Oxford University Hospitals NHS
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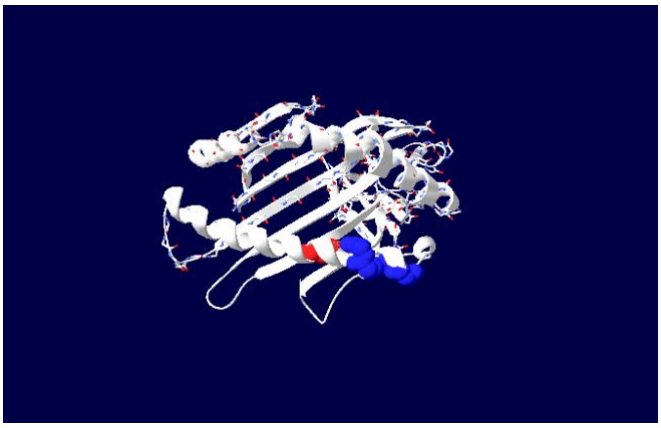
NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

UNIVERSITY OF OXFORD

OxKen: DPhil in inflammatory and musculoskeletal disease

2022 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 2022. Applications from current Oxford medical students are welcomed to start directly after preclinical training (Final Honours School) or after the first clinical year. The first cohort will start in October (or July for first year clinical students) 2022.

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:

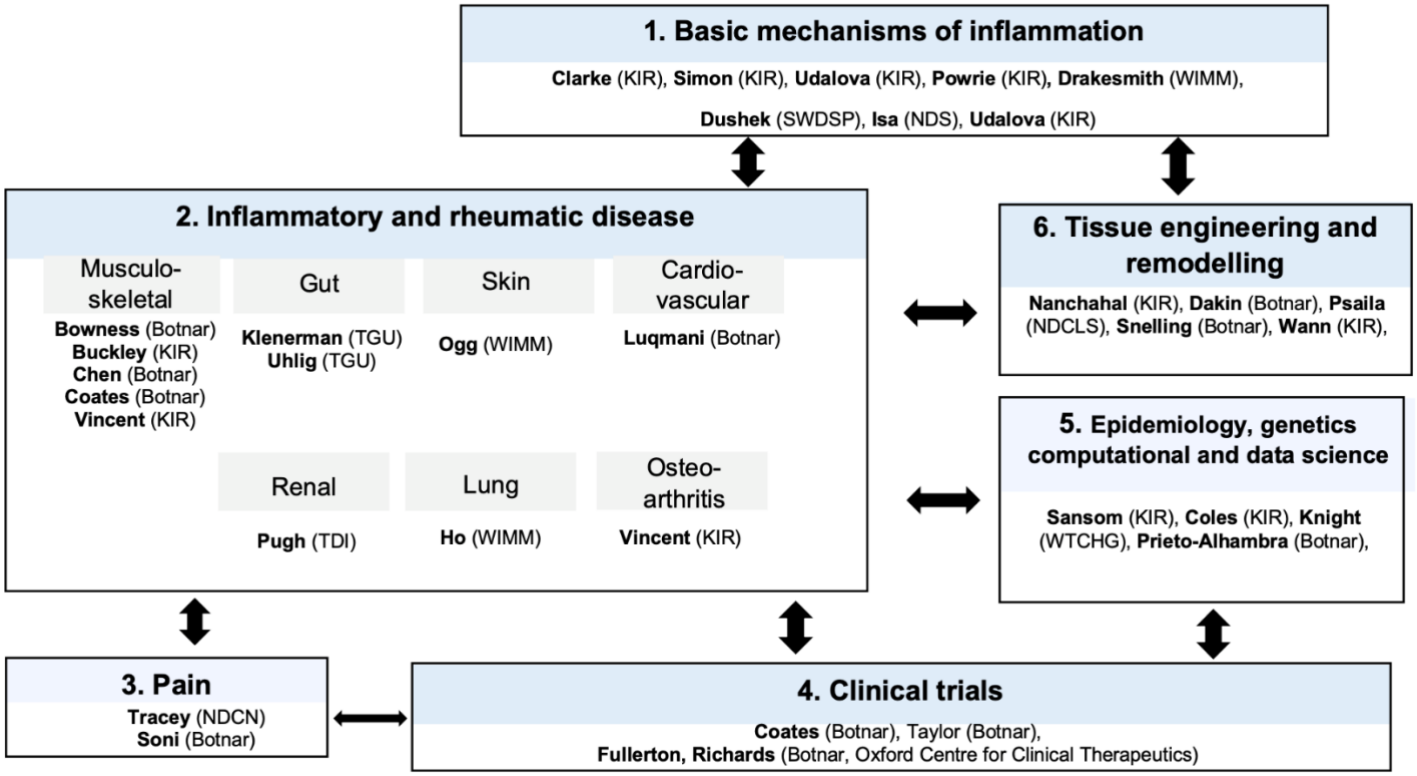
- have a thorough knowledge of the basic principles of research into inflammatory disorders including the relevant literature and a comprehensive understanding of scientific methods and techniques applicable to their research.
- be able to demonstrate originality in the application of knowledge, together 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. Pain
4. Clinical trials
5. Epidemiology, computational and data science
6. Tissue engineering and remodelling

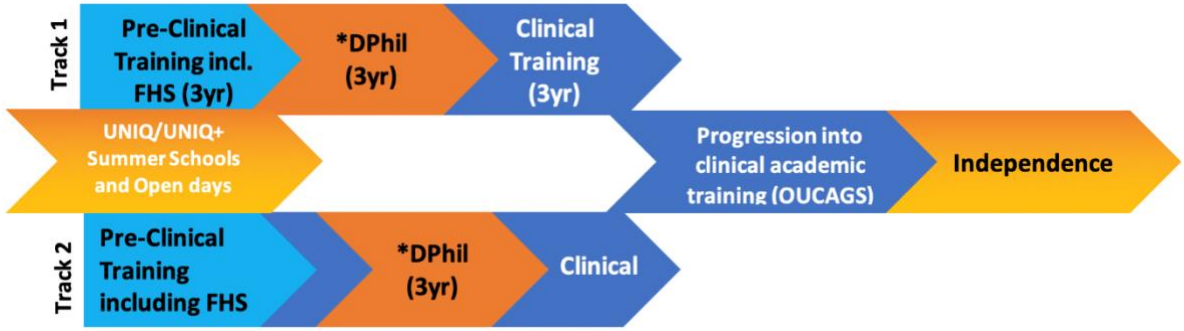
OxKEN Research Themes



Abbreviations used: KIR: Kennedy Institute of Rheumatology. WIMM: Weatherall Institute of Molecular Medicine. TGU: Translational Gastroenterology Unit. NDCN: Nuffield Department of Clinical Neurosciences. WTCHG: Wellcome Trust Centre for Human Genetics.

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 2022)
Application Track 2 – 1st year clinical students (to start 01 Aug 2022).

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 03 Dec 2021. 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 19 October2021- closing date 03 December 2021. Please apply through MSD DTC (DPhil in inflammatory and musculoskeletal disease). Colleges currently accepting OxKen students are listed at the end of this booklet.

It is our intention to invite shortlisted students to interview on Thursday 20th January (on Teams). Students are welcome to jointly apply for the OxCat and OxKen training programs
If successful, students will be allocated a project on the basis of their ranking during the review process.

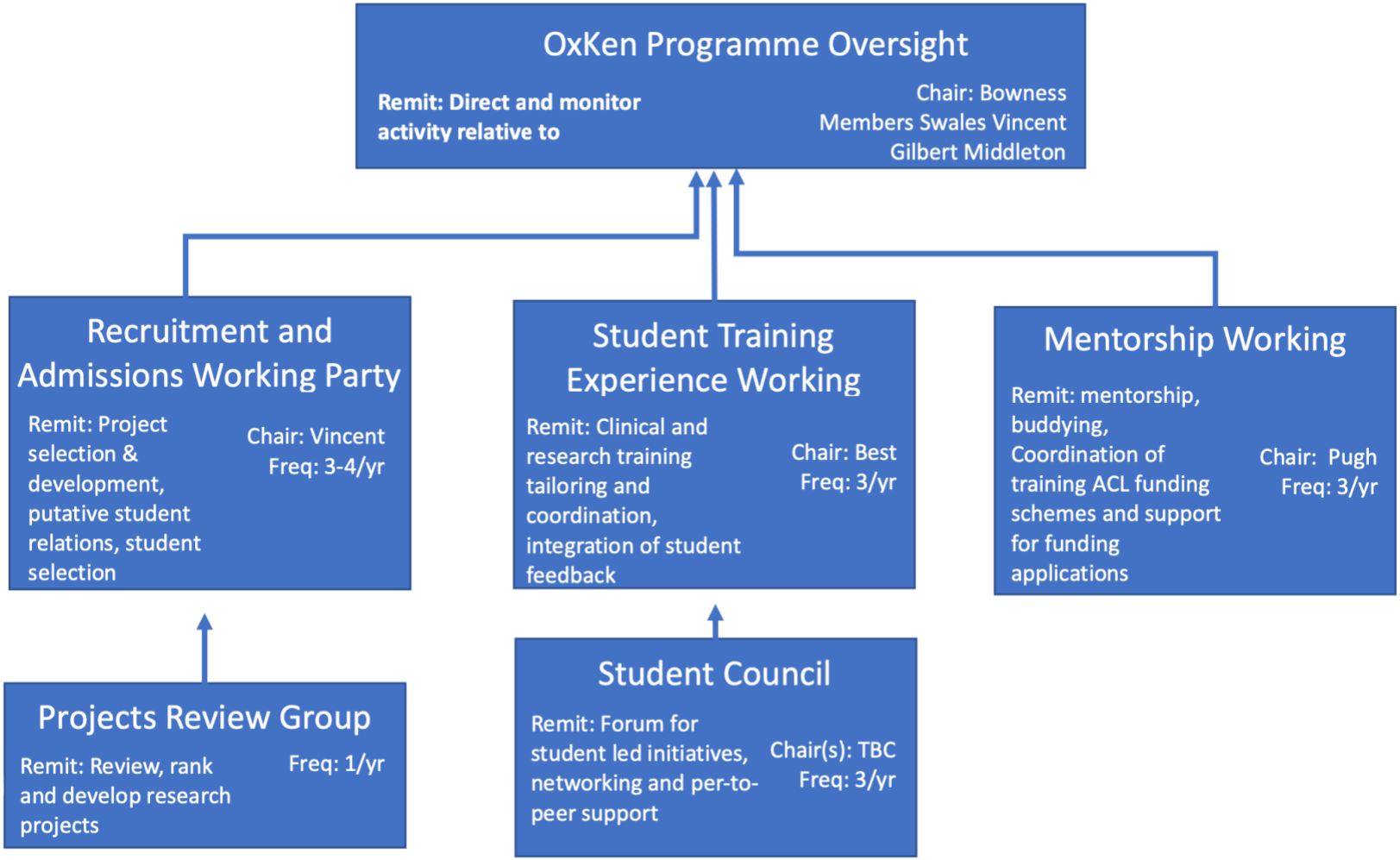
Projects at a Glance

Project ID	Title	Supervisor(s)	Themes
#OxKEN-2022/1	Influence of Modifiable factors in PsA contributing to treat to target success (the IMPACT study)	Supervisor 1: Laura Coates Co-Supervisor/s: Anushka Soni, Irene Tracey	4 (3)
#OxKEN-2022/2	Elucidating T cell phenotype and function in frozen shoulder	Supervisor 1: Stephanie G Dakin, Co-Supervisor/s: Christopher Buckley, Mark Coles	2 (5)
#OxKEN-2022/3	Co-prevalence of liver disease in psoriatic disease (COLIPSO)	Supervisor 1: Laura Coates Co-Supervisor/s: Paul Klenerman, Hussein Al-Mossawi	2 (4)
#OxKEN-2022/4	Tissue ecology in IBD development and pathophysiological function	Supervisor 1: Fiona Powrie Co-Supervisor/s: Matthias Friedrich, Mathilde Pohin	1
#OxKEN-2022/5	Delivering an ethnically diverse atlas of the inflamed and healthy human knee	Supervisor 1: Sarah Snelling Co-Supervisor/s: Chris Buckley, Mat Baldwin, Adam Cribbs	6
#OxKEN-2022/6	Exploring the cellular contribution of fibroblasts and chondrocytes in osteoarthritis pathogenesis.	Supervisor 1: Tonia Vincent Co-Supervisor 1: Chris Buckley Co-supervisor 2: Stefan Kluzek (University of Nottingham)	2
#OxKEN-2022/7	Understanding and exploiting antigen discrimination by T cells	Supervisor 1: Omer Dushek Co-Supervisor/s: P. Anton van der Merwe	1
#OxKEN-2022/8	Dissecting the fibrotic landscape in Dupuytren's disease	Supervisor 1: Jagdeep Nanchahal Co-Supervisor/s: Chris Buckley	6
#OxKEN-2022/9	Investigating functional consequences of disease-specific genomic enhancers in ankylosing spondylitis	Supervisor 1: Julian Knight Co-Supervisor/s: Carla Cohen, Matteo Vecellio	5

#OxKEN-2022/10	Application of single cell omics to dissect tissue-immune cell crosstalk and identify targetable mediators of tissue fibrosis	Supervisor 1: Beth Psaila, POTENTIAL co-SUPERVISORS: Dominic Furniss (Botnar) Adam Mead, Ling-Pei Ho; Svetlana Reilly. MRC Weatherall Institute of Molecular Medicine (Psaila, Mead, Ho groups) and Division of Cardiovascular Medicine (Reilly). University of Oxford	6
#OxKEN-2022/11	Gamma-delta intra-epithelial lymphocytes in coeliac disease	Supervisor 1 Paul Klenerman, Co-Supervisor/s: Michael FitzPatrick, Holm Uhlig	2
#OxKEN-2022/12	Investigation of neutrophil-vasculature interactions	Supervisor 1: Irina Udalova Co-Supervisor/s: Raashid Luqmani, Lihui Wang	2 (1)
#OxKEN-2022/13	Investigating interactions between oxygen-sensing pathways and autoimmunity	Supervisor 1: Fadi Issa Co-Supervisor/s: Katherine Bull; Joanna Hester; Chris Pugh	1
#OxKEN-2022/14	Iron control of immune responses	Supervisor 1: Hal Drakesmith Co-Supervisor/s: from: Tom Milne; Fadi Issa; Susie Dunachie (will depend on choice of project)	1
#OxKEN-2022/15	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	2 (5)
#OxKEN-2022/16	Mechanism to Therapy: Applying mechanism driven modelling to COVID-19 pathologies to accelerate therapeutic development for inflammatory disease.	Supervisor 1: Prof. Mark Coles Co-Supervisor/s: Prof. Helen Byrne	5
#OxKEN-2022/17	Identifying therapeutic combinations for immune	Supervisor 1: Prof. Mark Coles Co-Supervisor/s: Prof. Eamonn Gaffney	5

	mediated inflammatory disease using computational modelling, artificial intelligence and experimentation		
#OxKEN-2022/18	'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-2022/19	Elucidating the mechanisms of tissue regeneration by studying the myocardium after infarction	Co-Supervisor 1: Professor Jagdeep Nanchahal Co-Supervisor 2: Professor Paul Riley Co-supervisor 3: Professor Robin Choudhury Joint Supervisor(s): Dr Thomas Layton, Dr Ana Espirito Santo	6
#OxKEN-2022/20	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-2022/21	Investigation of DDR2 signalling to promote 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-2022/22	Parallel challenge paradigms to catalyse vaccine and immunomodulatory drug development	Supervisor 1: James Fullerton Co-Supervisor/s: Anita Milicic, Mark Coles	4

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: Anushka Soni, Irene Tracey

PROJECT OVERVIEW: (500 words maximum)

Psoriatic arthritis (PsA) is a type of arthritis that develops in around 30% of people with the skin condition psoriasis. In addition to PsA related inflammation in the joints and skin, other non-inflammatory processes contribute to pain and disability experienced, with some preliminary information that this may be different in women and men. This DPhil project will the first in-depth study to investigate both inflammatory (patterns of psoriasis/arthritis) and non-inflammatory processes (including underlying causes of pain, mood, sleep disturbance, and coping strategies) that prevent patients achieving treatment targets and minimal impact of disease.

Funding is already secured for a 300 patient cross-sectional study, across 10-15 UK centres, with measures of psoriasis and arthritis disease activity alongside a comprehensive assessment of non-inflammatory factors including: fatigue, self-efficacy, fibromyalgia, neuropathic pain, pain catastrophizing, anxiety, depression, and sleep disturbance.

This will be complemented by analysis in existing longitudinal data from the Dutch Early PsA Registry (DEPAR), for over 700 early PsA patients. There will be the opportunity for an exchange to visit or exchange with another PhD student with supervision from Professor Marijn Vis in Rotterdam. Logistic regression modelling will be used to identify predictors of good disease control and low patient impact. This will also be combined with a data driven approach, using cluster and principle component analyses, to identify novel patient subgroups and predictors of response.

We believe that this study will help to find a new way of grouping patients who have not achieved well-controlled disease, due to different combinations of inflammatory and non-inflammatory processes. This could be used to improve their outcome using specific tailored treatments for non-inflammatory factors (for example painkillers targeting nerve-related pain) alongside current psoriasis and arthritis treatments aimed at controlling inflammation.

KEYWORDS (5 WORDS): disease burden, psoriatic arthritis, pain, clinical study

TRAINING OPPORTUNITIES: biostatistics, big data, epidemiology, specialist psoriatic arthritis and combined rheum/derm clinics, presentations at national and international meetings, link into large European PsA consortium investigating predictors of PsA development.

KEY PUBLICATIONS (5 maximum):

1. Soni A, Wanigasekera V, Mezue M, Cooper C, Javaid MK, Price AJ, Tracey I. Central sensitisation in knee osteoarthritis: Relating pre-surgical brainstem neuroimaging and PainDETECT based patient stratification to arthroplasty outcome. Arthritis Rheumatol 2018.
2. Soni A, Santos-Paulo S, Segerdahl A, Javaid MK, Pinedo-Villanueva R, Tracey I. Hospitalization in fibromyalgia: a cohort-level observational study of in-patient procedures, costs and geographical variation in England. Rheumatology (Oxford) 2020;59(8):2074-2084.
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:

Laura Coates Email – laura.coates@ndorms.ox.ac.uk

Anushka Soni Email – anushka.soni@ndorms.ox.ac.uk

Irene Tracey Email – irene.tracey@ndcn.ox.ac.uk

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.

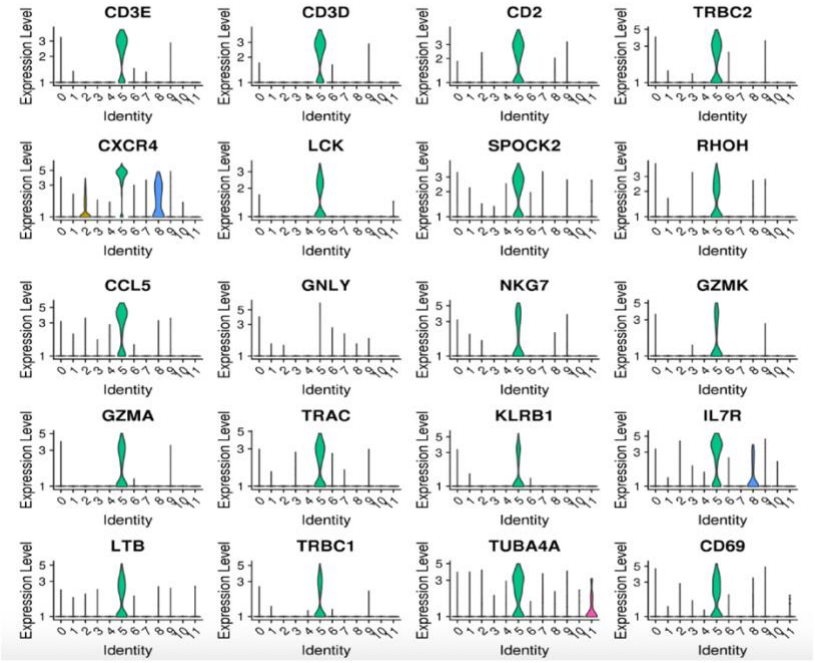


Figure 2A. ChipCytometry immunostaining of T cell markers in cryosections of frozen shoulder patient tissues.

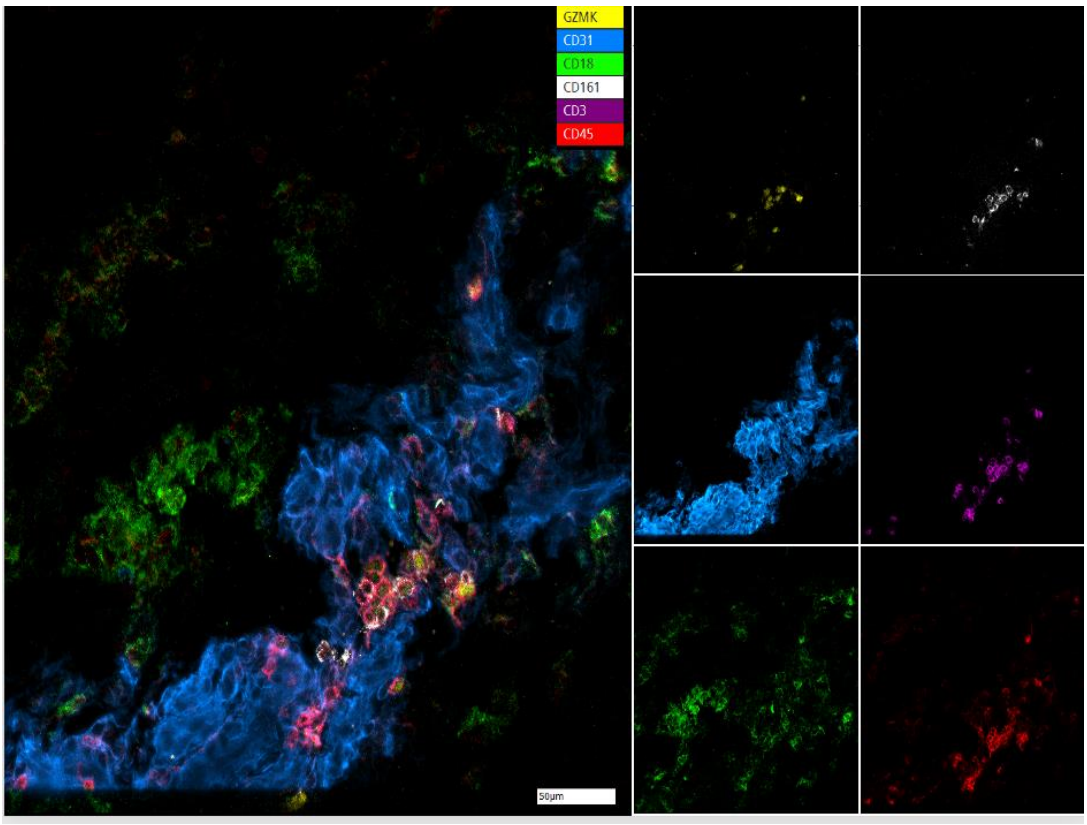


Figure 2A. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows GZMK (yellow), CD18 (green), CD161 (KLRB1, white), CD3 (violet), CD45 (red) and vascular endothelial marker CD31 (blue). Note the perivascular location of identified T cells. Scale bar = 50µm.

Figure 2B

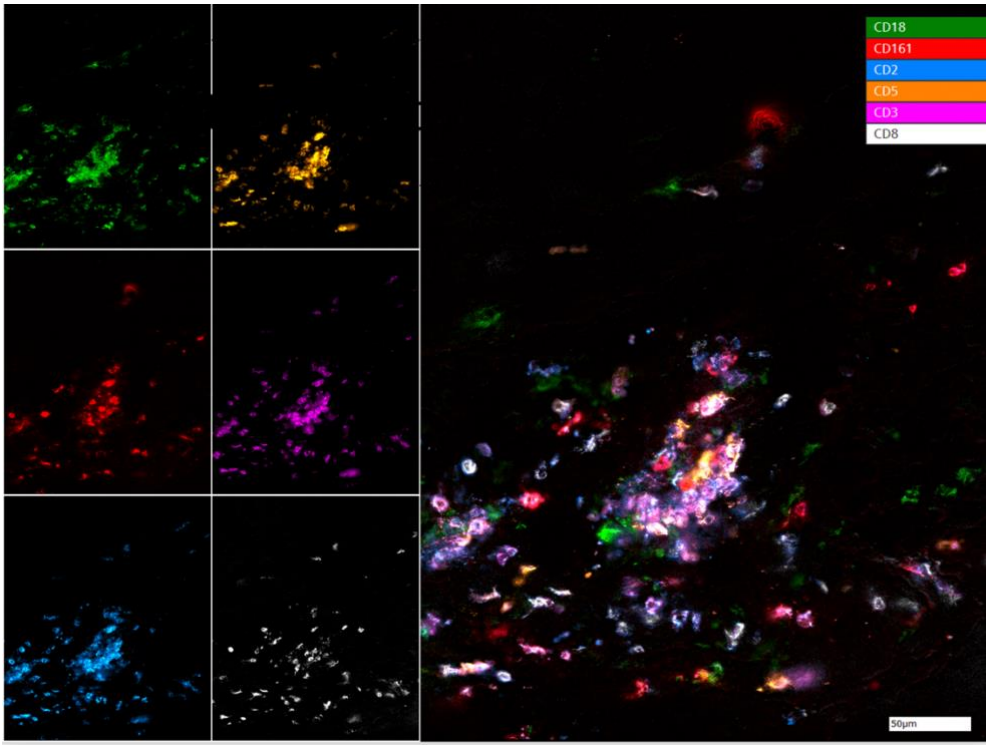


Figure 2B. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows CD18 (green) CD161 (KLRB1, red), CD2 (blue), CD5 (orange), CD3 (magenta), CD8 (white). Scale bar = 50µm.

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.

CONTACT INFORMATION OF ALL SUPERVISORS:

Email: stephanie.dakin@ndorms.ox.ac.uk

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:

Laura Coates Email – laura.coates@ndorms.ox.ac.uk

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

Hussein Al-Mossawi email – hussein.al-mossawi@ndorms.ox.ac.uk

4. Project Title: Tissue ecology in IBD development and pathophysiological function

Supervisor 1: Prof Fiona Powrie

Co-Supervisor/s: Dr Matthias Friedrich, Dr Mathilde Pohin

PROJECT OVERVIEW: (500 words maximum)

Inflammatory bowel diseases (IBDs) are chronic relapsing disorders manifesting in the inflammation of the gastrointestinal tract (1). The complex multifactorial nature of IBD results in considerable heterogeneity in the cell types and molecular processes that drive inflammation across patients. This heterogeneity also affects response rates to medical therapy in IBD, which is now dominated by the use of biologics (e.g., anti-TNF). Indeed, biologics fail in more than half of the patients treated, suggesting that in many cases these medicines do not target the specific tissue inflammatory processes driving disease in an individual. To date patient stratification is limited to clinical symptoms and phenotype (Crohn's disease, ulcerative colitis) which insufficiently captures the molecular and cellular nuances of tissue inflammation.

To better understand the heterogeneity of tissue inflammation and therapy response, we recently integrated bulk and single-cell transcriptomics with molecular pathology to identify and define distinct tissular responses in IBD termed 'pathotypes' [4]. Such pathotypes represent a novel way to stratify patients based on distinct intestinal tissue ecologies which involve the remodelling of tissue resident stromal cell populations (fibroblasts) and the activation of innate (neutrophils) and adaptive immune cell compartments (T-cells, plasma cells) [4]. Despite this study, we still have an incomplete understanding of the diverse inflammatory tissue ecologies in patients with IBD, how they develop and how they could be therapeutically targeted. In-depth knowledge of these processes would allow us to select the most efficient biologic therapy for each patient, moving towards personalised medicine. Our findings highlight that fibroblasts and cytokine rewiring are key drivers in establishing the pathotype niches we identified so far [3,4].

Utilising existing data on molecular, cellular and histopathologic hallmarks of pathotypes in IBD patients, the DPhil student will establish disease-positioned mouse models to reflect these. Specifically, the role of cytokine- and fibroblast-driven pathology will be interrogated. This will include the longitudinal study of pathotype development, dissecting cell type specific contributions, and testing of potential new therapies. Most promising therapeutic approaches identified through the *in vivo* models will then be validated in *ex vivo* organ culture systems derived from IBD patients' tissues, available through the Translational Gastroenterogy Unit at the John-Radcliffe Hospital.

Overall, this translational project offers the opportunity to apply cutting-edge technologies such as disease-positioned mouse models, spatial transcriptomics, proteomics, digital pathology and pre-clinical organoid/experimental mouse models to address and overcome pressing unmet clinical needs in IBD.

KEYWORDS (5 WORDS): inflammation, bowel, therapy, mouse, fibroblast

TRAINING OPPORTUNITIES: The DPhil student will develop expertise in establishing and characterising mouse models, and testing therapies in pre-clinical *in vivo* models and patient-derived organ culture systems. In addition, the project will allow the DPhil student to build an excellent network of academic (Universities of Oxford and Cambridge) and industrial (Janssen) partners involved in the project. Specific training opportunities will include but are not limited to:

- Expert understanding in intestinal tissular ecologies and disease pathogenesis
- Spatial transcriptomics (e.g., 10X Visium or GeoMx), proteomics (e.g., CellDive)
- Bioinformatic analysis of 'omic data
- *In vivo* disease-positioned pre-clinical mouse models
- *Ex vivo* patient-derived tissue culture models
- Presenting and networking with academic and industrial collaborators, including the opportunity of short stays
- Designing, conducting and publishing experimental studies and reviews
- Attending and presenting at national and international conferences

KEY PUBLICATIONS (5 maximum):

(1) Uhlig H and Powrie F. Translating Immunology into Therapeutic Concepts of Inflammatory Bowel Disease. ***Annual Reviews Immunology*** 2018;36:755

(2) Friedrich M *, Pohin M *, Powrie F. Cytokine Networks in the Pathophysiology of Inflammatory Bowel Disease. *Immunity* ***25th Anniversary Edition*** 2019;50(4):992.

(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 in mice and its abundance predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. ***Nature Medicine*** 2017; 23(5):579.

(4) Friedrich M *, Pohin M *, Jackson MA *, Korsunsky I, Bullers S, Rue-Albrecht K, Christoforidou Z, Sathananthan D, Ravindran R, Peres RS, Sharpe H, Wei K, Watts GFM, Mann EH, Geremia A, Thomas T, Attar M, Oxford IBD Cohort Investigators, Roche Fibroblast Network Consortium, McCuaig S, Thomas L, Collantes E, Uhlig HH, Sansom SN, Easton A, Raychaudhuri S, Travis SP, Powrie FM. IL-1-driven stromal-neutrophil interaction in deep ulcers definesa pathotype of therapy non-responsive inflammatory bowel disease. ***Nature Medicine*** (*in press*), *bioRxv 2021* (https://doi.org/10.1101/2021.02.05.429804)

CONTACT INFORMATION OF ALL SUPERVISORS:

fiona.powrie@kennedy.ox.ac.uk; powrie.pa@kennedy.ox.ac.uk Phone: +44 (0)1865 612659

matthias.friedrich@kennedy.ox.ac.uk, mathilde.pohin@kennedy.ox.ac.uk

5. Project Title: Delivering an ethnically diverse atlas of the inflamed and healthy human knee

Supervisor 1: Associate Professor Sarah Snelling

Co-Supervisor/s: Professor Chris Buckley, Dr Mat Baldwin, Dr Adam Cribbs

PROJECT OVERVIEW: (500 words maximum)

Worldwide, 20-33% of people live with painful and disabling musculoskeletal diseases. Diseases occur in all joints and particularly affect soft tissues especially the tendons, synovium, ligaments or fibrocartilage. While functionally diverse, these soft tissues possess a rich extracellular matrix (ECM), low cellularity and a predilection for 'degeneration' and consequent structural failure. Such pathologies are particularly prevalent in the knee, meniscal fibrocartilage or anterior cruciate ligament (ACL) tears each have an annual incidence of 60-70 cases per 100,000 people and pre-dispose to osteoarthritis. Blood vessel ingrowth, fibrosis, significant presence of inflammatory mediators and immune cell infiltration hallmark 'degenerative' soft tissue joint diseases – strongly implicating chronic inflammation in their onset and progression. However, it is unclear if shared or unique inflammatory processes underpin these clinically distinct diseases.

Unravelling the single cell signatures and molecular processes driving autoimmune joint diseases has revolutionised therapeutic development and repurposing. The lack of equivalent, comprehensive, assessment of the landscape underpinning 'degenerative' joint diseases limits treatments to broad-spectrum anti-inflammatories and surgical repair. Such therapies are at best ineffective and at worst harmful. The laboratory challenges of working with ECM-rich tissues and the clinical challenges of accessing tissues for delivery of representative cellular atlases has compounded current efforts to treat these diseases. Further, a paucity of pre-clinical models that recapitulate disease further hampers successful development of pharmacologic and surgical-biomaterial treatments for 'degenerative' diseases of the knee.

Goals

This mixed-methods project focuses on the knee, delivering an ethnically diverse comparative single-cell portrait of inflammation-driven degenerative soft tissue joint diseases of the knee, with concomitant development of *in-vitro* disease models. We will:

1. Generate comparative and ethnically diverse single cell maps of diseased (torn) and healthy patellar tendon, meniscus and ACL, and osteoarthritic synovium. Single nucleus RNAseq (SNucRNAseq) and imaging will identify the unifying and unique cellular features underlying knee soft tissue homeostasis and inflammation-driven disease.
2. Develop scalable, tractable and physiologically relevant *in-vitro* models of diseased soft tissues. We will culture human fibroblasts and immune cells on our synthetic, ECM-mimicking electrospun (naive and growth factor functionalised, and hydrogel biomaterials. We will assess which of these cell-instructive biomaterials best induce

recapitulation of the unifying and unique cellular signatures (WP1) of inflammation-driven degenerative diseases of knee soft tissues.

3. Concurrently analyse a national survey to exploring factors influencing participation in musculoskeletal tissue biobanking. This survey explores a number of domains including; privacy, autonomy, religious belief, monetary or health considerations and research design. The results of this survey will be used to build a focus group and improved educational material to better support ethnically diverse patients to participate in research.

Ultimately we aim to revolutionise the development and testing of effective treatments for inflammation-driven 'degenerative' soft tissue joint diseases (collaboration with Prof Duncan Richards and Prof Chris Buckley). Critically we aim for these advances to be developed to clearly benefit ethnically under-represented populations.

KEYWORDS (5 WORDS): Genomics, inflammation, ethnicity, musculoskeletal

TRAINING OPPORTUNITIES:

Alongside departmental training opportunities listed below we will ensure hands-on computational training to support analysis of single-cell RNAseq data and embedding within our international Tendon Seed Network to ensure laboratory guidance and support. The student will work on their unique project within an experienced and collaborative team. The qualitative work within this project will be supported by long-standing collaborations with our population health and clinical trial unit partners. 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 Institute 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 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 groups including the Oppermann, Cribbs and Buckley teams.

KEY PUBLICATIONS (5 maximum):

1. Histone H3K27me3 demethylases regulate human Th17 cell development and effector functions by impacting on metabolism. Cribbs et al. Proceedings of the

National Academy of Sciences Mar 2020, 117 (11) 6056-6066; DOI:10.1073/pnas.1919893117
2. Factors influencing public participation in biobanking. Ahram et al. *Eur J Hum Genet*. 2014;22(4):445-451. doi:10.1038/ejhg.2013.174
3. Augmenting endogenous repair of soft tissues with nanofibre scaffolds. Baldwin et al. J. R. Soc. Interface.2018. http://doi.org/10.1098/rsif.2018.0019

CONTACT INFORMATION OF ALL SUPERVISORS:

Sarah.snelling@ndorms.ox.ac.uk

Matthew.baldinw@ndorms.ox.ac.uk

Adam.cribbs@imm.ox.ac.uk

Christopher.buckley@kennedy.ox.ac.uk

6. Project Title: Exploring the cellular contribution of fibroblasts and chondrocytes in osteoarthritis pathogenesis.

Supervisor: Professor Tonia Vincent

Co-Supervisor 1: Professor Chris Buckley

Co-supervisor 2: Dr Stefan Kluzek (University of Nottingham)

Collaborators(s): Dr Jolet Mimpin (post doctoral fellow) and Dr Sarah Snelling

PROJECT OVERVIEW: (500 words maximum)

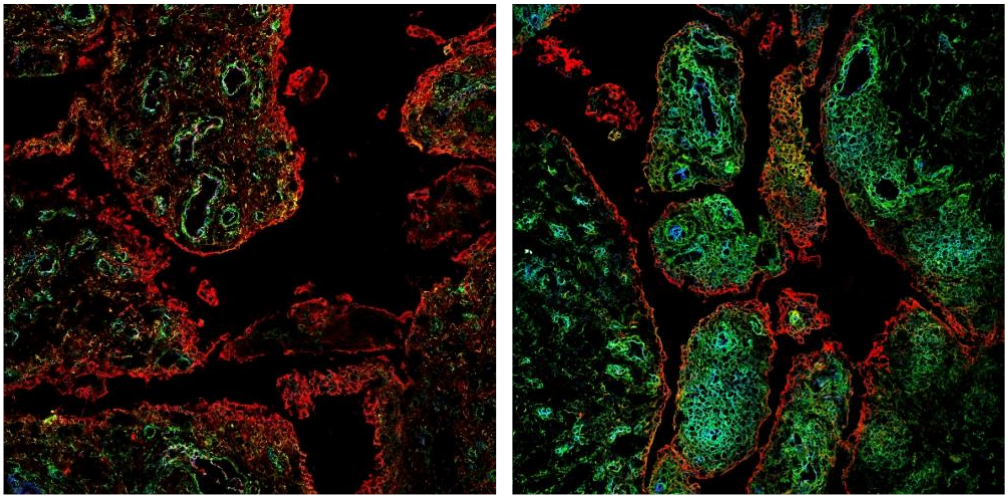
The cellular basis of osteoarthritis (OA) remains enigmatic. Pathogenesis in OA is in part due to loss of articular cartilage driven by direct sensing of chondrocytes to mechanical stress [1]. However, people with OA also have synovial inflammation (synovitis) and fibrosis, which correlates with disease severity and symptoms. The importance of the synovium in disease initiation and progression is unclear. The synovitis in OA is very distinct from synovitis in RA as it is low-grade, with low levels of the typical inflammatory markers observed in rheumatoid arthritis (RA) and associated with cytokines typically seen in fibrotic conditions. Like the articular cartilage, the synovium is also highly mechanosensitive. ***Together this has led to the concept that OA is a disease of 'mechanoflammation'; inflammation directly triggered by mechanical as opposed to soluble inflammatory stimuli*** *[2].*

Acute destabilising injuries of the joint lead to mechanoflammation and are common after sporting injuries (such as rugby and football). These confer a greatly enhanced risk of developing OA within 5-10 years [3]. OxKIC is a knee injury cohort in Oxford, in which synovial biopsies and clinical data have been collected prospectively in 134 individuals. Those usually represent moderate and mild synovial inflammation with a subset of normal non-inflammed synovium.The team also have access to a small number of normal healthy synovial samples.

The healthy synovium consists of two distinct anatomical compartments: a thin lining layer (LL) and a thicker sub-lining layer (SL). In health, the synovium is devoid of lymphocytes and consists of specialised synovial fibroblasts, adipocytes, endothelial cells as well as tissue-resident macrophages. GDF5 positive stem cells are also thought to derive from the synovium after joint injury. Although synovial pathology in OA remains poorly defined by comparison with normal healthy tissue, recent findings, including our own, have revealed cell types that are significantly expanded within OA compared with RA synovium. For example, FAP+CD90+ sub-lining fibroblasts are enriched in RA compared with OA synovium. In complete contrast, FAP+CD90- lining fibroblasts are expanded in OA compared with RA [4] (Figure below). A comparison of OA samples with normal synovium is an important gap in our current knowledge. As are the early changes that occur in the synovium after joint injury.

Osteoarthritis
CD90 lubricin CD146

Rheumatoid Arthritis
CD90 lubricin CD146



Expansion of lubricin+ CD90 negative lining fibroblasts in OA, compared to CD90+ sub lining fibroblasts in RA. CD146 is a mural cell marker found surrounding blood vessels

As LL fibroblasts derive from a shared ancestry, share many similarities with superficial chondrocytes, for example lubricin production, and are contiguous with the articular surface, in this project **we will test the hypothesis that LL synovial fibroblasts, along with articular chondrocytes, contribute to OA pathogenesis**. Using a combined human and mouse approach this studentship will:

1 Define the cellular and tissue structural differences between normal and osteoarthritic human synovium.
2 Explore the synovial histology at early points post joint injury and relate these to patient symptoms and outcome.
3 Determine the effects of deleting either LL fibroblasts and/or articular chondrocytes in well-established animal models of OA using transgenic cell deletion strategies (fibroblast/chondrocyte Cre drivers crossed with inducible DTR mice).

KEYWORDS (5 WORDS): Arthritis, fibroblast, chondrocyte, single cell RNA-sequencing, animal models

TRAINING OPPORTUNITIES: The successful candidate will be embedded within the Centre for OA Pathogenesis Versus Arthritis at the Kennedy Institute of Rheumatology, Oxford. They will benefit from supervision by an experienced team of clinician scientists interested in the cell biology of arthritis and deeply involved in clinical studies including drug induced perturbation studies. They will work closely with Kluzek (Institute for Sports Medicine Nottingham), as well as two collaborators with expertise in human OA tissue and biomaterials based in the Botnar Centre, Oxford.

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 OA tissue samples and

murine models of arthritis. There is support available from post-doctoral scientists and laboratory managers in our groups. In summary, you will be working within:

- Cutting-edge cell biology and next generation sequencing techniques available in-house, including tissue culture, cell sorting, arthritis models, multi-channel immunohistochemistry and single cell RNA-sequencing analysis
- Strong translational environment: findings from human and murine samples in conjunction with next generation sequencing to define and test putative therapeutic targets in OA
- 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 environment with expertise ranging from molecular and cell biology to *in vivo* models and computational biology / genomics analysis. You will also have the opportunity to participate in several other collaborations within the University of Oxford and with the Universities of Nottingham and Birmingham

KEY PUBLICATIONS (5 maximum):

1. Vincent, T.L., *Of Mice and Men; converging on a common molecular understanding of Osteoarthritis.* Lancet Rheumatology, 2020. **2**(10): p. E633-E645, .
2. Vincent, T.L., *Mechanoflammation in osteoarthritis pathogenesis | Elsevier Enhanced Reader.* Seminars in arthritis and rheumatism, 2019. **49**: p. S36-38.
3. Lohmander, L.S., et al., *The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis.* The American journal of sports medicine, 2007. **35**(10): p. 1756-1769.
4. Croft, A.P., et al., *Distinct fibroblast subsets drive inflammation and damage in arthritis.* Nature, 2019. **570**(7760): p. 246-251.

CONTACT INFORMATION OF ALL SUPERVISORS:

Email tonia.vincent@kennedy.ox.ac.uk

christopher.buckley@kennedy.ox.ac.uk

Stefan.Kluzek@nottingham.ac.uk

7. 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:

Email: omer.dushek@path.ox.ac.uk,

anton.vandermerwe@path.ox.ac.uk

8. Project Title: Dissecting the fibrotic landscape in Dupuytren's disease

Supervisor 1: Professor Jagdeep Nanchahal

Co-Supervisor/s: Professor Chris Buckley

PROJECT OVERVIEW: (500 words maximum)

Fibrotic diseases account for up to 45% of deaths in industrialised countries, yet there are few effective therapies. Important limiting factors are a lack of well characterised patient samples across the stages of disease, from the early to treatment refractory stages, as multiply passaged cells from limited samples usually from patients with late stage disease are not representative of the complex disease milieu, and animal models fail to recapitulate all the important aspects of the disease processes. To develop effective therapeutics in fibrosis we need to have a detailed understanding of the entire cellular ecosystem across tissues and the subtypes and functional properties of fibrotic stromal cells in particular.

Patients with localized fibrotic diseases are a rich source of readily accessible early stage tissue. Dupuytren's disease is a common and progressive fibroproliferative disorder of the palmar and digital fascia of the hand and, in Western populations affects 12% of those aged 55 years, increasing to 29% of people 75 years and older. The initial clinical presentation is the appearance of a firm nodule in the palm that expands into fibrous collagenous cords that case irreversible flexion contractures of the fingers. Dupuytren's nodules, which represent the early stage of the disease, are a highly cellular fibrotic ecosystem and are an important model to examine developing fibrosis in humans. Leveraging our ability to access a plentiful supply of clinical samples from patients with Dupuytren's disease we have demonstrated the key role of immune-stromal cell crosstalk in driving the disease (Izadi et al., 2019). Furthermore, our identification of key signalling pathways (Verjee et al., 2013) has translated through an ongoing phase 2b clinical trial of anti-TNF therapy in Dupuytren's disease (Nanchahal et al., 2018). We have also constructed a molecular taxonomy of stromal cells in human fibrosis using single cell RNA sequencing (Layton et al., 2020). Our single cell atlas of the fibrotic milieu elucidated functionally distinct stromal cell types and states, including fibroblast and myofibroblast subsets that mediate discrete pro-fibrotic functions. In addition, we developed functional and live cell imaging assays to functionally validate cellular biomarkers defined in the next generation sequencing.

This project will focus on the complex multicellular network in Dupuytren's disease to gain a complete molecular prospective of how discrete cell types contribute to fibrosis. Building on our discoveries of the stromal and immune cell populations present in human samples, a central goal of this project will be to characterize the vascular niche in fibrosis and define the precursors of mural cells such as myofibroblasts, the key effector cells in all fibrotic disorders. It will be powered by the integration of advanced next generation sequencing techniques, such as single cell RNA-seq and ChIP-seq, with established functional assays. Our expertise in

computational biology (Croft et al., 2019; Layton et al., 2020) will support the construction of a comprehensive single cell atlas of fibrosis and prioritise potential novel therapeutic targets.

KEYWORDS (5 WORDS): Musculoskeletal science, Dupuytren's disease, fibrosis, translational research, single cell RNA-sequencing

TRAINING OPPORTUNITIES: The successful candidate will benefit from supervision by a surgeon scientist with a focus on translational musculoskeletal science alongside a clinician scientist with expertise in computational biology and translational research. In addition, you will be supported by two junior supervisors with expertise in computational and cell biology, live imaging and molecular biology techniques.

You will be 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. There is support available from post-doctoral scientists and lab managers in our groups. In summary, you will be working with:

- Cutting-edge musculoskeletal and fibrosis biology and next generation sequencing techniques available in-house, including tissue culture, cell sorting and single cell RNA-sequencing analysis, spatial transcriptomics and imaging
- Emphasis on translational work: findings from human samples using advanced genomics techniques will enable a high impact on future therapeutic development
- 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 environment with expertise ranging from molecular and cell biology, live cell imaging and computational biology/genomics analysis. You will also have the opportunity to participate in several other collaboration within the University of Oxford and worldwide.

KEY PUBLICATIONS (5 maximum):

Croft, A.P., J. Campos, K. Jansen, J.D. Turner, J. Marshall, M. Attar, L. Savary, C. Wehmeyer, A.J. Naylor, S. Kemble, J. Begum, K. Durholz, H. Perlman, F. Barone, H.M. McGettrick, D.T. Fearon, K. Wei, S. Raychaudhuri, I. Korsunsky, M.B. Brenner, M. Coles, S.N. Sansom, A. Filer, and **C.D. Buckley**. 2019. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* 570:246-251.
doi: 10.1038/s41586-019-1263-7.

Izadi, D., T.B. Layton, L. Williams, F. McCann, M. Cabrita, A.I. Espirito Santo, W. Xie, M. Fritzsche, H. Colin-York, M. Feldmann, K.S. Midwood, and **J. Nanchahal.** 2019. Identification of TNFR2 and IL-33 as therapeutic targets in localized fibrosis. *Science Advances* 5:eaay0370.
doi: 10.1126/sciadv.aay0370.

Layton, T.B., L. Williams, F. McCann, M. Zhang, M. Fritzsche, H. Colin-York, M. Cabrita, M.T.H. Ng, M. Feldmann, S.N. Sansom, D. Furniss, W. Xie, and **J. Nanchahal**. 2020. Cellular

census of human fibrosis defines functionally distinct stromal cell types and states. *Nature Commununications* 11:2768.
doi: 10.1038/s41467-020-16264-y.

Nanchahal, J., C. Ball, D. Davidson, L. Williams, W. Sones, F.E. McCann, M. Cabrita, J. Swettenham, N.J. Cahoon, B. Copsey, E. Anne Francis, P.C. Taylor, J. Black, V.S. Barber, S. Dutton, M. Feldmann, and S.E. Lamb. 2018. Anti-Tumour Necrosis Factor Therapy for Dupuytren's Disease: A Randomised Dose Response Proof of Concept Phase 2a Clinical Trial. *EBioMedicine* 33:282-288.
doi: 10.1016/j.ebiom.2018.06.022.

Verjee, L.S., J.S. Verhoekx, J.K. Chan, T. Krausgruber, V. Nicolaidou, D. Izadi, D. Davidson, M. Feldmann, K.S. Midwood, and **J. Nanchahal**. 2013. Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target. *Proceedings of the National Academy of Sciences, U S A* 110:E928-937.
doi: 10.1073/pnas.1301100110.

CONTACT INFORMATION OF ALL SUPERVISORS:

Jagdeep Nanchahal (jagdeep.nanchahal@kennedy.ox.ac.uk)

Christopher Buckley (christopher.buckley@kennedy.ox.ac.uk)

9. Project Title: Investigating functional consequences of disease-specific genomic enhancers in ankylosing spondylitis

Supervisor 1: Prof Julian Knight

Co-Supervisor/s: Dr Carla Cohen, Dr Matteo Vecellio

PROJECT OVERVIEW: (500 words maximum)

Ankylosing spondylitis (AS) is the archetypal spondyloarthropathy, characterised by inflammatory arthritis of the spine and sacroiliac joints that frequently results in bony fusion. The polygenic associations with AS are well documented, and to date more than 100 genetic associations have been characterised, however, the exact mechanisms and SNPs involved remain poorly understood. In a handful of examples, such as the IL-23 receptor, and the aminopeptidase ERAP1, coding polymorphisms have been documented, but in the majority of cases it is likely that the functional SNP lies within a non-coding regulatory region such as gene enhancers or promoters. A recent unpublished study in the Knight lab in collaboration with Professor Bowness and Professor Wordsworth has used epigenomic profiling in subsets of immune cells from AS patients and healthy volunteers to identify hundreds of putative regulatory genomic regions that are specifically activated or repressed in cells from patients with active disease. These regulators typically act in a cell-type specific manner and are hypothesised to activate proximal genes or work over large genomic distances, as mediated by chromosome looping events. Consequently this work has identified a number of genomic regions that are strong candidates for further functional follow up, in order to define their role in disease pathogenesis and define new therapeutic targets in AS. This is essential if we are to capitalise on the results of genome wide association studies, using knowledge of the genes modulated by specific regulatory regions containing disease associated variants.

The aims of this DPhil project are:

(i) to perform chromosome looping experiments (such as Capture-C) to identify and confirm interactions between disease-specific regulatory elements and cognate genes

(ii) to perform reporter gene assays to confirm that putative regulatory regions have enhancer or suppressor activity in appropriate model systems

(iii) to use genomic editing methods involving CRISPR-Cas9 to experimentally manipulate putative regulatory regions, and identify effects on gene regulation

(iv) to perform functional immunological assays to establish the role of prioritised genes identified in earlier parts of the project

(v) to take forward targets for drug development in collaboration with colleagues in NDORMS and the Centre for Medicine Discovery

The analysis outlined in Aims (i)-(iii) will initially be performed on a small number of regions while the candidate becomes proficient in the relevant methods. However there is potential for medium-high throughput screening in later stages of the DPhil. These experiments will be performed in cell line model systems, complimented by application in primary human immune cells from AS patients and healthy volunteers (ethical approval is in place).

This project presents an exciting opportunity for a student undergoing medical training to become proficient in the field of functional genomics which has wide ranging applications in rheumatology and beyond.

KEYWORDS (5 WORDS): Ankylosing spondylitis, Epigenomics, Genome editing, Enhancers, Functional genomics

TRAINING OPPORTUNITIES:

This project presents the opportunity for the student to train in relevant core molecular and genetic laboratory methods, along with cutting edge techniques such as using CRISPR-Cas9. This will be done through local training with senior postdoctoral researchers experienced in these methods. Additionally, appropriate bioinformatics training will be provided so that the student can gain competency in analysing genomic datasets in statistical packages such as R. There will be opportunities to work alongside senior clinical rheumatologists, enabling the student to develop an understanding of how genomics research can be applied in the clinic. The establishment of the NHS genomic medicine service highlights the need for capacity building in genomics with cross disciplinary training and expertise. The Knight lab offers an excellent opportunity for medical students to gain this and become future leaders in the field.

KEY PUBLICATIONS (5 maximum):

1. Fang, H., U.-D. Consortium, H. De Wolf, B. Knezevic, K.L. Burnham, J. Osgood, A. Sanniti, A. Lledo Lara, S. Kasela, S. De Cesco, J.K. Wegner, L. Handunnetthi, F.E. McCann, L. Chen, T. Sekine, P.E. Brennan, B.D. Marsden, D. Damerell, C.A. O'Callaghan, C. Bountra, P. Bowness, Y. Sundstrom, L. Milani, L. Berg, H.W. Gohlmann, P.J. Peeters, B.P. Fairfax, M. Sundstrom, and J.C. Knight, *A genetics-led approach defines the drug target landscape of 30 immune-related traits.* Nat Genet, 2019. **51**(7): p. 1082-1091.
2. Al-Mossawi, H., Yager, N., Taylor, C.A., Lau, E., Danielli, S., de Wit, J., Gilchrist, J., Nassiri, I., Mahe, E.A., Lee, W., Rizvi, L., Makino, S., Cheeseman, J., Neville, M., Knight JC†, Bowness P† & Fairfax BP†. Context-specific regulation of surface and soluble IL7R expression by an autoimmune risk allele. Nature Commun, 2019. **10**: p.4575 (†joint senior authors).
3. Vecellio, M., A. Cortes, S. Bonham, C. Selmi, J.C. Knight, R. Fischer, M.A. Brown, B.P. Wordsworth, and C.J. Cohen, *A RUNX3 enhancer polymorphism associated with ankylosing spondylitis influences recruitment of Interferon Regulatory Factor 5 and factors of the Nucleosome Remodelling Deacetylase Complex in CD8+ T-cells.* Arthritis Rheumatol. 2020, Accepted Author Manuscript. https://doi.org/10.1002/art.41628.
4. Fairfax, B.P., P. Humburg, S. Makino, V. Naranbhai, D. Wong, E. Lau, L. Jostins, K. Plant, R. Andrews, C. McGee, and J.C. Knight, *Innate Immune Activity Conditions the Effect of Regulatory Variants upon Monocyte Gene Expression.* Science, 2014. **343**(6175): p. 1246949.
5. Roberts, A.R., M. Vecellio, L. Chen, A. Ridley, A. Cortes, J.C. Knight, P. Bowness, C.J. Cohen, and B.P. Wordsworth, *An ankylosing spondylitis-associated genetic variant in the IL23R-IL12RB2 intergenic region modulates enhancer activity and is associated with increased Th1-cell differentiation.* Ann Rheum Dis, 2016. **75**(12): p. 2150-2156.

CONTACT INFORMATION OF ALL SUPERVISORS:

Email

julian@well.ox.ac.uk

ccohen@well.ox.ac.uk

matteo.vecellio@ndorms.ox.ac.uk

10. Project Title: Application of single cell omics to dissect tissue-immune cell crosstalk and identify targetable mediators of tissue fibrosis

POTENTIAL SUPERVISORS: Beth Psaila, Dominic Furniss, Adam Mead, Ling-Pei Ho, Svetlana Reilly, NDORMS (Furniss), MRC Weatherall Institute of Molecular Medicine (Psaila, Mead, Ho groups) and Division of Cardiovascular Medicine (Reilly).

PROJECT SUMMARY: Advances in single cell technologies have revolutionized our ability to dissect cellular and molecular heterogeneity and identify the key cell-cell interactions in healthy and diseased tissues. This is a cross-disciplinary project that brings together scientific and clinical expertise in musculo-skleletal, bone marrow, cardiac and lung fibrosis. The goal is to develop and interrogate parallel single cell genomic datasets of samples from tissue fibrosis and to perform comprehensive analysis of a shared pathological pathway, to facilitate discovery of novel anti-fibrosis targets and to develop pre-clincial models to validate these 'hits'. We believe that a multi-organ and cross-disciplinary approach greatly increases the likelihood of identifying clinically-relevant targets, with potential for identifying a universal fibrosis 'hit' amenable to small molecule or antibody targeting.

BACKGROUND: Fibrosis is a pathological process in which healthy tissue is replaced by excessive, abnormal extracellular matrix proteins leading to loss of tissue architecture and function, and consequential morbidity and mortality[1]. This can occur secondary to repair from mechanical or chemical injury, in response to autoimmune reactions, or in association with malignant transformation (cancer-associated fibrosis). The overall burden of tissue fibrosis is substantial, and has been estimated as affecting 1 in 4 people globally[2]. There is major unmet clinical need for effective strategies to reverse or prevent tissue fibrosis, and the potential clinical and commercial impact of a successful anti-fibrosis therapy is great, given the relevance to many common disorders affecting different body organs, including the musculoskeletal system (e.g. Dupytren's Disease, keloid scarring, scleroderma, frozen shoulder), heart, lungs, skin, liver, kidneys and bone marrow. Many studies have implicated a key role for interactions between inflammatory myeloid cells and stromal cells in fibrotic disorders. Advances in single cell technologies now offer an opportunity to conduct a more comprehensive and unbiased assessment of the cellular and molecular pathways involved than has previously been possible using studies of tissue samples in 'bulk'. In this project, we propose applying state-of-the-art single cell transcriptomic and proteomic assays and in-house computational pipelines to perform parallel studies of pulmonary, cardiac and bone marrow fibrosis.

METHODS/TECHNIQUES TO BE USED:

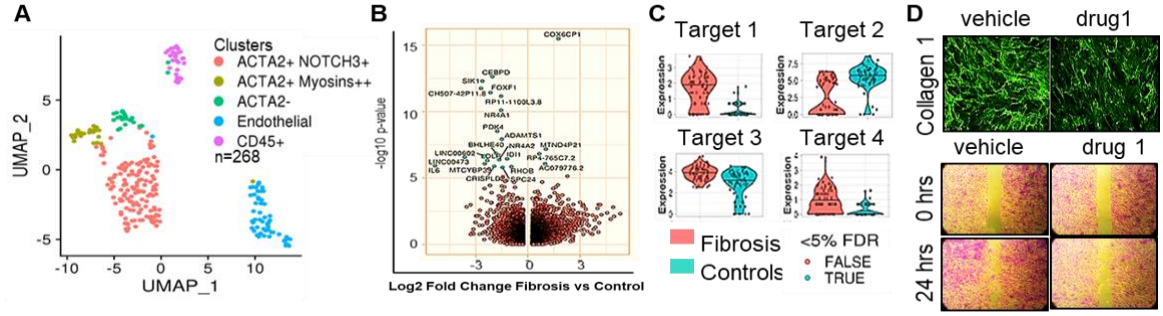
(1) Single cell multi-omic analysis of **primary tissue biopsies** from patients and appropriate controls, including biopsies from **Dupytren's Disease, Frozen Shoulder, human myocardium**[3,4], lung tissue from patients with **idiopathic pulmonary fibrosis**[5-7] and bone marrow biopsies from patients with **bone marrow fibrosis**[8,9]. All ethical approvals are in place and extensive tissue banks collated.

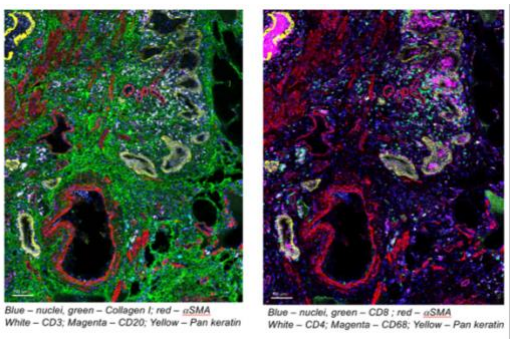
(2) With support from an experienced computational biologist, you would apply computational pipelines to analyse the data and identify disease-specific cell types and cell-cell interactions. The ability to compare **multiple distinct tissue types and in malignant and non-malignant**

pathologies would greatly increase the power of the study and likelihood of identifying a clinically relevant, tractable target.

(3) Validate targets using ***in vitro*** **fibrosis deposition assays**[3,10] and animal models.

Example data from cardiac biopsy: Fig. 1. Trascriptional clusters of scRNAseq of human cardiac fibrobalsts (**A**) and differentially expressed genes (**B-C)** assessed by SMART-seq2 scRNAseq in matched patients with fibrosis and controls; assessmen of collagen-1 accumulation (by scar-in-a-jar, top, **D**) and cell migration (by wound healing assay, bottom, **D**) in human cardiac fibroblasts.





Hyperion imaging mass cytometry showing collagen deposition in lung tissue: Fig. 2. widespread collagen deposition in IPF lungs (left panel) and macrophage and CD8 T cells in close proximity around alveolar epithelium (right). L. PSR staining reflecting fibrosis in lungs of bleomycin model of lung injury, fibrosis and resolution over time M. PSR staining of lung sections of representative mouse from bleomycin model.

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5. Mann E, Menon M, Knight S, et al. Longitudinal immune profiling reveals distinct features of COVID-19 pathogenesis. *Science Immunology (in press)*. 2020.
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CONTACT INFORMATION OF ALL SUPERVISORS:

Beth Psaila (bethan.psaila@ndcls.ox.ac.uk); Dominic Furniss (dominic.furniss@ndorms.ox.ac.uk); Adam Mead (adam.mead@imm.ox.ac.uk); Ling-Pei Ho (ling-pei.ho@imm.ox.ac.uk); Svetlana Reilly (Svetlana.reilly@cardov.ox.uk). NDORMS (Furniss), MRC Weatherall Institute of Molecular Medicine (Psaila, Mead, Ho groups) and Division of Cardiovascular Medicine (Reilly).

11. 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:

Michael FitzPatrick Email – michael.fitzpatrick@ndm.ox.ac.uk

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

12. Project Title: Investigation of neutrophil-vasculature interactions

Supervisor 1: Professor Irina Udalova

Co-Supervisor/s: Professor Raashid Luqmani, Dr Lihui Wang (post-doc)

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.

Inflammatory responses trigger the release of functionally distinct immature neutrophils into the circulation and tissues in different diseases, including severe COVID-19, where we, and others, identify the presence of neutrophil progenitors (**2**). Our recent work on 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 (**3**). 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 (**4**).

To further investigate the cellular and molecular mechanisms of neutrophils function on vasculature, we will adopt and modify the recently developed model system of human vascular organoids (**5**). The system is a revolutionary technological breakthrough enabling in-depth study of human vasculature in diseases that lack relevant animal models. Using this vascular organoid system we will (1) monitor the interactions of neutrophils at different maturation stages with the vessels, (2) examine the effect of neutrophil ROS and NET generation on vascular damage and (3) assess the effect of new drugs under trials in inflammatory diseases and the inhibitors of the identified molecular regulators (**4**) for their effect on vasculature state.

The outcome of this study is expected to contribute significantly to the establishment of vascular organoids as a model to dissect the fundamental cellular and molecular events of neutrophils in vasculitis. Knowledge obtained from the novel neutrophil-vascular organoids system will advance the 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): Vascular organoids, Neutrophils, Vasculitis, 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. Confocol 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 signaling 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) Oxford Covid-19 Immunology Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. 10.1101/2021.05.11.21256877.

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

(4) 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, in press.

5) Wimmer RA, Leopoldi A, Aichinger M, Wick N, Hantusch B, Novatchkova M, Taubenschmid J, Hämmerle J, Esk C, Bagley JA, Lindenhofer D, Chen G, Boehm M, Agu CA, Yang F, Fu B, Knoblich Zj, Kerjaschki D & Penninger JM. Human blood vessel organoids as a model of diabetic vasculopathy ***Nature*** 2019 565: 505–510.

CONTACT INFORMATION OF ALL SUPERVISORS:

Email

Professor Irina Udalova Irina.udalova@kennedy.ox.ac.uk

Professor Raashid Luqmani raashid.luqmani@ndorms.ox.ac.uk

Dr Lihui Wang lihui.wang@kennedy.ox.ac.uk

13. 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.

14. Project Title: Iron control of immune responses

Supervisor 1: Hal Drakesmith

Co-Supervisor/s: from: Tom Milne; Fadi Issa; Susie Dunachie (will depend on choice of project)

PROJECT OVERVIEW: (500 words maximum)

Inflammatory responses include upregulation of the iron hormone, hepcidin. Hepcidin drives serum iron down, and this state of hypoferraemia is an ancient highly conserved innate immune defence mechanism that protects against some (bacterial, malaria) infections. However, our recent work shows that hypoferraemia profoundly impairs the development of adaptive immunity, with inhibition of primary CD4, CD8 and B-cell responses and reduced immunological memory. This nutrient trade-off has implications for understanding immunity in the contexts of chronic inflammatory disorders, iron deficiency (the most common micronutrient deficiency worldwide). Furthermore, the concept suggests new methods to control the immune response, via regulation of iron availability to lymphocytes by controlling hepcidin. There are several directions the follow-up research is taking, and a student would be able to choose the specific project that were more interested. In essence, work spans from investigations as to why lymphocytes are so dependent on iron and the consequences of iron deficiency on immune cell function, to much more translational work. Opportunities include: 1) Multi-omic analysis of T-cell metabolism, epigenetic regulation and transcriptomics under conditions of hepcidin-induced hypoferraemia; 2) Tracing of iron trafficking in vivo in immune cells using animal models and humans via single-cell metallomics and imaging of lymph nodes; 3) Testing how iron and iron deficiency influence the immune response to vaccination; 4) Understanding how inflammation and iron control the development of ‘trained immunity’; 5) Manipulating hepcidin to control immune responses in the contexts of viral infection, or immuno-oncology, or transplantation. Each of these opportunities brings with them particular co-supervisors and collaborators and will necessitate the development of certain skill-sets. The student will be able to tailor a project to their own interests to a large degree.

KEYWORDS (5 WORDS): Hepcidin; inflammation; hypoferraemia; T-cells; adaptive immunity

TRAINING OPPORTUNITIES: Animal models, flow and mass cytometry; bioinformatics, ‘omics approaches, combining physiology with immunology, human studies

KEY PUBLICATIONS (5 maximum):

Frost et al, Hepcidin-Mediated Hypoferremia Disrupts Immune Responses to Vaccination and Infection. Med, 19th November, 2020. https://doi.org/10.1016/j.medj.2020.10.004

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Prentice et al, Respiratory infections drive hepcidin-mediated blockade of iron absorption leading to iron deficiency anemia in African children. Sci Advances, March 2019. https://advances.sciencemag.org/content/advances/5/3/eaav9020.full.pdf

Pasricha et al, Reducing anaemia in low income countries: control of infection is essential. BMJ, 2018. https://doi.org/10.1136/bmj.k3165

Drakesmith and Prentice, Hepcidin and the iron-infection axis. Science, Nov 2012. https://science.sciencemag.org/content/338/6108/768.abstract

CONTACT INFORMATION OF ALL SUPERVISORS:

Email: alexander.drakesmith@imm.ox.ac.uk

15. 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.

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CONTACT INFORMATION OF ALL SUPERVISORS:

Email:

mark.coles@kennedy.ox.ac.uk

Christopher.buckley@kennedy.ox.ac.uk

16. Project Title: Mechanism to Therapy: Applying mechanism driven modelling to COVID-19 pathologies to accelerate therapeutic development for inflammatory disease.

Supervisor 1: Prof. Mark Coles
Co-Supervisor/s: Prof. Helen Byrne

PROJECT OVERVIEW: (500 words maximum)

COVID-19 pathologies result from inappropriate inflammatory immune responses to the infection rather than the virus infection per say, leading to patient morbidity and mortality. Even for patients that recover from severe COVID infection long term COVID pathologies can persist having significant effects on well-being and capacity to work. Understanding the molecular and cellular mechanisms driving the interlinked pathological events in severe COVID-19 will help stratify patient treatment and provide new insights into novel potential therapeutic approaches for these patients including drug repurposing and timing of therapeutic delivery. In Oxford a large scale collaboration between investigators has led to the formation of the Oxford COMBAT dataset that contains deep phenotyping on COVID-19 patients including tracking clinical parameters with scRNAseq, ATACseq, genetics, high dimensional cytometry, antibody profiles, and functional assays. Although machine learning and topological data analytical based techniques have provided key insights from these datasets into disease mechanisms, translating these insights into new clinical treatments and novel patient stratification is more limited due the challenge of capturing time in datasets a key factor dictating clinical outcomes. Mathematical (ordinary and partial differential equations (ODE/PDE)) and computational (agent based models (ABM)) mechanistic simulations can be used to address temporal questions about how pathways identified from high dimensional data analysis impact on human pathology.

Initial analysis of these datasets are consistent with changes to innate immune cell production and function, is different between mild and severe patients which correlates with change in iron and oxygen levels, the mechanisms driving these pathological events and how the intersection between different biological systems lead to severe outcomes is unclear. Based on analysis of the COMBAT datasets we hypothesise that interplay between hypoxia, iron metabolism, inflammatory cytokines and activation of complement drive a set of intersecting autocrine and paracrine inflammatory loops leading to emergence of immature neutrophils from the bone marrow and hyperinflammation driving damage to secondary tissues leading severe COVID symptoms and development of long term pathology. Mechanistic mathematical biology built on well understand molecular and cellular pathways will permit analysis of the contribution of individual pathways and how the intersections between these different cellular and molecular pathways can drive pathological autocrine and paracrine feedback loops. This will permit exploration of potential therapeutic approaches to complex disease pathologies.

In this PhD project we will bring together a team of mathematicians, immunologists and clinical expertise to address this key problem in a project with three key aims: 1) to develop multiple different mathematical models of individual inflammatory/pathological events (e.g. emergence of immature neutrophils), 2) to link model parameters in these models to the data from the COMBAT dataset, 3) analyse how the intersection between the different models might synergise to drive severe pathology.

This project will develop the mathematical models that can provide a basis for models to accelerate stratification of patients at higher risk of severe pathology and identify potential therapeutic combinations that can be applied to virtual clinical trials accelerating and de-risking clinical development of new therapies to prevent formation of long-term patient pathologies.

KEYWORDS (5 WORDS): COVID-19, Mathematical Modelling, Systems Immunology, Inflammation

TRAINING OPPORTUNITIES: The student will gain training in computational and systems immunology including modelling methodologies and modelling tools including Matlab and other programming environments (e.g. Python or C++). The student will be undertaking an interdisciplinary project brining together mathematics, systems biology and immunology.

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.

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Abnormal morphology biases hematocrit distribution in tumor vasculature and contributes to heterogeneity in tissue oxygenation, Proc Natl Acad Sci U S A, 2020 Nov 10;117(45):27811-27819. doi: 10.1073/pnas.2007770117.

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CONTACT INFORMATION OF ALL SUPERVISORS:

Email: mark.coles@kennedy.ox.ac.uk

helen.byrne@maths.ox.ac.uk

17. 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

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CONTACT INFORMATION OF ALL SUPERVISORS:

Email:

mark.coles@kennedy.ox.ac.uk

eamonn.gaffney@maths.ox.ac.uk

18. 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.

https://www.ndorms.ox.ac.uk/team/antonella-delmestri

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.

https://www.ndorms.ox.ac.uk/team/gary-collins

Current DPhil Students within the research group: 10

Current Postdocs within the research group: 7

Email

sara.khalid@ndorms.ox.ac.uk

daniel.prietoalhambra@ndorms.ox.ac.uk

antonella.delmestri@ndorms.ox.ac.uk

laura.coates@ndorms.ox.ac.uk

gary.collins@csm.ox.ac.uk

19. Project Title: Elucidating the mechanisms of tissue regeneration by studying the myocardium after infarction

Co-Supervisor 1: Professor Jagdeep Nanchahal

Co-Supervisor 2: Professor Paul Riley

Co-supervisor 3: Professor Robin Choudhury

Joint Supervisor(s): Dr Thomas Layton, Dr Ana Espirito Santo

PROJECT OVERVIEW: (500 words maximum)

Heart disease is the leading cause of morbidity and mortality in the West. Every year 205,000 people in the UK and 805,000 people in the US suffer a myocardial infarction. For patients who survive the initial event, the damaged cardiac muscle is replaced by fibrous tissue. Forty percent of these patients eventually develop heart failure, which affects 38 million people worldwide, with the current 6.6 million in USA projected to increase to >8 million by 2030. Despite healthcare expenditure for heart failure in the USA exceeding $30Bn per year and expected to increase to $70Bn by 2030, 5 year survival is only ~60%, worse than most cancers. Current treatments are aimed at limiting ventricular dysfunction and there is no approved therapy for promoting myocardial regeneration, reducing fibrosis and leading to sustained improvement in cardiac function (Cahill et al., 2017).

We have previously shown that exogenous administration of fully-reduced HMGB1 (FR-HMGB1) promotes regeneration of bone, skeletal muscle and blood following injury, where it acts on resident stem and progenitor cells to transition them to G_{Alert} (Lee et al., 2018). We have recently shown that intravenous administration of FR-HMGB1 at the time of myocardical infarction in mouse model leads to 40% improvement in left ventricular function. Others have shown in a large animal model that local injection of HMGB1 leads to improved cardiac function, in part by promoting cardiomyocyte survival and angiogenesis (Bauza et al., 2019). We have also shown that the heart contains a population of progenitor cells (Smart et al., 2011) and demonstrated the crucial role of immmune cells following acute myocardial infarction (Klotz et al., 2015).

This project will profile the dynamic cellular landscape of heart regeneration following myocardial infarction. Using established murine models and advanced sequencing techniques, including single cell and bulk RNA-sequencing, we will define how FR-HMGB1 orchestrates myocardial regeneration to identify central regulators of cardiomyocyte repair and homeostasis, including intracellular signalling pathways. Our expertise in computational biology and cardiovascular medicine will support the construction of a single cell atlas of heart repair and uncover key cell types and states that govern this process. A range of functional assays developed in our group will support validation of cell subsets identified in addition to a novel multiplex imaging platform enabling cellular biomarkers to be spatially mapped *in vivo*. In addition, this project will define the intracellular signalling pathways activated by FR-HMGB1.

KEYWORDS (5 WORDS): cardiac regeneration, myocardial infarction, single cell RNA-sequencing, HMGB1 signalling

TRAINING OPPORTUNITIES: The successful candidate will benefit from supervision by a surgeon scientist with a focus on translational medicine, two renowned authorities on the cardiac regeneration and a clinical cardiologist. In addition, you will be supported by two junior supervisors with expertise in HMGB1 biology and computational biology.

You will be 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. The project will use a combination of human samples and murine models of myocardial infarction. There is support available from post-doctoral scientists and lab managers in our groups. This project will benefit from:

- Cutting-edge cardiac biology and computational biology techniques available in-house, including tissue culture, flow cytometry and cell sorting, myocardial infarction models, MRI and next generation sequencing including single cell RNA-sequencing analysis

- Emphasis on translational work: murine cardiac models optimised for therapeutic development and integration in a team working on translational research spanning from bench to bedside

- 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 environment with expertise ranging from molecular and cell biology to *in vivo* models and computational biology / genomics analysis. You will also have the opportunity to participate in several other collaboration within the University of Oxford and worldwide.

KEY PUBLICATIONS (5 maximum):

Bauza, M.D.R., C.S. Gimenez, P. Locatelli, A. De Lorenzi, A. Hnatiuk, M.C. Capogrossi, A. Crottogini, L. Cuniberti, and F.D. Olea. 2019. High-dose intramyocardial HMGB1 induces long-term cardioprotection in sheep with myocardial infarction. *Drug Deliv Transl Res* 9:935-944. doi: 10.1007/s13346-019-00628-z.

Cahill, T.J., R.P. Choudhury, and **P.R. Riley**. 2017. Heart regeneration and repair after myocardial infarction: translational opportunities for novel therapeutics. *Nat Rev Drug Discov* 16:699-717. doi: 10.1038/nrd.2017.106.

Klotz, L., S. Norman, J.M. Vieira, M. Masters, M. Rohling, K.N. Dube, S. Bollini, F. Matsuzaki, C.A. Carr, and **P.R. Riley**. 2015. Cardiac lymphatics are heterogeneous in origin and respond to injury. *Nature* 522:62-67. doi: 10.1038/nature14483.

Lee, G., A.I. Espirito Santo, S. Zwingenberger, L. Cai, T. Vogl, M. Feldmann, N.J. Horwood, J.K. Chan, and J**. Nanchahal**. 2018. Fully reduced HMGB1 accelerates the regeneration of multiple tissues by transitioning stem cells to GAlert. *Proc Natl Acad Sci U S A* 115:E4463-E4472. doi: 10.1073/pnas.1802893115.

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CONTACT INFORMATION OF ALL SUPERVISORS:

jagdeep.nanchahal@kennedy.ox.ac.uk

paul.riley@dpag.ox.ac.uk

robin.choudhury@cardiov.ox.ac.uk

ana.espiritosanto@kennedy.ox.ac.uk

thomas.layton@kennedy.ox.ac.uk

20. 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

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CONTACT INFORMATION OF ALL SUPERVISORS:

Dominic.furniss@ndorms.ox.ac.uk

Fadi.issa@nds.ox.ac.uk

21. Investigation of DDR2 signalling to promote synovial cell invasion into cartilage in rheumatoid arthritis

Supervisor 1: Prof Yoshifumi Itoh

Co-Supervisor/s: Prof Chris Buckley; Prof 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 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), mediaties cartilage collagen signal to synovial fibroblasts and upregulate 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 efficient manner. These findings suggest that DDR2 acts as a sensor to detect 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 RELEVANT 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

C. Buckley: christopher.buckley@kennedy.ox.ac.uk

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

22. Project Title: Parallel challenge paradigms to catalyse vaccine and immunomodulatory drug development

Supervisor 1: James Fullerton

Co-Supervisor/s: Anita Milicic, Mark Coles

PROJECT OVERVIEW: (500 words maximum)

Despite promising pre-clinical data, many vaccine and drug candidates fail to translate into effective therapies for humans. The majority of development programmes are now terminated upon introduction into man (Phase I) or patients (Phase II) with lack of efficacy the principal reason for non-continuation. Recent data suggest that inadequate assessment of pharmacology, physiological mechanism-of-action and the use of non-representative animal models are key contributors to attrition.

In vivo human inflammo-immune challenge model systems afford one potential solution to this problem. By permitting the controlled exploration and therapeutic modulation of pathways not present or activated during homeostasis in the target species, they can help bridge the 'translational gap', allowing unique biological and pharmacological insight early in a drug's development. The availability of parallel or 'mirror' animal models further enhances their utility, allowing in depth mechanistic characterisation of drug action and permitting dynamic forward/reverse translation.

Using keyhole limpet hemocyanin (KLH) as a standardised 'model' immunogenic neo- and recall antigen, this project seeks to establish parallel challenge paradigms in both healthy humans and mice (creating a phenocopy). The end result would be a novel multi-species translational platform capable of rapidly and efficiently establishing proof of mechanism for diverse (inhibitory or stimulatory, stromal/microenvironmental, metabolic, innate or adaptive immune cell targeting) therapeutics, as well as informing vaccine design.

Participants and mice will be systematically exposed to sub-unit KLH (Immucothel, Biosyn) alone and in combination with clinically-approved adjuvants (e.g. aluminium hydroxide, squalene-in-water emulsion) via the same route, at allometrically scaled doses to elicit a T-cell dependent antibody response. Intra-dermal re-challenge with KLH will be employed to trigger delayed-type hypersensitivity. The nature, magnitude and kinetics of the elicited immune response will be sequentially characterised (cellular and humoral in blood, lymph nodes, spleen, and skin) and directly compared inter-species. Pharmacological equivalence in therapeutic modifiability of key response elements will be determined. These observations will be extended, using the murine model, to existing and novel clinically relevant adjuvants, successively bridging the translational gap.

Different adjuvants are anticipated to elicit divergent immune response profiles. This will expose discrete molecular pathways relevant to different disease states (e.g. autoimmune) to interrogation, increasing the utility of this model system. Further, verification of murine mimicry of human biology with known adjuvants will increase confidence in results obtained using novel immunomodulatory drug candidates as well as help catalyse new vaccine development.

KEYWORDS (5 WORDS): Immunomodulation, vaccines, adjuvants, drug development, pharmacology.

TRAINING OPPORTUNITIES:

The student will be trained and mentored by a diverse supervisory team with complementary interdisciplinary skills in human and mouse immunology, vaccine adjuvants and clinical pharmacology and therapeutics.

Full training in good experimental design and research practice in applied immunology using human and murine models will be coupled with exposure to the clinical immune-evaluation of the experimental compounds, bridging the mouse-human immunology gap in therapeutics development.

The student will be trained in vaccine preparation and formulation approaches, standard immunological techniques for evaluating the systemic and localised immune responses, quantification and qualitative evaluation of humoral and cellular immunity using ELISA, ELISpot, flow cytometry, comparative data analysis, in vivo (non-invasive) imaging techniques and single cell genomic and proteomic technologies, as required.

Oxford graduate training includes compulsory core workshops, seminars, career events and online resources enabling the development of the 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.

KEY PUBLICATIONS (5 maximum):

1. Luchner, M., Reinke, S., & *Milicic, A.* (2021). TLR Agonists as Vaccine Adjuvants Targeting Cancer and Infectious Diseases. *Pharmaceutics*, *13*(2).

2. Reinke, S., Thakur, A., Gartlan, C., Bezbradica, J. S., & *Milicic, A*. (2020). Inflammasome-mediated immunogenicity of clinical and experimental vaccine adjuvants . *Vaccines*, *8*(3).

3. *Milicic, A.,* Rollier, C. S., Tang, C. K., Longley, R., Hill, A. V. S., & Reyes-Sandoval, A. (2017). Adjuvanting a viral vectored vaccine against pre-erythrocytic malaria. *Scientific Reports*, *7*(1).

4. Motwani MP, Flint JD, De Maeyer RP, *Fullerton JN* et al. Novel translational model of resolving inflammation triggered by UV-killed E. coli. *The Journal of Pathology Clinical Research* 2016;2(3):154-65

CONTACT INFORMATION OF ALL SUPERVISORS:

Email:

james.fullerton@ndorms.ox.ac.uk

anita.milicic@ndm.ox.ac.uk

mark.coles2@kennedy.ox.ac.uk

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
Hertford	Hertford College Catte St, Oxford OX1 3BW graduate.admissions@hertford.ox.ac.uk
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
Lincoln College	Richard Little Admissions Officer Lincoln College richard.little@lincoln.ox.ac.uk
New College	Dr. Beth Psaila CRUK Advanced Clinician Scientist & Group Leader, MRC Weatherall Institute of Molecular Medicine. Haematology Consultant, Oxford University Hospital NHS Trust Senior Fellow of New College Oxford bethan.psaila@ndcls.ox.ac.uk
Pembroke	Nancy Braithwaite Academic Director Pembroke College nancy.braithwaite@pmb.ox.ac.uk
Reuben	Dr Caroline Mawson Senior Tutor Reuben College University of Oxford senior.tutor@reuben.ox.ac.uk
St Catherine's	Cressida Chappell Academic Registrar St Catherine's College college.office@stcatz.ox.ac.uk
St Hilda's	Dr Sarah Norman Senior Tutor & Tutor for Admissions St Hilda's College University of Oxford Oxford OX4 1DY sarah.norman@st-hildas.ox.ac.uk
St John's	Professor Jaideep J Pandit Professor of Anaesthesia University of Oxford St John's College Oxford OX1 3JP jaideep.pandit@sjc.ox.ac.uk
Somerville	daniel.anthony@pharm.ox.ac.uk senior.tutor@some.ox.ac.uk
The Queen's College	Mark Buckley Tutor for Graduates The Queen's College

	buckley@psy.ox.ac.uk rosie.mcmahon@queens.ox.ac.uk
Trinity	Professor Valerie Worth, MA DPhil Senior Tutor, Trinity College University of Oxford valerie.worth@trinity.ox.ac.uk>
Wadham	Dr Mike Froggatt Acting Senior Tutor & Tutor for Admissions Wadham College Oxford OX1 3PN michael.froggatt@wadham.ox.ac.uk
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