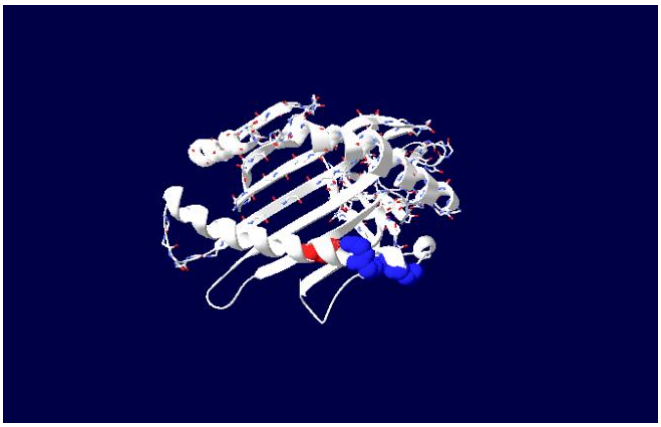
OxKen: DPhil in inflammatory and musculoskeletal disease

2021 Intake Project Book



28 Jan2021

OxKen: DPhil in inflammatory and musculoskeletal disease
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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 2021. 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) 2021.

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 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

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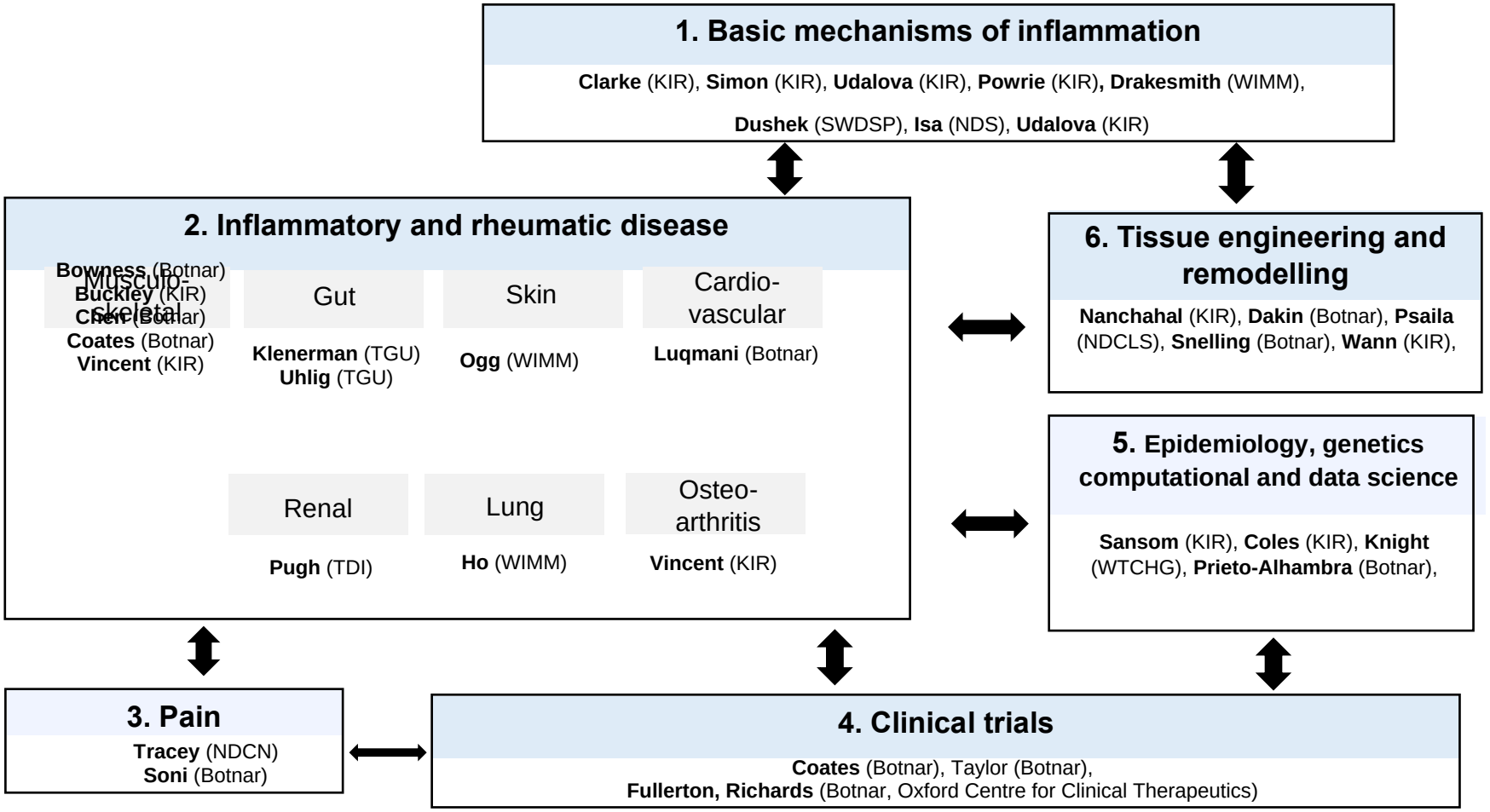
OxKen research themes



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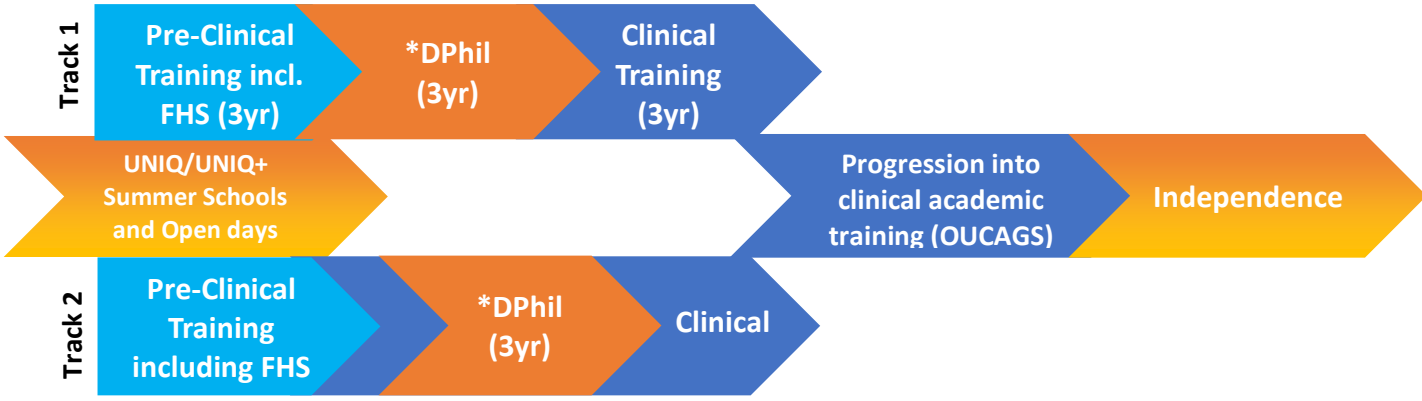
Abbreviations used: KIR: Kennedy Institute of Rheumatology. WIMM: Weatherall Institute of Molecular Medicine. TGU: Translational Gastroenterology Unit. NDCN: Nuffield Department of Clinical Neurosciences. WTCHG: Wellcome Trust Centre for Human Genetics.

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 Oct 2021)
Application Track 2 – 1st year clinical students (to start 01 July 2021).

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 02 March 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 01 February 2021 - closing date 02 March 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.

Shortlisted students will be invited to interview on 23 March 2021 pm (on teams).

If successful, students will be allocated a project on the basis of their ranking during the review process.

Projects at a Glance

No	Title	Supervisor(s)	Themes
1.	Machine learning to predict the development of psoriatic arthritis	Supervisor 1: Dani Prieto-Alhambra Co-Supervisor/s: Laura Coates, Sara Khalid	5
2.	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)
3.	Elucidating T cell phenotype and function in frozen shoulder	Supervisor 1: Stephanie G Dakin, Co-Supervisor/s: Christopher Buckley, Mark Coles	2 (5)
4.	Co-prevalence of liver disease in psoriatic disease (COLIPSO)	Supervisor 1: Laura Coates Co-Supervisor/s: Paul Klenerman, Hussein Al-Mossawi	2 (4)
5.	Tissue ecology in IBD: Diagnostic and therapeutic implications	Supervisor 1: Fiona Powrie Co-Supervisor/s: Matthias Friedrich	1
6.	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
7.	Molecular pathogenesis of Marfan Syndrome	Supervisor 1: Tonia Vincent Co-Supervisor/s: Angus Wann	2
8.	Understanding and exploiting T cell antigen discrimination	Supervisor 1: Omer Dushek Co-Supervisor/s: To be determined	1
9.	Dissecting the fibrotic landscape in Dupuytren's disease	Supervisor 1: Jagdeep Nanchahal Co-Supervisor/s: Chris Buckley	6

10.	Human intradermal Staphylococcal challenge as a novel translational model to explore physiology, pathology and pharmacology	Supervisor: James Fullerton Co-Supervisor/s: Graham Ogg (Prof Dermatology), Duncan Richards (Prof Clinical Therapeutics, Director of OCTRU)	4
11.	Investigating functional consequences of disease-specific genomic enhancers in ankylosing spondylitis	Supervisor 1: Julian Knight Co-Supervisor/s: Carla Cohen, Matteo Vecellio	5
12.	Exploring HLA-B*27-targeted RNAi therapy for Ankylosing Spondylitis	Supervisor 1: Liye Chen Co-Supervisor/s: Paul Bowness	2
13.	A single-cell genomics based investigation of spondyloarthritis	Supervisor 1: Stephen N Sansom Co-Supervisor/s: Paul Bowness	5
14.	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
15.	Understanding the role of lysosomal signalling in autoimmunity	Supervisor 1: Katja Simon Co-Supervisor/s: Alex Clarke	1
16.	Gamma-delta intra-epithelial lymphocytes in coeliac disease	Supervisor 1 Paul Klenerman, Co-Supervisor/s: Michael FitzPatrick, Holm Uhlig	2
17.	Immune cell atlas of giant cell arteritis: the interplay between neutrophil and T cell	Supervisor 1: Irina Udalova Co-Supervisor/s: Raashid Luqmani, Lihui Wang	2
18.	Investigating interactions between oxygen-sensing pathways and autoimmunity	Supervisor 1: Fadi Issa Co-Supervisor/s: Katherine Bull; Joanna Hester; Chris Pugh	1

19.	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
20.	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)
21.	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
22.	Identifying therapeutic combinations for immune mediated inflammatory disease using computational modelling, artificial intelligence and experimentation	Supervisor 1: Prof. Mark Coles Co-Supervisor/s: Prof. Eamonn Gaffney	5
23.	Immunometabolism in human adipose tissue – crosstalk between macrophages and adipocyte progenitors driving sex-specific adipose tissue expansion	Supervisor 1: Prof Fredrik Karpe, OCDEM-RDM Supervisor 2: Prof Jelena Bezbradica Mirkovic, Kennedy-NDORMS Co-Supervisor/s: Dr Marijana Todorcevic, OCDEM-RDM	1

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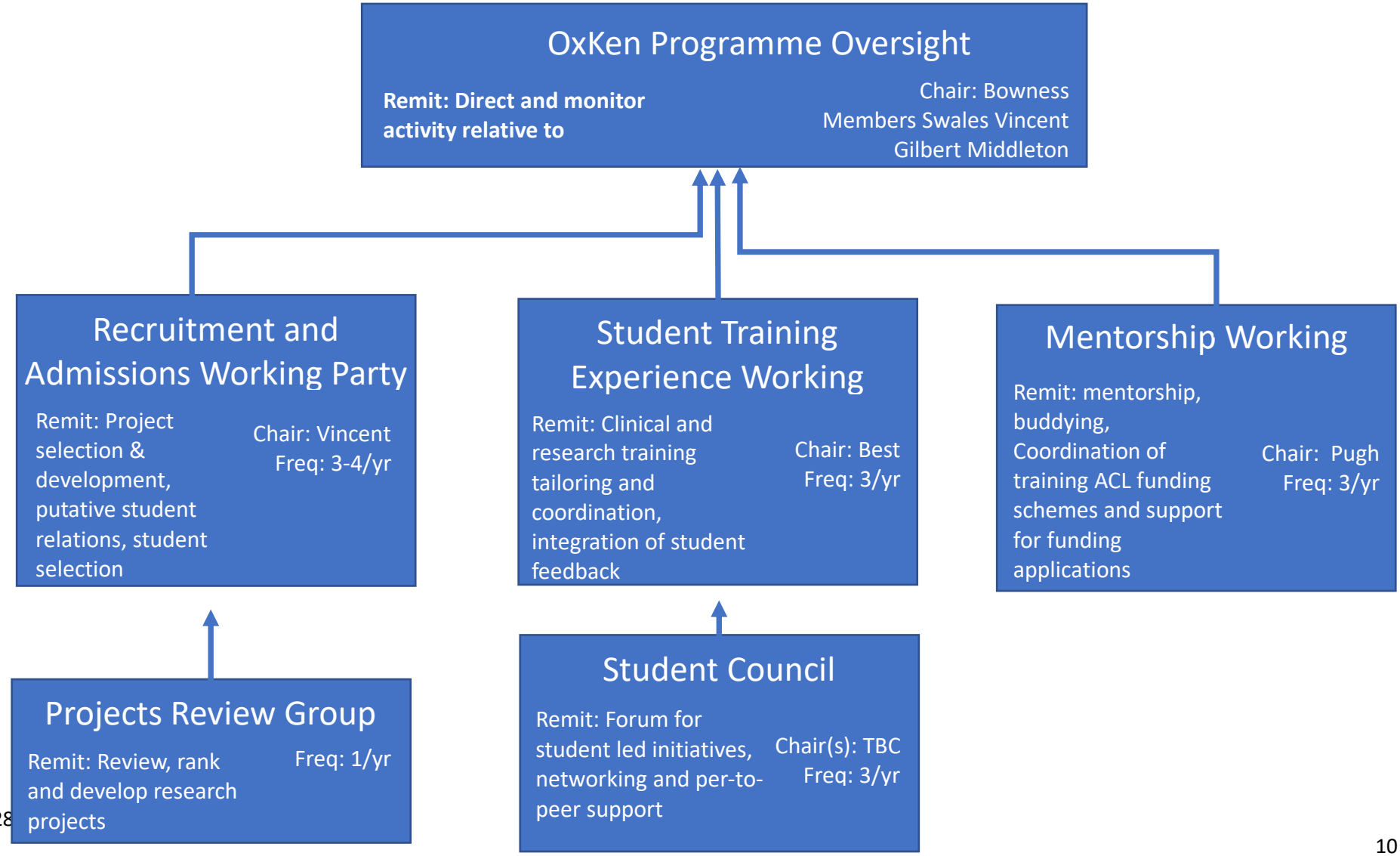
OxKEN Governance Structure



Project Proposals

1. Project Title: Machine learning to predict the development of psoriatic arthritis

Supervisor 1: Dani Prieto-Alhambra

Co-Supervisor/s: Laura Coates, Sara Khalid

PROJECT OVERVIEW: (500 words maximum)

This project will use routinely collected clinical data from electronic medical records across Europe to develop machine learning algorithms for the identification of subjects at high risk of developing psoriatic arthritis amongst those with a diagnosis of psoriasis.

The data have all been previously mapped to a common data model (as used in the EHDEN project - www.ehden.eu) and so can be combined for federated analysis. Large databases of primary care electronic medical records including >20 million UK subjects (CPRD GOLD and AURUM) will be used to develop machine learning algorithms. Embedded within the large epidemiology group led by Dani, you will be taught how to apply different machine learning methods including Regularized logistic regression, Random forests, Gradient boosting machines, Decision trees, Naive Bayes, K-nearest neighbours, Neural networks and Deep learning (Convolutional neural networks, Recurrent neural network and Deep nets) methods.

The best performing algorithms will be made available to the community in an interactive web environment (see here for an example of prediction algorithms for the identification of subjects with rheumatoid arthritis at risk of infections, cardiovascular disease, and cancer).

This work will feed into a large European consortium aiming to predict the development of PsA and will inform future projects including development of an interventional study aiming to prevent PsA in people with psoriasis. This work will particularly inform the identification of patients at increased risk for PsA by clarifying the optimal inclusion and exclusion criteria to define an at-risk population for the future interventional trial.

KEYWORDS (5 WORDS): disease inception, psoriasis, machine learning, epidemiology, psoriatic arthritis

TRAINING OPPORTUNITIES: biostatistics, big data, epidemiology, machine learning, 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. 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.
2. 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.
3. Lane JCE, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, Alser O, Alshammari TM, Biedermann P, Banda JM, Burn E, Casajust P, Conover MM, Culhane AC, Davydov A, DuVall SL, Dymshyts D, Fernandez-Bertolin S, Fišter K, Hardin J, Hester L, Hripcsak G, Kaas-Hansen BS, Kent S, Khosla S, Kolovos S, Lambert CG, van der Lei J, Lynch KE, Makadia R, Margulis AV, Matheny ME, Mehta P, Morales DR, Morgan-Stewart H, Mosseveld M, Newby D, Nyberg F, Ostropolets A, Park RW, Prats-Uribe A, Rao GA, Reich C, Reps J, Rijnbeek P, Sathappan SMK, Schuemie M, Seager S, Sena AG, Shoaibi A, Spotnitz M, Suchard MA, Torre CO, Vizcaya D, Wen H, de Wilde M, Xie J, You SC, Zhang L, Zhuk O, Ryan P, Prieto-Alhambra D; OHDSI-COVID-19 consortium. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. Lancet Rheumatol. 2020 Nov;2(11):e698-e711. doi: 10.1016/S2665-9913(20)30276-9.
4. Roca-Ayats N, Balcells S, Garcia-Giralt N, Falcó-Mascaró M, Martínez-Gil N, Abril JF, Urreizti R, Dopazo J, Quesada-Gómez JM, Nogués X, Mellibovsky L, Prieto-Alhambra D, Dunford JE, Javaid MK, Russell RG, Grinberg D, Díez-Pérez A. GGPS1 Mutation and Atypical Femoral Fractures with Bisphosphonates. N Engl J Med. 2017 May 4;376(18):1794-1795.
5. Bayliss LE, Culliford D, Monk AP, Glyn-Jones S, Prieto-Alhambra D, Judge A, Cooper C, Carr AJ, Arden NK, Beard DJ, Price AJ. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. Lancet. 2017 Apr 8;389(10077):1424-1430. doi: 10.1016/S0140-6736(17)30059-4.

CONTACT INFORMATION OF ALL SUPERVISORS:

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Daniel Prieto-Alhambra – daniel.prietoalhambra@ndorms.ox.ac.uk

Sara Khalid – sara.khalid@ndorms.ox.ac.uk

2. 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:

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

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

3. 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.

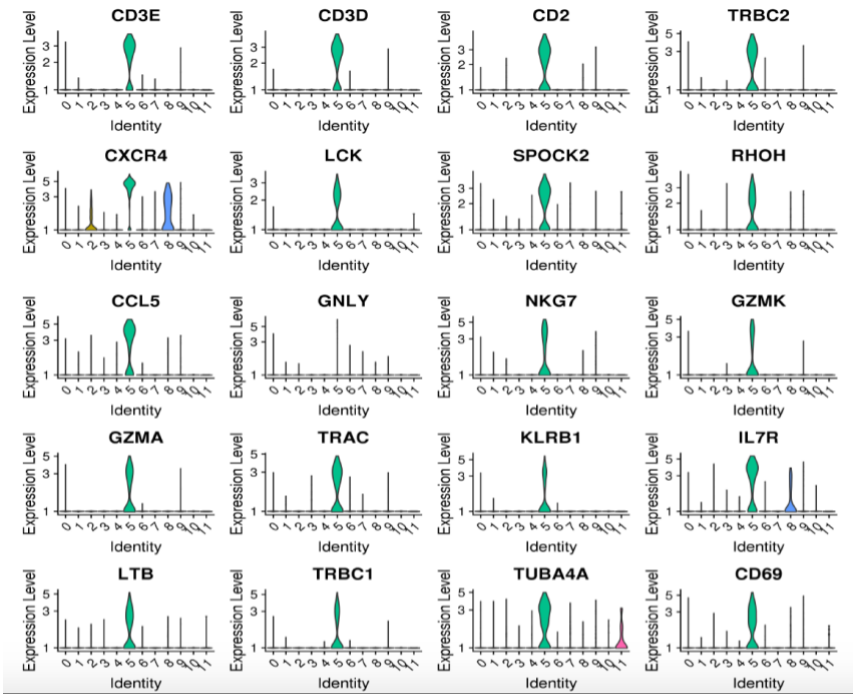

Figure 1. Profile of capsular T cells identified by scRNAseq. Violin plots showing differentially expressed genes in T cells residing within the shoulder joint capsule. Data are generated from tissues collected from 6 non-diseased comparator and 3 frozen shoulder donors.

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

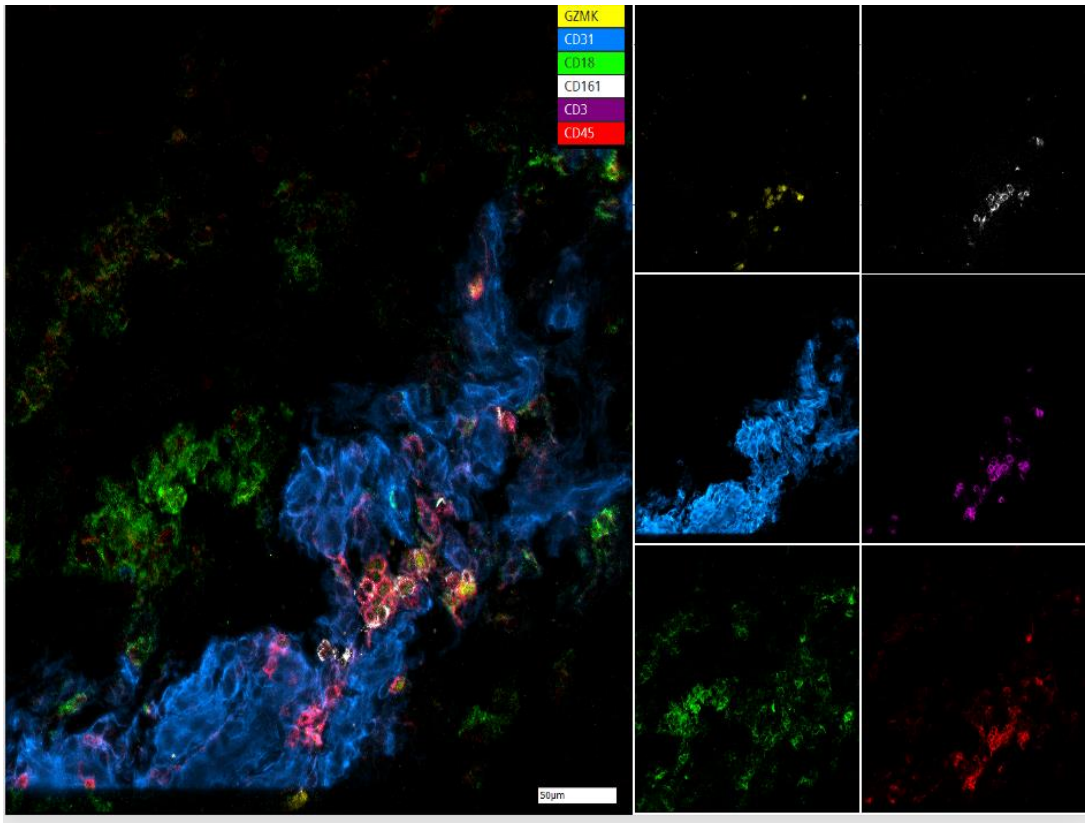

Figure 2A. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows GZMK (yellow), CD18 (green), CD161 (KLRB1, white), CD3

(violet), CD45 (red) and vascular endothelial marker CD31 (blue). Note the perivascular location of identified T cells. Scale bar = 50µm.

Figure 2B

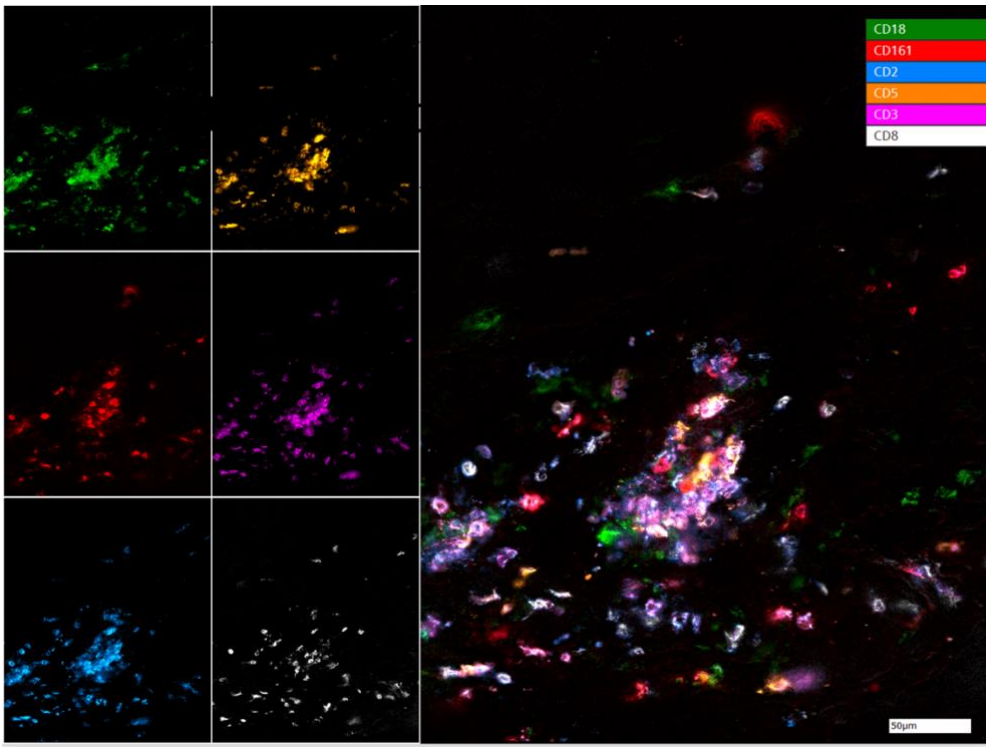

Figure 2B. Immunostaining of frozen shoulder patient tissues for T cell markers. Representative image shows CD18 (green) CD161 (KLRB1, red), CD2 (blue), CD5 (orange), CD3 (magenta), CD8 (white). Scale bar = 50µm.

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:

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Email: markcoles2@kennedy.ox.ac.uk

4. 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):

6. 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.
7. 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
8. 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.
9. 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.
10. 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.

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5. Project Title: Tissue ecology in IBD: Diagnostic and therapeutic implications

Supervisor 1: Prof Fiona Powrie

Co-Supervisor/s: Dr Matthias Friedrich

PROJECT OVERVIEW: (500 words maximum)

The inflammatory bowel diseases (IBDs) are a heterogeneous group of chronic relapsing disorders involving inflammation of the gastrointestinal tract (1). Current long-term therapy in IBD is now dominated by the use of biologics (e.g., anti-TNF), which target inflammatory mediators with high specificity (2). The response to biologics in IBD is heterogeneous, suggesting in some cases these medicines do not target the specific tissue inflammatory processes driving disease. Indeed, biologics fail in more than half of the patients with IBD, and uncontrolled inflammation can lead to the surgical removal of the affected bowel parts, or accelerate tissue fibrosis (3).

Our recent work has highlighted how the complex multifactorial nature of IBD results in considerable heterogeneity in the cell types and molecular processes that drive inflammation (4). This is also reflected at the microscopic level, where observed features range from mucosal lymphoid aggregates to epithelial ulceration with granulocyte presence. The diverse inflammatory tissue ecologies in patients with IBD are currently not well described. The molecular and cellular hallmarks of these ecologies could however allow us to select the most efficient biologic therapy for each patient, moving towards personalised medicine in IBD.

By combining molecular and histologic phenotyping of IBD patient cohorts, as well as *in vitro* and *in vivo* approaches, this project will interrogate the tissue ecologies in IBD that are associated with poor outcome, in particular the non-response to biologics, fibrosis and surgery. This translational project offers the opportunity to apply cutting edge technologies such as transcriptomics, mass spectrometry, digital pathology and pre-clinical organoid/experimental mouse models to address key unmet clinical needs in IBD.

KEYWORDS (5 WORDS):

inflammation, bowel, therapy, fibrosis, surgery

TRAINING OPPORTUNITIES:

The candidate will have the opportunity for training in the analysis of tissue samples obtained from patients with IBD and mouse models. This will include but is not limited to:

- Analytical transcriptomics (e.g., RNAseq), proteomics (e.g., mass spectrometry) and cellular phenotyping (e.g., FACS)
- *In silico* data mining of public datasets
- *In vitro* tissue culture systems (e.g., intestinal organoids)
- *Ex vivo* primary tissue models (e.g., patient tissue explants)
- *In vivo* experimental models of intestinal inflammation and fibrosis (e.g. models of experimental colitis)

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 M, et al. IL-1-driven stromal-neutrophil interaction in deep ulcers identifies a pathotype of therapy non-responsive inflammatory bowel disease. Submitted 2021.

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6. 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

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7. Project Title: Molecular pathogenesis of Marfan Syndrome

Supervisor 1: Professor Tonia Vincent

Co-Supervisor/s: Dr Angus Wann

PROJECT OVERVIEW: (500 words maximum)

Background: Marfan Syndrome (MFS) is an autosomal dominant condition occurring in one in 5,000-10,000 individuals. It is driven by mutations in fibrillin-1 (FBN1), an extracellular matrix (ECM) protein, that forms part of the elastin rich filament of large arteries. This can result in aortic dissection, the principal life-threatening complication of MFS. In recent years it has emerged that loss of fibrillin-1, rather than simply causing weakness of the matrix, alters the bioavailability of a key repair growth factor, TGFβ. Targeting TGFβ arrests aortic dilation in mice with MFS and improves vascular outcomes in patients (1, 2). This, combined with regular surveillance (echocardiography) and improved surgical repair, means that the life expectancy in MFS has greatly increased.

Musculoskeletal complications in MFS are common and cause significant disability, increasingly so in the ageing patient population. In addition to disproportionately long arms and legs, changes include scoliosis, chest wall deformities and hind foot abnormalities. In young individuals with MFS, complaints are often around deformity, affecting self-esteem, posture and ability to cope with the diagnosis. In older individuals, pain may occur as osteoarthritis develops at stress points e.g. the concavity of the scoliotic spine.

We have recently performed detailed characterisation of the skeletons of mice with a human knock-in fibrillin-1 mutation, and shown that they exhibit all of the expected features of disease including long arms and legs, kyphoscoliosis, chest wall abnormalities and hypognathism (small jaw) (unpublished data) (Figure 1). Previously our group has described a number of matrix bound growth factors that are sequestered in the pericellular matrix of articular cartilage and released in response to injury (3-5). Pilot microscopy data of the growth plates of MFS mice indicate that the growth plate is of normal size but there is a reduction in matrix bound latent TGFβ that is normally apparent prominent around the hypertrophic chondrocytes. TGFβ co-localises with perlecan, a heparan sulfate proteoglycan, similar to what we have seen in articular cartilage. A number of important questions have emerged:

(i) What is the temporal development of the skeletal abnormalities in MFS mice pre-and post-natally?
(ii) Is there aberrant TGFβ signalling in the growth plate (as seen in the aortas) and to what extent is this driving the skeletal phenotype?
(iii) Are other perlecan bound growth factors also affected in MFS (e.g. FGF2) and does this contribute to pathobiology of disease?
(iv) Are the musculoskeletal features of MFS amenable to pharmacological intervention, and if so, what is the optimal treatment window?

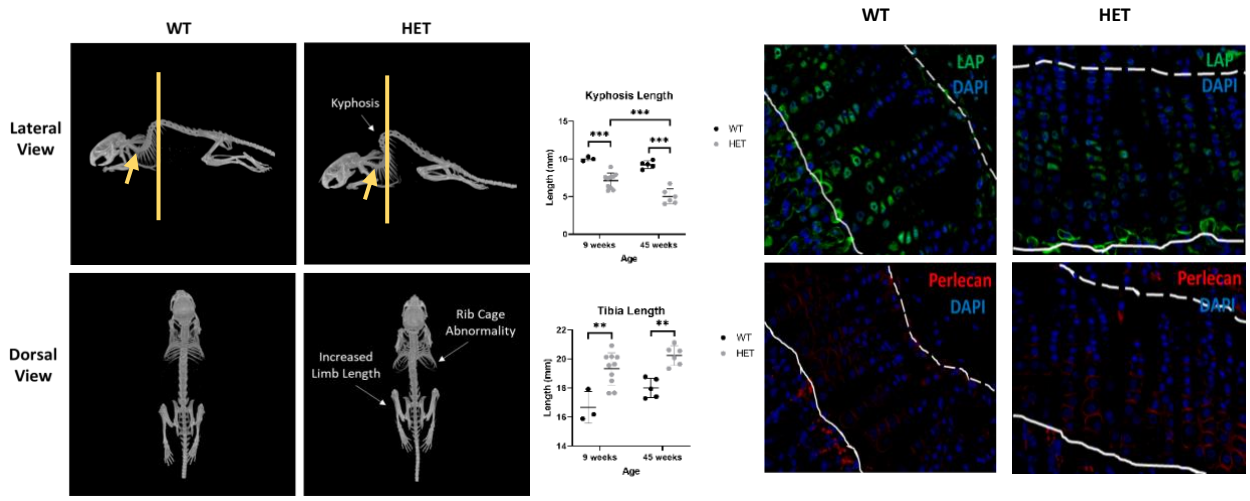

Figure 1. Musculoskeletal features of mice carrying a human type mutation in fibrillin-1. MicroCT images were taken of wild type (WT) and MFS mice (HET) at either 9 or 45 weeks of age. Lateral views of mice show excessive kyphosis in HET which is quantified as a reduced distance from the peak of kyphosis to first rib (kyphosis length). Dorsal view shows abnormal rib cage, and increased tibial length. Immunohistochemistry showing latent TGFb (LAP) and perlecan in the growth plate (between hashed and solid white lines) of WT and HET mice. Note distinctive LAP staining in basal cells of WT mice that is less lost in HETs.

The student will be embedded within the Kennedy Institute of Rheumatology where they will interact with clinical and non-clinical scientists working across inflammatory and other rheumatological diseases. They will be part of a large multidisciplinary cohort of DPhil students at the Kennedy and the wider NDORMS, and take advantage of multiple training opportunities through seminars and departmental and University courses. They will present their data regularly to group and Centre meetings. If desired, they will have the opportunity to attend bi-monthly MFS clinics in Oxford with Vincent.

KEYWORDS (5 WORDS):

Marfan syndrome

Scoliosis

Skeletal development

Growth plate biology

TGFb and FGF2 signalling

TRAINING OPPORTUNITIES:

- Characterisation of the phenotype of MFS in vivo using ex vivo tissue, microCT scanning.

- Confocal microscopy of long bone growth plates.
- In vivo protein turnover studies including SILAC labelling and proteomics.
- RNA Scope (in situ RNA labelling of individual cells within the growth plate).
- Design of a pharmacological trial in mice to test whether the skeletal complications in MFS are modifiable.

KEY PUBLICATIONS (5 maximum):

1. M. M. van Andel *et al.*, Long-term clinical outcomes of losartan in patients with Marfan syndrome: follow-up of the multicentre randomized controlled COMPARE trial. *Eur Heart J* 10.1093/eurheartj/ehaa377 (2020).
2. M. Mullen *et al.*, Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet* **394**, 2263-2270 (2019).
3. X. Tang *et al.*, Connective tissue growth factor contributes to joint homeostasis and osteoarthritis severity by controlling the matrix sequestration and activation of latent TGFβ. *Annals of the rheumatic diseases* 10.1136/annrheumdis-2018-212964 (2018).
4. T. Vincent, M. Hermansson, M. Bolton, R. Wait, J. Saklatvala, Basic FGF mediates an immediate response of articular cartilage to mechanical injury. *Proc Natl Acad Sci U S A* **99**, 8259-8264 (2002).
5. T. L. Vincent, C. J. McLean, L. E. Full, D. Peston, J. Saklatvala, FGF-2 is bound to perlecan in the pericellular matrix of articular cartilage, where it acts as a chondrocyte mechanotransducer. *YJOCA* **15**, 752-763 (2007).

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8. Project Title: Understanding and exploiting T cell antigen discrimination

Supervisor 1: Omer Dushek

Co-Supervisor/s: To be determined

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. We have recently shown using a reductionist experimental system that the co-signalling receptors CD2 and LFA-1 can increase not only antigen sensitivity but also antigen discrimination whereas the co-receptor CD8 increases antigen sensitivity but decreases antigen discrimination. This is important because it suggests that reducing off-target responses to lower-affinity antigens may be possible without impacting on-target responses to higher-affinity antigens. 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. By tampering with individual co-signalling receptors, their impact on antigen sensitivity and discrimination can be quantitatively assessed.

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) T cells exhibit unexpectedly low discriminatory power and can respond to ultra-low affinity peptide-MHC ligands. Submitted (BioRxiv: https://www.biorxiv.org/content/10.1101/2020.11.14.382630v1)

Huhn et al (2021) The discriminatory power of the T cell receptor. Submitted (BioRxiv: https://www.biorxiv.org/content/10.1101/2020.11.16.384495v1)

*Trendel N, *Kruger P, Nguyen J, Gaglione S, Dushek O (2021) Perfect adaptation of CD8+ T cell responses to constant antigen input over a wide range of affinity is overcome by costimulation. Science Signalling (in press, BioRxiv)

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

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

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9. 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.
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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.

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

10. Project Title: Human intradermal Staphylococcal challenge as a novel translational model to explore physiology, pathology and pharmacology

Supervisor: Dr James Fullerton (Associate Professor of Clinical Therapeutics)

Co-Supervisor/s: Prof Graham Ogg (Professor of Dermatology), Prof Duncan Richards (Professor of Clinical Therapeutics, Director of OCTRU)

PROJECT OVERVIEW: (500 words maximum)

Inflammation represents an evolutionarily conserved host response to noxious stimuli. Whilst vital to help combat infection and trigger healing from injury, significant inter- and intra-individual variability in the magnitude and duration of a response is recognised, which in itself may be pathogenic. This may relate to insufficiency (failure to clear an infection), over-exuberance (sepsis, severe Covid-19), lack of regulation (auto-immunity) or chronicity (e.g. atherlosclerosis). In the case of bacterial infections, the character and kinetics of the reaction - both local and systemic - relate to properties of both the pathogen and host, and their subsequent interaction.

The majority of work undertaken to study the fundamental biology of inflammation and the associated immune response has been undertaken in non-human species. Whilst possessing some clear advantages, this approach has well-recognised translational limitations, especially in relation to drug development. Human experimental medicine approaches, where healthy or diseased individuals are deliberately (but safely) exposed to stimuli and/or drugs represent a crucial, if under-utilised, method to interrogate basic molecular and cellular pathways, explore inter-individual variability and elucidate pharmacology in the target species for most therapeutics.

With regards to inflammation, it's regulation and how it may be pharmacologically manipulated, skin challenge models have found a particular role, the response being visible, measurable and accessible. To date, several approaches have been taken to trigger a local inflammatory response: chemical (cantharidin), heat, UV light, physical (negative pressure), allergic (house dust mite) and abrasion. A recently developed and particularly promising approach is injection of UV-killed bacteria intra-dermally with subsequent biopsy or suction blister formation over the site. This permits acquisition of both the infiltrating cells and associated humoral mediators at different phases of the inflammatory response to a relevant stimulus in an intact tissue matrix *in vivo*. To date, this has only been conducted with *E.coli* and *E.coli*-derived endotoxin, a Gram-negative bacteria that is not associated with clinical skin infection.

This project seeks to develop this model further, employing UV-killed Gram-positive Staphylococcal species (*S. aureus* and *S. epidermidis*), including substrains with known discrete pathogenic factors, as stimuli for the local inflammatory response. These common skin commensals are of direct pathogenic relevance in different clinical populations and alternate Staphylococcal colonisation patterns, as well as their host-recognition and handling, are associated with allergic skin disease. The response to intra-dermal injection will be temporally characterised locally and systemically, clinically, physiologically and immunologically, and divergences in response explored. Once established, it is anticipated that these standardised models will be employed by the student in both pre-defined populations to explore clinically-relevant biology (e.g. age-related changes in immune function), and in healthy vs. diseased cohorts (e.g. atopic dermatitis) to detect drivers of an alternate response and thus potential therapeutic targets. The highly translational nature of this project is expected to be of immediate impact, being of relevance in both academia and

also the industrial setting, where it is anticipated to be of value in both pre-clinical and early phase studies seeking to establish proof-of-mechanism.

KEYWORDS (5 WORDS):

Experimental medicine

Immunology

Inflammation

Clinical pharmacology

Dermatology

TRAINING OPPORTUNITIES:

The successful applicant will benefit from a supervisory team comprised of experts in immunology, clinical pharmacology, early phase drug discovery and human *in vivo* challenge models. They will be encouraged to integrate these disciplines to generate novel, impactful paradigms that promote translational science and accelerate the discovery of therapeutics. Independent thought and the challenging of established dogma will be actively encouraged.

The student would be based at the Botnar Research Centre but with access to the MRC Weatherall Institute of Molecular Medicine. Experimental studies will be conducted initially at the NIHR Clinical Trials Unit (Nuffield Orthopaedic Centre). At all sites there are excellent core facilities, infrastructure and expertise readily available. The student would receive training in experimental medicine approaches (including associated clinical skills), molecular and cellular techniques and would gain experience in handling human skin biopsies and skin tissue fluid and cells, with concomitant assays including imaging (e.g. Hyperion), RNAseq, rtPCR and cytokine bead array. Initial hands-on support will enable the rapid accruing of skills and the ability to undertake work independently. The student would also learn about regulatory issues surrounding the use and storage of human samples including ethics, hospital R&D, GCP and HTA. The student would attend GCP, statistical courses and relevant conferences as well as the excellent internal and guest speaker programmes available in Oxford. They will be expected to present data regularly to the department, attend and disseminate data at national and international conferences as well as publish in high-impact journals.

KEY PUBLICATIONS (5 maximum):

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

De Maeyer RPH, van de Merwe RC, Louie R, et al. Blocking elevated p38 MAPK restores efferocytosis and inflammatory resolution in the elderly. *Nat Immunol* 2020;21(6):615-25.

Chen YL, … *Ogg G*. Re-evaluation of human BDCA-2+ DC during acute sterile skin inflammation. *J Exp Med*. 2020 Mar 2;217(3)

Hardman CS, … *Ogg G*. CD1a presentation of endogenous antigens by group 2 innate lymphoid cells. *Sci Immunol*. 2017 Dec 22;2(18):pii: eaan5918

Jarrett R, … *Ogg G*. Filaggrin inhibits generation of CD1a neolipid antigens by house dust mite derived phospholipase. *Science Translational Medicine*. 2016;8:325ra18

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11. 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.

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12. Project Title: Exploring HLA-B*27-targeted RNAi therapy for Ankylosing Spondylitis

Supervisor 1: Liye Chen

Co-Supervisor/s: Paul Bowness

PROJECT OVERVIEW: (500 words maximum)

Ankylosing Spondylitis (AS) is a common form of arthritis with an unusually strong genetic association with HLA-B*27 (90% in AS vs 5% in healthy control). Theories proposed to explain HLA-B27's role in AS pathogenesis include 1) presentation of arthritogenic peptide(s), 2) intracellular and cell surface expression of HLA-B27 free heavy chains (FHC). HLA-B27 FHCs enhance interleukin (IL)-17 production in AS through binding to KIR3DL2 expressed on T cells [1]. Both HLA-B*27 peptide presentation and FHC cell surface expression can be modulated through the suppression of endoplasmic reticulum aminopeptidase 1 (ERAP1, another genetic risk in AS) [2 3]. However, development of drugs targeting HLA-B*27 FHC or ERAP1 have proven challenging due to technical reasons or safety concerns. Thus, despite the genetic and biological evidence highlighting the key role of HLA-B*27 in AS, drugs targeting HLA-B*27 have not been developed.

RNA interference (RNAi) was discovered twenty years ago but its development for clinical application has been halted for a long time due to stability and delivery issues. These issues have been solved recently, leading to the development of the first successful RNAi drug approved for hereditary ATTR amyloidosis in 2018. Earlier this year, RNAi targeting PCSK9, a genetic risk for coronary artery disease, was approved as the low-density lipoprotein cholesterol (LDL-C) lowering treatment. PCSK9 RNAi shows an afficacy similar to that of PCSK9 antibodies but is cheaper and only requires twice-yearly dosing, thus saving the healthcare cost.

This project aims to explore the translational value of HLA-B*27 RNAi in AS. Patients with AS have enhanced lymphocyte IL-17 responses and monocyte TNF-alpha response [4 5], with antibodies blocking IL-17 and TNF-alpha currently used for AS treatment. In this project you will firstly investigate the impact of HLA-B*27 knockdown/knockout on the IL-17 and TNF-alpha response in lymphocytes and monocytes from HLA-B*27+ AS patients. You will stimulate patient cells, including whole blood, synovial fluid and T cells and monocytes isolated from these sources, with T cell activators including cytokines, pathogen-derivatives and whole bacteria under different conditions. The role of HLA B27 and its mechanism of action will then be studied especially for lymphocyte IL-17 production, which is largely unknown.

KEYWORDS (5 WORDS):

Ankylosing Spondylitis, HLA-B*27, RNAi therapy, TNF-alpha, IL-17

TRAINING OPPORTUNITIES:

You will receive broad training in immunology and molecular biology including: 1) human primary T cell and monocyte culture, 2) designing and performing inflammation-relevant cellular assays using primary immune cells (techniques including ELISA, flowcytometry, qPCR and western blot), 3) gene RNAi knockdown and CRISPR-knockout in primary T-cells and monocytes (techniques including standard molecular biology techniques, lentivirus production for gene knockdown and overexpression), 4) bulk and/or single cell RNA-seq for mechanistic study, 5) designing cellular assays to model inflammation-driven disease for translational investigation.

A core curriculum of lectures will be taken in the first term to provide a solid foundation in a broad range of subjects including musculoskeletal biology, inflammation, epigenetics, translational immunology, data analysis and the microbiome. Students will also be required to attend regular seminars within the Department and those relevant in the wider University. Students will be expected to present data regularly in Departmental seminars, lab meeting within Chen and Bowness groups and to attend external conferences to present their research globally, with limited financial support from the Department.

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

KEY PUBLICATIONS (5 maximum):

1. Bowness P, Ridley A, Shaw J, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. *J Immunol* 2011;186(4):2672-80. doi: 10.4049/jimmunol.1002653 [published Online First: 2011/01/21]
2. Chen L, Fischer R, Peng Y, et al. Critical role of endoplasmic reticulum aminopeptidase 1 in determining the length and sequence of peptides bound and presented by HLA-B27. *Arthritis Rheumatol* 2014;66(2):284-94. doi: 10.1002/art.38249 [published Online First: 2014/02/08]
3. Chen L, Ridley A, Hammitzsch A, et al. Silencing or inhibition of endoplasmic reticulum aminopeptidase 1 (ERAP1) suppresses free heavy chain expression and Th17 responses in ankylosing spondylitis. *Ann Rheum Dis* 2016;75(5):916-23. doi: 10.1136/annrheumdis-2014-206996 [published Online First: 2015/07/02]
4. Al-Mossawi MH, Chen L, Fang H, et al. Unique transcriptome signatures and GM-CSF expression in lymphocytes from patients with spondyloarthritis. *Nat Commun* 2017;8(1):1510. doi: 10.1038/s41467-017-01771-2 [published Online First: 2017/11/17]
5. Shi H, Chen L, Ridley A, et al. GM-CSF Primes Proinflammatory Monocyte Responses in Ankylosing Spondylitis. *Front Immunol* 2020;11:1520. doi: 10.3389/fimmu.2020.01520 [published Online First: 2020/08/09]

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Paul Bowness: paul.bowness@ndorms.ox.ac.uk

13. Project Title: A single-cell genomics based investigation of spondyloarthritis

Supervisor 1: Assoc. Prof. Stephen N Sansom

Co-Supervisor/s: Prof. Paul Bowness

PROJECT OVERVIEW: (500 words maximum)

In our groups, we investigate the molecular basis of inflammatory arthritis[1,2] (https://sansomlab.org ; https://www.ndorms.ox.ac.uk/research-groups/immunology-of-Ankylosing-Spondylitis). This project focuses on ankylosing spondylitis (AS), a common and highly heritable form of arthritis which characteristically involves inflammation of the sacroiliac joints and spine. To discover the cellular and molecular causes of this disease, we are applying state-of-the-art multi-modal single-cell genomics technology directly to patient biopsy samples. With this approach, we can simultaneously capture the transcriptome, surface protein profile and TCR sequences of thousands of cells. For your DPhil research, you will perform computational analysis of the resulting datasets to identify the cellular circuits, biological pathways and genes that drive pathogenesis.

This work is vital as current therapeutics do not work in all patients and cannot induce disease remission. Inflammation in AS is known to involve the IL-23/IL-17 immune pathway[3] but the cellular and molecular origins of the disease remain mysterious. The strong genetic association of AS with the human leukocyte antigen (HLA) class I molecule HLA-B*27 suggests that inflammation is triggered by an 'arthritogenic' peptide, but there is also evidence for several other models of disease pathogenesis[4]. This project will involve comparison of cells from patients with spondylitis with those from other forms of arthritis as well as from healthy joints (which we are generating as part of the Human Cell Atlas project).

Working closely with clinical and experimental colleagues you will have the opportunity to contribute to the wet-lab aspects of the project. This will include designing and performing follow-up experiments to test hypotheses using the latest functional genomics approaches such as CRISPR-based gene editing. Ultimately, this research will provide a rational basis for the development of more effective therapeutics that target the causes, rather than the symptoms, of AS. This research is supported by funding from Versus Arthritis.

KEYWORDS (5 WORDS):

inflammation; immune mediated inflammatory disease; arthritis; single cell genomics; computational biology; bioinformatics

TRAINING OPPORTUNITIES:

The Kennedy Institute is a world-renowned research centre, housed in a brand new, state-of-the-art facility at the University of Oxford. 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. Students will become fluent in computational genomics and acquire an expert understanding of chronic inflammatory disease. Training will be provided in data science techniques including the writing of computational pipelines (see e.g. https://github.com/sansomlab/tenx) with Python, the use of Linux high-performance compute clusters, and statistical data analysis and visualisation with R. Students will have the opportunity to utilise machine learning approaches, to work closely with world-leading statistical geneticists, and will perform integrated analyses with “big data” from sources such as the Human Cell Atlas (https://www.humancellatlas.org/) and ImmGen projects. You will be expected to develop a close understanding of experimental research through regular attendance of wet-lab group meetings. You will have the opportunity to be closely involved in the generation of functional genomics data and to learn the various immunological techniques that are up and running in the Bowness lab. For more information on our work please visit our websites: https://www.kennedy.ox.ac.uk/research/computational-genomics (Sansom group), https://www.ndorms.ox.ac.uk/research-groups/immunology-of-Ankylosing-Spondylitis (Bowness group).

A core curriculum of lectures will be taken in the first term to provide a solid foundation in a broad range of subjects including musculoskeletal biology, inflammation, epigenetics, translational immunology, data analysis and the microbiome. Students will attend regular seminars within the department and those relevant in the wider University. Students will be expected to present data regularly in the departmental PGR seminars, Sansom and Bowness group meetings and to attend external conferences to present their research globally.

Students will have access to various courses run by the Medical Sciences Division Skills Training Team and other departments. All students are required to attend a 2 - day Statistical and Experimental Design course at NDORMS.

KEY PUBLICATIONS (5 maximum):

(1) Distinct fibroblast subsets drive inflammation and damage in arthritis. Adam P. Croft, et. al. Nature, 2019
(2) Unique transcriptome signatures and GM-CSF expression in lymphocytes from patients with spondyloarthritis. Al-Mossawi et. al. Nature Communications, 2017
(3) Progress in our understanding of the pathogenesis of ankylosing spondylitis. Simone D, Al Mossawi and Bowness P. Rheumatology (Oxford), 2018
(4) HLA-B27. Bowness P. Annual Review Immunology, 2015

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14. PROJECT TITLE: Application of single cell omics to dissect tissue-immune cell crosstalk and identify targetable mediators of tissue fibrosis

POTENTIAL 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).

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:

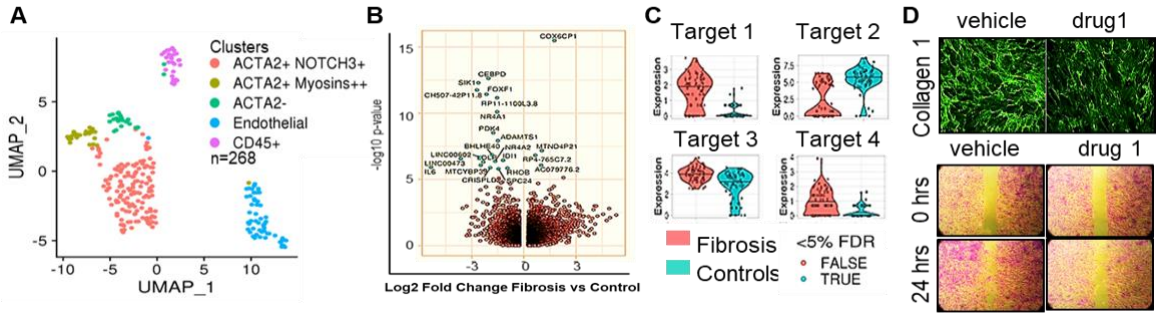
(1) Single cell multi-omic analysis of **primary tissue biopsies** from patients and appropriate controls, including biopsies from **Dupytren's Disease, Frozen Shoulder, human myocardium**[3,4], lung tissue from patients with **idiopathic pulmonary fibrosis**[5-7] and bone marrow biopsies from patients 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**

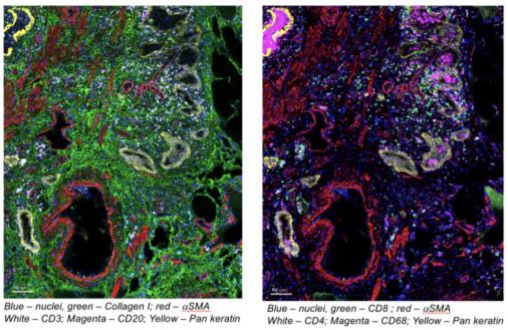
pathologies would greatly increase the power of the study and likelihood of identifying a clinically relevant, tractable target.

(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.



REFERENCES:

1. Eckes B, Eming SA. Tissue fibrosis: a pathomechanistically unresolved challenge and scary clinical problem. *Exp Dermatol*. 2017;26(2):135-136.
2. Zhao X, Kwan JYY, Yip K, Liu PP, Liu FF. Targeting metabolic dysregulation for fibrosis therapy. *Nat Rev Drug Discov*. 2020;19(1):57-75.
3. Moreira L, Takawale A, Hulsurkar M, et al. Calcitonin paracrine signaling controls atrial fibrogenesis and arrhythmia. . *Nature*. 2020;In press.
4. Reilly SN, Liu X, Carnicer R, et al. Up-regulation of miR-31 in human atrial fibrillation begets the arrhythmia by depleting dystrophin and neuronal nitric oxide synthase. *Sci Transl Med*. 2016;8(340):340ra374.
5. Mann E, Menon M, Knight S, et al. Longitudinal immune profiling reveals distinct features of COVID-19 pathogenesis. *Science Immunology (in press)*. 2020.
6. E Fraser, L Denney, K Blirando, et al. Type-1 IFN primed monocytes in pathogenesis of idiopathic pulmonary fibrosis. *BioRxiv* 2020;doi 10.1101/2020.01.16.908749.
7. Peng Y, Mentzer AJ, Liu G, et al. Broad and strong memory CD4(+) and CD8(+) T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat Immunol*. 2020.
8. Psaila B, Wang G, Rodriguez-Meira A, et al. Single-Cell Analyses Reveal Megakaryocyte-Biased Hematopoiesis in Myelofibrosis and Identify Mutant Clone-Specific Targets. *Mol Cell*. 2020;78(3):477-492 e478.
9. Rodriguez-Meira A, Buck G, Clark SA, et al. Unravelling Intratumoral Heterogeneity through High-Sensitivity Single-Cell Mutational Analysis and Parallel RNA Sequencing. *Mol Cell*. 2019;73(6):1292-1305 e1298.
10. Colombo M, Brierley C, Wang G, et al. A novel tissue-specific platform for prioritisation and validation of novel inhibitors of bone marrow fibrosis using human bone marrow stromal cells. *European Haematology Association Annual Meeting Abstract* 2020.

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28 Jan2021

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15. Project Title: Understanding the role of lysosomal signalling in autoimmunity

Supervisor 1: Katja Simon

Co-Supervisor/s: Alex Clarke

PROJECT OVERVIEW: (500 words maximum)

Lysosomes are the essential recycling machinery of the cell, receiving and degrading biological macromolecules, and liberating their components for reuse.

They are also multifunctional signalling platforms, with critical roles in sensing cellular nutrient status, controlling apoptosis, and in immunity against microbes, including HIV, SARS-CoV2, and cholera.

Shortly after their identification in the late 1960s, it was noted that lysosomes accumulate in the immune cells of patients with the often severe and not infrequently fatal autoimmune disease systemic lupus erythematosus (SLE). However, why this happens and what the consequences are for autoimmunity remains essentially unknown. This is important, because SLE has great unmet treatment needs, with limited and often ineffective options.

We've recently shown that autophagy, a fundamental process for transferring intracellular cargo to the lysosome, is defective in SLE, and that genetic variants in lysosome signalling adapters can predispose to the disease. We've also found that lysosomal function can be modulated, with important effects on the immune system.

In this project, you will examine the hypothesis that a build-up of self-nucleic acids and antigens in a defective lysosomal system triggers an immune response which drives SLE. Lysosomes are vital to terminate signalling by toll like receptors (TLRs) in endosomes, which recognise self-nucleic acids. This may also contribute to the inflammatory state seen in aging, again associated with lysosomal defects.

Our aim is to translate lysosomal modification into novel treatment approaches for SLE and other autoimmune diseases.

To do so, you will start work with human patients, using a full spectrum of advanced techniques to image lysosomes and analyse their function in immune cells. Following on will be detailed mechanistic study, using experimental models of autoimmune disease and lysosomal dysfunction. Finally restoration of lysosomal function using genetic and pharmacologic approaches will be tested in disease models to provide a foundation for clinical use.

KEYWORDS (5 WORDS):

Lysosome

SLE

Autoimmunity

Autophagy

Innate immunity

TRAINING OPPORTUNITIES:

This project will provide comprehensive coverage of standard and advanced human and experimental immunology techniques, including flow cytometry, confocal imaging, *in vitro* cell culture, and quantification of lysosomal function. The student will have the opportunity for patient contact to collect samples, and develop clinical research skills. There will be opportunities to acquire skills in bioinformatic analysis of large data sets generated by genomic techniques during the project. The student will develop detailed understanding of genetically modified models of cellular function and disease, and their role in developing mechanistic and therapeutic insights.

KEY PUBLICATIONS (5 maximum):

Ballabio A, Bonifacino JS. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat Rev Mol Cell Biol* Feb;21(2):101-118 (2020)

Clarke, A. J. *et al.* Autophagy is activated in systemic lupus erythematosus and required for plasmablast development. *Ann Rheum Dis* **74,** 912–920 (2015).

Bonam, S. R., Wang, F. & Muller, S. Lysosomes as a therapeutic target. *Nat Rev Drug Discov* 1–26 (2019).

Clarke, A. J. & Simon, A. K. Autophagy in the renewal, differentiation and homeostasis of immune cells. *Nat Rev Immunol* 1–14 (2019).

Zhang H et al. Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence. *Mol Cell* Oct 3;76(1):110-125 (2019)

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16. 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).

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

17. Project Title: Immune cell atlas of giant cell arteritis: the interplay between neutrophil and T cell

Supervisor 1: Professor Irina Udalova

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

PROJECT OVERVIEW: (500 words maximum)

Giant cell arteritis (GCA) is the most common form of vasculitis, which affects mainly the aging population leading to permanent blindness without timely diagnosis and medical intervention (1). GCA patients are 17 times more likely to develop cardiovascular complications compared to the healthy controls. Similar cardiovascular commodity is also observed in other rheumatic diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ANCA (anti neutrophil cytoplasmic antibody) associated vasculitis (2).

However, the underlying pathogenesis of GCA remains poorly understood. we have recently discovered novel immature neutrophils populations in the blood of GCA patients to be unequivocally associated with both the clinical phenotype and response to treatment (3) Moreover, the release of immature neutrophils into the circulation has been described in SLE, RA, and infectious diseases, such as sepsis or severe COVID-19 (5). We further demonstrated that immature neutrophils remained in the vasculature for a prolonged time, interacted with platelets, extravasated into the tissue surrounding the temporal arteries and generated high levels of extracellular reactive oxygen species (ROS) affecting vascular barrier in vitro (3).

Based on our findings, we hypothesize that immature neutrophils are the key players in initiating vascular inflammation and propose the following 3-stage model of neutrophils in GCA pathogenesis. **Stage 1:** ongoing chronic inflammation in patients causes release of immature neutrophils into the circulation with an extended life span. **Stage 2:** immature neutrophils enter from both lumen and capillaries and adhere to the elastic lamina for prolonged periods of time to release ROS in an inflammatory microenvironment, which results in the accumulation of small breaks and lesions in elastic lamina. **Stage 3:** other immune cells, including monocytes, T cells, and DCs, infiltrate into the vessels via the initial lesions and gradually lead to formation of giant cells and/or granulomas culminating in severe vessel inflammation. Specifically, disbalance in T cell repertoire, i.e. expansion of Th1 and Th17 cell and reduction in Treg cells, has been well-documented in GCA patients (2). This project will investigate the interaction between immature neutrophils and dysfunctional T cells and its contribution to the GCA pathogenesis.

The study will be conducted in three key stages.

S1) Mapping the geographical distribution of neutrophils and T cells subsets and their direct physical cell interaction in the biopsies of newly diagnosed GCA patients (4) using Hyperion, imaging mass cytometry of up to 40 markers.

S2) Immunophenotyping T cell subsets in the blood of GCA patients using CyTOF and FACS analyses.

S3) In vitro analysis of neutrophil and T cell interactions, such as T cell proliferation assay in the presence of neutrophils; b) profiling of growth factors and cytokines released by neutrophils and T cells, which sustain proliferation, recruitment etc.

Insight from studying neutrophil and T cell interplay in GCA will aid discovery of new molecular mechanisms behind inflammatory vasculature diseases and may lead to alternative neutrophil – T cell targeted therapies.

KEYWORDS (5 WORDS):

Giant cell arteritis, vascular inflammation, neutrophils, t cells, hyperion

TRAINING OPPORTUNITIES:

The candidate will benefit significantly from the established and productive framework of translational medical research between the Udalova and Luqmani groups based at Kennedy institute and Botnar research centre respectively. The Kennedy Institute hosts state-of-art core research facilities from single cell mass cytometry (CyToF), imaging mass cytometry (Hyperion), FACS sorting to advanced imaging technologies including confocal, whole tissue and live cell imaging. The candidate will be trained to acquire those advanced cellular technologies which offer unprecedented potential to tackle challenging biomedical questions. The Botnar team lead by Professor Luqmani will provide training on the design of biomedical research, analysis of large medical dataset and organisation of clinical sample recruitments and processing.

The candidate will learn basic molecular techniques at the Udalova group including human blood PBMC isolation; cell purification, isolation and ex vivo tissue culture; western, ELISA and rt-PCR. A rare opportunity associated with the proposed project is to establish a 3D microvessel culture to model the interaction between neutrophils and t cells in GCA pathogenesis. The 3D cell culture on-a-chip system can be modified and adapted to other organoid systems in a high throughout format that will be very useful for disease target identification and drug screening in medical research.

The project will be in active collaboration with other groups of various expertise in and outside Oxford. For instance, multiplex luminex in collaboration with Luzheng Xue group at Nuffield department of medicine will be conducted to investigate growth factors and cytokines released by neutrophils in vitro and in the plasma of GCA patients. Hyperion will be in collaboration with Ling-pei Ho group at WIMM.

Scientific writing, data analysis and communication skills are an integral part of the D.Phil program. The candidate will be required to present and attend lab meetings, encouraged to attend both external and internal Kennedy seminars and journal clubs, relevant workshops on cutting edge technologies, data analysis tools/software and to present at local and national conferences related to the proposed program. Discoveries made from the research will be highly encouraged to be published at high impact journals.

KEY PUBLICATIONS (5 maximum):

1) C. Ponte, A. F. Rodrigues, L. O'Neill, R. A. Luqmani, Giant cell arteritis: Current treatment and management. *World J Clin Cases* **3**, 484-494 (2015)

2) D. M. Schwartz, A. M. Burma, M. M. Kitakule, Y. Luo, T cells in autoimmunity-associated cardiovascular diseases. Front. Immunol. **11**: 588776 (2020)

3) L. Wang *et al.*, ROS-producing immature neutrophils in giant cell arteritis are linked to vascular pathologies. *JCI Insight* **5**, (2020).

4) R. Luqmani et al., The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess **20**, 1-238 (2016).

5) A. Silvin *et al.*, Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19. *Cell* **182**, 1401-1418 e1418 (2020).

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

18. 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.

19. 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

Shah et al, Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19. Crit Care, June 2020. https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03051-w

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

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

Supervisor 1: Prof. Mark Coles

Co-Supervisor/s: Prof. Christopher Buckley

PROJECT OVERVIEW: (500 words maximum)

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

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

Project Aims:

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

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

TRAINING OPPORTUNITIES: The student will be based in the Kennedy Institute of Rheumatology taking advantage of world leading technologies in the institute including confocal microscopy, high dimensional Cell Dive imaging and 3D light sheet microscopy. obtain training in key cutting-edge technologies including: 3D light sheet and multi-plex high dimensional imaging; Spatial genomics and big data analysis; Organoid culture systems; biomechanical forces; Human Developmental Biology

KEY PUBLICATIONS (5 maximum):

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

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

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

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

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

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21. 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.

Aschenbrenner D, Quaranta M, Banerjee S, Ilott N, Jansen J, Steere B, Chen YH, Ho S, Cox K, Arancibia-Cárcamo CV, Coles M, Gaffney E, Travis SP, Denson L, Kugathasan S, Schmitz J, Powrie F, Sansom SN, Uhlig HH. Deconvolution of monocyte responses in inflammatory bowel disease reveals an IL-1 cytokine network that regulates IL-23 in genetic and acquired IL-10 resistance, Gut. 2020 Oct 9:gutjnl-2020-321731. doi: 10.1136/gutjnl-2020-321731A covid

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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.

Bull JA, Mech F, Quaiser T, Waters SL, Byrne HM, Mathematical modelling reveals cellular dynamics within tumour spheroids, PLoS Comput Biol, 2020 Aug 18;16(8):e1007961. doi: 10.1371/journal.pcbi.1007961

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helen.byrne@maths.ox.ac.uk

22. 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.

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23. Project Title: Immunometabolism in human adipose tissue – crosstalk between macrophages and adipocyte progenitors driving sex-specific adipose tissue expansion

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Co-Supervisor/s: Dr Marijana Todorcevic, OCDEM-RDM

PROJECT OVERVIEW: (500 words maximum)

The metabolic risk of obesity leading to type 2 diabetes and premature heart disease is conveyed by the imbalance in the opposing function of upper and lower body fat stores. An upper body fat and visceral fat accumulation are strongly associated with metabolic complications and chronic inflammation whereas expansion of lower body fat stores is protective. This fits well with physiological studies observing functional differences between abdominal and gluteofemoral adipose tissue (AT) but the key drivers for sex-specific expansion of the protective lower body fat stores are poorly understood. In type 2 diabetes, chronic inflammation in AT is caused by the enhanced recruitment of pro-inflammatory macrophages. The role of an innate immune response in AT is understood for cellular turnover but less is known about the role of immune cells in tissue remodelling. Recent pilot data from our laboratory suggest the involvement of an immunometabolic cross talk between tissue macrophages and adipocyte progenitor cells stimulated by the female specific sex hormone oestrogen. Using a newly developed co-culture system of iPS-derived macrophages and human regional-specific adipocyte progenitor cells we showed that oestrogen is inducing a phenotypic change in the macrophages, but only in the presence of gluteofemoral pre-adipocytes and not with abdominal cells. In turn, only in the presence of macrophages, oestrogen induced a proliferative response in the gluteofemoral pre-adipocytes. With these findings we postulate a priming signal from gluteofemoral pre-adipocytes to macrophages and the release of a proliferative signal from the macrophages. The aim of this studentship is to characterise the cross-talk between tissue macrophages and adipocytes to understand the regulation of tissue remodelling and inflammation.
The project will involve the following steps:

- Establish and fine-tune the co-culture and organoid systems between iPS-derived macrophages and human adipose cells.
- Characterise the phenotypic changes of macrophages when in contact with adipocytes, in the presence or absence of oestrogen, towards pro-inflammatory polarization, and its impact on tissue remodelling
- Identify signals exchanged between macrophages and adipocytes and signalling pathways activated that convey a proliferative response on gluteofemoral pre-adipocytes in the presence of oestrogen
- Access human whole AT from humans with defined fat distribution (recall-by-phenotype in the Oxford Biobank) to provide *in vivo* verification of findings.

This project has great potential for discovery of poorly understood signals in normal sex-specific human tissue development and novel therapeutic strategies for immunometabolic disease.

KEYWORDS (5 WORDS):

Inflammasome, matrix remodelling, single cell RNASeq, android and gynoid

TRAINING OPPORTUNITIES:

- Human adipocyte cell culture systems including organoids
- RNA silencing and genetic modification of iPS macrophages and adipocytes
- In vivo and vitro tissue/cell phenotyping, microscopy, RNASeq
  Human genetic models, handling human tissues

KEY PUBLICATIONS (5 maximum):

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