MB-PhD Supervisor Profiles & Project Outlines

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Project Title: The impact of psychological factors on outcomes in psoriatic arthritis

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Supervisor 2: Professor Chris Armitage; School of Health Sciences, Division of Psychology & Mental Health; Email: chris.armitage@manchester.ac.uk

Supervisor 3: Dr Mark Lunt; School of Biological Sciences, Division of Musculoskeletal & Dermatological Sciences; Email: mark.lunt@manchester.ac.uk

Project Description

Background

Psoriatic Arthritis (PsA) is a chronic debilitating form of immune-mediated inflammatory arthritis that is associated with the common skin condition psoriasis. PsA affects up to 30% of people with psoriasis and the impact of disease is profound. PsA leads to significant joint swelling, damage and disability. There is currently no cure for PsA, and biologic disease modifying anti-rheumatic drugs (bDMARDs), such as TNF inhibitors, are used to control the inflammation. Not everyone, however, responds to the drugs and the complex interplay between psychological distress and inflammation has yet to be elucidated. The traditional thought that pain and disability leads to psychological distress in patients with inflammatory disease is simplistic and evidence for a more complex immune-psychology interplay is emerging. Depression and anxiety are associated with higher levels of joint inflammation in patients with PsA and TNF-driven systemic inflammation may affect psychiatric symptoms demonstrating the complex interaction between inflammation and psychological distress.

Hypotheses

1. Baseline psychological factors affect response to TNF inhibitors in patients with psoriatic arthritis
2. Active psoriatic arthritis joint inflammation results in psychological distress

Approach

PsA patients will be identified from the OUtcome of Treatment in Psoriasis and Psoriatic Arthritis Study Syndicate (OUTPASS, REC 13/NW/0068; CI - JBluett) Study, a large (n=600) prospective observational cohort study of patients with PsA about to be commenced on a bDMARD. Psychological and clinic-demographic variables are taken at baseline and patient response, psychological measures (General Self-Efficacy Scale, Hospital Anxiety and Depression Scale and Brief Illness Perception Questionnaire) and self-reported adherence are measured at 3, 6 and 12 months.

Utilising a cohort approach of patients with and without psychological comorbidities at baseline the student will explore the influence of pre-existing psychological comorbidities and PsA response to TNF inhibitors (as measured by swollen and tender joint count), adjusting for potential confounding factors (hypothesis 1).

Using random effects models to allow for within subject correlation, the student will investigate whether patients with active inflammation, despite TNF inhibitor therapy, experience a higher burden of psychological distress over time. The applicant will gain experience in biostatistics including statistical modelling, handling missing data and develop an understanding of how psychological factors influence disease response in inflammatory conditions (hypothesis 2).

The development of skills in statistics and complex modelling will be essential for students to be able to undertake analysis in other disease areas in the future and not just rheumatology or psychology.

OUTPASS has ethical approval in place and has recruited more than 600 PsA patients to date. Therefore further

prospective data collection or ethical approvals will not be required to ensure successful completion of the project.

Background to research of supervisory team

James Bluett is the Chief Investigator of OUTPASS. He has supervised clinicians throughout the training spectrum including medical students, academic foundation years and a specialty trainee who is currently completing their PhD. He has a research interest in stratified medicine approaches in inflammatory arthritis including pharmacogenomics, clinical trials and the development of complex health interventions. He is currently the chief investigator of a clinical trial of an adherence intervention.

Christopher J. Armitage is Professor of Health Psychology at the University of Manchester. He researches psychological theory (e.g., transtheoretical model) to develop tools for behaviour change (e.g., medication adherence) among diverse populations (e.g., patients with arthritis). He has published more than 150 peer-reviewed articles on these topics and has received funding to support this research from numerous sources, including the MRC.

Mark Lunt is Reader in Medical Statistics at the University of Manchester, based in the Centre for Epidemiology Versus Arthritis. His focus is on ensuring that researchers from the Centre use appropriate statistical methodology in their work, and has a particular interest in causal inference from observational data, since most of the Centre's work is with such data. He has over 250 peer-reviewed publications, and a current h-index of 82.

Supervision and lab culture

The supervisory team currently supervises 23 PhD students between them. The student will be paired with a peer mentor and assigned an academic advisor and postgraduate research tutor who in addition to their supervisory team are responsible for monitoring student progress and assessment. The Unit has an ethos of close and regular contact between supervisors and students. Weekly formal meetings will be held to provide updates on progress and discuss future plans. The student will undertake the centers statistics course as part of their training and be encouraged to undertake clinical attachments to maintain their clinical knowledge and skills.

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Project Title: Identification of novel biomarker profiles to define subgroups of Systemic Autoimmune Rheumatic Diseases

Supervisor 1: Prof Ian Bruce; School of Biological Sciences, Division of Musculoskeletal & Dermatological Sciences; Email: ian.bruce@manchester.ac.uk

Supervisor 2: Dr Madhvi Menon; School of Biological Sciences, Infection, Immunity & Respiratory Medicine, Lydia Becker Institute of Immunology and Inflammation; Email: madhvi.menon@manchester.ac.uk

This programme requires co-leadership from an academic clinician and basic science researcher. Please add details of additional supervisors if required.

Project Description

Our proposal is well-aligned with the objectives of the Kennedy Trust Inflammation IMPACT MBPhD programme through integration of clinician science and immunology capabilities. The PhD student will have access to an existing cohort of patients (n=350) and is therefore not reliant on recruitment of new patients.

Background: Systemic Autoimmune Rheumatic Diseases (SARDs) are a group of multisystem autoimmune disorders with overlapping clinical and serological manifestations. Patients may transition between clinical disease categories

over time; some evolve from an undifferentiated connective tissue disease (UCTD) to a specific disease type (eg. lupus, Sjogren's, scleroderma etc), whilst others develop an overlap syndrome. The significant commonalities in clinical features and autoantibody profiles suggest a shared molecular aetiology to particular conditions or features.

Among autoimmune rheumatic diseases, systemic lupus erythematosus (SLE) is especially challenging due to its clinical diversity. A substantial number of SLE cases exhibit overlap features of other rheumatic diseases, summarised as SLE-overlap syndrome. One of the hallmarks of human SLE is the type-I interferon (IFN-I) gene signature, present in ~60-80% of patients. This refers to an upregulation of IFN-I-stimulated genes (ISGs) by peripheral blood cells; found to directly correlate with disease severity and serum IFN levels. We have recently discovered that the elevated IFN-I signature in SLE patients directly correlates with the number of autoantibodies in circulation, thus supporting a plausible role for IFN-I signalling in a subgroup of SARDs patients with SLE-overlap syndrome.

Hypotheses: Defining subgroups of SARD patients based on their molecular and immune profiles will identify biomarkers to predict disease trajectory. - IFN-I signature may identify a subgroup of SARD patients with SLE-overlap syndrome.

Plan of investigation: We are currently conducting an independent study entitled Lupus Extended Autoimmune Phenotype (LEAP) to identify novel subsets within a cohort of patients with SARDs. The student will utilise cross-sectional and longitudinal blood and serum samples from our existing cohort recruits (n=350), as well as patients with UCTD and overlap syndromes (n=50).

Aim1: To identify subgroups of SARD patients based on baseline biomarker profiles. Using existing baseline samples from the LEAP cohort, the student will identify the autoantibody profile (ELISAs), serum proteomic profile (mass spectrometry), whole blood transcriptomic and genetic profiles (sequencing), and the immune phenotype of peripheral blood cells (flow cytometry). Analysis focused on combining measured biomarkers will allow identification of unique patient subgroups based on immunopathogenesis. As B cells as central to SARD pathogenesis, we will focus on how B cell responses associate with biomarker profiles (eg.IFN-I) to further disentangle overlap syndromes.

Aim2: To investigate how biomarker profiles associate with disease trajectories. The student will compare biomarker profiles at baseline and follow-up visits, in order to determine how stable the patient subgroups are and to define the variables that may shift SARD patients from one subgroup to another.

Expected outcome: Using biomarker profiles to define subgroups of SARD patients may provide a better prediction of the disease course in individual patients. This novel approach could therefore offer new opportunities for trial design by enabling early disease stratification and treatment choice.

Background to research of supervisory team

The Lupus and Connective Tissue Diseases research team is a multidisciplinary group and the student will have access to the full team for support. We run regular journal clubs and weekly seminars and share and troubleshoot operational issues. Our research assistants and postdoctoral Fellows are available to advise on all aspects of study development including ethics, protocol development, regulatory issues and laboratory techniques and approaches. Wider training is available through seminars at the Lydia Becker Institute of Immunology and Inflammation and the Manchester Biomedical Research Centre, and will give the student access to generic research skills training over and above the University's standard PhD training programmes.

MM is a Presidential Research Fellow at the Lydia Becker Institute of Immunology and Inflammation. Her research focusses on understanding aberrant B cell responses in autoimmune diseases and other chronic inflammatory disorders. She has successfully completed high-impact research projects that include evaluating B cell interactions in autoimmune diseases (SLE and RA) as well as identifying inflammatory pathways driving age-related macular degeneration and Alzheimer's disease. Her expertise in B and T lymphocyte immunology established over the course of her training will be critical to the project.

Supervision and lab culture
Supervision will be by the PIs co-supervising the student (IB and MM) and this will give a clinical and scientific viewpoint for the project. Day-to-day supervision will focus on the clinical and laboratory work to be undertaken and will be supported by laboratory post-doctoral fellows and clinical research staff including Clinical Fellows (4) and research assistants (3). Both the laboratory teams and clinical teams hold regular research operational and scientific meetings for the student to attend. The student will meet with their supervisors on a weekly basis to discuss study plans, results and analysis etc. Formal meetings mandated by the University will be scheduled in advance of deadlines and an adviser will be appointed to provide independent input to the student for any additional support required.

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Project Title: Investigating how early rheumatoid arthritis signatures associate with treatment response and clinical trajectories

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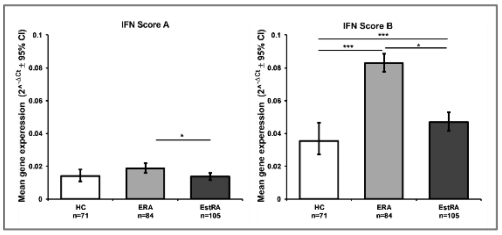
Supervisor 2: Dr Madhvi Menon; School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine, Lydia Becker Institute of Immunology and Inflammation; Email: madhvi.menon@manchester.ac.uk

Project Description
Our proposal clearly aligns with the 'IMPACT' programme objectives through integrated clinical science and immunology. The student will access an already acquired bioresource from unique new-onset RA trial cohorts. This eliminates feasibility concerns in the current clinical-research climate, providing security for a 3-year PhD.

Background: Immunotherapies have transformed outcomes for patients with rheumatoid arthritis (RA). Nevertheless, drug responses are variable, reflecting the heterogeneous nature of RA. TNF, IL-6, GM-CSF are centrally implicated cytokines. Our preliminary analysis of a broad CyTOF panel in new RA suggests key roles for B/T lymphocytes. Recent synovial tissue single-cell characterisation has further informed on key immune phenotypes and pathways.



We have recently discovered a peripheral blood type-I interferon (IFN-I) response gene signature in pre-clinical RA, when autoimmunity is evident, prior to development of joint inflammation. This is also evident on transitioning to RA (Fig.1/Factor B), and comprises distinct genes to those observed in lupus (factor A; El-Sherbiny YM, et al. Scientific Reports). Synovial tissue gene expression clusters in treatment-naïve RA have also been reported: higher inflammation groups exhibiting IFN-1 responsive genes and TNF, IL-6, and a less inflammatory group with stromal genes. The relevance of each of the signatures at time of diagnosis, change with treatment and association with response/longer-term outcomes remains ill-defined.

Hypotheses:
- New-onset RA immune-cell and transcriptional signatures hold prognostic relevance and diversify with disease progression
- Type-I IFN in new-onset RA-subgroup may offer the opportunity of therapeutic targeting (directly and/or with JAK-inhibition)

Research questions:
1. Does IFN-I at time of new-onset RA reflect earlier/milder disease or in a subgroup, persist over time?
2. What are the additional immune phenotypes and gene profiles at time of diagnosis?
3. Do these profiles have prognostic significance and specific treatment predictive capability?
4. Do further immune phenotypes emerge with disease progression?

Methods: The student will utilise longitudinal peripheral blood/synovial tissue (n=140/40) from highly-characterised early RA trial patients treated with methotrexate, anti-TNF or tocilizumab/anti-IL-6, offering the most robust form of clinical data. Additional patients can be recruited (ethics in place) for validation work.

WS1: Detailed peripheral blood immune phenotyping and gene expression profiling: the student will use available cell-subset microarray and CyTOF data to inform detailed longitudinal immune phenotyping. Multiparameter flow cytometry will characterise immune cell subsets, activation/exhaustion states, and migratory profiles; with PCR to validate novel gene signatures identified from the microarray data.

WS2: Comparing peripheral blood to synovial tissue signatures: Using matched tissue samples, we will use in-situ hybridization, immunofluorescence+/-flow cytometry to compare signatures identified in the blood to the tissue site. If we secure additional funds, we will use spatial transcriptomics to analyse the transcriptome of lymphocytes at the tissue.

WS3: Functional assays: based on the outcome of workstreams1-2

Importance and novelty: Most immune phenotype and prediction studies have comprised observational, established RA and short-term outcomes. Our proposal provides a unique opportunity to interrogate blood-tissue signatures at time of diagnosis, when disease is unperturbed by previous treatment; evaluating association with 3 treatments and clinical trajectories.

Results/Output: High-resolution understanding of biological diversity of inflammation in new-onset RA towards target discovery and tractable therapeutics.

Background to research of supervisory team
MHB is Director of Experimental Medicine, Centre for Musculoskeletal Research (and Visiting Professor at the University of Leeds where she maintains active collaborative links). She is an International leader in clinical and translational research in rheumatoid arthritis and targeted therapies, and cardiovascular pathology in immune-mediated inflammatory diseases (IMID). She directs a broad research portfolio spanning clinical trials and complex observational investigation to experimental studies in blood and synovial tissue; in order to advance understanding of RA disease and inform on optimal therapeutic strategies. She has additional clinical and research interests in the rare disease, scleroderma. Her research programme aligns with national initiatives and strategies. She is Chair of the NIHR UK Musculoskeletal Translational Research Collaboration; NIHR-BHF cardiovascular partnership steering committee member (lead of CVD in IMID workstream) and lead of the 'CARDIO-IMID UK Network'. These provide significant opportunity to lead and collaborate on high impact multi-disciplinary biomedical research and provides further prospects for her research group members.

MM is a Presidential Research Fellow at the Lydia Becker Institute of Immunology and Inflammation. Her research focusses on understanding aberrant B cell responses in autoimmune diseases and other chronic inflammatory disorders. She has successfully completed high-impact research projects that include evaluating B cell interactions in autoimmune diseases (SLE and RA) as well as identifying inflammatory pathways driving age-related macular degeneration and Alzheimer's disease. Her expertise in lymphocyte immunology and type-I interferons established over the course of her training will be critical to the project.

Supervision and lab culture
MHB has established a translational group, comprising clinical and non-clinical scientists (currently n=3, UnivManchester; n=2 UnivLeeds). This reflects her clinically driven research programme that uses clinical science and

observations to raise meaningful hypotheses for testing in order to understand mechanisms of disease and improve treatment use. MM is an experienced post-doctoral research fellow with significant experience in all techniques mentioned within this proposal; she will be able to guide the PhD student through the experiments. Her expertise in lymphocyte immunology and type-I interferons has helped develop the rationale for this project.

MHB and MM share a common ethos of nurturing collaboration and integrating immunology and clinical science investigation to address key unmet needs in the management of RA and autoimmune diseases more generally.
MHB and MM will hold weekly one to one supervision meetings with the student where similarly integrated training and guidance can be provided. The student will also attend a weekly MHB group meeting when they will present their results to the wider group and critique journals, and benefit from similar discussion from the rest of the group. MM will also join this meeting as needed. The student will also attend wider scientific meetings held at the DMDS and LBII to consolidate their knowledge and training.

There will also be opportunity to join cross-institutional meetings held by MHB, notably in her capacity as Visiting Professor at the University of Leeds.

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Project Title: Identifying Biomarkers of Myositis Treatment Response Using UK-Wide Longitudinal Data to Personalise Patient Management

Supervisor 1: Professor Hector Chinoy; Division and School: Centre for Musculoskeletal Research, School of Biological Sciences; Email: hector.chinoy@manchester.ac.uk

Supervisor 2: Dr Janine Lamb; School of Health Sciences, Division and School: Division of Population Health, Health Services Research & Primary Care; Email: janine.lamb@manchester.ac.uk

Supervisor 3: Dr James Lilleker; School of Biological Sciences, Centre for Musculoskeletal Research

Supervisor 4: Dr Alexander Oldroyd; School of Biological Sciences, Centre of Epidemiology Versus Arthritis

Project Description
Idiopathic inflammatory myopathies (IIMs) are rare autoimmune diseases characterised by muscle inflammation (myositis). Whilst prolonged, high-dose glucocorticoids and immunosuppressants can reduce disease activity/damage, clinicians are unable to predict who will best respond to a particular drug.

Aims: To identify laboratory, serological and/or clinical biomarkers of treatment response in people with IIM.

Methods:
Data
The student will use existing data collected from the MRC-funded MYOPROSP study. MYOPROSP collected repeated longitudinal data from >200 people with IIM. Blood samples are stored and available for use at the University of Manchester, and 95 have >/=3 serial samples collected over time.
Analysis

1. Quantify individual participant response to treatment instigation (e.g. rituximab initiation). Disease activity will be quantified using a validated response criteria.
2. Use latent growth mixture modelling, a machine-learning method, to identify groups within the cohort with distinct trajectories of treatment response, e.g. “rapid responders”, “late responders”, “relapsers”, “non-responders”.
3. Characterise the genetic, serological, clinical, and demographic profile of each group.

4. Use multi-level mixed effects logistic regression modelling to identify individual variables associated with treatment response.

Feasibility of successful completion

- All data has been collected and will be fully available from the start of the PhD.
- The supervisory team have the necessary range of expertise available to closely supervise the student in each stage of the study. Any further required expertise can be quickly sought from the supervisory team's global network of researchers.

PPI/E

A focus group of people living with myositis, recruited via Myositis UK, will meet with the student and supervisory team on a yearly basis. Methods, findings, implications and dissemination plans will be discussed and agreed. Patients and other service users have already been involved in formulating these research ideas through the CfMR Research Users Group.

Impact

- **Personalisation of care –** The identification of characteristics associated with treatment response to several commonly used medications in IIM patient care will allow clinicians to identify treatments more likely to confer benefit.
- **Quantification of real-world treatment response –** Results from this study will help quantify the degree to which commonly used medications benefit people with IIM, thus focusing pre-treatment counselling of patients.
- **Identification of treatment response in under-represented groups –** The MYOPROSP study collected data on many patients typically under-represented in drug trials. Quantification of treatment response in such groups may provide patients and clinicians with valuable information, thus empowering patients to make informed pre-treatment decisions.

How does this project fit the inflammation brief?

- The ability to predict IIM treatment response can facilitate personalisation of treatment and expedite remission, defined as resolution of inflammation, thus improving long-term outcomes.
- This study will provide mechanistic insights to understand which factors initiate and propagate the inflammatory response in IIM, and how these interact with treatment decisions and other interventions.

Background to research of supervisory team

The supervisory team, all members of the MMRG (www.manchester.ac.uk/myositis/), carries out cutting-edge multi-disciplinary research into the IIMs with the aim of improving diagnosis, treatment and long-term outcomes:

- Professor Hector Chinoy:
  - Professor of Rheumatology and Musculoskeletal Medicine; research on translation medicine in idiopathic inflammatory myopathy. Chief Investigator of upcoming interventional clinical trial of JAK inhibition in IIM.
- Dr Janine Lamb:
  - Reader in Complex Human Genetics/Genomics; research focuses on genetic susceptibility to several human disorders to increase understanding of aetiology and pathogenesis
- Dr James Lilleker:
  - Consultant Neurologist and Honorary Senior Lecturer with a current focus on muscle imaging and cell therapy and previous experience in epidemiology and statistical modelling in IIM.
- Dr Alexander Oldroyd:
  - NIHR Clinical Lecturer with expertise in epidemiology, statistical computation (including using "R"), longitudinal analysis, machine learning, and clinical translation.

The group regularly publish in high-impact journals (47 in 2019-2020) and secure competitive funding (see above section). Crucially, research findings are disseminated and integrated into clinical care via clinical academic members of the MMRG, strong links with NIHR Manchester BRC and the established UK-wide MYONET community.

The MMRG have extensive experience in recruiting to and analysing collected data from national and international IIM registries. The MYOPROSP study and analysis to be carried out in the proposed PhD project will build on this

experience.

Supervision and lab culture

Structure and size of group

- The student be part of the Manchester Myositis Research Group (MMRG), within the Centre for Musculoskeletal Research (CfMR). The MMRG is an enthusiastic multi-disciplinary team of 8 researchers including 3 clinical academics, one current PhD student and one study coordinator.
- Twice monthly MMRG team meetings (currently virtually) to advance projects, develop new projects and foster collaborations.
- The group has strong links with Salford Royal Hospital and the Manchester NIHR Biomedical Research Centre, where study participants are recruited from the tertiary myositis clinic run by MMRG members.
- The MMRG has a strong network of international collaborators – the student will therefore develop skills in network formation and establishing productive collaborations.

Regularity of meetings

- The student will have weekly one-on-one 1-hour supervisory meetings with the Supervisors. Ad-hoc meetings will also be possible. Close project supervision will be tailored to the student's progress to foster incremental independence.

Work/life balance

- All MMRG members prioritise the importance of work/life balance. A sensible working pattern tailored to the student's personal circumstances will be encouraged.
- The MMRG is a friendly, collaborative and supportive research team – the student will be supported and assisted during disruptive events, e.g. research difficulty, inter-personal conflict or journal/conference submission rejection.

Multi-disciplinary environment

The student will be equipped with skills vital for future translational research within multi-disciplinary environments.

- Core and IIM-specific research
- Research dissemination
- Machine-learning
- This rare combination of skills will allow the student to be a key member of future studies both within and outside MMRG

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Project Title: Discovery and clinical translation of small molecule biomarkers of inflammation in asthma

Supervisor 1: Professor Stephen Fowler; School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine; Email: stephen.fowler@manchester.ac.uk

Supervisor 2: Professor Clare Mills; School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine; Email: clare.mills@manchester.ac.uk

Dr Waqar Ahmed (PDRA); School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine; Email: waqar.ahmed@manchester.ac.uk

Project Description

Asthma is a very common inflammatory airways disease that causes significant breathing difficulties that may result in hospitalisation or even death. Despite this we lack robust diagnostic and prognostic biomarkers, and asthma is associated with very high costs and strain on healthcare. Measuring small molecules (called volatile organic compounds) in the breath is a promising area of research which aims to identify metabolic biomarkers of disease. Several studies have shown that volatile metabolites can differentiate different types of asthma with high diagnostic accuracy. However, little is yet known of their cellular and metabolic origin; such knowledge will be critical for understanding and applying these biomarkers, and potentially in identifying future targets for new drugs.

As part of the MD-PhD project, the student will develop an air-liquid interface epithelial cell culture model. They will then stimulate a cellular inflammatory response and identify phenotypic molecules that can then be sought in the breath. Biomarkers will be validated using samples and data from an ongoing clinical study at MFT-Wythenshawe Hospital (BRC RADicA - Rapid Access Diagnostics for Asthma, https://www.radica.org.uk/home.htm).

In the first year, the student will be based in Professor Clare Mills' lab at Manchester Institute of Biotechnology. Here, the student will be trained in relevant cell biology and analytical chemistry methods e.g. mass spectrometry and cell culture. The student will be exposed to a highly interdisciplinary lab research environment and there may be opportunities to further expand their training and development to supplement the project aims (e.g. flow cytometry and proteomics from cell supernatant).

During the second year, it is expected the student will apply their training to design and run experiments under supervision. Here, the student will begin to formulate and answer project objectives, for example 1) Define the molecular profile of type I and type II pneumocytes in co-culture with eosinophils, 2) Analyse the change in the molecular profile after stimulation with inflammatory cytokines,

In the first six months of the final year, the student will translate their *in vitro* findings to search for *in vivo* biomarkers in patient exhaled breath using data from samples currently being acquired in the RADicA study. Using their medical background and data analysis knowledge gained from laboratory experiments, the student will apply data cleaning, transformation, and statistical analysis to search for biomarkers in clinical sample data. To develop their research skills, the student will be encouraged and guided through disseminating their work through internal school meetings, and external conferences and publications if deemed appropriate.

Background to research of supervisory team

SF is a clinical academic and consultant in the regional severe asthma service at Manchester University Foundation Trust. Research interests include breath analysis in respiratory disease, and asthma diagnostics and phenotyping.
CM is professor in molecular allergology at the University of Manchester. Based in the Manchester Institute of Biotechnology and part of the UoM Respiratory and Allergy Research team she is now applying molecular science to understand, better diagnose and treat allergic and associated respiratory disease.
WA is a postdoctoral research associate in the group of SF researching clinical breath analysis and molecular analysis of cell cultures.

Supervision and lab culture

This supervisory team provides a strong multidisciplinary mix of supervisors with backgrounds in academic respiratory medicine, biological sciences, and analytical chemistry. For the first year, the student will be based at the Manchester Institute of Biotechnology (MIB) within the Mills group. Here the student will be exposed to a basic research environment including biological and analytical science methods. Through the MD-PhD the student will be exposed to the respiratory and allergy research group at both the University of Manchester and Wythenshawe hospital.

The Mills group currently has 2 PDRAs, and 2 PhD students based at the MIB. The Fowler group is split across the MIB (breathomics group in the lab of CM) and Wythenshawe hospital and currently has 3 PDRAs, and 4 PhD students (2 as main supervisor).

The student will take part in weekly meetings lab group meetings of both groups and get involved in other activities such as journal clubs. Quarterly progress meetings will also be planned with the student with the supervisors. Other supervisors will provide *ad-hoc* support to the student. Day-to-day supervision and support will be provided by other supervisors (WA) and research staff within both groups.

If appropriate, the student would also have the opportunity to gain relevant clinical experience in the regional severe asthma service at Wythenshawe, for example by participating in a clinic and/or MDTM every fortnight under the direct supervision of SF.

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Project Title: Using Artificial Intelligence to Better Understand Multimorbidity and Treatment Outcomes in Patients with Rheumatoid Arthritis

Supervisor 1: Professor Kimme Hyrich (Academic Clinician), School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: Kimme.hyrich@manchester.ac.uk

Supervisor 2: Professor Goran Nenadic; School of Engineering, Department of Computer Science; Email: Goran.nenadic@manchester.ac.uk

Supervisor 3: Professor Nophar Geifman; Professor of Health & Biomedical Informatics
The University of Surrey; Email : n.geifman@surrey.ac.uk

Project Description

Overview: Chronic inflammatory diseases such as rheumatoid arthritis (RA) are potentially life-ruining. Not only is the condition itself associated with significant pain and disability, patients are more likely to be diagnosed with other co-morbid conditions, both as a consequence of chronic inflammation as well as its treatments. This multimorbidity will also influence disease status (such as remission) and choice and safety of medications. The ways these comorbidities develop and cluster over time and their association with anti-rheumatic medications and disease activity is not well understood. Artificial intelligence approaches to analysing big-data offer a new opportunity to explore this further, with the potential to reveal previously unrecognised patterns of illness over time, which could have direct impact on the way these conditions are managed in routine care.

The British Society for Rheumatology (www.bsrbr.org) has been capturing significant clinical data from >30000 patients with RA since 2001. Free-text adverse event and comorbidity data (>140000 records) have been recorded and manually coded; however manual coding is laborious and introduces the potential for inconsistencies in disease identification over time. Natural language processing (NLP) through use of text-mining software to automatically "machine-code" adverse event and comorbidity data offers a new opportunity to better harmonise outcome data over time. Unsupervised machine learning (ML) (a type of artificial intelligence), such as Latent Class Analysis and Topological Data Analysis, can subsequently be applied to these data to look for relations and patterns of disease clustering and their relationship to medication and the underlying arthritis disease activity over time.

Hypotheses: There are distinct multimorbidity disease clusters which develop over time in relation to chronic inflammation (poor disease control) and/or treatment.

Proposed plan with yearly aims:
Year 1: Literature reviews on (1) multimorbidity in RA and (2) utility of NLP/ML for discovery of "disease status". Tailoring and application of text-mining software to free text data in study.

Year 2: Clustering based on comorbidity patterns, application of latent class analysis (and other methods) to cross-sectional snapshot of all accumulated events and relating back to outcomes (drug exposure, remission status, etc.).

Year 3: Longitudinal analysis of morbidity patterns - identifying disease/adverse event sequences using ML approaches; write up and submit PhD

This project would be well suited to a student interesting in pursuing research in epidemiology, data science and AI/machine learning.

Background to research of supervisory team

The supervisory team already have an existing track record of collaboration.

Professor Hyrich has been a clinical academic within DMDS for 20 years and is a Consultant Rheumatologist at Manchester Foundation Trust. She runs a highly successful pharmacoepidemiological and outcomes research

programme with strong collaboration across laboratory science, adult and paediatric rheumatology and psychology. She has a strong focus on precision medicine and is the national Co-Lead of the MRC Juvenile Idiopathic Arthritis Precision Medicine Consortium CLUSTER.

Professor Nenadic's research focuses on making sense of large-scale free-text healthcare. He is based in the Department of Computer Science, University of Manchester, and is also a Fellow at the Alan Turing Institute, the UK national institute for data science and AI. He leads the UK healthcare text analytics network (Healtex), which has been funded by EPSRC to identify the main opportunities and challenges in processing healthcare free text. With his team, he has worked on combining knowledge and data-intensive methods to unlock evidence from clinical notes, healthcare social media and literature to support clinical practice and epidemiological research.

Professor Geifman is a Professor of Health and Biomedical Informatics at University of Surrey. Her research centers on data sciences within medical research, precision medicine and biomarker discovery; improving patient-centric predictions, treatment and outcomes. She leads on data-driven Machine-Learning endotype discovery within three of the MRC-funded stratified medicine initiative national consortia.

Supervision and lab culture
The divisions (DMDS and DIIDS) already host a number of PhD students and offer a number of opportunities for training and wider learning within the research field. The student will be welcomed into all regular seminars and study groups already running within the 2 departments which cover a wide range of skills and interests in the related disciplines of epidemiology, biostatistics and data science. Based on the students existing knowledge and experience, further bespoke training in NLP/text-mining/ analysis with R, Python and other computing packages, will be offered.

The student will be jointly supervised across 2 divisions. The supervisors already have a track record of working together and it is anticipated that this will continue in a similar fashion with the student spending time with both groups, including co-location. Professor Hyrich, Epidemiologist and Clinical Rheumatologist will be the main supervisor. Professor Nenadic will oversee NLP. Dr Geifman will oversee machine learning approaches.

We anticipate that the frequency of meetings will be driven by the time in PhD as well as the needs of the student. We will start with weekly meetings which over time can be reassessed in their timing and frequency. Within our groups we also have a number of post-docs that will help navigate the students through the complex datasets and new analytical approaches. The anticipated outcomes would be a series of high impact publications focussing both on methodology and clinical outcomes. Strong methodological skills which could be built upon or transferred to post-doctoral work are anticipated.

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Project Title: Using cellular and zebrafish disease modelling to study the relationship between inflammasomes and cholesterol metabolism in haemorrhagic stroke

Supervisor 1: Dr Paul Kasher; School of Biological Sciences, Division of Neuroscience & Experimental Psychology; Email: paul.kasher@manchester.ac.uk

Supervisor 2: Dr Adrian Parry-Jones; School of Biological Sciences, Division and School: Division of Cardiovascular Sciences; Email: adrian.parry-jones@manchester.ac.uk

Supervisor 3: Professor David Brough; School of Biological Sciences, Division of Neuroscience & Experimental Psychology; Email: david.brough@manchester.ac.uk.

Project Description
Hypocholesterolemia is a clinical risk factor for intracerebral haemorrhage (ICH) and is associated with worse outcomes (PMID: 32973669). Almost immediately following ICH, the toxic influx of blood into the brain initiates inflammation via activation of microglia and peripheral leukocytes, subsequently driving acute brain injury. If the

patient survives, neuroinflammation gradually resolves at later, more chronic time points. The inflammasome is a multi-molecular protein complex that drives inflammatory responses. Recent experimental evidence implicates inflammasome activation during the acute injury phase following ICH (PMID: 32856203), however the regulatory mechanisms associated with this are not well understood.

We have recently characterised the pathological and inflammatory consequences of spontaneous ICH in a zebrafish larval model (PMID: 30473780). Preliminary evidence indicates that expression of the cholesterol 25-hydroxylase (ch25h) gene is significantly reduced in macrophages during the acute injury phase post-ICH. Furthermore, preliminary immunohistochemistry experiments using post-mortem ICH patient brain material indicates that CH25H is strongly expressed in inflammatory cells in the peri-haematomal region during the chronic injury phase. Therefore, our data suggest an inverse relationship between ch25h and inflammation may exist in ICH. Interestingly, Ch25h is an interferon-stimulated gene encoding an enzyme that converts cholesterol into 25-hydroxycholesterol (25-HC) – an oxysterol that can regulate inflammasome activation (PMID: 25104388). Therefore we hypothesise that loss of ch25h following ICH during acute stages allows for increased inflammasome activation which can drive brain injury.

To study this, the student will test whether specific blood molecules (haemin, haemoglobin, thrombin) inhibit ch25h to subsequently elevate inflammasome activation using established in-vitro systems. The student will also investigate whether 25-HC treatment can suppress inflammasome activation and brain injury in a zebrafish model of ICH. Unlike surgically invasive rodent models, ICH in zebrafish larvae occurs spontaneously, thus more closely mimicking the patient scenario. Furthermore, experimentation with zebrafish larvae is relatively high-throughput and therefore more amenable to a cross-disciplinary 3 year PhD, in comparison to rodent disease modelling. The student will perform further immunohistochemistry experiments in a cohort of post-mortem ICH brain samples to profile CH25H and inflammasome-related protein expression in acute and chronic phases. Furthermore, we have access to banked patient haematoma and blood which the student can utilise for additional analyses. Our overall aim is to determine if CH25H / 25-HC regulates inflammasome activation in ICH and whether targeting these molecules represents a therapeutic avenue.

This study aligns directly with an ongoing MRC NIRG-funded project to PK (see above) which funds a PDRA (Dr Victor Tapia) who will work alongside and train the MB-PhD student. Furthermore, resources/funding from this grant can support aspects of this PhD project, to enable successful completion of the study within 3 years.
The student will develop a core understanding of inflammasome biology and its role in driving injury processes following stroke. They will also develop translational skills by interpreting how fundamental immunology may inform the clinical setting and lead to developing candidate strategies for therapies. The student will also generate novel, publishable data to improve our knowledge of how cholesterol metabolism can regulate inflammation under disease conditions.

Background to research of supervisory team
The supervisory team are all PI's within the Brain Inflammation group. PK is a Stroke Association funded lecturer with specific expertise in pre-clinical stroke research using zebrafish disease modelling. A key aspect of his current research is focused on understanding the regulation of cholesterol and inflammation in the context of cerebrovascular disease. APJ is a stroke neurologist and a Stroke Association funded reader. Immediately prior to the Stroke Association Award, APJ was funded by an NIHR Clinician Scientist Award, funding a programme of work investigating the inflammatory response to ICH. DB is a professor of neuroinflammation and expert on inflammasome biology. Furthermore DB is the Neuroimmunology theme lead and management board member of the Geoffrey Jefferson Brain Research Centre (GJBRC) which is a partnership between the University and the Northern Care Alliance.

Supervision and lab culture
The student will be based in the Brain Inflammation group and the GJBRC, a large multi-disciplinary group whose focus is on understanding the contribution of inflammation to cerebrovascular disease. Research in this group spans from molecular studies in cell based systems, through preclinical (animal) models of disease to clinical studies/trials. Full training in all techniques will be done in-house. The student will also work closely with pathologists at the Manchester Brain Bank (based within the GJBRC) in obtaining and preparing post-mortem brain tissue. The MB-PhD students will receive day-to-day supervision from researchers within the lab groups of PK and DB, who collaborate and co-supervise

projects with APJ. APJ will provide complimentary clinical training and opportunities to join stroke clinics at Salford Royal. The student will join weekly lab meetings held by each individual supervisor, and meet the entire supervisory team fortnightly to discuss specific plans.

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Project Title: Using genetics to predict disease outcomes, severity and treatment response in childhood inflammatory arthritis

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Supervisor 3: John Bowes; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: j.bowes@manchester.ac.uk

Project Description

Juvenile idiopathic arthritis (JIA) is the most common immune-mediated paediatric rheumatological condition, which is estimated to affect 1 in 1000 children in the UK. JIA comprises distinct and heterogeneous subtypes of childhood arthritis that differ in their clinical presentation. However, irrespective of subtype, children diagnosed with JIA are first given a single drug therapy, but this is only successful in ~50% of patients, and the remainder must then try other treatments until they find one that works for them. To date, there are no validated clinical/biological tools to predict disease severity or outcome, or to predict response to treatment. The overall aim of this project is to use genome-wide association study (GWAS) data in JIA patient collections to identify genetic variants that differentiate disease subtypes, severity or response to treatment. The project will benefit from access to unique resources that are available to the supervisory team, including GWAS and extensive clinical and biological data from studies contributing to the CLUSTER Consortium (https://www.clusterconsortium.org.uk/), which brings together four independent patient collections of more than 5,000 children. The project will also make use of state-of-the-art statistical methods under development by the supervisory team that maximise opportunities for discovery of genetic variants with "heterogeneous" effects between disease subtypes or patients that respond to a specific treatment. These novel genetic discoveries will: (i) provide novel insight into biological processes and molecular mechanisms that drive differences between disease subtypes and treatment response; and (ii) enable development of genetic prediction algorithms that, when combined with baseline clinical data, can be used to inform treatment choices for JIA patients. Taken together, the findings of this research will enable accurate patient stratification and drug choices so that each child has an opportunity to receive their optimal first-line treatment regime. This "personalised" approach would be expected to increase early remission rates, reduce the suffering of patients, improve long-term outcomes, and reduce the economic costs of many years of treatment with ineffective drugs.

Background to research of supervisory team

The shared research focus of the multidisciplinary supervisory team is to revolutionize treatment opportunities for juvenile idiopathic arthritis (JIA) by personalizing the best first-line treatment for each child. The team collaborate as part of several national projects, including the CLUSTER Consortium (https://www.clusterconsortium.org.uk/), which brings together unique patient collections and internationally recognized researchers in JIA, bioinformatics and industry to predict disease outcomes for childhood arthritis. Kimme Hyrich is an epidemiologist at the Centre for Musculoskeletal Research and a Consultant Rheumatologist in the Kellgren Centre for Rheumatology. Her main research interests are to understand the short and long-term outcomes in adult and childhood inflammatory arthritis, including a greater understanding of the role treatments play in these outcomes. John Bowes and Andrew Morris are statistical geneticists at the Centre for Genetics and Genomics Versus Arthritis. John's main research interests include understanding the genetic contribution to a range of rheumatological disorders with a specific focus on inflammatory joint disease, and he has led the largest genome-wide association study of JIA to date. Andrew's research focuses on the development of novel statistical methods for the analysis of genetic and genomic studies of human diseases. These

methods enhance understanding of the biological processes through which genetic variation impacts on disease, providing novel opportunities for treatment development and personalization.

Supervision and lab culture
The student will primarily be based in the JIA Genetics and Genomics Group at the Centre for Genetics and Genomics Versus Arthritis (CfGG). The group (led by Steve Eyre) currently consists of seven members, including one PhD student and three PDRAs. The group meet bi-monthly to provide updates on research projects and discuss recent publications and innovations relevant to JIA. The student will also join the inter-disciplinary "Children and Young People's Rheumatology Research Programme" (CHYRRP), which brings together epidemiologists, clinicians and geneticists working on JIA in the Centre for Musculoskeletal Research for monthly meetings. The CfGG hosts monthly Genetics Group meetings, which offers an opportunity for junior researchers to present data and results, discuss challenges and bottlenecks in their research work, and review recent publications. The primary supervisor will meet with the student each week, and the supervisory team will meet monthly.

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Project Title: The impact of the lipidome on drug response in psoriatic arthritis

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Supervisor 2: Dr James Bluett (academic clinician), School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: james.bluett@manchester.ac.uk

Supervisor 3: Dr Sebastien Viatte (basic clinical/science researcher); School of Biological Sciences, Musculoskeletal and Dermatological Sciences; Email: sebastien.viatte@manchester.ac.uk

Project Description
Background. Psoriatic Arthritis (PsA) is a chronic debilitating form of immune-mediated inflammatory arthritis. It ranges from mild to severe erosive disease affecting the spine, entheses and peripheral joints, significantly reducing quality of life. PsA patients have increased death rate compared to the general population (~60%), mainly from cardiovascular disease, while obesity is a risk factor. The underlying molecular mechanisms are attributed to T-cell-driven autoinflammation processes, involving Th1, Th2, Th17 and pro-inflammatory cytokines. The development of biologic disease-modifying-anti-rheumatic drugs (bDMARDs) revolutionised PsA treatment outcomes. However, none are universally effective and treatment choice is often based on cost as there are currently no biomarkers of response to inform early treatment decisions.

Bioactive lipids (prostaglandins, ceramides, phospholipids) mediate inflammatory and immune reactions, gene activation and signalling. Lipidomics addresses the analysis and functionality of the complete set of lipids (*lipidome*), measured by mass spectrometry. Lipids are altered in inflammation and regulate T-cell function, important feature of PsA. Our pilot data shows increased levels of proinflammatory lipids in PsA plasma, that appear unaffected by bDMARDs.

Hypotheses, Aim and Objectives: We hypothesise that quantifying changes in the PsA blood lipidome following bDMARD treatment, can give insight into the pathogenic role of lipids, provide a biomarker of drug response and identify therapeutic opportunities. Our aim is to investigate the utility of the lipidome as a biomarker of response in PsA patients treated with bDMARDs.

Our objectives are to (A) quantify blood lipidomic changes in PsA patients with good (n=30) and poor (n=30) response to bDMARD and (B) assess potential correlations between lipids and immune cells in PsA patients following bDMARD treatment (n=12).

Experimental Design and Resources: In objective (A) we will use existing bio-banked serum samples from OUTPASS, a large prospective observational cohort study of PsA patients commencing bDMARDs, and includes clinical and

demographic data. This approach will allow the student to gain lab skills, and produce data without any delay, ensuring the success of the project. The lipidome of good (n=30) and poor responders (n=30) will be measured at baseline and 3-months of treatment. For objective (B) we will collect plasma and PBMC samples (n=12), biobank and analyse in yr3. This will provide the student with access to the clinic, training on patient identification, sample collection and bio-banking. These objectives are designed to bridge the gap between the lab and the clinic.
Blood samples. PsA patients will be identified via extreme phenotype selection. Lipidomics will be performed by UPC^2/ESI-MS/MS using existing, optimised and validated technologies. Plasma and PBMCs will be collected from OUTPASS patients. PBMCs will be extracting using ficoll fractionation and analysed by CyTOF following antibody treatment through existing protocols.

Fit with inflammation brief: PsA is a disease with strong inflammatory component. Literature and pilot data indicate that pro-inflammatory lipid mediators that affect T-cell function are upregulated in the disease and may be indicative of patients' response to bDMARDs. Exploring the PsA lipidome for markers of response to PsA treatment and assessing potential correlations between lipids and PBMSs provides a significant advancement of inflammation research.

Background to research of supervisory team
Anna Nicolaou: My research focuses on the molecular mechanisms underpining the role of fatty acids, eicosanoids, endocannabinoids, ceramides and phospholipids in inflammation, cellular communications and tissue responses. I use mass spectrometry-based lipidomics, metabolic, signalling and expression studies to explore lipid networks in health and disease. I have a strong interest in translational research, the mechanism of action of pharmaceuticals and biologics, and lipid biomarkers. Current projects focus on skin, the cardiovascular and reproductive systems, cancer and lupus.

James Bluett: Chief Investigator of OUTPASS. He has supervised clinicians throughout the training spectrum including medical students, academic foundation year Doctors and a Rheumatology Specialty Trainee who is currently completing their PhD. He has a research interest in stratified medicine approaches in inflammatory arthritis including pharmacogenomics, clinical trials and the development of complex health interventions.

Sebastien Viatte: translational research to bridge the gap between basic science and clinical research. Main current area of research is the investigation of immune cell types under the genetic control of rheumatoid arthritis (RA) susceptibility polymorphisms. Understanding the mechanisms of disease etiology in RA will lead to the identification of genetic, clinical and immunological biomarkers of RA outcome to guide clinical decision making for stratified / personalized / precision medicine.

Supervision and lab culture
The student will join active and well-funded research labs (Lipidomics; Rheumatology; Centre for Genetics and Genomics) that have all the facilities and equipment needed to deliver the project in a timely manner. This includes mass spectrometers dedicated to lipidomics (Nicolaou) and cyTOF (Viatte), and access bio-banked clinical samples (Bluett).

Our laboratories have an ethos of close and regular contact between supervisors and students. We hold weekly lab meetings where the students give short (every 2 weeks) and long (every 4 weeks) presentations. Training will be provided by the supervisors, postdocs and research technicians. During their first year, the student will also have a weekly one-to-one meeting with the main supervisor and monthly meetings with the project supervisory team. During years 2-3, we will continue with the monthly meetings and offer one-to-one meetings as needed.

Importantly, there will be options for clinical attachments (supervised by Bluett) to ensure the medical student keeps up to date with their clinical training. The student will have the opportunity to receive further training through the faculty Doctoral Academy and BB training courses (e.g. medical statistics). The student will be assigned an academic advisor and postgraduate research tutor who, in addition to their supervisory team, are responsible for monitoring student progress and assessment.

Our lab environment is friendly and supportive, offering peer mentorship with other PhD students and postdocs. PhD

students are actively encouraged to submit their work to national and international conferences, attend seminars and contribute to divisional, school and faculty research and widening-participation events.

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Project Title: Functional dissection of disease associated genetic loci in rheumatoid arthritis

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Supervisor 2: Anne Barton, academic clinician; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: anne.barton@manchester.ac.uk

Project Description

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by inflammation of the joints that affects 1% of the population. It has a high socioeconomic burden and is one of the major causes of disability. RA has no cure and many patients do not respond appropriately to currently available treatments. Understanding the biological mechanisms that drive disease is essential to improve patient care and prognosis.

The most important factor contributing to RA susceptibility is genetics. Through the application of genome wide association studies (GWAS), our group has identified over 100 genetic variants that are associated with RA risk. However, 90% of them lie outside protein coding genes and, therefore, their potential role in pathological mechanisms is not obvious. There is strong evidence that disease associated variants are involved in transcriptional regulation by disrupting enhancers, short DNA elements that bind transcription factors and other proteins to increase transcription of genes. These enhancers can have an effect on multiple genes, and they influence expression of genes that can be located at long distances through chromatin interactions.

The aim of the project is to identify and characterize regulatory elements that are affected by RA-associated variants, and to determine the genes, biological pathways and mechanisms by which these variants act in specific cell subtypes in RA patients to increase the risk of disease.

We will map chromatin accessibility using ATAC-Seq and active enhancers using H3K27ac and H3K4me1 ChIP-Seq in CD4+ T-cells isolated from blood from RA patients with high disease activity (high inflammation) and patients in remission (no inflammation). In addition, we will map chromatin interactions using Hi-C in the same sample types. These experiments will be complemented with RNA-Seq transcriptomic analysis.

Next, we will model the relationship between enhancers and gene regulation (how strong the enhancer is and how frequently the enhancer interacts with gene promoters) using the omics data generated from RA patients' samples and publicly available datasets, together with existing GWAS data, assigning the most likely causal genetic variants, effector genes and cell types through which they operate.

We will also explore how genetic variation influences the relationship between enhancers and gene expression. Finally, we will use genome editing (CRISPR-Cas9) to verify target genes and the functional importance of identified elements containing RA associated variants.

This project will therefore contribute to the identification of fundamental genes and biological pathways that mediate RA pathology and inflammation, which will in turn inform novel therapeutic targets discovery and drug repurposing.

We have already collected all the samples necessary for the Hi-C and RNA-Seq experiments. We have around 40 aliquots fixed with formaldehyde ready to generate Hi-C libraries. RNA-Seq data has already been obtained for all these samples. The student will have the chance to collect more samples for the ATAC-seq and ChIP-Seq experiments, whilst performing the Hi-C experiments on the already collected samples. All the necessary laboratory techniques and analysis pipelines have already been stablished in the lab. All this ensures that the project will be feasible in 3 years.

Background to research of supervisory team

The supervisory team are the director (Barton) and deputy director (Orozco) of the Centre for Genetics and Genomics Versus Arthritis (CfGG). We have an international reputation for conducting high quality research around inflammatory arthritis. Our work in the field of GWAS has been pivotal for the identification of hundreds of genetic loci that contain variants associated with rheumatoid arthritis (RA), psoriatic arthritis and juvenile idiopathic arthritis. Our goal now is to translate this genetic knowledge into the clinic.

Currently, our research is divided into two main programmes of work:
1) Translational genetics, which aims to translate our findings about susceptibility and outcomes of disease into prevention, predicting treatment response and developing personalised treatments (Barton). Prof Barton is PI for the largest sample collections from RA patients in the world (BRAGGSS and the National Repository), which underpin much of the work in the Centre. She has led work to identify genetic risk factors for rheumatoid arthritis and genetic/genomic biomarkers of treatment response.
2) Functional genomics, which aims to determine the genes, biological pathways and mechanisms that lead to disease (Orozco). We use functional genomics (ATAC-Seq, ChIP-Seq, RNA-Seq, Hi-C) and genome editing techniques (CRISPR-Cas9) to map and characterize non-coding regulatory elements important in disease and their target genes, and to understand how disease associated variants alter the function of these regulatory elements. We integrate in house generated and publicly available genetic and omics data to identify disease mechanisms and pathways, and in turn, identify potential drug targets and drugs for repositioning.

Supervision and lab culture

The CfGG is a diverse and multi-disciplinary research group encompassing basic scientists, clinician scientists, computational biologists, bioinformaticians and experts in statistical genetics and clinical trials, with strong links with the Lydia Becker Institute, the Centre for Epidemiology, the Centre for Dermatology Research and the Centre for Respiratory Research. The student will have the chance to interact and collaborate closely with researchers and students across the Centers and will therefore be exposed to a wide range of research topics and methodologies.
The supervisory team will meet with the student on a weekly basis.

Day to day supervision will be provided by Dr Orozco and her team (two postdocs, one technician and two PhD students). In the lab, the student will be supported by a senior postdoc, a technician and a PhD student who can train and assist the student with all the relevant wet lab techniques required for the completion of the project. The student will be provided with training and support in bioinformatics and statistical analysis by one postdoc and a PhD student member of Dr Orozco's team.

Prof Barton will provide clinical expertise and her team will facilitate the recruitment of patient samples and clinical data. Prof Barton will also provide mentorship in terms of clinical academic career planning and progression.
The student will also have the opportunity to attend and present at the CfGG weekly lab meetings, where a wide range of topics are discussed, and will be encouraged to submit abstracts to national and international conferences.

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Project Title: Characterisation of longitudinal peripheral immune cellular changes in post-stroke dementia

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Supervisor 2: Professor Stuart Allan; School of Biological Sciences, Division of Neuroscience and Experimental Psychology; Email: stuart.allan@manchester.ac.uk

Supervisor 3: Dr John Grainger; School of Biological Sciences, Division of infection, immunity and respiratory medicine; Email: john.grainger-2@manchester.ac.uk

Project Description

Introduction: Stroke is a major cause of death and disability worldwide. In stroke survivors one of the most distressing complications is dementia, which occurs in up to a third of individuals within five years and impacts significantly on quality of life.

Dysregulated inflammatory and immune pathways are strongly implicated in the pathophysiology of cerebrovascular disease and dementia. Innate immune cells, such as microglia and monocytes, play a key role in the response to brain injury and are thought to modulate subsequent recovery and repair. Using flow cytometry, we have recently identified specific changes in peripheral blood dendritic cell and monocyte subsets early after stroke. These subsets are also increasingly implicated in development of dementia after stroke. Our overarching hypothesis is that innate immune alterations in the acute phase of stroke shape chronic maladaptive neuroimmune responses that compromise long-term structural and functional brain integrity, and contribute to the development of vascular dementia.

Aims: The main aim of this project is to investigate the association between peripheral blood immune status after stroke, with a focus on myeloid sub-sets, and development of vascular dementia in patients.

Methods: The project will align with an ongoing prospective cohort study (Stroke Immune Mediated Pathways and Cognitive Trajectory [Stroke-IMPaCT]; https://stroke-impact.org/) of patients with acute ischemic stroke, with longitudinal follow-up, serial blood sampling, blood bio-banking, and clinical/cognitive assessments, funded by a prestigious Leducq Foundation Transatlantic Network of Excellence Award (https://www.fondationleducq.org/). Serial blood samples will be drawn for evaluation of immunophenotype and function of myeloid subsets using state of the art multicolour flow cytometry, RNA sequencing and immunoassay of related plasma inflammatory markers. Computational immunology algorithms will be applied to the flow cytometric analyses and single-cell RNA sequencing. Relationships with baseline clinical factors and both cognitive and functional outcomes will be explored. Blood samples have already been processed and banked in 85 participants with acute stroke, with ongoing recruitment of around 8 new participants per month.

Anticipated outcome: Comprehensive training will be provided in clinical research methodology, assessment of stroke and cognition, translational neuroscience, immunology and bioinformatics. The work will parallel pre-clinical studies within the Stroke IMPaCT network and benefit from bidirectional hypothesis generation between the clinical study and these experimental studies. The project will provide novel insights into how the immune system is altered over time after stroke and how this relates to cognitive trajectory and possible therapeutic or preventative targets. It will also identify potential immune targets to enable development of therapies to prevent the devastating effects of post-stroke dementia.

Resources available: The project will receive additional financial and infrastructure support from the existing Leducq award. The student will receive support from the LCRN acute research delivery team at MCCN and will have access to both bioinformatics and statistical support and benefit from interactions within the brain inflammation group, GJBRC and Lydia Becker Institute. They will join the wider Stroke-IMPaCT network, giving a unique opportunity to interact and collaborate with other leading international groups in the field of stroke immunology, which will include travel to collaborating laboratories to present data and learn techniques. The student will also be encouraged to engage with opportunities for training in clinical neurosciences at MCCN.

Background to research of supervisory team

Professor Smith has extensive experience of investigating the role of inflammation in patients with stroke, with experience in leading cohort studies and randomised trials of anti-cytokine therapies [interleukin-1 receptor antagonist (IL-1Ra)]. These have incorporated measurement of plasma inflammatory markers and immune cellular function, and their interpretation in relation to infection and clinical outcomes.

Professor Allan has extensive experience in investigating inflammatory and immune mechanisms in experimental models of stroke and dementia, demonstrating the importance of peripheral inflammation in determining outcomes in these models, and the potential of IL-1 blockade as a treatment in stroke.

Dr Grainger has particular expertise in understanding the cellular mechanisms that underlie function of innate immune

populations, particularly monocytes and macrophages, in health and during inflammation, using preclinical models and clinical samples.

The supervisory team have established a collaborative programme of clinical studies undertaking immunophenotyping and functional evaluation of the peripheral blood immune compartment in stroke using state of the art flow cytometry (e.g. https://onlinelibrary.wiley.com/doi/epdf/10.1111/cei.13551). Our focus is on innate immunity, infection and the role of the IL-1 axis. We have recently observed stroke-induced changes to innate-like B cell, monocyte and dendritic cell populations, and evaluation of the functional and clinical relevance of these observations is ongoing. We have a Leducq Foundation Transatlantic network award (Stroke-IMPaCT), for which Professor Allan is the European Coordinator, and Professor Smith is the UK PI for the clinical cohort study investigating the role of peripheral innate and adaptive cellular reprogramming in post-stroke dementia. This study will form the basis for the proposed MB-PhD studies.

Supervision and lab culture
The student will be embedded in a dynamic and supportive research environment within the Brain Inflammation Group (BIG), Grainger lab and MCCN. BIG comprises over 40 Masters and PhD students, PDRAs and Research Fellows with multiple PIs with over 20 years experience of working together (https://www.braininflamelab.org/). Research in BIG has a major focus on translation, benefitting from the input of clinical academics (including Professor Smith) on interdisciplinary projects within the group. The stroke human immunology research bridges BIG and the Grainger lab and benefits from monthly focused meetings to discuss results and future plans. BIG have weekly lab meetings with members of the group presenting roughly every 4 months. There are regular journal clubs organized along thematic lines which all students in the group are encourage to attend. The Stroke and Dementia theme within the GJBRC hold quarterly research meetings with a specific topic focus each time.

It is anticipated that the student will work between clinical research activities at the Greater Manchester Comprehensive Stroke Centre (the largest stroke service in the country) at MCCN, and the Grainger/Allan lab. The supervisory team is therefore ideally placed to provide the necessary interdisciplinary supervision and training for the student, both in the clinical research environment and the laboratory.

Keywords
Stroke; Immunology; Inflammation; Dementia

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Project Title: The moderating effect of socioeconomic factors on the association between alcohol consumption, long-term inflammation and risk of rheumatoid arthritis.

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Supervisor 2: Dr James Gwinnutt; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: james.gwinnutt@manchester.ac.uk

Supervisor 3: Dr Jenny Humphreys (clinical researcher); School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: jenny.humphreys@manchester.ac.uk

Project Description

Alcohol consumption may have anti-inflammatory properties, with studies reporting an association between alcohol consumption and lower risk of rheumatoid arthritis (RA), an inflammatory auto- immune disease. However, the relationship between alcohol consumption and systemic inflammation level / risk of RA is "U-shaped": low-moderate alcohol consumption is associated with lower inflammation / risk of RA and no consumption or high consumption associated with increased risk[1-4]. Heavy alcohol consumption may lead to low-level gut bacterial translocation and consequently increased levels of pro-inflammatory cytokines[4].

An alternative explanation could be that socioeconomic disparities are moderating the effect of alcohol on systemic inflammation and RA incidence, causing the "U-shaped" functional form. Most studies in meta-analyses only reported limited confounding adjustments, primarily demographics (age, gender, BMI), smoking status and some comorbidities[1 5]. Given that socioeconomic factors are correlated with inflammation[6], RA onset[7] and alcohol use[8], socioeconomic indicators (e.g. education, work status, social environment) could be confounding or moderating the relationship between alcohol consumption, systemic inflammation and RA onset.

A U-shaped relationship between alcohol consumption and progression of certain RA outcomes has also been reported (radiographic progression[9], remission[10]), although evidence is limited. This relationship could also be moderated by sociodemographic factors.

Therefore, the objectives of this project are:

1) To perform a literature review on the association between socioeconomic disparities and systemic inflammation (e.g. C-reactive protein [CRP] level)
2) To analyse the functional form (e.g. non-linear relationship) of the association between alcohol use and (i) longitudinal inflammation and (ii) risk of RA and osteoarthritis (non-inflammatory condition [negative control])
3) To estimate the moderating effect of socioeconomic indictors (education, wealth, occupation, area level deprivation) on the above relationships
4) To analyse the functional form of the association between alcohol use and longitudinal outcomes (disease activity/remission, disability, pain) in people with early RA
5) To estimate the moderating effect of socioeconomic indictors on the above relationship

Background to research of supervisory team

Dr Suzanne Verstappen is a Reader in musculoskeletal epidemiology. Her research focuses on the impact of rheumatic and musculoskeletal diseases (e.g. work outcomes) and predictors of response, adverse events, and adherence to methotrexate treatment.

Dr James Gwinnutt is a musculoskeletal epidemiologist investigating the onset and long-term outcomes of people with rheumatoid arthritis (RA), including mortality, disability and cognition. Dr Gwinnutt is particularly interested in modifiable lifestyle factors that influence onset and progression of RA, such as diet and exercise. He has significant

experience with a range of statistical and machine learning methods and has experience working with multiple longitudinal cohorts, including ELSA and RAMS.

Dr Jenny Humphreys is a senior clinical research fellow and consultant rheumatologist. Her current University of Manchester Presidential Fellowship research focuses on socioeconomic disparities in health and social care of patients with musculoskeletal disease. She has extensive research experience in the epidemiology of rheumatoid arthritis and she has previously published on the association between alcohol exposure and transaminitis risk in rheumatoid arthritis (Ann Rheum Dis, 2017, 76(9)).

Supervision and lab culture
The Centre for Epidemiology Versus Arthritis is a large (~70 members) and diverse group studying the epidemiology of musculoskeletal conditions (such as rheumatoid arthritis). The research group includes rheumatologists, physiotherapists, epidemiologists, statisticians, data scientists and qualitative researchers. The Centre is a highly collaborative environment, with multiple recurring meetings such as: scientific meetings, analysis meetings, statistics and programming groups, and journal clubs. The centre also hosts two in-house training series: 'Statistical Inference using Stata' and 'Introduction to Epidemiology, Genetic Epidemiology and Biostatistics'. All of these meetings and courses have been migrated online due to the current pandemic. The Centre hosts a Research User Group (RUG) made up of people with musculoskeletal conditions and carers or parents. Members of the Centre can approach the RUG with project ideas and collaborate with RUG members on research projects, thus ensuring all research is relevant to people with musculoskeletal conditions. Therefore, there are multiple opportunities for prospective PhD students to learn and collaborate with other members of the centre.

The Centre also has strong links with other departments, providing opportunities to collaborate externally. The foremost is the enduring relationship with the Centre for Genetics and Genomics Versus Arthritis, which houses expertise in genetic/genomics and bioinformatics. The centre also collaborates with the Centre for Biostatistics (statistical expertise), Health e-Research Centre / Department of Mathematics (machine learning), the School of Social Science / Division of Population Health / Cathie Marsh Institute (social science and socioeconomic determinants of public health) and the Manchester Biomedical Research Centre.

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Project Title: Immunology of treatment response in autoimmune diseases (rheumatoid arthritis)

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Supervisor 3: John Grainger (basic science researcher); School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine; Email: john.grainger-2@manchester.ac.uk

Project Description
Background: Rheumatoid arthritis (RA) is an autoimmune disease of unknown aetiology [1]. Disease course and response to treatment are partially genetically determined [2]. Our lack of understanding of RA pathophysiology results in a trial and error in the prescription of biologic drugs with 30% of patients failing to respond. A few pathogenic immune cell types involved in the aetiology of RA have been recently identified [3,4,5], but their role in treatment response is unknown. A multidisciplinary approach is necessary to answer this question, as RA is a heterogeneous disease: a clinical team is required to collect blood samples; a team of immunologist to deeply immunophenotype these samples; a team of geneticists and data analysts to correct for the effect of genetic heterogeneity.

Aims / Objectives: To identify an immune cell type in the blood of RA patients which will predict treatment response.

Methods: We will use the worlds largest prospective cohort of RA patients undergoing treatment with biologics, the BRAGGSS cohort. Peripheral blood from over 100 patients has already been biobanked. Demographic and clinical patients' characteristics have been collected before and after treatment to determine treatment response. Three flow cytometry panels have been developed to determine the level and functions of lymphocyte and myeloid cell subsets, including those recently published [3,4,5] by our collaborator Prof. Raychaudhuri (Harvard Medical School). Genome-wide genetic profiles have already been determined. Immune cells will be stained with the available 3 flow cytometry panels to determine their levels in patients. Data will be analysed using in house developed unbiased advanced computational strategies and clustering algorithms to define cellular clusters agnostically. This pipeline allows for the integration of genetic profiles to adjust for variations in cell levels caused by genetic factors and also tests for associations between immune cell types and response to treatment.

Training: This project represents a fantastic opportunity for the successful candidate to acquire multidisciplinary skills (immunology; bioinformatics; genetics; clinical sciences / rheumatology). The student will also have the opportunity to interact directly with Prof. Soumya Raychaudhuri (Manchester/Harvard) on several aspects of the data analysis.

[1] Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. Nat Rev Rheumatol. 2013;9(3):141-153. **[2]** Viatte S, Plant D, Han B, et al. Association of HLA-DRB1 haplotypes with rheumatoid arthritis severity, mortality, and treatment response. JAMA. 2015;313(16):1645-1656. **[3]** Rao DA, Gurish MF, Marshall JL, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature.* 2017;542(7639):110-114. **[4]** Zhang F, Wei K, Slowikowski K, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nat Immunol*. 2019;20(7):928-942. **[5]** Fonseka CY, Rao DA, Teslovich NC, et al. Mixed-effects association of single cells identifies an expanded effector CD4+ T cell subset in rheumatoid arthritis. *Sci Transl Med*. 2018;10(463).

Background to research of supervisory team

Translational research to bridge the gap between basic science and clinical research. Main current area of research is the investigation of immune cell types under the genetic control of rheumatoid arthritis (RA) susceptibility polymorphisms. Understanding the mechanisms of disease etiology in RA will lead to the identification of genetic, clinical and immunological biomarkers of RA outcome to guide clinical decision making for stratified / personalized / precision medicine.

Supervision and lab culture

The Arthritis Research UK Centre for Genetics and Genomics provides an ideal environment for this programme for many reasons. First, there is the availability of all the necessary techniques, technologies and analytical skills in order to see this project through to fruition, including wet laboratories with cell culture facilities. Second, the Unit has an existing programme of work investigating genetic, genomic and immunological predictors of treatment response. Third, extensive collaborations exist with other relevant groups within The University of Manchester, in particular with the Manchester Centre for Collaborative Integrated Research (MCCIR); Sebastien Viatte is an Associate Member of the MCCIR and already supervises a PhD student in Immunology based at that Institute and is already accessing the infrastructure of the MCCIR to immunophenotype patients with RA by flow cytometry. S. Viatte is also a longstanding collaborator of John Grainger. Both Centres (Centre for Musculoskeletal Disease and MCCIR / Lydia Becker Institute for Immunology) provide extensive training opportunities for PhD students with regular journal clubs and lab meetings and provide a critical mass of PhD students, including a large number of medical students / doctors at all stages of their career, which will represent a stimulating environment for the candidate. Day-to-day supervision will be provided by a postdoctoral researcher (lab work) or directly by Sebastien Viatte (data analysis). Weekly supervisory meetings with Sebastien Viatte. Regular monthly meetings with every member of the supervisory team.

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Project Title: Using functional genomics and genetic engineering (CRISPR) techniques to investigate the JAKi pathway in Psoriasis

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Supervisor 2: Professor Stephen Eyre; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: s.eyre@manchester.ac.uk

Project Description

Genome wide association studies (GWAS) in psoriasis have strongly implicated TYK2 as being important in risk of disease. Several single nucleotide polymorphisms (SNPs) both within exons of TYK2 and proximal to the gene are independently associated with risk of psoriasis (Ps), along with a range of autoimmune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis, type 1 diabetes and systemic lupus erythematosus.
In addition GWAS studies in Ps also indicate how IL23R is associated with risk of disease (supported by recent biological therapeutics), along with SNPs proximal to STAT3 and IFNAR1/IFNAR2 , implicating the specific IL23/IL23R/TYK2/STAT3 Th17 axis in risk of disease.

The associated SNP, rs34536443, results in the P1104A substitution in TYK2, affecting the kinase domain and reducing the function of the gene This reduction of function is sufficient to offer protection for autoimmune diseases, but not so great as to increase risk of infection. The SNP results in reduced TYK2 function, but this is only manifested with reduced downstream STAT phosphorylation in specific contexts – INF-A/B stimulation or IL12/IL23 stimulation

Hypotheses/Aims:

- How do these variants impact on the TYK2 pathway and patient risk/response to treatment?
- Does carriage of SNP variants in other TYK2 pathway genes (STAT3, IFNAR) result in a synergistic/compounded effect in samples heterozygous for the TYK2 protective variant? For example, does being heterozygous at the TYK2 protective SNP, allied with protective variants at the STAT3/IFNAR locus, have a similar magnitude in the perturbation of this pathway as being homozygous for the TYK2 SNP?

By better understanding why the loss of TYK2 only has effects in specific celluolar contexts, and why this is compensated for in other settings will we better understand why some patients respond differently to treatment, and why a TYK2 disease associated variant can lead to protection for Ps, through the Th17 pathway perhaps due to other variants (e.g. IL23R/STAT3)?) carried by at risk cohorts.

Resources:

The Eyre lab has established all the necessary laboratory techiques, including CRISPRa, CRISPRi in relevant cell lines (MyLa, HaCat), RNA-seq, scRNA-seq, CyTOF, FACS and qPCR. The plan will include;

- Chronicity CRISPR in CD4+/CD8+ cell lines. K/O, edit, CRISPRa/I, TYK2 in these cells, stimulate and look for how pathways change over time.
- Stimulate, inhibit, knock-out, edit CD4+ and CD8+ T cell lines at the key genes (TYK2, STAT3, IL23R) and measure downstream affect with and without TYK2 drug, using RNA-seq, FACS, CyTOF, qPCR
- CRISPR disruption/base editing of primary cells
- Repeat experiments in patient samples from involved/uninvolved plagues
- Perturb-seq – knock-out TYK2 in primary CD4+ and CD8+ T cells and look at downstream affect on both expression and cell subtype composition.

Fit to the inflammation brief:

This project will primarily fit the inflammation brief through to new technologies (CRISPR, scRNA-seq, RNA-seq, CyTOF) that improve treatments and clinical trials (stratify patients based on genetics and cellular context).

Background to research of supervisory team

Eyre has been involved in researching the genetic susceptibility to complex disease for over 20 years. In recent years his lab has focussed on understanding the mechanisms by which DNA variants lead to an increase risk of disease. In collaboration with Peter Fraser developing methods to interrogate the regions that are associated with disease, mainly regulatory enhancer regions, to determine the interacting gene targets. Using this Capture HiC methodology discovering how long range interactions regulate gene expression. In addition established collaborations with to look at the immunological, epigenetic and non-coding RNA consequences of the RA associated regions. These methods include ChIP, ATAC-Seq, RNA-seq and CRISPR genome editing.

Professor Richard Warren is a consultant dermatologist in Manchester, UK. He graduated from Liverpool University with a first-class honours degree in Pharmacology and gained his medical degree with honours one year later. His work in dermatology has focused on pharmacogenetics, the genetic susceptibility to psoriasis and biologic therapies in the treatment of psoriasis. He has received national and international awards for his research and regularly publishes in high impact factor journals including the Lancet. He has supervised 12 PhDs all completed within 4 years and is currently delivering successful grants for the MRC and NIHR. Warren is a member of several national committees, including the British Association of Dermatologist Biologics Registry, and is current EU Editor of the Journal of Dermatology and Therapy. He has published widely in the field of dermatology with > 300 abstracts, articles and book contributions on topics related to psoriasis.

Supervision and lab culture

The Eyre lab is situated within the Versus Arthritis Centre of Excellence in the AV Hill building. The Eyre group itself consists of Research Fellows, Post-docs and PhD students. The lab is closely linked to the Orozco lab, also with a team of post-doc and research assistants/technicians, and Professor Andrew Morris, a statistical geneticist. The groups have regular, shared lab meetings, themed into lab; statistical genetics; immunology and functional biology. The PhD student will gain from support of these dynamic groups and will meet with Professor Eyre Weekly, and with both supervisors on a monthly basis.

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