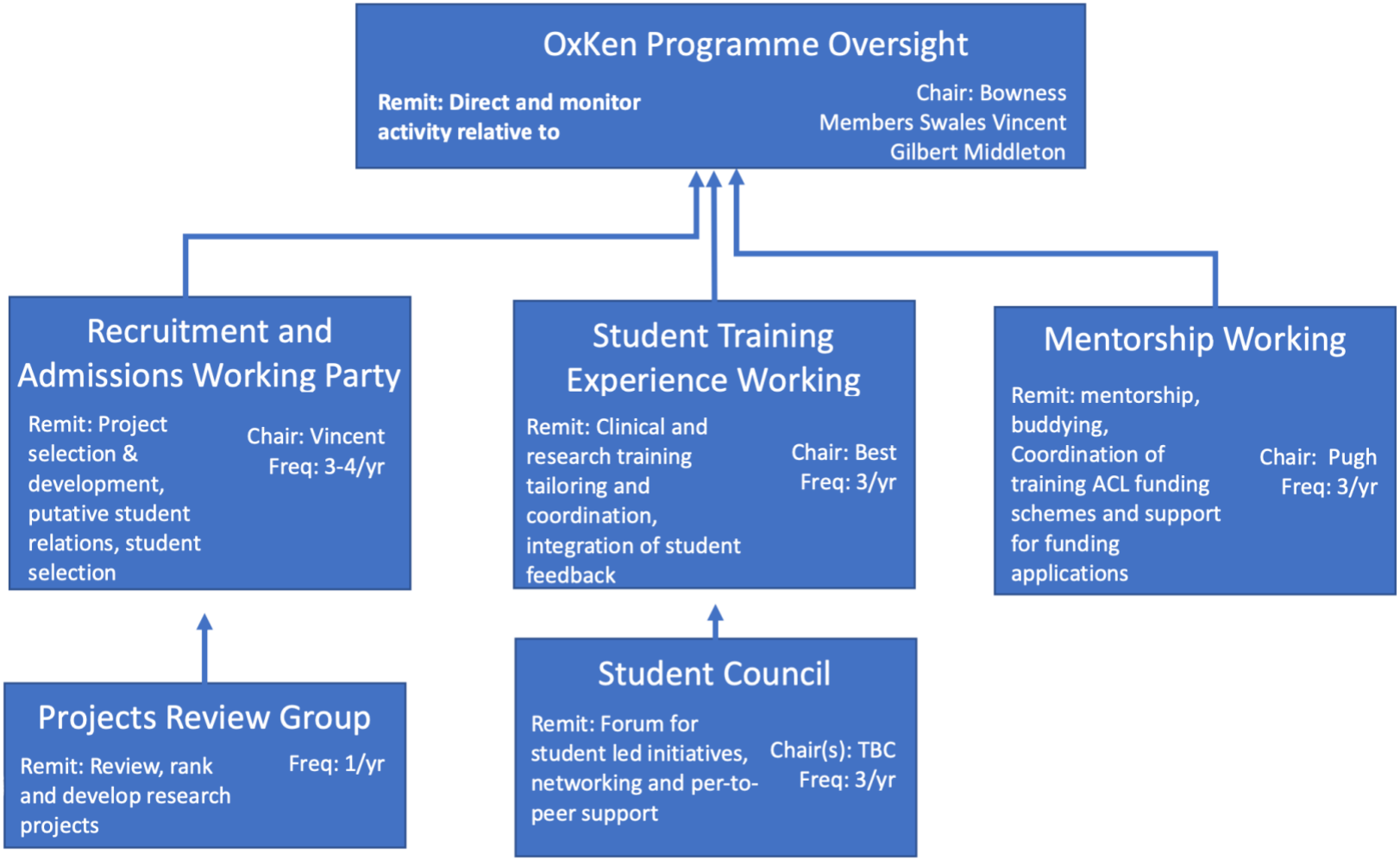
OxKen Governance Structure



Project Proposals

1. Project Title: Influence of Modifiable factors in PsA contributing to treat to target success (the IMPACT study)

Supervisor 1: Laura Coates

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

PROJECT OVERVIEW: (500 words maximum)

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.

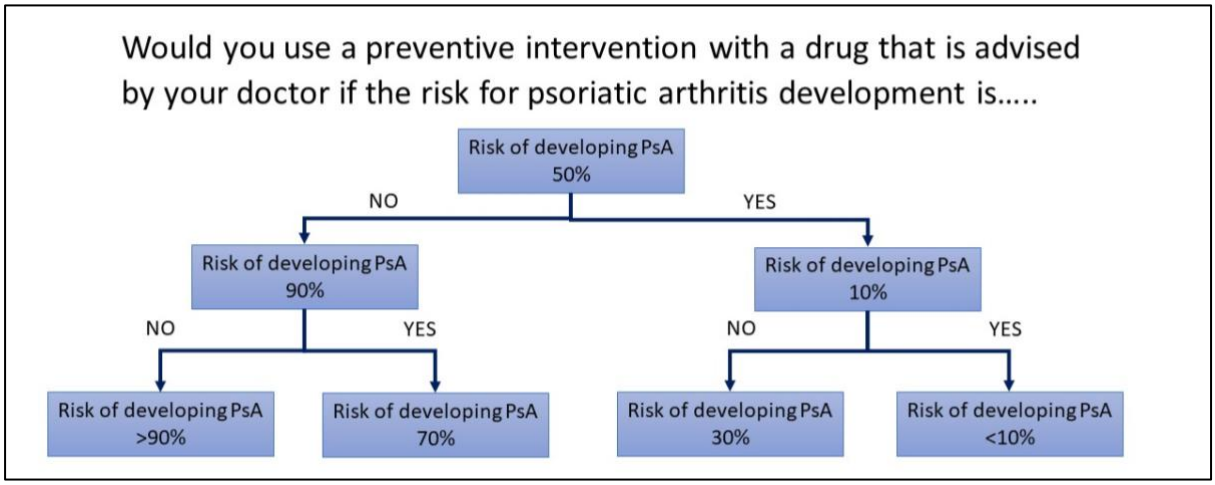
This DPhil project will establish the acceptability of preventative treatment for PsA amongst people with psoriasis. It will help us to design a future interventional study aiming to prevent the progression to psoriatic arthritis.

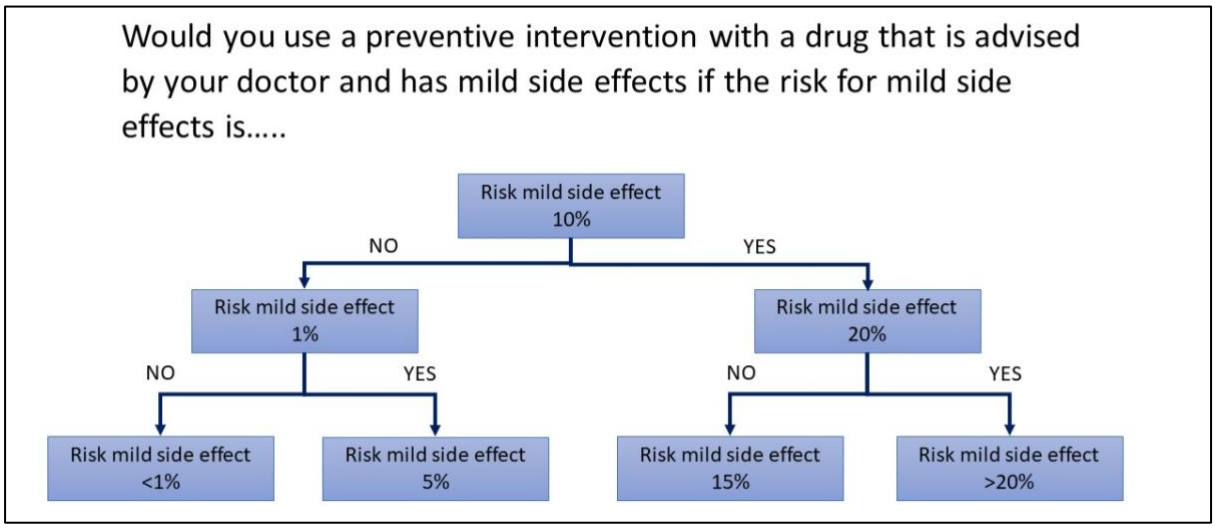
Whether people would be happy to join a preventative study is likely to depend on a lot of factors, Training will be provided in qualitative research techniques to lead focus groups of people with psoriasis. This qualitative work will explore the different factors that would influence their choice about 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 (5 WORDS): 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 (5 maximum):

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
4. Simons G, **Veldwijk J**, Disantostefano RL, Englbrecht M, Radawski C, Bywall KS, Valor Méndez L, Hauber B, Raza K, **Falahee M**. Preferences for preventive treatments for rheumatoid arthritis: discrete choice survey in the UK, Germany and Romania. Rheumatology (Oxford). 2022 Sep 7:keac397. doi: 10.1093/rheumatology/keac397. Online ahead of print.PMID: 36068022
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.

CONTACT INFORMATION OF ALL SUPERVISORS:

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Email – emma2.dures@uwe.ac.uk

Email – m.falahee@bham.ac.uk

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2. Project Title: Elucidating T cell phenotype and function in frozen shoulder

Supervisor 1: Prof Stephanie G Dakin, **Co-Supervisor/s: Prof Christopher Buckley & Prof Mark Coles**

PROJECT OVERVIEW: Frozen shoulder is a disabling condition affecting 10% of the working population. Disease causes significant pain and immobility of the shoulder joint, reducing life quality of affected patients. Frozen Shoulder is an inflammatory fibrotic disease localised to the shoulder joint capsule. Curiously the disease is self-limiting, as symptoms almost always resolve, albeit over 2-3 years. Frozen shoulder is therefore a unique example of a chronic inflammatory fibrotic disease that resolves. The cellular basis underpinning how inflammatory fibrosis resolves in frozen shoulder is currently unknown. Understanding this cellular basis of resolution will 1)identify new treatments to accelerate resolution of frozen shoulder and 2)inform the biological cues to push persistent inflammatory fibrotic diseases like arthritis down a resolving pathway.

In the absence of animal models that accurately recapitulate human disease, we set up the ICECAP clinical study, enabling us to collect well-phenotyped shoulder capsule tissues from patients undergoing surgery for frozen shoulder. We also collect comparator capsular tissues from patients undergoing shoulder stabilisation or arthroplasty procedures. Our pilot scRNAseq data identify that the human shoulder capsule is comprised of distinct tissue-resident stromal cell subsets. We have identified a unique subset of CD3+CD8+CD69+ T cells which appear to be resident in the capsule. These cells also highly express *GRANZYME K, GRANULYSIN, IL7R, CXCR4 and KLRB1* (Figure 1). We confirmed expression of these proteins in sections of frozen shoulder patient tissues using ChipCytometry (Figure 2A&B). These T cells exhibit a profile akin to the SCT5 subset identified by Zhang *et al*. in synovial tissues from patients with rheumatoid arthritis[1]. This preliminary data suggests that T cells in frozen shoulder may be enriched for cytotoxicity. However their precise phenotype(s), biological function(s) and how these cells might change in frozen shoulder remain unknown. Pereira *et al*. identified that Sestrins can induce the re-programming of non-proliferative senescent-like CD8+ T cells, enabling them to acquire broad-spectrum, innate-like killing activity[2]. We therefore hypothesise that T cells in the shoulder capsule are implicated in killing senescent capsular fibroblasts, contributing to resolution processes during frozen shoulder.

The over-arching aim of this project is to elucidate the biological role of T cells in the resolution of frozen shoulder. The specific objectives to address this aim are to:

1. Expand the scRNAseq dataset to identify transcriptomic T cell signature(s) in capsular tissues collected from non-diseased comparator and frozen shoulder patient tissues.
2. Confirm T cell protein signatures in sections of capsular tissues from comparator and frozen shoulder patients
3. Use organoid cultures comprised of patient-derived cells to understand how T cells interact with capsular stromal cells to resolve inflammatory fibrosis in frozen shoulder
4. Bioinformatically compare the profiles of capsular T cells in resolving frozen shoulder with T cells in non-resolving fibrotic diseases

In addition to discovering new therapeutic strategies for frozen shoulder, this work will also provide novel insights into the cellular mechanisms of intractable soft tissue inflammatory and

fibrotic diseases affecting the lung, liver, kidney and skin which ultimately contribute to 45% of all-cause mortality[3], leading towards potential new treatment paradigms.

Figure 1. Profile of capsular T cells identified by scRNAseq. Violin plots showing differentially expressed genes in T cells residing within the shoulder joint capsule. Data are generated from tissues collected from 6 non-diseased comparator and 3 frozen shoulder donors.

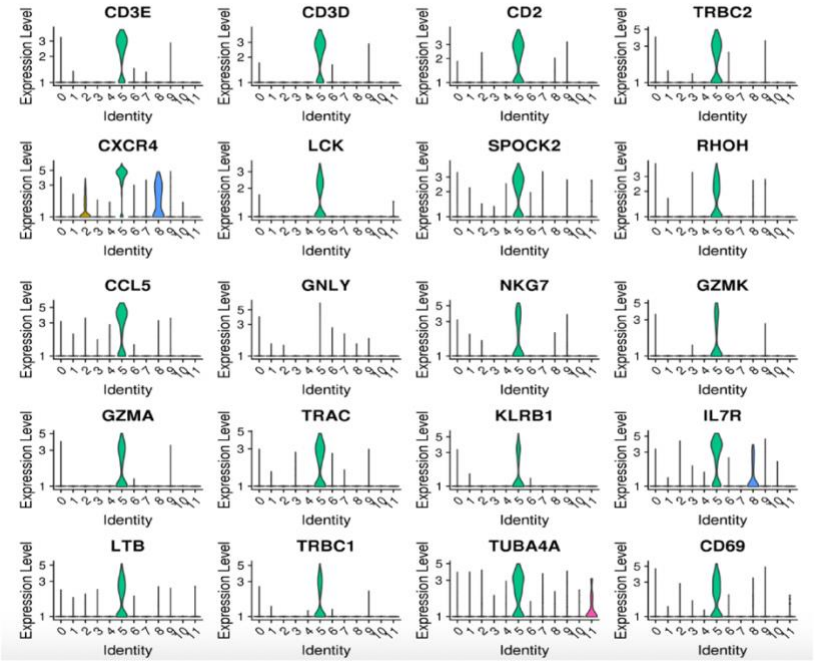

Figure 2A. ChipCytometry immunostaining of T cell markers in cryosections of frozen shoulder patient tissues.

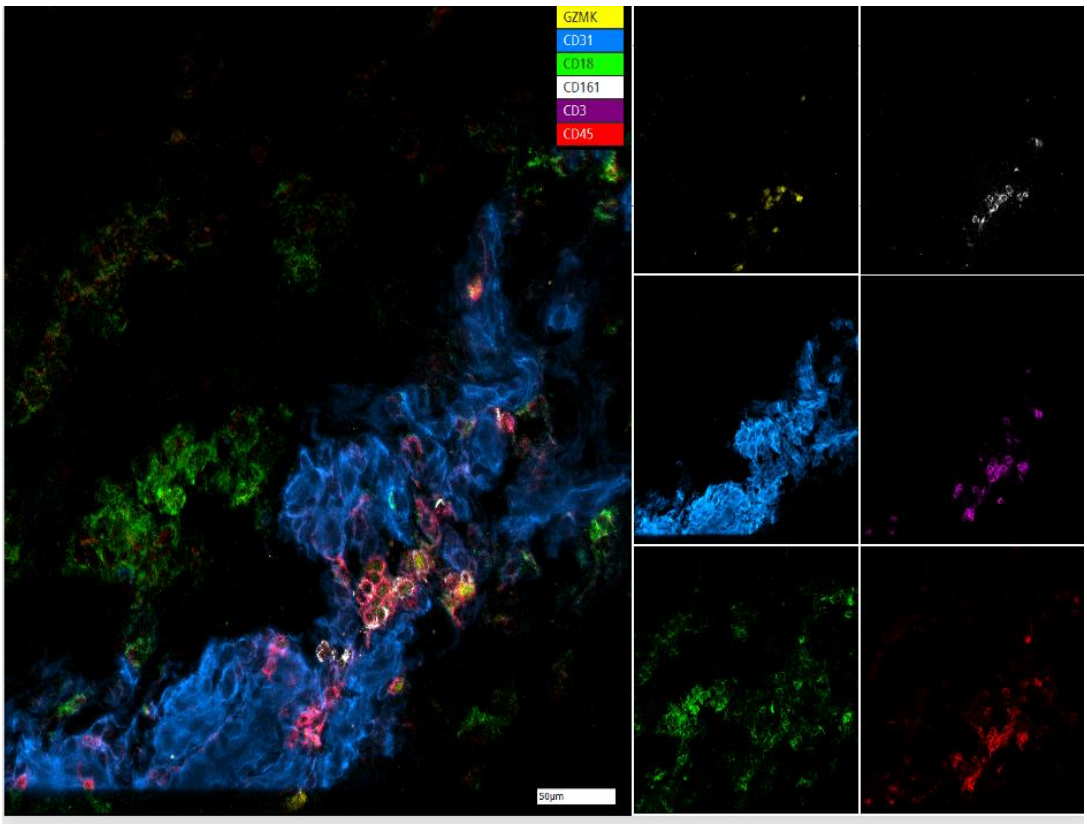

Figure 2A. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows GZMK (yellow), CD18 (green), CD161 (KLRB1, white), CD3 (violet), CD45 (red) and vascular endothelial marker CD31 (blue). Note the perivascular location of identified T cells. Scale bar = 50µm.

Figure 2B

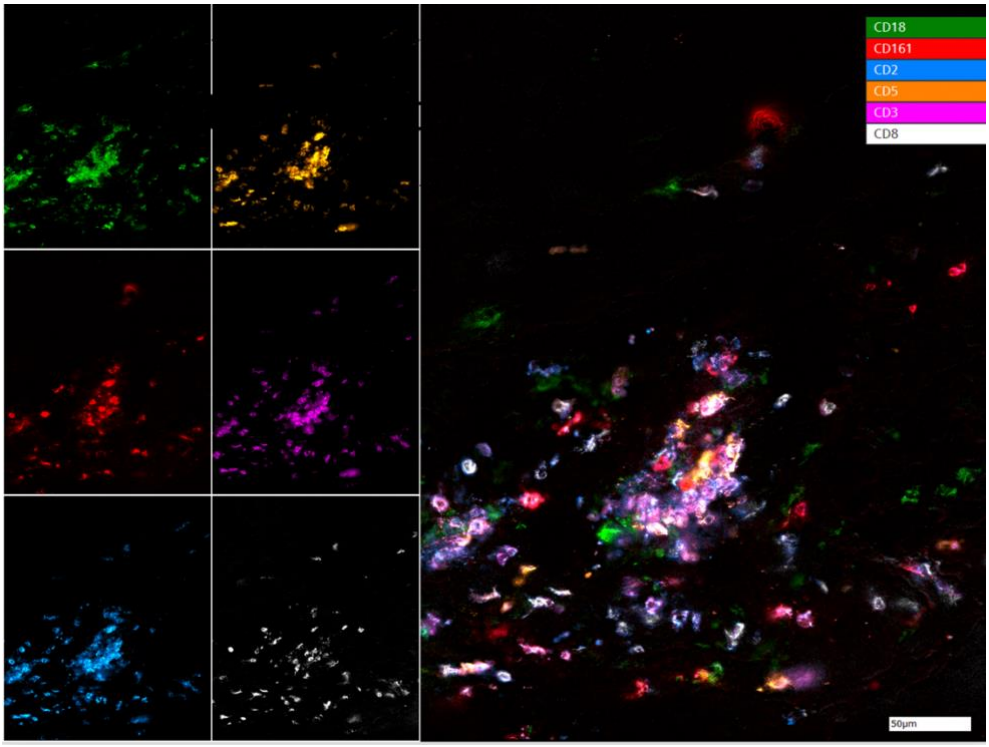

Figure 2B. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows CD18 (green) CD161 (KLRB1, red), CD2 (blue), CD5 (orange), CD3 (magenta), CD8 (white). Scale bar = 50µm.

KEYWORDS (5 WORDS): Musculoskeletal, inflammation, fibrosis, T cells, frozen shoulder

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) Preparation of capsular patient tissues for NGS and immunostaining
2) Analysis of Next Generation Sequencing (NGS) data sets for mechanistic study of T cell gene function
3) Bioinformatic modelling of T cell focused ligand-receptor and protein-protein interactions
4) Multiplex imaging of stained capsular tissues

Dakin has significant experience in DPhil supervision, having successfully supervised 8 DPhil students over the past 6 years and has 2 current DPhil students (due to complete in 2022 and 2023). Buckley and Coles have extensive supervision experience, having successfully supervised 14 & 20 DPhil students respectively. The Dakin, Buckley & Coles labs possess the expertise and access to necessary patient tissue samples, resources and equipment required for wet-lab based experiments to complete this project.

KEY PUBLICATIONS (5 maximum):

Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, Savary L, Wehmeyer C, Naylor AJ, Kemble S, Begum J, Dürholz K, Perlman H, Barone F, McGettrick HM, Fearon DT, Wei K, Raychaudhuri S, Korsunsky I, Brenner MB, **Coles M**, Sansom SN, Filer A, **Buckley CD**. Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature. 2019 Jun;570(7760):246-251. doi: 10.1038/s41586-019-1263-7. Epub 2019 May 29. PMID: 31142839; PMCID: PMC6690841.

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.

Dakin SG, Rangan A, Martinez F, Brealey S, Northgraves M, Kottam L, Cooper C, **Buckley CD,** Carr AJ. (2019) Tissue inflammation signatures point towards resolution in adhesive capsulitis. Rheumatology (Oxford). 2019 Jan 27. doi: 10.1093/rheumatology/kez007.

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**. 7 (311); 311ra173. doi: 10.1126/scitranslmed.aac4269.

Kendal AR, Layton T, Al-Mossawi H, Appleton L, **Dakin SG**, Brown R, Loizou C, Rogers M, Sharp R, Carr AJ. Multi-omic single cell analysis resolves novel stromal cell populations in healthy and diseased human tendon. Sci Rep. 2020 Sep3;10(1):13939.

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Email: christopher.buckley@kennedy.ox.ac.uk

Email: markcoles2@kennedy.ox.ac.uk

3. Project Title: Co-prevalence of liver disease in psoriatic disease (COLIPSO)

Supervisor 1: Laura Coates

Co-Supervisor/s: Paul Klenerman, Hussein Al-Mossawi

PROJECT OVERVIEW: (500 words maximum)

Patients with psoriatic disease (psoriasis and psoriatic arthritis) have a much higher risk of developing non-alcoholic liver disease. This is a difficult clinical problem as many disease-modifying drugs used for psoriasis and arthritis (e.g. methotrexate) may worsen the liver disease. Previously the only tests available for this have been liver function tests (often normal until the liver is quite damaged) or a liver biopsy (an invasive and risky procedure). LiverMultiScan is a novel, CE-marked and FDA-cleared product (Perspectum Diagnostics Ltd, UK https://perspectum-diagnostics.com/) that can non-invasively quantify liver tissue characteristics based on magnetic resonance imaging (MRI).

Our hypothesis is that this completely novel method of liver disease quantification using MRI LiverMultiScan technology can be applied in psoriatic disease allowing quantification and further understanding of this comorbidity. The aims are to:

- Quantify the true extent of liver disease in people with psoriatic disease compared to UK Biobank controls.
- Investigate the causal pathological relationship between systemic inflammation, gut microbiome dysbiosis and liver disease in people with psoriatic disease
- Explore the impact of commonly used psoriatic therapies such as methotrexate and biologics on liver inflammation and fibrosis.

The role of gut dysbiosis in psoriatic disease is becoming more evident but the potential impact of this dysbiosis on the liver, which is the first site of processing for microbial metabolites, has not yet been investigated. In particular, we plan to study a population of resident mucosal invariant T cells (MAIT) found in the liver which recognise microbial metabolites and are capable of producing pro-inflammatory type 17 cytokines such as IL-17A and F. MAIT cells have been associated with the pathogenesis of psoriatic disease and thus uniquely poised to link gut dysbiosis with Th17-driven joint inflammation. The gut microbiome profile of individuals will be correlated with the MAIT cell transcriptomic signature.

Funding is already secured for a 100 patient cross-sectional study, across 2 UK centres, recruiting patients with psoriasis and PsA who are about to start disease-modifying therapy. We will perform clinical assessments, LiverMultiScan MRI and collect blood/stool samples pre and post treatment.

KEYWORDS (5 WORDS): non-alcoholic fatty liver disease, psoriasis, psoriatic arthritis, imaging, MAIT cells.

TRAINING OPPORTUNITIES: FACS sorting, RNA sequencing, PCR, microbiome sampling, biostatistics, specialist psoriatic arthritis and combined rheum/derm clinics, presentations at national and international meetings,

KEY PUBLICATIONS (5 maximum):

1. MAIT Cells in Health and Disease. Provine NM, Klenerman P.Annu Rev Immunol. 2020 Apr 26;38:203-228. doi: 10.1146/annurev-immunol-080719-015428. Epub 2019 Jan 27.
2. Cole S, Murray J, Simpson C, Okoye R, Tyson K, Griffiths M, Baeten D, Shaw S, Maroof A. Interleukin (IL)-12 and IL-18 Synergize to Promote MAIT Cell IL-17A and IL-17F Production Independently of IL-23 Signaling. Front Immunol. 2020 Nov 20;11:585134. doi: 10.3389/fimmu.2020.585134
3. Coates Laura C, Moverley Anna R, McParland Lucy, Brown Sarah, Navarro-Coy Nuria, O'Dwyer John L, Meads David M, Emery Paul, Conaghan Philip G, Helliwell Philip S. (2015) Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet; 386(10012):2489-98.
4. van Mens Leonieke JJ, van de Sande Marleen GH, van Kuijk Arno WR, Baeten Dominique, Coates Laura C. (2018) Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. Ann Rheum Dis;77(2):251-257.
5. Coates LC, FitzGerald O, Merola JF, Smolen J, van Mens LJJ, Bertheussen H, Boehncke WH, Callis Duffin K, Campbell W, de Wit M, Gladman D, Gottlieb A, James J, Kavanaugh A, Kristensen LE, Kvien TK, Luger T, McHugh N, Mease P, Nash P, Ogdie A, Rosen CF, Strand V, Tillett W, Veale DJ, Helliwell PS. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology Consensus-Based Recommendations and Research Agenda for Use of Composite Measures and Treatment Targets in Psoriatic Arthritis. Arthritis Rheumatol. 2018 Mar;70(3):345-355.

CONTACT INFORMATION OF ALL SUPERVISORS:

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4. Project Title: Understanding and exploiting antigen discrimination by T cells

Supervisor 1: Omer Dushek

Co-Supervisor/s: P. Anton van der Merwe

PROJECT OVERVIEW: (500 words maximum)

T cells use their T-cell receptors (TCRs) to discriminate between lower-affinity self and higher affinity non-self pMHC antigens. Although this process has been widely studied, the underlying mechanisms remain unclear. In particular, it is presently unclear whether co-signalling receptors, including those routinely used for cancer immunotherapy (e.g. PD-1), only impact antigen sensitivity or also impact antigen discrimination. The objective of this project will be to investigate the contribution of various co-signalling receptors to the process of antigen discrimination by T cells and to exploit this information to improve T cell therapies as appropriate. The work will rely on primary human T cells transduced or transfected with a defined TCR to which a panel of pMHC antigens have been identified that bind with a spectrum of affinities (as described in Pettmann et al (2021) eLife). By tampering with individual co-signalling receptors, their impact on antigen sensitivity and discrimination can be quantitatively assessed and rationally exploited for improved T cell based therapies.

KEYWORDS (5 WORDS): T cells, T cell receptor, Antigen discrimination, Co-signalling receptors, T cell therapy

TRAINING OPPORTUNITIES: Primary human T cells (isolation, culture, genetic medication, stimulation), Flow cytometry, Biophysical analysis of TCR/pMHC interactions, Quantitative data analysis, Mathematical modelling

KEY PUBLICATIONS (5 maximum):

Pettmann et al (2021) The discriminatory power of the T cell receptor. eLife

Lever et al (2016) Architecture of a minimal signalling pathway explains the T cell response to a 1,000,000-fold variation in antigen affinity and dose. PNAS

Dushek & van der Merwe (2014) An induced rebinding model of T cell antigen discrimination. Current opinions in Immunology

Lever et al (2014) Phenotypic models of T cell activation. Nature Reviews Immunology

CONTACT INFORMATION OF ALL SUPERVISORS:

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anton.vandermerwe@path.ox.ac.uk

5. Project Title: Gamma-delta intra-epithelial lymphocytes in coeliac disease

Co-Supervisor/s: Paul Klenerman, Michael FitzPatrick, Holm Uhlig

PROJECT OVERVIEW: (500 words maximum)

Celiac disease is common, increasing in prevalence, and leads to significant morbidity and impaired quality of life for patients. Treatment with a gluten-free diet is burdensome, and there is a significant unmet need for improved diagnostics and therapeutics. *Celiac disease also serves as an important model for inflammatory diseases – one where the triggering antigen is clearly defined and the tissue pathology (in disease and resolution) readily available for sampling.*

Whilst the role of the gluten-specific CD4+ T cell in the immunopathology of celiac disease is well-studied, the cytotoxic CD8+ and γδ+ T cell populations that accumulate in the mucosa during inflammation are less well understood. In particular, the involvement of γδ T cells, which are hugely increased in number in the epithelium in coeliac disease, remain an enigma. *Such cells are likely important in a range of inflammatory diseases but Celiac disease offers an important opportunity to study their role in tissue.*

Recent evidence indicates that the T cell receptor (TCR) repertoire of this population is perturbed in coeliac disease, suggestive of an antigen-driven role of γδ T cells in celiac disease. However, these antigens remain unknown, as does the functional role of these intriguing cells in the gut in coeliac disease and elsewhere. This project aims to use novel molecular biology approaches and *in vitro* assays to answer these questions.

Project aims:

1. Characterize the phenotype and transcriptional state of circulating and intestinal γδ T cell populations in health and celiac disease, using single cell RNA sequencing and flow cytometry as well as new spatial (in situ) methods.

2. Explore the functional responses of T cell clones derived from disease-associated intestinal γδ T cells.

3. Identify putative TCR ligands for disease-associated γδ T cells *in vitro* using intestinal-derived T cell clones.

Unpublished data from our lab shows that CD8+ and γδ+ T cells in the gut in coeliac disease show skewed TCR repertoires, with candidate disease-associated TCR sequences identified. These populations also differ in their transcriptional profile, suggesting that these two cell types play different roles in the disease process. Funding is secured for sequencing and *in vitro* work to examine these populations in coeliac disease. In addition, we are analysing a recent, large-scale single-cell RNA sequencing project, which will provide further insights into the interactions between these CD8+ and γδ+ T cells and the epithelial cells in coeliac disease, in particular about potential ligands and antigens. These interactions can be

addressed using newer spatial methods including high content staining approaches and spatial transcriptomics.

The lab is based in the Translational Gastroenterology Unit, a world-class translational immunology facility at the JR Hospital. The unit works closely with the clinical department, with opportunities to experience specialist clinics and gastrointestinal endoscopy. The close-knit lab group is a supportive training environment, with extensive experience of training clinician-scientists in DPhil research.

KEYWORDS (5 WORDS): Gastrointestinal immunology, coeliac disease, γδ T cells, Intra-epithelial lymphocytes, transcriptomics

TRAINING OPPORTUNITIES: Human tissue processing, conventional and spectral flow cytometry, FACS sorting, bulk and single-cell RNA sequencing, cell culture, PCR, biostatistics, specialist coeliac disease and gastro-immunology clinics, gastrointestinal endoscopy, research and clinical journal clubs, presentations at national and international meetings.

KEY PUBLICATIONS (5 maximum):

Provine, N.M., Binder, B., FitzPatrick, M.E.B., Schuch, A., Garner, L.C., Williamson, K.D., van Wilgenburg, B., Thimme, R., Klenerman, P., Hofmann, M., 2018. Unique and Common Features of Innate-Like Human Vδ2+ γδT Cells and Mucosal-Associated Invariant T Cells. Front. Immunol. 9, 120–32. doi:10.3389/fimmu.2018.00756

FitzPatrick, M.E.B., Provine, N.M., Garner, L.C., Powell, K., Amini, A., Irwin, S., Ferry, H., Ambrose, T., Friend, P., Vrakas, G., Reddy, S., Soilleux, E., Klenerman, P., Allan, P.J., 2019. Human intestinal tissue-resident memory CD8+ T cells comprise transcriptionally and functionally distinct subsets. Cell Reports (In Press).

CONTACT INFORMATION OF ALL SUPERVISORS:

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Paul Klenerman Email – paul.klenerman@medawar.ox.ac.uk

6. Project Title: Investigating the role of neutrophil subsets in vascular inflammation

Supervisor 1: Professor Irina Udalova

Co-Supervisor/s: Professor Raashid Luqmani, Dr Kristina Zec (Versus Arthritis Fellow)

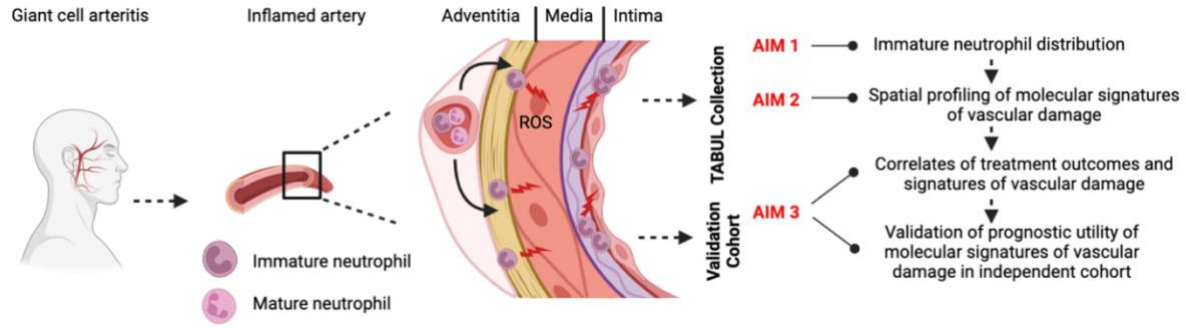
PROJECT OVERVIEW: (500 words maximum)

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 (**2**).

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 (**3**). Our recent work on auto-immune vasculitis has shown that immature neutrophils can generate dysregulated ROS to cause vascular leakage and damage that may lead to systemic vascular pathology (**4**). Moreover, we have unravelled novel cell-intrinsic molecular regulators of neutrophil maturation and phenotype and function that may lead to multiple therapeutic strategies tailored to specific conditions (**5**).

This project will profile core pathways and processes of vascular damage associated with immature neutrophils in Giant Cell Arteritis (GCA)-affected arteries by performing multiplex gene and protein expression analyses using the state-of-the-art spatial biology approaches, such as multi-parameter confocal microscopy and single cell spatial transcriptomics. Specifically the Cell Dive platform which allows for multiplex imaging of a single sample by iterative staining, will be used to expand our analysis of neutrophil- and oxidative tissue damage-associated biomarkers in GCA biopsies. Correlations between molecular signatures of vascular damage associated with immature neutrophils and treatment outcomes will be assessed in a clinically well-defined cohort and validated in an independent replication cohort (Fig overview). To further investigate the cellular and molecular mechanisms of neutrophils function on vasculature, the system of human vascular organoids will be adopted.

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 (5 WORDS): 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) and imaging (immunofluorescence on tissue sections) approaches. This rare opportunity to develop vascular organoids will involve stem cell reprogramming and culture. The candidate can benefit from the hands-on experience with these techniques in the Udalova lab, and from access to clinical samples and expertise in their immune analysis in the Luqmani group. Primary human neutrophils and plasma will be prepared from blood samples of patients with well phenotyped forms of vasculitis recruited by Prof Luqmani's research team. Confocal microscopy will be applied routinely to validate organoid structure and to image neutrophil-vasculature interaction and vascular damages. Multiplex assays such as the Luminex assay will be used for patient plasma profiling to identify key signalling molecules that modulate neutrophil-vasculature interaction. 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 organoids development.

KEY PUBLICATIONS (5 maximum):

(1) Ponte C, Martins-Martinho J, **Luqmani RA**. Diagnosis of giant cell arteritis. ***Rheumatology (Oxford).*** 2020 May 1;59(Supplement_3):iii5-iii16***.***

(2) 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.

(3) 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.

(4) **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

(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.

CONTACT INFORMATION OF ALL SUPERVISORS:

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

7. Project Title: Investigating interactions between oxygen-sensing pathways and autoimmunity

Supervisor 1: Fadi Issa

Co-Supervisor/s: Katherine Bull; Joanna Hester; Chris Pugh

PROJECT OVERVIEW: (500 words maximum)

Hypoxia complicates most human diseases, and the immune system operates in the resultant environment. Oxygen-homeostatic transcriptional responses are controlled by the hypoxia-inducible factor (HIF) pathways, regulated by the oxygen-sensing HIF hydroxylases (PHD 1-3 and FIH) [1]. We recently discovered that **global silencing of PHD2, the major oxygen-sensitive hydroxylase controlling HIF, results in spontaneous development of systemic lupus erythematosus (SLE)-like autoimmunity**, associated with impaired regulatory T cell (Treg) function in mice. Importantly this phenotype is reversible when PHD2 is re-expressed [2].

More recently, we tested the immune effects of environmental hypoxia on normal unchallenged adult mice to investigate whether the magnitude of HIF hydroxylase inhibition resulting from physiologically tolerable levels of hypoxia would be sufficient to influence immune status. Systemic hypoxia did produce a small HIF2α-dependent increase in lymph node size, milder than that seen with PHD2 silencing, but associated with an increased incidence of anti nuclear antibody (ANA) positivity (but little evidence of tissue inflammation). Furthermore, we have found that the ability of splenocytes to kill mycobacteria in vitro is enhanced following BCG immunisation combined with hypoxic exposure compared to BCG immunisation alone, mediated at least in part through HIF system effects in Tregs. Importantly, HIF induction via prolyl hydroxylase inhibition is already being used as a treatment for renal anaemia [3] and drugs inhibiting HIF2 dimerisation are showing promising results in the treatment of renal cancer [4].

In this project we will test the **hypotheses** that 1) HIF pathway induction can potentiate autoimmune responses/phenotypes and 2) that blocking endogenous HIF pathway induction or suppressing HIF2α can enhance immune regulation and ameliorate autoimmune phenotypes. Specifically, we will examine the effects of manipulating the HIF pathway (genetically, by altering oxygen supply, or pharmacologically) in mouse models of autoinflammatory and autoimmune conditions. Initial studies will focus on two models of SLE, TLR7 agonism with Imiquimod, which induces self-reactive antibody production and immune complex mediated renal damage consistent with lupus nephritis and MRL/lpr mice which provide a good polygenic model of multi-system human lupus. Both models can be combined with hypoxic or pharmacological manipulation of the HIF pathway and the Imiquimod model can be applied to mice with genetic HIF pathway manipulations. Sharpin deficient and NOD mice are also available and these experiments are all covered by existing animal licence permissions.

We will then extend this work to investigate the **underlying mechanisms** linking changes in HIF2α activity to changes in Treg phenotype, but potentially considering effects in other cell types highlighted by the models. Mechanistic studies will **combine state of the art approaches** including single cell and bulk sequencing, targeted CRISPR and/or small molecule interventions using both animal (perhaps including our humanised mouse models [5]) and in vitro assays (using human or mouse leukocytes). The goal of this latter work being

not only to advance knowledge and relate findings to human disease but also to **identify intermediary targets that could allow the immune response to be reversibly and precisely tuned** without entraining the wide effects of the entire HIF transcriptional pathways.

KEYWORDS (5 WORDS): Hypoxia; autoimmunity; SLE; Treg; HIF

TRAINING OPPORTUNITIES:

Generic skills training would be provided through access to the resources of the University's Graduate School (see https://www.medsci.ox.ac.uk/study/skillstraining). This covers areas such as experimental design, literature searching, coding, statistics, research presentations and scientific writing.

The project work would involve training in specific skills including, but not restricted to:

- use of animal models;
- informatics relating to single cell sequencing, including RNA velocity;
- signal pathway analysis;
- use of tissue culture models;

and potentially

- Cas9/CRISPR based genetic modification of cells;
- small molecule or RNAi based screens.

Attendance at meetings run by both the Hypoxia Biology Group and Transplantation Research and Immunology Group would ensure a broad grounding in the field of studies. Attendance at seminar series run across the University and meetings held with BMS would add diversity, exposure to a commercial mind-set and exposure to other methodologies.

In addition, the recipient of the Fellowship would receive support from the Oxford University Clinical Academic Graduate School which Chris Pugh directs. This would help with career development and acquisition of skills necessary to progress a clinical academic career, including advice about future grant applications and access to Clinical Lectureships.

KEY PUBLICATIONS (5 maximum):

1. Pugh, C. W. & Ratcliffe, P. J. *Exp Cell Res* 356(2):116-121 (2017).

2. Yamamoto et al. *J Clin Invest* 130, 3640-3656 (2019).

3. Chen et al. *N Engl J Med* 381(11):1011-1022(2019).

4. Courtney et al. *J Clin Oncol* 36, 867-874 (2018).

5. Adigbli et al. doi: 10.1097/TP.0000000000003177 *Transplantation.* (2020).

CONTACT INFORMATION OF ALL SUPERVISORS:

Email: Fadi.issa@nds.ox.ac.uk; bullk@well.ox.ac.uk; Joanna.hester@nds.ox.ac.uk; chris.pugh@ndm.ox.ac.uk.

8. Project Title: Form meets function in synovium: Did the evolution of power and precision grip drive development of rheumatoid arthritis?

Supervisor 1: Prof. Mark Coles

Co-Supervisor/s: Prof. Christopher Buckley

PROJECT OVERVIEW: (500 words maximum)

Rheumatoid arthritis (RA) and osteoarthritis (OA) have very different underlying biological pathways and process driving disease pathology leading to either bone destruction (RA) or bone creation (OA). RA is a classically leukocyte driven inflammatory disease leading to expansion of sublining layer stroma with inflammatory monocyte and lymphocytic inflammation and loss of synovial lining layer integrity. OA involves a non-lymphocytic disease process with inflammation and expansion of the lining layer leading to a mechanical fibrotic like disease. Interestingly in the human fingers OA occurs in the distal interphalangeal (DIP) joint in contrast RA occurs in the proximal interphalangeal (PIP) joint, implying anatomical and physiological differences inherent to the individual joints is as important as genetic and underlying immunological processes are in disease formation. One of the key observations about the PIP joint is it is a uniquely human joint providing hominids with two key properties that drove brain enlargement, power grip and precision control permitting tool usage. Thus, this unique joint in the animal kingdom not only made us human but might act as the triggering microenvironment to precipitate rheumatoid arthritis through anatomical features that act as a disease trigger point.

To develop a mechanistic understanding of human joint formation and function we have developed a transcriptomic atlas of developing human DIP and PIP joints using single cell genomics and cytometry. This has been performed at three different human developmental stages. Even at early stages of development differences in cellular composition and gene expression were revealed indicating that mechanics alone are not responsible for disease formation. This work is now being extended to normal human finger DIP and PIP joints to develop a comprehensive atlas of a human joint. In this project this atlas will be used to map and test gene function in the DIP vs PIP joints. Specifically, in this project a combination of spatial genomics and functional assays to dissect the anatomical and physiological differences between DIP and PIP joints.

Project Aims:

1: *To develop a spatial genomic map of human DIP and PIP joints:* Using a combination of multi-plex high dimensional imaging, light sheet microscopy and transcriptomics to develop a spatial map of the joints characterizing cell – cell interactions in the developing joints and 3 dimensional organization of neurons, vasculature and synovial tissues.
2: *Utilize human joint organoid models to analyse developmental differences in DIP and PIP synovium:* We will utilise the cartographical map of the DIP and PIP joints to test gene expression and function in vitro using organoid culture systems and observing effect of cytokines and mechanical stresses.
3: *Analyse the differential role of neurons, vasculature and synovium in disease formation:* Patients with denervation lead to resolution of rheumatoid arthritis in the effected limb, in mouse models localized vasculature has been shown to be important in RA like disease induction. Organotypic

cultures containing either neuronal in growth and/or vasculature to determine the roles of these cell types in development of differential susceptibility to disease.

KEYWORDS (5 WORDS): Rheumatoid-Arthritis, human-developmental, systems-biology, imaging

TRAINING OPPORTUNITIES: The student will be based in the Kennedy Institute of Rheumatology taking advantage of 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; Organoid culture systems; biomechanical forces; Human Developmental Biology

KEY PUBLICATIONS (5 maximum):

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.

Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, Savary L, Perlman H, Barone F, McGettrick HM, Fearon DT, Wei K, Raychaudhuri S, Lorsunsky I, Brenner MB, Coles M, Sansom SN, Filer A, Buckley CD, Pathologically distinct fibroblast subsets drive inflammation and tissue damage in arthritis, Nature. 2019 Jun;570(7760):246-251. doi: 10.1038/s41586-019-1263-7

Nayar S, Campos J, Smith CG, Iannizzotto V, Gardner DH, Mourcin F, Roulois D, Turner J, Sylvestre M, Asam S, Glaysher B, Bowman SJ, Fearon DT, Filer A, Tarte K, Luther SA, Fisher BA, Buckley CD, Coles MC, Barone F, Immunofibroblasts are pivotal drivers of tertiary lymphoid structure formation and local pathology. Proc Natl Acad Sci U S A. 2019 Jun 18. pii: 201905301. doi: 10.1073/pnas.1905301116.

Juan-Colás J, Hitchcock IS, Coles M, Johnson S, Krauss TF.Quantifying single-cell secretion in real time using resonant hyperspectral imaging. Proc Natl Acad Sci U S A. 2018 Dec 26;115(52):13204-13209. doi: 10.1073/pnas.1814977115. Epub 2018 Dec 10.

Yang J, Cornelissen F, Papazian N, Reijmers RM, Llorian M, Cupedo T, Coles M, Seddon B. IL-7-dependent maintenance of ILC3s is required for normal entry of lymphocytes into lymph nodes. J Exp Med. 2018 Apr 2;215(4):1069-1077. doi: 10.1084/jem.20170518.

CONTACT INFORMATION OF ALL SUPERVISORS:

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9. Project Title: 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

PROJECT OVERVIEW: (500 words maximum)

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 (5 WORDS): 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 (5 maximum):

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.

Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, Savary L, Perlman H, Barone F, McGettrick HM, Fearon DT, Wei K, Raychaudhuri S, Lorsunsky I, Brenner MB, Coles M, Sansom SN, Filer A, Buckley CD, Pathologically distinct fibroblast subsets drive inflammation and tissue damage in arthritis, Nature. 2019 Jun;570(7760):246-251. doi: 10.1038/s41586-019-1263-7

Nayar S, Campos J, Smith CG, Iannizzotto V, Gardner DH, Mourcin F, Roulois D, Turner J, Sylvestre M, Asam S, Glaysher B, Bowman SJ, Fearon DT, Filer A, Tarte K, Luther SA, Fisher BA, Buckley CD, Coles MC, Barone F, Immunofibroblasts are pivotal drivers of tertiary lymphoid structure formation and local pathology. Proc Natl Acad Sci U S A. 2019 Jun 18. pii: 201905301. doi: 10.1073/pnas.1905301116.

Brown LV, Gaffney EA, Wagg J, Coles MC. An in silico model of cytotoxic T-lymphocyte activation in the lymph node following short peptide vaccination. J R Soc Interface. 2018 Mar;15(140). pii: 20180041. doi: 10.1098/rsif.2018.0041.

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10. Project Title: 'Towards equity in medicine with big health data, epidemiology, and Artificial intelligence'

Supervisor 1: Daniel Prieto-Alhambra

Co-Supervisor/s: Sara Khalid, Laura Coates, Gary Collins, Antonella Delmestri

PROJECT OVERVIEW: (500 words maximum)

The Covid pandemic has highlighted inequalities in health systems around the world. However, inequity is not limited to the pandemic – it is in fact a long-standing and multifaceted issue. In addition to socio-economic complexities, imbalances in healthcare technologies can worsen existing biases.

An example is the artificial intelligence technology behind clinical prediction models. If there are imbalances in the data used to train the models, or if there are algorithm biases within the analytical pipeline, the resulting models can be biased and result in mis-estimation of the health risks of patients in real-time. This in turn can lead to some groups of patients being under- or over-prioritised.

This research will develop prediction models that are based on bias-minimisation guidelines (developed by the Equator Centre UK housed in our department) and that are tailored to specific patient groups, including patients with different ethnic backgrounds, patients with rare conditions and patients with disabilities. By addressing any sources of bias in the data and in the analytical pipelines, prediction models can be made more targeted and equitable.

The project will use routinely collected data from the UK Clinical Practice Research Datalink, Hospital Episode Statistics (HES), and Office of National Statistics, as well as international data representing >500 million patients and 5 billion clinical records from across 5 continents. The project will have access to the OHDSI analytics pipeline (ohdsi.org) for standardized, rapid, and reproducible artificial intelligence.

Patient and public engagement and involvement will be an important element of this research.

KEYWORDS (5 WORDS): Personalised medicine, Big Data, Health Equity, Machine Learning, Observational Research

TRAINING OPPORTUNITIES:

The Botnar Research Centre plays host to the University of Oxford's Institute of Musculoskeletal Sciences and Centre for Statistics in Medicine.

Training will be provided in relevant related research methodology, including the handling and analysis of large health datasets, and advanced statistical and machine learning techniques, as well

as in patient and public engagement for research. Attendance at formal training courses will be encouraged, and will include the "Real world epidemiology" Oxford summer school and the "Big Data and Machine Learning for Healthcare" modules.

In addition, courses from the University's Centre for Teaching and Learning (https://www.ctl.ox.ac.uk/#/), Department of Computer Science (http://www.cs.ox.ac.uk/), and the Medical Science Division Skills Team (https://www.medsci.ox.ac.uk/study/skillstraining) on key skills for the completion of a successful PhD thesis will be available. Additional on-the-field training opportunities will arise, and the supervisors will encourage the student to pursue such opportunities.

Further, the Observational Health Data Sciences and Informatics (https://ohdsi.org/) global community of 300+ researchers will provide training and opportunities for international collaboration stretching beyond the project.

A core curriculum of lectures organized departmentally will be taken in the first term to provide a solid foundation in a broad range of subjects including epidemiology, machine learning, and statistics.

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 research group and to attend external conferences to present their research globally.

KEY PUBLICATIONS (5 maximum):

A. K. Clift *et al.*, "Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study," *BMJ*, vol. 371, p. m3731, Oct. 2020, doi: 10.1136/bmj.m3731.

S. Khalid *et al.*, "A standardized analytics pipeline for reliable and rapid development and validation of prediction models using observational health data," *medRxiv*, 2021.

S. Khalid and D. Prieto-Alhambra, "Machine Learning for Feature Selection and Cluster Analysis in Drug Utilisation Research," *Curr. Epidemiol. Reports*, vol. 6, no. 3, pp. 364–372, 2019.

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G. S. Collins *et al.*, "External validation of multivariable prediction models: a systematic review of methodological conduct and reporting," *BMC Med. Res. Methodol.*, vol. 14, no. 1, pp. 1–11, 2014.

CONTACT INFORMATION OF ALL SUPERVISORS:

Prof Daniel Prieto-Alhambra has published extensively in the field of pharmaco-epidemiology, and is recognised internationally as an authority on use of routine data for musculoskeletal pharmaco- and device epidemiology.

https://www.ndorms.ox.ac.uk/team/daniel-prieto-alhambra

Professor Laura Coates is an Associate Professor and honorary consultant rheumatologist with an interest in outcome measures, clinical trial design and patient and public involvement in research.

https://www.ndorms.ox.ac.uk/team/laura-coates

Dr Sara Khalid is a machine learning lead in the Centre for Statistics in Medicine, Oxford. She has an Oxford DPhil in Engineering Science, and has an excellent track record and experience in the use of big data methods including machine learning and similar methods.

https://www.ndorms.ox.ac.uk/team/sara-khalid

Dr Antonella Delmestri is an international expert in automation of data engineering, data mining and advanced curation of real-world health data routinely collected by doctors in primary and secondary care.

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Prof Gary Collins' research interests are focused on methodological aspects surrounding the development and validation of multivariable prediction models and has published extensively in this area. He is particularly interested in the role that big data and machine learning has in developing and evaluating prediction models.

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11. Project Title: Developing and testing a humanised mouse model of fibrosis

Supervisor 1: Prof Dominic Furniss, NDORMS

Co-Supervisor/s: Prof. Fadi Issa, NDS

PROJECT OVERVIEW: (500 words maximum)

Fibrosis is a final common pathway of disease in many organ system, and chronic fibroproliferative diseases are estimated to be responsible for 45% of all natural deaths in economically developed countries. However, there are no widely available therapeutics that target fibrosis, partly due to a poor understanding of the pathological process across different organs, and crucially a lack of animal models that accurately recapitulate human disease. In particular, there is a complex interaction between fibrotic tissue foci and the immune system that has not been previously modelled.

In this project, the student will use the combined expertise of the supervisory team to develop and test new **humanised** mouse models of two common fibrotic conditions – Dupuytren Disease and Keloid Scarring. There will be an opportunity to be trained in a very wide variety of laboratory techniques, and advanced data analytics.

Organ specific fibroses cause both morbidity and mortality. **Dupuytren disease (DD)** is a progressive fibroproliferative disease of the palmar fascia of the hand affecting 1-5% of adults. It causes flexion contractures of the involved digits, functional impairment and reduced quality of life. **Keloid scarring (KS)** is a fibroproliferative disorder of the skin, characterised by excessive, invasive scar formation after skin injury. It is more common in darkly pigmented skin, and in certain anatomical locations.

The student will develop and characterise a new model of DD and KS, using subcutaneous placement of excised tissue from patients in a humanised immune system (HIS) mice. They will implant a 5mm^3 piece of DD nodule under the under the flank, and harvest the tissue at 1, 3, and 6 weeks (n=3 per timepoint). They will analyse harvested DD tissues for engraftment, looking for vascular ingrowth and cell survival using qPCR and immunofluorescence microscopy from. They will then repeat the time-course using DD tissue and control tissue after re-constituting the immune system of the HIS mice with peripheral blood mononuclear cells (PBMCs) from the donor patient (n=6 disease and control per timepoint). They will determine immune infiltration using lymphocyte (CD3, CD4, CD8, FOXP3, CD19) and monocyte (CD14, CD16) markers by immunohistochemistry as well as examining general tissue architecture. They will use single cell RNA sequencing of the engrafted tissue, comparing it to the tissue processed directly from patients to demonstrate the survival of each of the cellular components of the tissues from the model with and without reconstitution of mice with donor PBMCs. Phenotypic and transcriptomic data will be compared to published datasets of fibrotic disease to determine overlap with human pathology. Further detailed characterisation of the immune cell components of the humanised mouse model and freshly harvested human samples will be undertaken. Finally, they will culture cells from engrafted tissue and perform functional assays, such as comparing cellular contraction, migration assays, and wound healing assays. Establishment

of this model will provide a useful platform for the assessment of anti-fibrotic therapies which may also be possible in the course of this project.

KEYWORDS (5 WORDS): Fibrosis, Humanised Mouse Model, Single Cell Sequencing

TRAINING OPPORTUNITIES:

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. 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. All students are required to attend a 2 - day Statistical and Experimental Design course at NDORMS. The student will attend regular seminars within the department and those relevant in the wider University.

The student will receive training in relevant related research methodologies including cell culture, in vivo techniques (including humanised mouse systems and surgical techniques), immunohistochemistry, molecular techniques, flow cytometry, and the handling and analysis of single cell sequencing datasets, and cross species analysis.

Additional on the job training opportunities will arise, and the supervisors will encourage the student to pursue such opportunities. Attendance at formal training courses will be encouraged. In addition, courses from the Oxford Learning Institute and the Oxford University Computer Sciences on generic skills for scientific research will be available and encouraged. Students will be expected to present data regularly in the departmental PGR seminars, Furniss group meetings, and to attend external conferences to present their research globally.

KEY PUBLICATIONS (5 maximum):

Layton TB, Williams L, McCann F, Zhang M, Fritzsche M, Colin-York H, Cabrita M, Ng MTH, Feldmann M, Sansom SN, Furniss D, Xie W, Nanchahal J. Cellular census of human fibrosis defines functionally distinct stromal cell types and states. *Nat Commun*. 2020 Jun 2;11(1):2768. doi: 10.1038/s41467-020-16264-y.PMID: 32488016

Ng M, Thakkar D, Southam L, Werker P, Ophoff R, Becker K, Nothnagel M, Franke A, Nürnberg P, Espirito-Santo AI, Izadi D, Hennies HC, Nanchahal J, Zeggini E, Furniss D. A Genome-wide Association Study of Dupuytren Disease Reveals 17 Additional Variants Implicated in Fibrosis. *Am J Hum Genet*. 2017 Sep 7;101(3):417-427.

Adigbli G, Hua P, Uchiyama M, Roberts I, Hester J, Watt SM, Issa F. Development of LT-HSC-Reconstituted Non-Irradiated NBSGW Mice for the Study of Human Hematopoiesis In Vivo. *Front Immunol*, 2021. doi: 10.3389.fimmu.2021.642198.

Adigbli G, Menoret S, Cross AR, Hester J, Issa F, Anegon I. Humanization of Immunodeficient Animals for the Modeling of Transplantation, Graft Versus Host Disease, and Regenerative Medicine. *Transplantation*, 2020. doi: 10.1097/TP.0000000000003177.

Allen RJ, Guillen-Guio B, Oldham JM, Ma SF, Dressen A, Paynton ML, Kraven LM, Obeidat M, Li X, Ng M, Braybrooke R, Molina-Molina M, Hobbs BD, Putman RK, Sakornsakolpat P, Booth HL, Fahy WA, Hart SP, Hill MR, Hirani N, Hubbard RB, McAnulty RJ, Millar AB, Navaratnam V, Oballa E,

Parfrey H, Saini G, Whyte MKB, Zhang Y, Kaminski N, Adegunsoye A, Strek ME, Neighbors M, Sheng XR, Gudmundsson G, Gudnason V, Hatabu H, Lederer DJ, Manichaikul A, Newell JD Jr, O'Connor GT, Ortega VE, Xu H, Fingerlin TE, Bossé Y, Hao K, Joubert P, Nickle DC, Sin DD, Timens W, Furniss D, Morris AP, Zondervan K, Hall IP, Sayers I, Tobin MD, Maher TM, Cho MH, Hunninghake GM, Schwartz DA, Yaspan BL, Molyneaux PL, Flores C, Noth I, Jenkins RG, Wain LV. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care* Med. 2019 Nov 11.

CONTACT INFORMATION OF ALL SUPERVISORS:

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Fadi.issa@nds.ox.ac.uk

12. Investigation of DDR2 signalling that promotes synovial cell invasion into cartilage in rheumatoid arthritis

Supervisor 1: Yoshifumi Itoh

Co-Supervisor/s: Chris Buckley; Richard Williams

PROJECT OVERVIEW: (500 words maximum)

A hallmark of rheumatoid arthritis (RA) is the destruction of cartilage and bone by inflamed synovial pannus tissue. The primary cell type that erodes cartilage in RA is synovial fibroblasts (RASF), and we have previously identified the crucial cartilage-eroding proteolytic enzyme, membrane-type 1 matrix metalloproteinase (MT1-MMP), which is highly expressed on the cell surface of RASF (Miller et al., 2009). Inhibition of MT1-MMP completely abolished cartilage invasion of RASF, and selective inhibition of MT1-MMP in a mouse model of arthritis also inhibited cartilage degradation (Kaneko *et al*., 2016).

MT1-MMP is highly expressed in the RASF at the interface between the pannus and cartilage, suggesting that cartilage may stimulate RASF to express MT1-MMP (Miller et al., 2009). We found that a collagen receptor tyrosine kinase, discoidin domain receptor 2 (DDR2), mediates cartilage collagen signal to synovial fibroblasts and upregulates the MT1-MMP gene (Majkowska *et al*., 2017). Interestingly, intact healthy cartilage does not activate the DDR2 signal, and cartilage needs to be partially damaged to activate DDR2 in an efficient manner. These findings suggest that DDR2 acts as a sensor detecting cartilage damage. In addition to MT1-MMP gene upregulation, DDR2 signalling also plays a role in regulating MT1-MMP function. Pharmacological inhibition of DDR2 inhibited MT1-MMP activity in RASF, although MT1-MMP is still expressed (Majkowska *et al*., 2017). These data suggest that the role of DDR2 signalling is not only in MT1-MMP gene upregulation but also modulates other gene expressions to activate synovial cells for tissue destruction.

Recently it was reported that DDR2 contributes to the progression of arthritis by upregulating IL-15 and Dkk-1 in the mouse model of arthritis. A lack of DDR2 and pharmacological inhibition of DDR2 abrogates joint damage in the mouse model of arthritis (Mu *et al*., Arthritis & Rheum, 2020), which supports our hypothesis of a broader role of DDR2 signalling. However, the mechanism of DDR2 signalling to activate synovial fibroblasts needs further understanding, and a systematic approach to unveil the role of DDR2 signalling is required.

This DPhil project aims to reveal the whole picture of DDR2 signalling and its effects that promote synovial cell invasion. To achieve the goal, we have the following four specific aims.

1. Identify the complete set of genes that DDR2 signalling activates in human synovial fibroblasts by RNAseq;

2. Investigate the roles of the identified genes in the synovial invasion;

3. Investigate the mechanism of DDR2 activation by cartilage;

4. Investigate the expression of the identified genes in the human RA and mouse model of arthritis.

Achieving this DPhil project would significantly deepen our understanding of RA disease progression and may identify novel means to prevent cartilage degradation in RA.

KEYWORDS (5 WORDS):

Rheumatoid Arthritis, Cartilage, DDR2, MT1-MMP, invasion

TRAINING OPPORTUNITIES:

The Kennedy Institute is a world-renowned research centre 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.

KEY PUBLICATIONS (5 maximum):

1. Gifford, V., and Itoh, Y. (2019) MT1-MMP-dependent cell migration: proteolytic and non-proteolytic mechanisms. ***Biochem Soc Trans***, 47 (3), 811-826

2. Itoh, Y. (2018) Discoidin domain receptors: Microenvironment sensors that promote cellular migration and invasion. ***Cell Adh Migr***. 12 (4), 378-385

3. Majkowska I, Shitomi Y, Ito N, Gray NS, Itoh Y (2017) Discoidin Domain Receptor 2 Mediates Collagen-Induced Activation of Membrane-Type 1 Matrix Metalloproteinase in Human Fibroblasts. *J Biol Chem*, 292(16):6633-6643

4. Kaneko K, Williams RO, Dransfield DT, Nixon AE, Sandison A and Itoh Y (2016) Selective inhibition of membrane-type 1 matrix metalloproteinase abrogates progression of inflammatory arthritis: synergy with TNF blockade. *Arthritis Rheum* 68 (2), 521-531

5. Miller MC, Manning HB, Jain A, Troeberg L, Dudhia J, Essex D, Sandison A, Seiki M, Nanchahal J, Nagase H, Itoh Y (2009) Membrane type 1 matrix metalloproteinase is a crucial promoter of synovial invasion in human rheumatoid arthritis. *Arthritis Rheum* 60(3)**:** 686-697

CONTACT INFORMATION OF ALL SUPERVISORS:

Y. Itoh: yoshi.itoh@kennedy.ox.ac.uk

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R. Williams: richard.williams@kennedy.ox.ac.uk

13. Project Title: Characterizing the ageing phenotype of fibroblast populations in the synovium of RA and OA patients.

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. These conditions have a very high medico-economic cost. Considerable advances in targeted therapy have improved outcomes in RA, yet a notable percentage of affected individuals still experience persistent inflammation and progressive disability, while for OA there is no effective therapy. Recent results demonstrate that resident cells of synovium, known as fibroblast-like synoviocytes (FLS), are not passive bystanders, but actively contribute to the inflammation and degradative processes in RA and OA. Different synovial fibroblast (SF) populations play key roles in mediating inflammation and bone/cartilage destruction. However, little is known about the molecular mechanisms that drive the different fibroblast behaviors observed in RA and OA; specifically, the enrichment of sublining, proinflammatory fibroblasts in RA compared to the enrichment of lining layer pro-destructive fibroblasts in OA. Differences in the cellular makeup of the synovium between RA and OA could be explained by differential ageing phenotype and senescence of SF subsets. Many studies report the negative effect of cellular senescence in SFs and chondrocytes in OA, yet the therapeutic induction of senescence in RA appears to reduce the activation of inflammatory SFs. This project will examine the role of age-related cellular senescence in determining the cellular structure of the synovium. We will use our combined expertise in fibroblast and ageing biology to test the hypothesis that ***differential senescence in synovial lining layer fibroblast subsets compared to sub-lining subsets underpins the degree of inflammation vs tissue damage between RA and OA.***

PROJECT AIMS:

This PhD studentship has three aims:

Aim1: Molecular characterisation of a panel of the ageing hallmark markers in synovial fibroblast lining and sub-lining layer fibroblast subsets in sex-matched patients across ages in OA and RA using different omics approaches.

Aim 2: Establish the anatomical localization of ageing fibroblast subsets in human OA and RA fibroblast synovium compared to inflammatory arthritis (CIA) and destabilisation of the medial meniscus (DMM) synovium using CellDive and RNA scope analysis to measure the ageing hallmark on transcript levels in parallel with the protein levels

Aim 3: Bioinformatic analysis of the relationship between the ageing hallmarks in the lining and sub-lining fibroblasts in human fibroblast subsets compared to subsets analyzed from established mouse models of inflammatory arthritis (CIA) and degenerative arthritis, the destabilization of the medial meniscus (DMM)

KEYWORDS (5 WORDS): 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).

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14. Project Title: 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: (500 words maximum)

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.

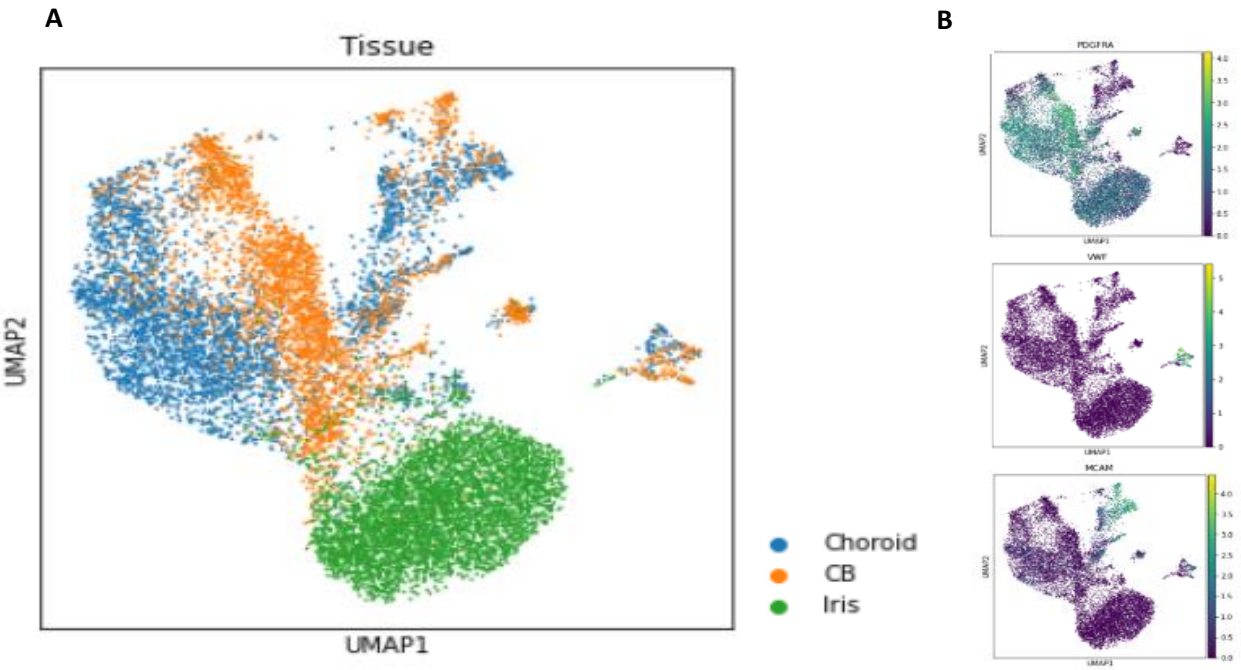

Figure 1. Single Cell RNA sequencing data demonstrates that fibroblasts of the iris (green) group separately to those of the ciliary body (orange) and choroid (blue) on single cell RNA sequencing.

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).

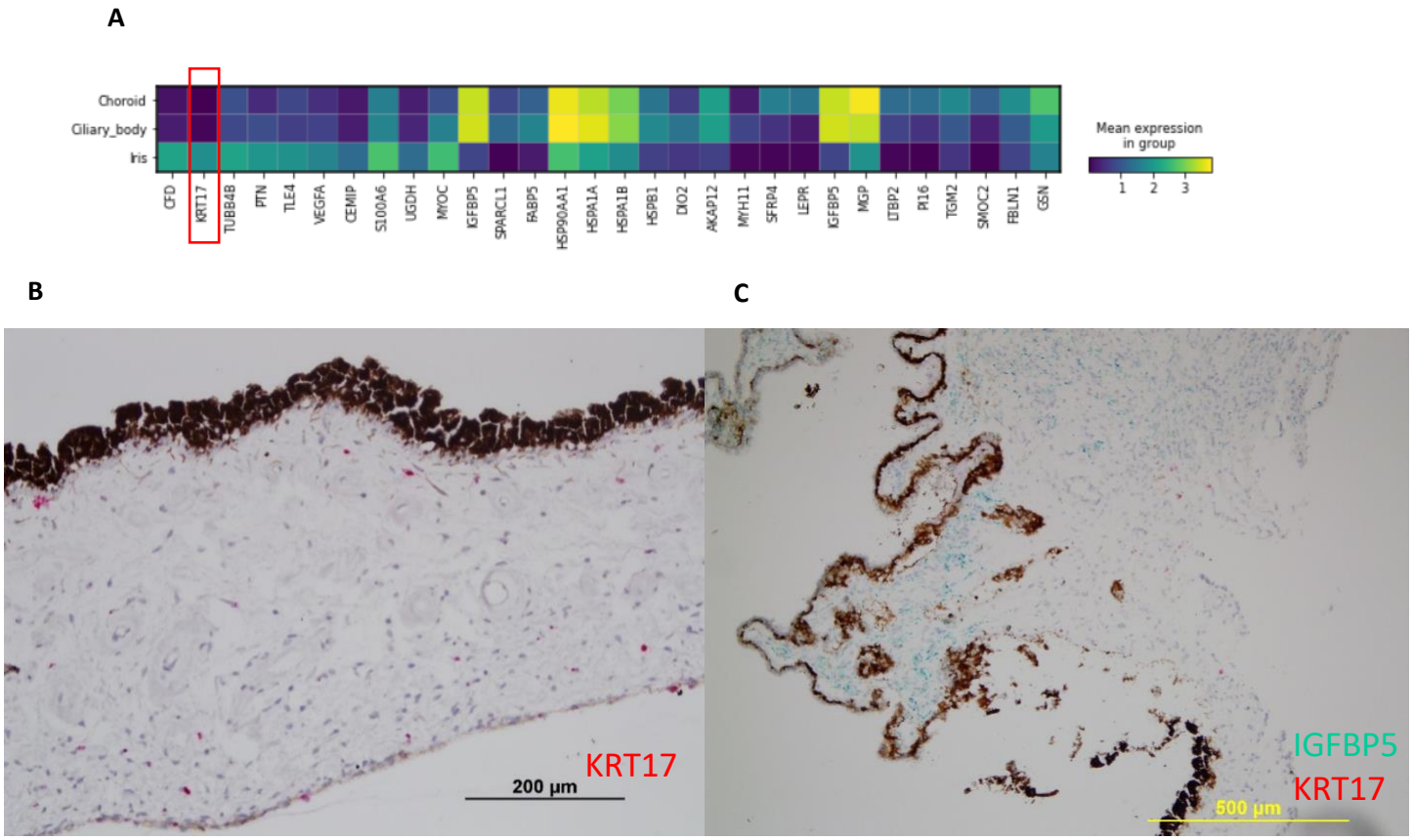

Figure 2. Kertain-17 expression is localised to the human iris.

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 (5 WORDS):

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 (5 maximum):

1. ET, E.C. and M. Zierhut, 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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15. Project Title: A cellular atlas of the human hip to understand the relationship between femeroacetabular impingement and hip osteoarthritis

Supervisors: Associate Professor Sarah Snelling, Associate Professor Adam Cribbs, Associate Professor Philippa Hulley, Dr Mat Baldwin. External Supervisor Mr Vikas Khanduja (Cambridge)

PROJECT OVERVIEW: (500 words maximum)

You will develop, optimise and deliver ancestrally diverse cellular maps of adult femoral bone, both in the laboratory and computationally. This project will be embedded within a partnership between the Human Cell Atlas and Chan Zuckerberg Initiative that utilise next generation transcriptomic sequencing to produce cellular maps of musculoskeletal tissues. A key aim of this partnership is to ensure cellular maps address important clinical questions and are globally relevant. To this end, the PhD student will work with teams at seven international clinical sites.

Bone is the major tissue of our musculoskeletal system and is commonly affected by femeroacetabular impingement (FAI) which leads to hip osteoarthritis (OA). Osteoarthritis (OA) is a major cause of loss of quality of life globally, with the hip particularly prone to disease. In FAI, additional bone growth occurs on the femoral neck - preventing smooth movement and causing pain. Hip OA itself is characterised by further bony changes ,including sclerosis, bone growth (osteophytes) and cystic change, alongside loss of cartilage. However, treatments for both femoroacetabular impingement (FAI) and hip OA are limited, partly due to a lack of understanding of the abnormal bone biology that occur in these conditions, alongside a paucity of data on the cellular composition of healthy bone of the hip joint.

The recruited student will build reference datasets of healthy bone, compare this to pathological conditions including FAI and OA to build understanding of disease mechanism(s) and identify treatment targets. As part of this DPhil you will process bone samples collected from the clinical team and generate libraries within the laboratory, carry out imaging validation and computationally analyse your data. You will work as part of a dynamic team of clinicians, engineers, computational biologists, epidemiologists, and biologists, who will provide an exciting range of training opportunities.

The outline for the DPhil will include:

1. Development of robust methods for single cell resolution analysis of femoral. You will compare and contrast single cell and single-nuclei ATACseq to improve cellular annotation.
2. Deliver an ancestrally diverse and temporal atlas of healthy human bone. You will use optimised methods to generate a single-cell resolution atlas of healthy bone collected by our clinical collaborators, will annotate these maps to identify cell

subsets that change with ageing and use spatial methods (e.g. CellDive imaging) to validate subsets and derive their locations.

3. Identify potential cellular drivers of FAI and hip OA at the bone level. You will use optimised methods to develop single cell atlases of FAI and hip OA and compare these to healthy reference datasets to identify potential cell subsets or pathways that may drive disease. Using in-house *in vitro* models, you will assess the importance of these identified subsets in driving pathological changes.

TRAINING OPPORTUNITIES

Alongside departmental training opportunities listed below we will ensure hands-on computational training to support analysis of single-cell RNAseq data. Embedding within our international Tendon Seed Network and Ancestrally Inclusive Musculoskeletal Network will also ensure laboratory guidance and support. Human primary bone organoid models containing functional sclerostin secreting osteocytes are available. A student would be supported to shadow relevant clinical work and to attend clinical and basic science conferences to enrich their studies –financial support is available for travel to conferences.

NDORMS hosts Oxford's Institute of Musculoskeletal Sciences, a centre for experimental medicine, the Kennedy Insititue of Rheumatology and a specialist trauma research unit. This enables and encourages research and education into the causes of musculoskeletal disease and their treatment.

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. All students are also required to attend a 2-day Statistical and Experimental Design course at NDORMS.Students will also be required to attend regular seminars within the Department and have access to a variety of other courses run by the Medical Sciences Division Skills Training Team https://www.medsci.ox.ac.uk/study/skillstraining and the wider University.

Finally,the student(s) will be expected to regularly present data in Departmental seminars, the Soft Tissue Repair group and within our linked goups internally and externally.

KEY PUBLICATIONS:

- Ramos-Mucci L, Sarmiento P, Little D, Snelling S (2022). Research perspectives-Pipelines to human tendon transcriptomics. *J Orthop Res*. doi: 10.1002/jor.25315
- Baldwin, M.J., Cribbs, A.P., Guilak, F. *et al.* Mapping the musculoskeletal system one cell at a time. *Nat Rev Rheumatol* 17, 247–248 (2021). https://doi.org/10.1038/s41584-021-00600-7
- Naoki Nakano & Vikas Khanduja (2018) Femoroacetabular impingement: the past, current controversies and future perspectives, The Physician and Sportsmedicine, 46:3, 270-272, DOI: https://doi.org/10.1080/00913847.2018.1478151

KEYWORDS (5 WORDS MAXIMUM): Genomics, osteoarthritis, hip, sequencing, therapeutics

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16. Project Title: Spatial exploration of hypoxic signalling and inflammation in chronic hepatitis B.

Supervisor 1: Jane McKeating

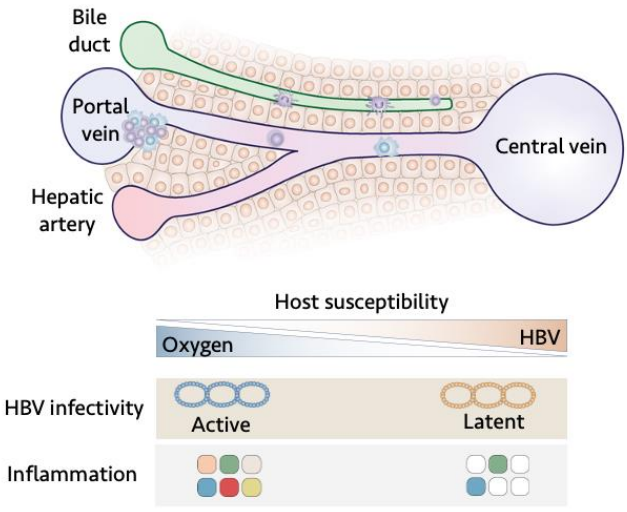
Co-Supervisor: Fadi Issa

PROJECT OVERVIEW:

Our research group is interested in the cellular basis of early infection events that define virus tropism and how this knowledge translates into new anti-viral strategies. We want to address the fundamental question of '**how, when and where viruses replicate'** and to understand how they evade immune recognition. Viruses are intracellular pathogens and understanding the host pathways that define susceptibility to infection and disease are essential for the design of new therapies. Viral replication is shaped by the cellular microenvironment and one key factor is local oxygen tension, where hypoxia regulates the transcription of genes involved in metabolism and inflammatory responses.

Hepatitis B virus (HBV) is a global health challenge and major cause of liver disease and cancer. Chronic hepatitis B is an inflammatory disease that reflects a dynamic interaction between the virus and host immune system. The liver is a naturally hypoxic organ and our recent studies identify a role for hypoxia inducible factors (HIFs) to activate HBV transcription. Hypoxia can also suppress anti-viral cellular immunity by recruiting regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) to low oxygen areas of the liver, thereby providing an environment for viral persistence. Understanding the pathways that define host susceptibility to viral mediated inflammation is the 'holy grail' of this field.

This DPhil will use Digital Spatial transcriptional Profiling (DSP) to identify immune cell populations and infected hepatocytes at the whole transcriptome level in liver biopsies. We will focus on immunosuppressive Tregs and assess whether hypoxic gene signatures impact on cell frequency, location and activation status. Nearest neighbour analysis will examine these cellular interactions at the micro-anatomic level. Staining liver sections for HBV RNAs will enable us to identify immune cells with intracellular viral nucleic acids.



For example, liver resident macrophages or Kupffer cells may scavenge HBV and identifying their sub-cellular localisation will uncover new aspects of immune surveillance. Key genes and immune cell types that associate with HBV replication parameters in the tissue will be validated using *in vitro* viral replication model systems. Pharmacological inhibitors of HIF signalling will define the mechanism underlying the hypoxic control of immune cell activity and virus regulation. The DPhil student will apply these exciting technologies allow us to study virus-host interplay at the single cell level in unprecedented detail. Collectively, this project will test our hypothesis that localised hypoxia regulates the accumulation and function of key effectors such as tissue resident memory T cells and localised suppressor mechanisms, providing new therapeutic insights.

KEYWORDS: Spatial, hepatitis, Inflammation, hypoxia, virus

TRAINING OPPORTUNITIES: The student will join a dynamic and lively team of biologists funded by a prestigious Wellcome Discovery Award that will provide a unique training environment to gain expertise in super resolution imaging techniques to visualize viral RNAs in complex tissues, digital spatial profiling and bio-informatic analysis of inflammatory transcriptomic data sets. Transferable skills include oral presentations at joint lab meetings, critical review of published scientific literature by contributing to journal clubs and scientific writing by reviewing and drafting manuscripts for publication. The student will work in Nuffield Department of Medicine Research Building and Department of Surgical Sciences (John Radcliffe Hospital, Oxford) and will have the opportunity to interface with a network of collaborators in Oxford, UK and internationally to translate their data to the wider biomedical community.

KEY PUBLICATIONS:

Wing PAC *et al*. Hypoxia inducible factors regulate hepatitis B virus replication by activating the basal core promoter. J Hepatol. 2021 Jul;75(1):64-73. doi: 10.1016/j.jhep.2020.12.034.

Wing PAC *et al.* Hypoxic and pharmacological activation of HIF inhibits SARS-CoV-2 infection of lung epithelial cells. Cell Rep. 2021 Apr 20;35(3):109020. doi:10.1016/j.celrep.2021.109020.

Wing PAC *et al*. Hypoxia inducible factors regulate infectious SARS-CoV-2, epithelial damage and respiratory symptoms in a hamster COVID-19 model. PLoS Pathog. 2022 Sep 6;18(9):e1010807. doi: 10.1371/journal.ppat.1010807.

Cross AR *et al*. Spatial transcriptomocs characterization of COVID-19 pneumonitis identifies immune circuits related to tissue injury. JCI Insights 2022, *in press.*

Bottomley MJ *et al*. Dampened Inflammatory Signalling and Myeloid-Derived Suppressor-Like Cell Accumulation Reduces Circulating Monocytic HLA-DR Density and May Associate With Malignancy Risk in Long-Term Renal transplant patients. Front Immunol 2022 Jul 1;13:901273.doi: 10.3389/fimmu

CONTACT INFORMATION OF SUPERVISORS:

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17. Project Title: Establishing the Insulin-like growth factor 1 (IGF-1) axis as a therapeutic target in carpal tunnel syndrome and trigger finger

Supervisor 1: Prof Dominic Furniss, NDORMS

Co-Supervisor/s: Prof Tonia Vincent, NDORMS; Prof Valentine Macaulay, NDS; Mr Akira Wiberg, NDORMS

PROJECT OVERVIEW: (500 words maximum)

Carpal tunnel syndrome (CTS) is a very common and disabling condition of the hand caused by compression of the median nerve as it travels through a bony tunnel in the wrist. It affects up to 10% of the population, and carpal tunnel decompression surgery is the most commonly performed elective hand operation worldwide. However, up to 25% of patients do not improve, or develop recurrent symptoms following surgery.

CTS is a typical complex disease, where genetic and non-genetic factors interact to affect overall phenotypic expression. We previously performed the first ever genome-wide association study (GWAS) of CTS, and identified 16 loci in the genome significantly associated with the disease, discovering a biologically plausible set of genes that contribute to CTS pathophysiology. In a subsequent study, we identified the Insulin-like growth factor 1 (IGF-1) axis as a driver of CTS pathophysiology. Our hypothesis is that overactivity of the IGF-1 pathway leads to fibrosis and proliferation of the sub-synovial connective tissues (SSCT), which are the connective tissues that surround the median nerve and the flexor tendons within the carpal tunnel. This fibrosis, in turn, causes tethering of the median nerve to surrounding structures, leading to nerve ischaemia and eventually nerve degeneration.

There are currently no effective drug treatments for CTS. The overarching aim of this DPhil project is to determine whether drugs that target the IGF-1 axis can be used in the treatment of CTS. Demonstrating, in vitro, that IGF-1 downregulation in the SSCT can reduce this tissue's propensity towards proliferation and fibrosis will demonstrate the proof-of-principle that the IGF-1 axis may be a viable therapeutic target in CTS patients.

In this project, the student will use the combined expertise of the supervisory team to
(i) Characterise the cellular and connective tissue microenvironment of the median nerve within the carpal tunnel using a combination of single-cell RNA sequencing and advanced imaging techniques.
(ii) Characterise where the IGF-1 receptor and its binding proteins are expressed within the SSCT.
(iii) Compare the expression of these genes and proteins between SSCT resected from CTS patients and healthy controls.
(iv) Study the functional effects of up- and down-regulation (using small molecule

inhibitors/monoclonal antibodies) of the IGF-1 pathway on cultured fibroblasts derived from the SSCT.

The student will be trained in a broad spectrum of experimental techniques, including (but not limited to) single-cell RNA sequencing, bulk-RNA sequencing, genotyping and qPCR, Western blotting, cell culture, confocal microscopy, and immunohistochemistry. There will also be training in advanced data analytics for processing and analysing the transcriptomic data. Furthermore, the student will gain valuable experience of a study involving human participants, including gaining a good grounding in research ethics, obtaining informed consent from participants, and collecting, processing and storing human tissues in accordance with the Human Tissue Act.

This is an exciting project that spans the translational medicine pipeline, and builds on existing collaborations between plastic surgeons, rheumatologists, and laboratory scientists. It is hoped that characterising and establishing the IGF-1 axis as a viable therapeutic target in the SSCT will form the foundations of a future experimental medicine human trial of anti-IGF-1 therapies in CTS patients.

KEYWORDS (5 WORDS): IGF-1, Single Cell Sequencing, Transcriptomics, Carpal Tunnel Syndrome, Nerve Injury

TRAINING OPPORTUNITIES:

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. The student will also be partly based in the modern building and laboratories of the Kennedy Institute of Rheumatology, a world-leading centre in the fields of cytokine biology and inflammation, with a strong emphasis on clinical translation.

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. All students are required to attend a two-day Statistical and Experimental Design course at NDORMS. The student will attend regular seminars within the department and those relevant in the wider University.

The student will receive training in relevant related research methodologies including cell culture, immunohistochemistry, molecular techniques, flow cytometry, and the handling and analysis of single cell sequencing datasets.

Additional on-the-job training opportunities will arise, and the supervisors will encourage the student to pursue such opportunities. Attendance at formal training courses will be encouraged. In addition, courses from the Oxford Learning Institute and the Oxford University Computer Sciences on generic skills for scientific research will be available and encouraged. Students will be expected to present data regularly in the departmental PGR seminars, Furniss and Vincent group meetings, and to attend external conferences to present their research globally.

KEY PUBLICATIONS (5 maximum):

1. Shared genetic susceptibility between trigger finger and carpal tunnel syndrome: a genome-wide association study. Patel B, Kleeman SO, Neavin D, Powell J, Baskozos G, Ng M, Ahmed WU, Bennett DL, Schmid AB, Furniss D, Wiberg A. Lancet Rheumatol. 2022 Aug;4(8):e556-e565. doi: 10.1016/S2665-9913(22)00180-1.PMID: 36043126

2. A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. Wiberg A, Ng M, Schmid AB, Smillie RW, Baskozos G, Holmes MV, Künnapuu K, Mägi R, Bennett DL, Furniss D. Nat Commun. 2019 Mar 4;10(1):1030. doi: 10.1038/s41467-019-08993-6.PMID: 30833571

3. Therapeutic Targeting of the IGF Axis. Osher E, Macaulay VM. Cells. 2019 Aug 14;8(8):895. doi: 10.3390/cells8080895.PMID: 31416218

4. Variants in *ALDH1A2* reveal an anti-inflammatory role for retinoic acid and a new class of disease-modifying drugs in osteoarthritis Zhu L, Kamalathevan P, Koneva L, Zarebska J, Chanalaris A, Ismail H, Wiberg A, Ng M, Muhammed H, Watt F, The Oxford Hand Surgical Team[4], Sansom S, Furniss D, Gardiner M, Vincent T. bioRxiv 3/11/2021. doi: https://doi.org/10.1101/2021.09.10.457848 (in revision)

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18. Matrix architecture in the perivascular niche: a master regulator of lymphocyte infiltration in inflammatory disease?

Supervisor 1: Prof Kim Midwood

Co-supervisors: Prof Dame Fiona Powrie, Dr Shirish Dubey, Mr. Jean-Baptiste Richard

Project overview: (500 words maximum)

Rheumatoid arthritis (RA) is an autoimmune disease of poorly understood aetiology, primarily characterised by inflammation and swelling of the joints, and which can lead to loss of function and disability (1). Under pathological conditions both the architecture and cellular landscape of the synovium, the primary site of RA inflammation, are significantly altered (2,3). The ingress and accumulation of lymphocytic cell subsets is a key feature of the histopathology of inflammatory arthritides and plays a crucial role in the establishment of a tissue-specific chronic inflammatory milieu (4). The primary focus of the Midwood group is on extracellular matrix (ECM) immunology in disease settings. While the ECM was long thought of as simply an inert scaffold in which cells are embedded, it is now evident that it plays key roles in defining tissue properties, cell spatial organisation and functional polarisation. ECM compositional biases are associated with growth, metastatic potential, and treatment refraction in cancer (5), and matrix dysregulation is also emerging as a key driver of inflammatory conditions, including RA (6,7).

Work focusing on elucidating the spatial and temporal dynamics of the poorly characterised ECM of the inflamed arthritic synovium reveals two distinct classes of matrix architecture that define blood and lymphatic vasculature respectively. This perivascular organization is conserved in different synovial diseases, and matrix composition in this niche significantly correlates with tissue lymphocyte levels in arthritis patient synovial biopsy sections. This project will investigate the hypothesis that the vascular architecture plays a key role in bidirectional lymphocytic trafficking in and out of inflamed tissues.

In this project, the DPhil student will assess whether type I and type II perivascular architecture is specific to the synovium, or a universal feature of blood and lymphatic vessels across human pathology, including inflammatory bowel disease, fibrotic diseases, and tumours. We will characterise the cellular landscape within each type of perivascular niche using multiplexed immunofluorescence to delineate cell lineage, phenotype and activation status, and spatial transcriptomics to uncover transcriptional conversations between niche-specific endothelial- or lymphatic-lymphocytic interaction networks. Analysis of T cell migration in vitro using artificial basement membrane constructs to recapitulate type I and II vasculature will provide a tractable model for gene expression

and pathway validation and to understand the mechanisms by which matrix composition controls lymphocyte trafficking.

Keywords: ECM, inflammation, arthritis, lymphocyte infiltration, omics

Training opportunities: Spatial transcriptomics and proteomics, multiplexed tissue imaging, bioinformatic analysis of omics data from published and generated datasets, developing expertise in *in vivo* and *in vitro* models of inflammation, expert understanding of links between tissue microenvironment and inflammation, presenting and networking in high profile academic settings.

Key publications:

1. Gulati M, Farah Z, Mouyis M. Clinical features of rheumatoid arthritis. Medicine. 2018 Apr 1;46(4):211–5.

2. Zhang F, Wei K, Slowikowski K, Fonseka CY, Rao DA, Kelly S, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. Nat Immunol. 2019 Jul;20(7):928–42.

3. Kurowska-Stolarska M, Alivernini S. Synovial tissue macrophages in joint homeostasis, rheumatoid arthritis and disease remission. Nat Rev Rheumatol. 2022 Jul;18(7):384–97.

4. Zhang F, Jonsson AH, Nathan A, Wei K, Millard N, Xiao Q, et al. Cellular deconstruction of inflamed synovium defines diverse inflammatory phenotypes in rheumatoid arthritis. bioRxiv; 2022. p. 2022.02.25.481990.

5. Henke E, Nandigama R, Ergün S. Extracellular Matrix in the Tumor Microenvironment and Its Impact on Cancer Therapy. Frontiers in Molecular Biosciences. 2020;6.

6. Friedrich M, Pohin M, Jackson MA, Korsunsky I, Bullers SJ, Rue-Albrecht K, et al. IL-1-driven stromal–neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies. Nat Med. 2021 Nov;27(11):1970–81.

7. Aungier SR, Cartwright AJ, Schwenzer A, Marshall JL, Dyson MR, Slavny P, et al. Targeting early changes in the synovial microenvironment: a new class of immunomodulatory therapy? Ann Rheum Dis. 2019 Feb;78(2):186–91.

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Dr Shirish Dubey - Shirish.Dubey@ouh.nhs.uk
Jean-Baptiste Richard email – jean-baptiste.richard@new.ox.ac.uk

19. The dark side of hypoferremia: does iron deficiency disable innate immunity in humans?

Supervisor 1: Associate Prof James Fullerton

Co-Supervisor/s: Prof Hal Drakesmith

PROJECT OVERVIEW: (500 words maximum)

During infection iron is sequestered from plasma via the regulatory hormone hepcidin. Classically, this is a beneficial 'nutritional immune' mechanism that protects against extracellular siderophilic bacterial pathogens. However, it is now recognised there is a 'dark side' to hypoferremia. Prolonged reduction in serum iron not only reduces erythropoiesis, causing the anaemia of chronic disease, but additionally impacts on leukocyte function.

Observational studies in individuals with hypoferremia have repeatedly highlighted functional deficits in both the innate and adaptive immune systems with consequent susceptibility to infection and impairment of responses to immunisation. Furthermore, individuals possessing mutations in the TFRC gene that encodes transferrin receptors experience a severe combined immune deficiency, with recurrent infection, neutropenia and hypogammaglobulinaemia.

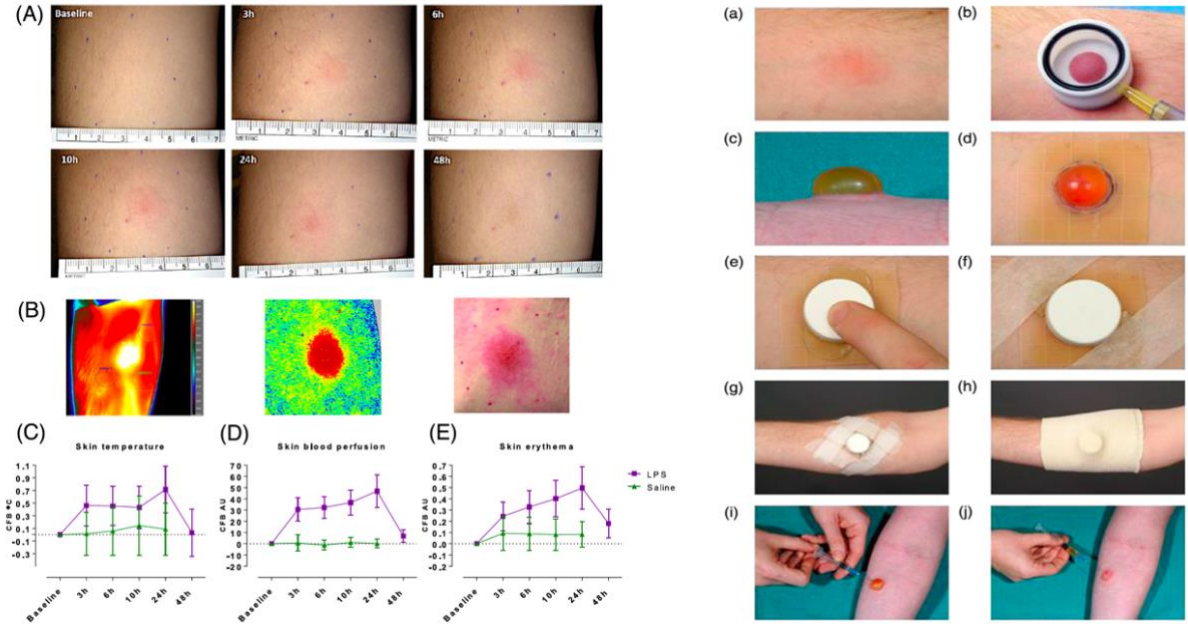
Recent work in the Drakesmith lab (see Frost et al 2022) has dissected the pivotal role of serum iron in neutrophil production and function. Experimentally induced hypoferremia in mice caused a specific reduction in both baseline and inflammation-induced granulopoesis, highlighting sensitivity to iron availability. Those neutrophils that were released displayed reduced reactive oxygen species generation, impaired phagocytosis of Gram positive and negative organisms, attenuated cytokine release, altered NETosis and reduced bacterial killing: all consistent with clinical susceptibility to infection and immunopathology. This data supports hypoferremia as a key and, most importantly, clinically modifiable modulator of innate immune function.

In this project we seek to translate this work using human experimental challenge paradigms. Self-reported healthy volunteers (18-40) will have their iron status screened for occult iron deficiency (ID) and cohorts of those with confirmed ID (transferrin saturation [TSAT] <10%), borderline ID (TSAT 10-20%) and normal iron status (TSAT >20%) recruited. *Ex-vivo* functional assays using granulocytes and peripheral blood mononuclear cells (PBMC) obtained from blood will be performed to explore specific neutrophil, monocyte and lymphocyte functional deficits between groups. Recapitulation of observed deficits in those with hypoferremia *in vitro* via deprivation of iron to effector cells will be evaluated, as will therapeutic rescue with replenishment.

The three groups will subsequently be challenged with intradermal injection (ID) of lipopolysaccharide (LPS, see Buters et al 2022 and Figure) to elicit a transient local inflammatory response in the skin, akin to cellulitis. The clinical response will be quantified via multispectral imaging (erythema, oedema) and laser Doppler (vascular reactivity) prior to formation and aspiration of a blister over the site (via negative pressure, see Figure) at

multiple time points (24h, 48h, D7). Flow cytometric and transcriptomic analysis of the cellular component alongside elucidation of the humoral cytokine profile will determine if functional deficits observed *in vitro* are replicated *in vivo*. Within subject repetition of the challenge in those with ID post therapeutic replacement will enable incontrovertible proof of the link between iron status and innate immune deficiency.

This novel work is expected to have significant impact, not only on our understanding of how iron mechanistically regulates protection from infection in the common contexts of iron deficiency and inflammatory disease in humans, but on the management of the circa ~1.5 billion individuals worldwide who are ID.



Left Panel (Buters et al 202, DOI: 10.1111/bcp.149992: Timecourse of intradermal (ID) LPS injection. Right Panel (Akbar et al 2013, DOI: 10.1111/cei.12107): Formation and aspiration of aspiration of a suction blister over an ID challenge

KEYWORDS (5 WORDS): Iron; inflammation; experimental medicine; neutrophils; innate immunity

TRAINING OPPORTUNITIES:

The successful student will train in a truly translational environment, being mentored by an experienced supervisory team with complementary interdisciplinary skills in human and mouse immunology, experimental medicine and clinical pharmacology and therapeutics.

Placement in the Oxford Centre for Clinical Therapeutics (OCCT, Fullerton) will afford full exposure to the design, initiation and conduct of early phase clinical trials. In addition, via working alongside exisiting clinical and non-clinical post docs and DPhil students, the accrual of a unique skillset in both the practical conduct of human challenge studies and their interpretation will be facillitated. Studies will principally be conducted in the new NIHR Experimental Medicine Clinical Research Facility (https://www.ndorms.ox.ac.uk/oxford-emcrf) with access to laboratories at the Botnar Research Centre and Kennedy Institute of

Rheumatology for sample processing. The student will additionally be expected to participate in and contribute to OCCT meetings and events where the evaluation of new and exisiting medicinal compounds are discussed, shaping their therapeutic development.

Through the MRC Human Immunology Unit (Drakesmith) the student will be trained in standard immunological techniques for evaluating the systemic and localised immune responses, including the functional assessment of innate immune responses (e.g. neutrophil chemotaxis, phagocytosis and reactive burst). To complement these, flow and mass cytometry, imaging, bioinformatics and 'omics approaches, will be employed to quantify and qualitatively describe the immunological response, linking *in vitro* and *ex vivo* observations to those made *in vivo*.

Oxford graduate training additionally includes core workshops, seminars, career events and online resources to enable the development of intellectual and technical research capabilities, capacity for independent and team-work, and skills to effectively communicate research to the broader scientific community and general public.

We encourage anyone interested in applying to make contact with us.

KEY PUBLICATIONS (5 maximum):

Frost et al, Plasma iron controls neutrophil production and function. Science Advances, 2022. https://doi.org/10.1126/sciadv.abq5384

Bonnadonna et al, Iron regulatory protein (IRP)–mediated iron homeostasis is critical for neutrophil development and differentiation in the bone marrow. Science Advances, 2022. https://doi.org/10.1126/sciadv.abq4469

Buters et al, Intradermal lipopolysaccharide challenge as an acute in vivo inflammatory model in healthy volunteers. Br J of Clinical Pharmacology, 2022 https://doi.org/10.1111/bcp.14999

Frost et al, Hepcidin-Mediated Hypoferremia Disrupts Immune Responses to Vaccination and Infection. Med, 2020. https://doi.org/10.1016/j.medj.2020.10.004

Maini et al, A Comparison of Human Neutrophils Acquired from Four Experimental Models of Inflammation. PLoS One, 2016**.** https://doi.org/10.1371/journal.pone.0165502

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20. A clinically-relevant musculoskeletal humanoid shoulder for studying joint instabilities and diseases

Supervisors: Pierre-Alexis Mouthuy, Julie Stebbins, Steve Gwilym

PROJECT OVERVIEW: (500 words maximum)

Shoulder dislocations are events which most typically affect younger adults, although can occur in people of all ages. Dislocations occur in those with predispositions due to joint hypermobility ('born loose") and in those who sustain a significant traumatic event ("torn loose"). When a dislocation occurs there is usually damage sustained to the glenoid cartilage, labro-capusular structures, and humeral bone. They can predispose to future instability and osteoarthritis (OA). Treatments currently aim to repair torn labro-capsular structures, but no treatments currently exist to address the cartilage or bone damage on the glenoid or humerus.

Tissue engineering is a promising repair strategy that involves the development of bioreactors that generate tendon tissue *in vitro* using the patient's cells, scaffolds and mechanical stimulation. Current bioreactors mostly provide uniaxial cyclic loadings, while evidence suggests that they should provide multiaxial stresses, similar to those found physiologically. In this context, we have recently developed a unique bioreactor system that uses a musculoskeletal (MSK) humanoid robotic arm to mimic the motion and forces observed at the human shoulder joint and actuate cell-materials samples (EPSRC-funded Humanoid Bioreactor project, EP/S003509/1; see references below).

MSK humanoids aim to replicate the inner structures and the biomechanics of the human body using string actuators. They have seen major developments in recent years but have not been originally designed for biomedical applications and therefore need improvement. For instance, MSK humanoid shoulders offer a limited range of motion, in part due to the poor design of the joint capsule and the fact that the scapula has not been replicated. Mimicking more closely the human shoulder's biomechanics and anatomy would be greatly beneficial to our investigation of the potential of these robotic systems for biomedical applications. Besides its use for tissue engineering application, the novel joint bioreactor could lead to an improved *in vitro* tissue culture platform for studing joint disease such as OA and for testing implants.

This PhD project will focus on the development of a clinically relevant shoulder model combine with a bioreactor chamber suitable for the study of shoulder joint disease. The main goals of the project are as follow:

1) Designing a suitable joint capsule that also acts as a bioreactor chamber by taking into account the anatomy and biomechanics of the human shoulder.

2) Evaluate the performances (range of motions and forces) of the novel biomimetic robotic shoulder through a motion study and compare them to the human shoulder and the original (unmodified) robotic shoulder.
3) Identify and characterise an existing biphasic biomaterial for bone and cartilage growth (osteochondral scaffold) that can be positioned in the glenoid cavity
4) Demonstrate the potential of the novel robotic bioreactor shoulder for studying shoulder instability and OA in the presence of healthy or diseased human cells and under clinically relevant mechanical stimulation
5) Characterise the cell-scaffold contructs through viability assays, mechanical testing, histology, gene expression analysis, confocal microscopy, scanning electron microscopy, etc.

This is a highly multidisciplinary project that involves various aspects of tissue engineering and biomechanics. Although a clear end medical application is proposed here, a much wider range of biomedical applications might benefit from this work, including implant testing and mechanotransduction studies.

KEYWORDS (5 WORDS): humanoid robots, motion studies, bioreactors, shoulder joint disease, biomaterials

TRAINING OPPORTUNITIES:

The student will be able to learn about the hardware and software involved in the MSK robotic platform developed by Devanthro.They will be able to participate to relevant workshops such as biomechanics (3D motion capture techniques and motion analysis), CAD design and 3D printing. They will be trained for basic biological and physical assays for tissue construct and material characterisation.

The student will be encouraged to take skill training modules offered by the Medical Science Division (www.medsci.ox.ac.uk/study/skillstraining) and the university. These include topics such as how to meet the standards of excellent research, how to safely use research equipment and how to work effectively in their research environment. As part of their continuous learning and training, the student will contribute to regular group meetings and departmental seminars through presentations and research discussions. They will also participate in other events typically attended by the host groups such as conferences and outreach events (e.g. open days).

Further expertise in biomechanics, tissue engineering and solid-fluid mechanics will be accessible through the network of experts collaborating on the Humanoid Bioreactor project (across NDORMS, Engineering Science and the Mathematical Institute). The student will have access to all NDORMS's facilities, which include wet laboratories for material and tissue culture work as well as laboratories mechanical characterisation and motion studies. The student will have access to a shared engineering workshop and various 3D printers.

The supervisory team will include:

- Prof Pierre-Alexis Mouthuy, with expertise in bioengineering, biomaterials and bioreactors. His multidisciplinary team includes bioengineers, computational engineers, medical doctors, textile scientists and biotechnicians.
- Dr Julie Stebbins, expertise in motion capture in the field of clinical biomechanics, including gait and upper limb.
  (See: https://www.ndorms.ox.ac.uk/research/research-groups/roam)
- Prof Steve Gwilym: is an expert shoulder surgeon and clinician scientist with a research interest in shoulder trauma, pain and osteoarthritis

External support and supervision will also be available at Devanthro through Mr Rafael Hostettler, CEO, with expertise in musculoskeletal humanoid robots and leading the Roboy musculoskeletal robot project

KEY PUBLICATIONS (5 maximum):

P.-A. Mouthuy, S. Snelling, R. Hostettler, A. Kharchenko, S. Salmon, A. Wainman, J. Mimpen, C. Paul, A. Carr, Humanoid robots to mechanically stress human cells grown in soft bioreactors, Communications Engineering 1(1) (2022) 2.

I.L. Sander, N. Dvorak, J.A. Stebbins, A.J. Carr, P.-A. Mouthuy, Advanced Robotics to Address the Translational Gap in Tendon Engineering, Cyborg and Bionic Systems 2022 (2022) 9842169.

P.-A. Mouthuy, A. Carr, Growing tissue grafts on humanoid robots: A future strategy in regenerative medicine?, Science Robotics 2(4) (2017).

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21. Project Title: 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: (500 words maximum)

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 (5 WORDS): 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 (5 maximum):

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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simon.travis@kennedy.ox.ac.uk

22. Project Title: Interrogating immune-mediated inflammatory disease via cutaneous human immune challenge

Supervisor 1: Assoc Prof James Fullerton

Co-Supervisor/s: Prof Chris Buckley

PROJECT OVERVIEW: (500 words maximum)

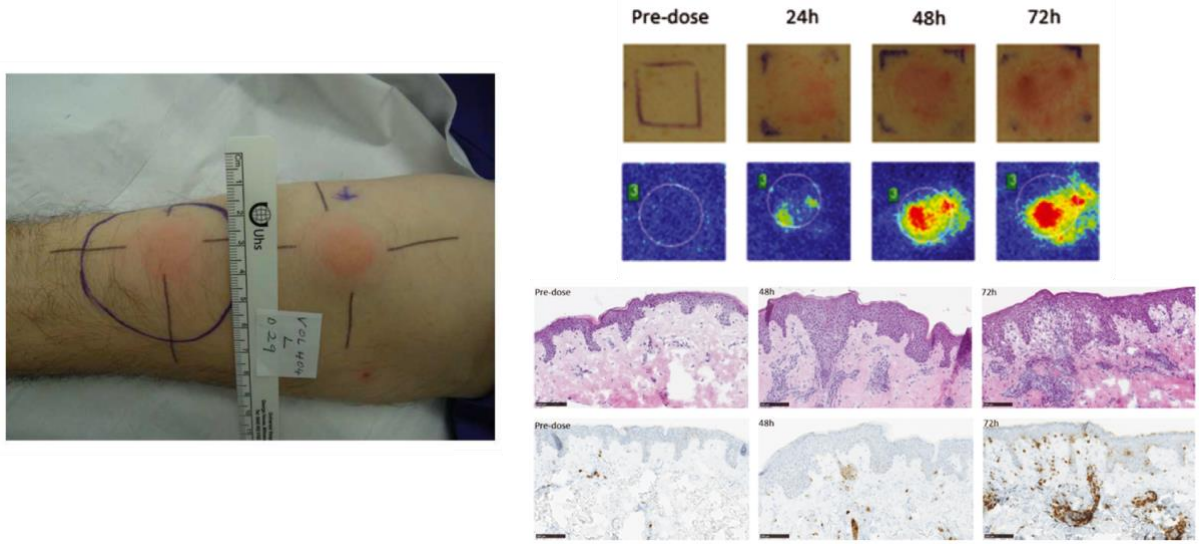
Human immune challenge (HIC), where an exogenous stimulant is employed to transiently induce normally quiescent pathways, cell populations and genes in healthy volunteers (HV), permits unique insights into fundamental biology at high temporal and spatial resolution. Through the elicitation of disease-relevant targets or biomarkers they additionally allow the therapeutic potential of existing and novel drug candidates to be evaluated, rapidly confirming pre-clinical data and gaining early proof-of-mechanism and pharmacology, including at the biophase (target tissue) of interest, prior to entering a patient population. Despite clear scientific and economic advantages over alternate approaches (e.g. animal models) HIC remains under utilised in both discovery biology and drug development programmes largely through insufficient characterization, heterogeneity in methodology and a historical failure to exploit the access to mechanism-related end-points they afford.

Several cutaneous HIC paradigms exist that induce a self-resolving inflammatory reaction via chemical (e.g. cantharidin), physical (e.g. UV-light) or pathogen-derived (e.g. endotoxin) stimuli. The subsequent immunological response can then be quantified clinically over time and the humoral and cellular elements accessed via blistering or skin biopsy. These approaches can be used not only to 'model' inflammatory dermatological conditions such as psoriasis or atopic dermatitis, but also to employ the skin as an exemplar tissue bed: gaining insight into pathological processes that occur in others (e.g. the lung or kidney). The problem is that we do not currently have a clear idea *which* stimuli best induce pathways relevant to different immune-mediated inflammatory diseases (IMID), *what* dose of stimuli to employ and both *when* and *how* to sample the skin to derive the greatest biological insight and optimally inform drug development decisions.

This experimental medicine project seeks to directly address this gap, comparing the response to alternate cutaneous HIC stimuli both within and between HV, hypothesizing that they will selectively elicit immunological pathways relevant to different IMID (e.g. rheumatoid arthritis or Crohn's). Further, it will seek to explore the immune response over time from the acute phase through resolution, using different sampling methods (blister vs. biopsy) to catalogue the infiltrating cells and explore their interaction with the local milieu. Finally, the relative sensitivity of the HIC paradigms to both locally and systemically administered immunomodulatory drugs will be explored *ex* and *in vivo*: a key step in validating their transaltional relevance.

Specifically, the molecular, cellular and transcriptional profile of samples (blood and skin) arising from discrete human skin challenges including cantharidin, endotoxin, imiquimod, UV-light and keyhole limpet haemocyanin (following immunization, to induce delayed type hypersensitivity) will be sequentially interrogated down to single cell resolution (spectral flow cytometry and RNA sequencing) and compared to library samples from patients with IMID.

The utility and relevance of each approach to specific disease states will be determined and a tissue atlas formed to inform future drug development and translational science programs. Within-subject studies using medicines with established mechanisms and known biological effects (e.g. corticosteroids, anti-IL6 agents) will then be conducted to determine the different HIC paradigms response characteristics and suitability for evaluating novel therapeutics.



Left Panel (Belson et al 2016, https://doi.org/10.1007/s00011-016-0923-4). Delayed type hypersensitivity response following antigen rechallenge. Right panel. Erythema, vascular reactivity and histology following imiquimod challenge (Van der Kolk et al 2020, https://doi.org/10.1111/cts.12563)

KEYWORDS (5 WORDS): Experimental medicine; immunomodulation; autoimmune diseases; drug development; pharmacology

TRAINING OPPORTUNITIES:

The successful applicant will benefit from regular hands-on training and supervision by experienced laboratory and clinical scientists both at the Kennedy Institute and Botnar Research Centre. As well as developing core 'wet lab' skills (flow cytometry, cell culture etc) they will gain exposure to a range of cutting-edge techniques (including single-cell RNA sequencing) and analysis. Most uniquely, they will work in conjunction with clinically qualified colleagues in the new NIHR Experimental Medicine Clinical Research Facility to undertake and obtain samples from the HIC paradigms; literally moving from 'bed to benchside'.

The development of outstanding communication and project management skills is expected as they take on the significant responsibility of establishing and running an experimental medicine trial. To achieve this they will be supported, trained and mentored by experienced clinicians and clinical/industrial science experts throughout. Daily interaction with fellow clinical and non-clinical PhD students and post-doctoral researchers will be supplemented by frequent supervisory meetings with Dr Fullerton and Prof Buckley. Regular attendance and participation at both Prof Buckley and Prof Mark Coles' (Stromal Immunology, https://www.kennedy.ox.ac.uk/team/mark-coles) lab meetings and those of the Oxford Centre for Clinical Therapeutics (led by Prof Duncan Richards, https://www.ndorms.ox.ac.uk/team/duncan-richards) will be required. Presentation at international conferences and publication in leading biomedical journals is expected. The

quality, relevance and impact of the students work will be guaranteed by the inter-linked nature of this work with existing research programmes (e.g. A-TAP https://www.kennedy.ox.ac.uk/about/translational-research/atap) and industrial collaborations (e.g. Oxford-Bristol Myers Squibb Fellowship), with associated expertise and funding.

KEY PUBLICATIONS (5 maximum):

Buters et al. Intradermal lipopolysaccharide challenge as an acute in vivo inflammatory model in healthy volunteers. Br J of Clinical Pharmacology, 2022 https://doi.org/10.1111/bcp.14999

Florian et al. Translational drug discovery and development with the use of tissue-relevant biomarkers: Towards more physiological relevance and better prediction of clinical efficacy. Exp Dermatol 2020. https://doi.org/10.1111/exd.13942

Saghari et al. A randomized controlled trial with a delayed-type hypersensitivity model using keyhole limpet haemocyanin to evaluate adaptive immune responses in man. Br J of Clinical Pharmacology, 2020. https://doi.org/10.1111/bcp.14588

Van der Kolk et al. Comprehensive, Multimodal Characterization of an Imiquimod-Induced Human Skin Inflammation Model for Drug Development. Clin Transl Sci 2018. https://doi.org/10.1111/cts.12563

Jenner et al. Characterisation of leukocytes in a human skin blister model of acute inflammation and resolution. PLoS One, 2014. https://doi.org/10.1371/journal.pone.0089375

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23. Project Title: Developmental engineering models of skeletal ciliopathies.

Supervisor: Dr Angus Wann

Co-Supervisor 1: Professor Tonia Vincent

Collaborators(s): Dr Dagan Jenkins, Prof Phil Beales (University College London), Prof M. Knight (QMUL, Emulate organ-on-chip Centre

PROJECT OVERVIEW: (500 words maximum)

Mutations in genes associated with the primary cilium underlie the congenital ciliopathies. An expanding collective of mutations have been associated with skeletal ciliopathies [1]. For example, mutations in IFT80, a protein component of the intraflagellar transport (IFT) system cause Jeune asphyixiating thoracic dystrophy (JATD) [2] and short rib polydactyly (SRP) type III. Both diseases are autosomal recessive chondrodysplasia and share clinical and radiological similarities. These include long bone shortening and constriction of the thoracic cage, the result of impaired endochondral ossification. Murine [3] and cell models have begun to build our molecular and cellular understanding of these disorders, but many open questions remain.

As part of a programme seeking to understand the biology of limb morphogenesis [4] and pathology, the Wann group is already exploiting a developmental engineering approach to model endochondral ossification. The project will exploit a validated chondro-osseous, scaffold supported organoid model [5], seeded with mouse and human mesenchymal stem cells carrying CRISPR edits (disease-causing mutations) and/or patient-derived iPSC. The model transitions from stem-cartilage-bone enabling a qualitative and quantitative tracking and assessment of molecular, cellular and matrix changes associated with mineralisation. It will be used here to model skeletal disorders such as JATD and SRP to understand disease mechanisms and, in the longer term, offer platforms for therapeutic screening. This work will run in parallel to collaborative analysis of IFT80 mouse models (UCL Cilia disorders laboratories). Other synergistic projects use the model to understand fundamental limb mechanobiology and other chondropathies including osteoarthritis.

The project will exploit the model to test the hypothesis that chondro-hypertrophic-bone transition mechanisms regulated by primary cilia underpin faulty endochondral ossification in JATD/SRP type III

Using this *in vitro* model of endochondral transitions this studentship will:

1 Generate CRISPR mutant (IFT80) stem cells/ explore iPSC use.
2 Validate *in vitro* tissue model of skeletal ciliopathies, comparing with *in vivo* mouse models.
3 Explore the molecular, cellular and matrisomal phenomena associated with impaired endochondral transitions, modelling JATD/SRP type III.

4 Trial gene therapy/small molecule interventions in *growth plate on a chip* model (With Emulate centre).

KEYWORDS (5 WORDS): Organoid, Chondrodysplasia, Mineralisation, Ciliopathy, Organ-on-Chip

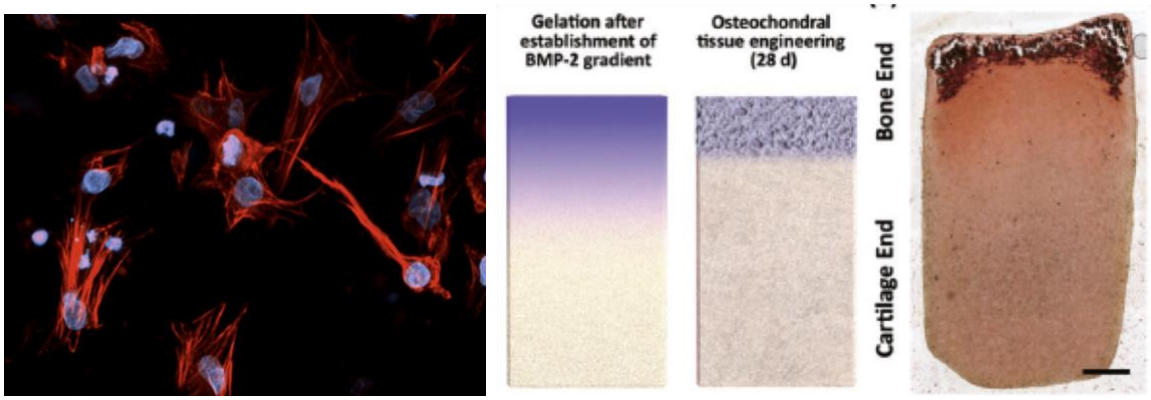

Figure 1. Stem cells seeded with GelMA scaffold (left). Middle images: Buoyancy established gradient and (Right) histological section of chondro-osseous model [5].

TRAINING OPPORTUNITIES: The successful candidate will be embedded within the Centre for OA Pathogenesis Versus Arthritis at the Kennedy Institute of Rheumatology, directed by Professor Vincent. They will benefit from supervision by an experienced team of clinician and basic scientists interested in the cell biology of MSK disease. They will work closely with genetics and clinical (ciliopathy) expertise at UCL, Cilia disorders laboratories and collaborate with Emulate Organ-on-a-chip predictive models centre.

You will be based in the laboratories of the Kennedy Institute of Rheumatology, a world-leading centre in the fields of tissue biology, inflammation, and repair, with a strong emphasis on clinical translation. The project will use a combination of human stem cells carrying disease-causing mutations and an *in vitro* developmental engineering model. There is support available from post-doctoral scientists and laboratory managers in our groups. In summary, you will be working within:

- Cutting-edge cell and tissue biology, imaging and next generation sequencing techniques available in-house, including 3D tissue culture, multi-channel immunohistochemistry analysed using world-class imaging facilities including light sheet microscopy and single cell RNA-sequencing analysis
- Strong translational environment.
- Well-established DPhil programme with defined milestones, ample training opportunities within the University and Department, and access to university/department-wide seminars by world-leading scientists
- Highly collaborative local environment and opportunities to participate in several other clinical and bioengineering collaborations with UCL and Emulate centre for predictive models at QMUL.

KEY PUBLICATIONS (5 maximum):

1. Huber, C. and V. Cormier-Daire, *Ciliary disorder of the skeleton.* Am J Med Genet C Semin Med Genet, 2012. **160C**(3): p. 165-74.
2. Beales, P.L., et al., *IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy.* Nat Genet, 2007. **39**(6): p. 727-9.
3. Rix, S., et al., *An Ift80 mouse model of short rib polydactyly syndromes shows defects in hedgehog signalling without loss or malformation of cilia.* Hum Mol Genet, 2011. **20**(7): p. 1306-14.
4. Coveney, C.R., et al., *Ciliary IFT88 Protects Coordinated Adolescent Growth Plate Ossification From Disruptive Physiological Mechanical Forces.* J Bone Miner Res, 2022.
5. Li, C., et al., *Buoyancy-Driven Gradients for Biomaterial Fabrication and Tissue Engineering*. Adv Mater, 2019. **31**(17): p. e1900291.

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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 there is no NHS Bursary to cover the initial clinical year; 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 DPhil, you will receive support as part of the MB DPhil funding to offset this.

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.

2. 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 helpf 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 "derisk" projects.

We ensure that all projects have a clinical supervisor or cosupervisor 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

Colleges Accepting OxKEN Applications

College	Contact
Balliol	Adam Smyth Professor of English Literature and the History of the Book Tutor for Graduate Admissions Balliol College, Oxford University graduate@balliol.ox.ac.uk
Brasenose	Dr Simon Smith Tutor Brasenose College Radcliffe Square, Oxford OX1 4AJ simon.smith@bnc.ox.ac.uk
Christchurch	Stephanie J Cragg MA DPhil Professor of Neuroscience Dept Physiology, Anatomy and Genetics University of Oxford OX1 3PT Stephanie.cragg@dpag.ox.ac.uk
Corpus Christi	Rachel Clifford Academic Registrar rachel.clifford@ccc.ox.ac.uk
Exeter	Dr Chris. Ballinger Academic Dean [Senior Tutor] & Official Fellow Exeter College Oxford OX1 3DP admissions@exeter.ox.ac.uk *Do not take for the graduate entry medicine programme
Green Templeton	Dr Alison Stenton Senior Tutor Green Templeton College, University of Oxford alison.stenton@gtc.ox.ac.uk
Harris Manchester	Professor Bee Wee CBE FRCP FRCGP SFFMLM PhD Hon DSc Associate Professor and Fellow of Harris Manchester College, Oxford University Email: bee.wee@ouh.nhs.uk Senior Tutor lesley.smith@history.ox.ac.uk Tutor for Admissions ashley.walters@hmc.ox.ac.uk
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Jesus	Dr Alexandra Lumbers Academic Director Jesus College, Turl Street, Oxford, OX1 3DW alexandra.lumbers@jesus.ox.ac.uk www.jesus.ox.ac.uk
Lady Margaret Hall	Dr Fiona Spensley Tutor for Graduates and Director of Visiting Students tutor.graduates@lmh.ox.ac.uk
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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 bethan.psaila@ndcls.ox.ac.uk
Pembroke	Nancy Braithwaite Academic Director Pembroke College nancy.braithwaite@pmb.ox.ac.uk
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Wolfson	Fiona Maguire (temp Senior Tutor) Wolfson College, Oxford senior.tutor@wolfson.ox.ac.uk
Worcester	Dr Michael Mayo Equalities Officer | Tutor for Graduates | Director of the Visiting Student Programme Worcester College, Oxford michael.mayo@worc.ox.ac.uk

OXKEN Co-applicants

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

Tonia Vincent, Deputy 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

Robert Gilbert: Director, Medical Sciences Division Graduate School

Chris Pugh: Professor of Renal Medicine, 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: 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