The Kennedy Trust IMPACT Inflammation MB-PhD

MB-PhD Supervisor Profiles & Project Outlines

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- Exploring how inflammation influences circadian disruption in critical care. (Dr JF Blaikley, Prof Andrew Hazel)

The impact of psychological factors on outcomes in psoriatic arthritis

Supervisor 1: Dr James Bluett; School of Biological Sciences, Division of Musculoskeletal & Dermatological Sciences; Email: james.bluett@manchester.ac.uk

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.

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

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.

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 for Musculoskeletal Research

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. Biological 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:
    - 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 (71 papers since 2023) 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 will be part of the Manchester Myositis Research Group (MMRG), spanning the Centre for Musculoskeletal Research (CfMR) and Division of Population Health. The MMRG is an enthusiastic multi-disciplinary team of researchers including clinical and non-clinical academics, clinical research fellows, PhD students, research assistant and study coordinator.
- Weekly MMRG team meetings to advance projects, develop new projects, foster collaborations and discuss relevant papers.
- 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 supervisory meetings. 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

Discovery and clinical translation of small molecule biomarkers of inflammation in asthma

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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.

Clinical relevance: Osteoarthritis (OA) has a strong genetic basis but we don't yet know how genetic changes act to cause disease. If we want to develop better treatments and ultimately cure disease, we first need to understand how these genetic changes affect biological pathways. It is a really exciting time for genetic diseases because we now have methods that allow us to manipulate DNA and see the effect (genome editing using CRISPR-Cas9, the pioneers of which were awarded the Nobel prize in 2020). Whilst the project is focussed on OA, the techniques could be applied in many disease areas.

Functional dissection of disease associated genetic loci in osteoarthritis

Supervisor 1: Gisela Orozco, basic science researcher; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: gisela.orozco@manchester.ac.uk

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

Supervisor 3: Steve Eyre, basic science researcher; School of Biological Sciences, Division of Musculoskeletal and Dermatological Sciences; Email: steve.eyre@manchester.ac.uk

Project Description

Osteoarthritis (OA) is the most common form of arthritis, affecting ~300 million people worldwide. The most important factor contributing to the risk of developing OA is genetics. The clinical challenge presented by OA is that despite GWAS identifying 100 robust loci for disease susceptibility, there remain no predictive molecular biomarkers and no targeted therapeutic interventions. 90% of genetic variants associated with OA lie outside protein coding genes; it is likely that they act by altering regulatory elements that control the expression of genes. Regulatory elements that are active in key tissues in OA have not been characterised, limiting understanding of the molecular processes driving disease and therefore hindering translation of GWAS findings.

The aim of the project is to identify the genes, biological pathways and mechanisms by which risk variants act to increase the risk of disease. We will use cutting-edge techniques such as ATAC-Seq, ChIP-Seq and chromosome folding studies in cartilage from OA patients to study how genetic variation influences the relationship between the genetic variants associated with OA and gene expression. Finally, we will use genome editing (CRISPR-Cas9) to change the DNA sequence variants to determine their effect on genes. This work will identify the fundamental genes and biological pathways that are disturbed in OA, and could identify new targets for drug development.

We have already collected some of the samples necessary, and there will be an opportunity for the student to collect more. All the necessary laboratory techniques are already established in the lab to ensure that the project will be feasible in 3 years.

The skills developed can be applied in any aspect of medicine and are state-of-the-art.

Background to research of supervisory team

The supervisory team are the director (Orozco) and deputy director (Eyre) of the Centre for Genetics and Genomics Versus Arthritis (CfGG) and the director of the Manchester Biomedical Research Centre (BRC) (Barton). We have an international reputation for conducting high quality research around arthritis. 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). 2) Functional genomics, which aims to determine the genes, biological pathways and mechanisms that lead to disease (Orozco, Eyre).

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. We host >10 PhD students at any one time so it is a vibrant and exciting department to work in. Students across the Center will 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 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. The student will be encouraged to write manuscripts for publication based on the results.

The role of the immune system in post-stroke dementia

Supervisor 1: Professor Craig James Smith; School of Medical Sciences, Division of Cardiovascular Sciences; Email: craig.smith-2@manchester.ac.uk

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. Post-stroke cognition and dementia are currently untreatable and remain a top research priority for stroke survivors.

Dysregulated inflammatory and immune pathways are strongly implicated in the pathophysiology of cerebrovascular disease and dementia. Innate immune cells, such as microglia and monocytes, and cells of the adaptive immune system 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 multiple immune cell subsets early after stroke. Our overarching hypothesis is that immune cellular 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 how changes in immune status after stroke contribute to blood-brain barrier leakage, neurodegeneration and development of vascular dementia.

Methods:

Several projects are available depending on the interests of prospective students. These align with our international Stroke Immune Mediated Pathways and Cognitive Trajectory [Stroke-IMPaCT]; https://stroke-impact.org/) Network, which includes both clinical and pre-clinical workstreams in patient cohorts and *in-vivo* experimental stroke models. The Stroke IMPaCT clinical study is a longitudinal cohort of patients with acute ischemic stroke and control participants without previous stroke, with longitudinal follow-up, serial blood sampling, advanced brain MRI, blood bio-banking, and clinical/cognitive assessments, funded by a prestigious Leducq Foundation Transatlantic Network of Excellence Award (https://www.fondationleducq.org/) and NIH. Immunological methodology includes evaluation of immunophenotype and function of immune cell 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, imaging and functional outcomes will be explored. Parallel studies in experimental stroke models will characterize longitudinal changes in systemic immunity and how these relate to

neuroinflammation, blood-brain barrier integrity and cognition. Preclinical studies will make use of advanced in vivo imaging (MRI, functional ultrasound, 2-photon), behavioural assessments of function and detailed post-mortem analyses of pathological changes, focusing on both central and systemic changes. Wherever possible we will make comparable parallel measures in the experimental studies to these being performed clinically. Identification of key immune and inflammatory mechanistic pathways will enable testing of potential candidate treatments to prevent cognitive decline in pre-clinical studies.

Anticipated outcome:

Depending on the particular interests of the student, comprehensive training will be provided in clinical research methodology, assessment of stroke and cognition, translational neuroscience, experimental stroke models, MR imaging, immunology and bioinformatics. The work will parallel other 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.

Resources available:

The project will receive additional financial and infrastructure support from the existing Leducq award and other ongoing work. Support from the LCRN acute research delivery team at MCCN is available for clinical projects and students will have access to both bioinformatics and statistical support and benefit from interactions within the brain inflammation group, GJBRC (including the Manchester Neuroimaging Group), 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 may 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

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.

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.

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 worked together for over 8 years, establishing a collaborative programme of clinical and experimental pre-clinical studies undertaking immunophenotyping and functional evaluation of the peripheral blood immune and brain 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 Allan is the European Coordinator, and 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 and aligned pre-clinical studies in experimental models 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). Research in BIG has a major focus on translation, benefitting from the input of clinical academics (including 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 and the Grainger lab have weekly lab meetings with members of the group presenting roughly every 4 months. There are regular journal clubs and seminars organized along thematic lines which all students in the group are encouraged to attend. The Stroke and Dementia theme within the GJBRC hold quarterly research meetings with a specific topic focus each time.

The student will have the opportunity to 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.

The supervisory team are all tenured so are in a position to provide a strong commitment to coordinated ongoing support and academic development of the student after completion of their PhD. In addition, Smith and Allan bring particular experience from contributing to the organisation and content of the annual NIHR-British Association of Stroke Physicians UK Stroke Research Workshop, which is a forum for engaging medical students and junior doctor ECRs in stroke research to boost capacity building.

The supervisory team will provide ongoing mentorship and supervision for the student during completion of their undergraduate medical training, their transition to junior doctor posts and beyond. This will include support with ongoing research related to the completed PhD (e.g. additional manuscript preparation, presentation of data at meetings), accessing further research activities and opportunities within the group (e.g. APEP project, applying for small funding awards) and engaging with research training and educational opportunities (e.g. GJBRC, BIG, Lydia Becker, MCCN seminars, events and teaching). In addition, Smith will provide mentorship and supervision with career advice, balancing a clinical and academic career, CV development and application for academic training posts (Specialist Foundation Doctor Programme, ACF etc).

Keywords
Stroke; Immunology; Inflammation; Dementia

The association between disease related factors and medication use with co-morbidity and mortality in patients with inflammatory polyarthritis

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Primary location(s) where student will undertake work: Centre for Musculoskeletal Research, Stopford Building, University of Manchester

People living with inflammatory polyarthritis (IP), including rheumatoid arthritis (RA) are at increased risk of developing other morbidities and increased risk of mortality. We have previously shown that the rates of morbidity such as cardiovascular diseases, cancer and lung disorders are relatively high in patients with IP/RA. The co-occurrence of these morbidities will result in an additional socio-economic burden not only for the individual patient but also for the society. It is important to further understand which factors contribute to this increased risk of other diseases in patients with IP/RA. To address this question a large cohort of patients is required with long-term follow-up and detailed information on disease related factors and medication use. The Norfolk Arthritis Register (NOAR) started in 1989 and is a long-term study of inflammatory arthritis in the community. The study recruits people who have developed inflammatory arthritis whilst living in Norfolk, and who are willing to take part in research. All patients (aged ≥16 years) newly identified with IP (i.e. have two or more swollen joints lasting four or more weeks), either presenting in primary or secondary care, are eligible to be referred to NOAR by GPs and local rheumatologists in Norwich and surrounding areas. A subset of the patients with IP develop rheumatoid arthritis (RA). The purpose of the register is to study the natural history of arthritis and to identify genetic and non-genetic factors (e.g. smoking, age, gender, disease activity) which may be related to the onset of arthritis, response to treatment, and to long-term outcomes such as morbidity. Data collected in NOAR will be linked with mortality data and NHS Digital morbidity data. To date there have been over 5000 recruits to the register.

The specific objectives of this project are:

To understand which factors (e.g. metabolic factors, inflammation and anti-rheumatic drugs) contribute to an increased or decreased risk for developing other diseases (e.g. CVD, lung disease) and increased mortality risk.

To investigate the interaction of genetic and disease specific factors with excess morbidity.

Risk prediction model – To develop a risk prediction model to identify people with IP/RA at increased risk of developing specific comorbidities allowing targeted, early intervention. The development of integrated risk models combining clinical and genetic data will improve risk prediction.

Inflammation brief

The focus of this study is on people with inflammatory arthritis who are at increased risk of developing co-morbidities. The increased risk may be partly explained by inflammatory processes. Suppression of inflammation can also result in a reduced risk of morbidities and mortality. Understanding which factors are associated with an increased or reduced risk will inform future clinical practice including treatment recommendations and personalized medicine approaches.

Professor Suzanne Verstappen is a Professor in Epidemiology with a main research interest in long-term outcomes in people with inflammatory arthritis including comorbidities, work outcomes and disability. She is the lead of several national and international research projects. She is also the Director for Equality, Diversity and Inclusion in the School of Biological Sciences.

Supervision and lab culture

The Centre for Musculoskeletal Research is a large centre (>100 staff) has an extensive track-record for supervising clinical and non-clinical PhD students (with many externally funded by the MRC, ESRC, NIHR, Wellcome Trust, Versus Arthritis and others) both during and beyond their courses. The Centre is a collaborative and supportive environment and provides multiple training opportunities (e.g. statistics, (advanced) epidemiology, and critical appraisal training), allowing students to acquire a well-rounded skill-set, important for completing their PhDs and for continuing their research careers post-PhD. The centre partners with many external departments (both internally and externally), providing many opportunities for PhD students to interact with the wider research community. Cross-disciplinary collaborations with these departments offers further support and mentoring based on the project needs. In first instance the PhD student will meet weekly with the supervisory team to discuss project and literature review. Thereafter bi-weekly meetings with at least the supervisor will take place. The progress of the PhD will be evaluated regularly by the supervisory team. The PhD student will also get the opportunity to visit the NOAR team in Norfolk to gain a better understanding about NOAR. All PhD students are encouraged to actively participate in CfMR journal clubs, statistics analysis meetings and other relevant research meetings. Depending on expertise PhD students, internal or external training will be provided. The Centre also convenes the 'UK Researchers in Musculoskeletal Epidemiology' (UK-RIME) network. The UK-RIME network is a collaboration of centres across the UK interested in musculoskeletal epidemiology. Job advertisements are regularly posted across the network, and collaboration between centres is encouraged and

supported.

Once students finish their PhDs, the centre continues to support them via training sessions and when applying for fellowships by providing seed funding for pilot grants and funding to go on research visits to external centres.

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

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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.

Understanding Clock control of Airway Barrier Function in Asthma and Allergic Airways Disease: Implication for treatment.

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Primary location(s) where student will undertake work:

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Project Description

Asthma is a prevalent chronic inflammatory disease of the airway; in the UK, 1 in 12 adults have asthma[1], and 3 people die from asthma everyday[2]. Asthma-mortality is strongly time-of-day dependent, peaking overnight[3]. Asthma is a highly rhythmic inflammatory disease with symptoms of asthma worsening overnight[4] coincident with exaggerated airway narrowing and airway inflammation (sputum eosinophilia) peaking at 04:00[5].

Fluctuation in airway narrowing in asthma is not simply passive to behavioural routine but shows a significant contribution from the internal circadian clock[6].

JG has previously shown that the Club cell present in the airway epithelium is the main pacemaker for the lung[7]. Jafar Cain (JC), who has recently completed a Kennedy Trust PhD in our group, showed that the molecular clock expressed in Club cells, regulates airway and endothelial barrier integrity by time of day, so controlling the movement of inflammatory cells to and from the lungs and airways, resulting in diurnal fluctuations in airway inflammation. JC has shown that a clock modulating ligand restores rhythmic barrier function in an Air Liquid Interface (ALI) model generated from Club Cell specific clock knock out cells. The airway epithelium is a crucial site for the biology of asthma and is also the site of action of inhaled therapies in asthma (e.g. inhaled corticosteroids, ICS). ICS are used to treat patients with mild/moderate asthma, work from our group has shown that the time of day at which ICS are taken significantly alters efficacy. ***We are interested in determining the mechanism by which the molecular clock in Club cells regulates airway barrier function through the day. Understanding this mechanism could lead to novel chrono-therapeutic targets in asthma.***

Hypothesis: The molecular clock regulates rhythmic airway barrier function through controlling the rhythmic expression of key factors (e.g. Eotaxin, prostoglandins, glucocorticoid receptors) by the Club cell.

Aims:

1. Use RNA Sequencing to identify key differences in the expression of genes in airway epithelial cells isolated from mice harbouring knock out of Club cell *clock gene* expression compared to littermate controls.

2. Investigate potential targets identified in Aim 1, using a well-established pre-clinical, in vivo model of allergic airways disease, AAD (house dust mite model), as well as tissue specific clock gene knock out mice (already housed in Manchester). You will explore how peripheral clocks present in the airway epithelium regulate rhythmic inflammation. Flow cytometry will be used to measure the time-of-day variation in the cellular environment of the lung and fluorescence-assisted cell sorting will be used to isolate specific cell populations of interest to map temporal transcriptional signatures.

3. Ex-vivo models such as the lung slice model, and the air liquid interface (ALI) model will be used to determine how cell specific clocks regulate airway epithelial barrier function, and to provide an assay for testing inhaled clock modulating compounds as a therapeutic strategy.

[1]www.asthma.org.uk.[2]WHO.[3]Cochrane*Thorax*1975.[4]TurnerWarwick*AmJMed*1988.[5]Durrington*AJRCCM*2018, [6]Scheer FAJL, PNAS 2021.[7]Gibbs et al. Nat Med 2014

Background to research of supervisory team

JG is a Professor of Chronobiology and heads a research laboratory focusing on circadian control of inflammation. Having completed a 5 year Versus Arthritis Career Development Fellowship in 2019, she was awarded a Versus Arthritis Senior Fellowship in 2021. Using pre-clinical models of inflammatory disease her group studies the influence of biological timers on disease initiation, progression and resolution and explores how understanding relationships between the timing system and inflammatory networks can be utilised for patient benefit.

HD is a Senior clinical Lecturer and an Honorary Respiratory Consultant Physician at Wythenshawe Hospital, with a specialist interest in asthma. Her research interests lie in understanding the circadian biology of asthma, with the aim to improve the diagnosis and treatment of asthma. She is fully translational in her research:

- **Clinical Studies-** investigating changes in biomarkers measured in healthy and asthmatic subjects over 24 hours in a real life setting. This work was published in AJRCCM and ERJ. HD is currently running a chronotherapeutics study investigating the impact of timing of inhaled corticosteroids in patients with asthma.
- **Epidemiology Studies** using the UK Biobank. We have shown that the risk of asthma (and particularly severe asthma) is increased in shift workers (published in Thorax in 2020).
- ***In vivo/ex vivo* studies**- We have shown the importance of the molecular clock in determining the time of day response of the airway to allergen challenge, (published in ERJ 2020).

HD also runs a weekly asthma clinic at Wythenshawe Hospital.

Supervision and lab culture

The combined labs of Gibbs and Durrington currently encompass 2 PIs, 3 PDRAs and 4 PhD students. Both PIs are situated next to each other on the 3rd floor of the AV Hill Building, ensuring a good working relationship. Both the Durrington and Gibbs labs have weekly lab meetings where students and post-doctoral staff present their recent findings and review journal publications. In addition to becoming involved in these, the recruited MB-PhD student will attend a weekly supervisory meeting with both supervisors to monitor training and progress of the project and discuss ideas. Training will be provided by both the supervisors and appropriate members of their team. Both supervisors have active laboratories with members of the team available to help the student as required. JG runs a vibrant and exciting program of seminars for the Centre for Biological Timing and the MB-PhD student will be expected to attend, as well as present to colleagues and peers several times a year. The MB-PhD student will undertake the Home Office Training Course.

HD runs a weekly asthma clinic at Wythenshawe Hospital, and the MB-PhD student will be welcome to attend to keep up their clinical skills, although in a purely educational capacity. The MB-PhD student will also have the opportunity to experience how to design and run clinical studies should they wish.

HD is a Clinician Scientist who undertook a Wellcome Clinical Training Fellowship, University of Cambridge 2006-2009, as a Specialist Registrar. In 2010 she became an NIHR Academic Clinical Lecturer first at the University of Cambridge and then at the University of Manchester, supported by an award (and mentor) from the Academy of Medical Sciences. In 2014 she became an Asthma UK Career Development Fellow and in 2017 the Dean's Clinical Fellow. In 2021 she was awarded a MRC Clinician Scientist Fellowship. HD is keen to use her experience to mentor the MB-PhD student after completion as they apply for an Academic Foundation Programme, and subsequently an NIHR ACL and Intermediate Fellowship. HD's previous PhD student secured an ACL post and she is co-supervisor for 2 other medics pursuing PhDs.

JG has a tenured position with the University. She is currently the sponsor/mentor for a former MRC Clinical Research Training Fellow who, after undertaking their PhD in her lab, was recently awarded an Academic Clinical Lectureship. JG has acted as academic advisor and internal PhD examiner for past and current CRTFs. She collaborates with a number of clinical academics at various stages of their career, often supporting the *in vivo* elements of their programme of work in her capacity as Home Office project license holder.

Structural immunology of smoking relating lung disease

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Primary location(s) where student will undertake work: Lydia Becker Institute, CTF building, 46 Grafton Street, M13 9WU

Project Description

Chronic obstructive pulmonary disease (COPD) is the third largest cause of death in the world. Our definition of COPD is defined physiologically, but there are a plethora of different structural changes in the lung caused by smoking that contribute to the end point of COPD. We have hypothesized that distinct patterns of inflammation may associate with different lung structural changes and influence how the lung responds to future insults and therapies. Furthermore, COPD patients are at a higher risk of lung cancer and specific types of inflammation are suspected to 'nurture' early pre-malignant lesions into aggressive lesions. This studentship will test the hypothesis that lung structure influences immunity in COPD through analysing immune cells in their tissue specific context in the lung. We will test any associations in structure and immune phenotype through novel *in vitro* models using primary human cells.

Resources

This studentship will be conducted in the Lydia Becker Institute, which has well developed facilities for phenotyping immune cells. We have access to imaging mass cytometry, flow cytometry and a wealth of expertise on site to ensure that the analysis in this studentship is of the highest quality. Prof Hussell is leading a BRC funded initiative for a new specialist experimental officer in immune phenotyping, who will be able to provide advice and expertise throughout this project.

The supervisory team have previously demonstrated the concept of 'trained immunity' where historical inflammatory insults have long-term effects on tissue resident innate immune cells, which can control the tone of inflammation in future insults. This studentship will bring this concept into COPD research, examining the cross-talk between immune cells and lung structure and how this may influence future disease trajectory and response to future insults.

Professor Hussell is a world leading immunologist, director of the Lydia Becker Institute and President of the British Society of Immunology. She has a strong track record in innate immune research and pioneered the concept of 'trained immunity' that is central to this studentship.

Dr Knight is an academic respiratory physician. His clinical interests include using immunology to uncover new concepts in lung conditions. This has included a landmark study in COVID-19 in collaboration with Prof Hussell and other investigators at the Lydia Becker. More recently, he has developed a collaboration with engineering colleagues at the Royce Institute to develop *in vitro* airway models to examine how the immune system influences pre-malignant lesions to evolve into aggressive cancers. He also has active collaborations with COPD researchers on a range of projects complementary to this PhD plan.

Supervision and lab culture

Dr Knight and Prof Hussell work in close collaboration with another Lydia Becker PI (Madhvi Menon). Our weekly lab meetings are shared and there are usually more than 10 lab members at each meeting. All members work on a common thread in immunology but use a diversity of techniques applied to conditions spanning both organ specific and multi-organ systems. Dr Knight meets once per week with all under his supervision, but we have an open door policy and lab members frequently visit for ad hoc meetings to work through specific issues as they arise. The student will also contribute to our Wednesday morning seminars and we also have a regular external speakers' program where prominent researchers from around the country are invited to present and discuss their work.

Dr Knight is a former MB PhD graduate and has a unique insight to impart on the academic journey after completing a PhD in medical training. He is actively supporting several aspiring academic clinicians at varying stages of their careers. He has inspired his first intercalating medical student to apply for an academic clinical fellowship and is actively supporting a junior doctor who completed her PhD more than 10 years ago to develop a research profile in the Lydia Becker Institute.

This proposal links a fundamental immunology concept of 'trained immunity' to a clinical disease. The skills imparted will be transferrable to any clinical specialty that the student decides to work in given that immune cells pervade all organ systems.

Epigenetic mechanisms linking maternal inflammation-induced transcriptional changes to adult behavioural impairment in a neurodevelopmental rat model

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Primary location(s) where student will undertake work: Michael Smith B2075/D1415

Project Description

A fundamental unknown in understanding mechanisms of inflammation induced disease, and therefore improving therapy, is how stressors experienced during critical developmental periods influence the genesis or 'programming' of adult disease (Estes & McAllister 2016). In particular, stressors experienced during pregnancy such as maternal inflammation may increase the likelihood of offspring developing cognitive disorders across their lifespan (Knuesel et al. 2014). Whether this is due to changes directly affecting brain development in utero, altered maternal behaviour, adolescent brain development or a combination of these, is unclear, and the mechanistic pathways underpinning affected traits remain poorly defined.

Maternal inflammation caused by viral infection result in epigenetic modifications in placental tissue and offspring brain, and are likely to be key candidate mechanisms leading to altered gene expression and thus developmental changes in the brain resulting in cognitive and behavioural disturbances (Woods et al. 2021).

The placenta plays a crucial role in maternal-fetal interactions. Modulation of fetal adaptive responses may lead to an increased susceptibility to development of neurodevelopmental disorders and neuropsychiatric disease later in life. Placental development is affected by maternal inflammation but how this links to cognitive impairment in offspring is unclear. We have recently established a link between reduced placenta weight, dysfunctional amino acid transport and increased risk for schizophrenia (Kowash et al. 2022). We propose that epigenetic mechanisms mediate the effects of maternal inflammation on placental function leading to altered brain development and later impaired cognitive development.

The proposed project capitalizes on our recently established neurodevelopmental rat model of maternal immune activation (Murray et al. 2019, Kowash et al. 2022, Potter et al 2023), seeking to investigate both prenatal effects of maternal immune activation on placental function and adult behavioural phenotypes linked to schizophrenia development. We will use multidisciplinary approaches to map functional changes along a developmental timeline that links placental functional development with fetal brain development and adolescent environmental conditions to offspring behavioural traits. Evaluation of placental development and function, molecular array studies for candidate genes and inflammation markers, epigenomic, histological and functional analyses in brain together with behavioural interactions, cognitive and behavioural analyses in our rodent neurodevelopmental model will be conducted. The project offers broad scientific training covering mammalian disease and behavioural research, histology, physiology, molecular biology, epigenetic and gene expression analyses. This multidisciplinary project will suit candidates who wish to apply their skills to a significant research question using cutting-edge technologies.

Background to research of supervisory team

The Hager laboratory will provide training in *in vivo* skills such as behavioural phenotyping (maternal-offspring behaviours), experimental designs, statistical and bioinformatics analysis, epigenetic assays and analysis. The Harte laboratory will provide training in handling, dosing of rodents and detailed analysis of neurobiology through qPCR, immunohistochemistry and western blotting. Training in behavioural testing, analysis and development will be provided, e. g. testing in social behaviour analysis and paradigms investigating cognition and affect such as attentional set shifting and affective bias. The Glazier laboratory will provide training in placental physiology and fetal growth analyses, including placental histology, placental nutrient transport assays, as well as developmental expression analyses using qPCR, immunohistochemistry, biochemical assays and Western blotting.

Dr Bromley is a clinical-academic with a background as a paeditric neuropsychologist who has 19 year's experience in investigating neurodevelopmental outcomes in human offspring following in utero exposures including stressor caused by inflammation. She is the current lead the Manchester based Fetal Exposure to Medicines Service. She will provide clinical and human epidemiological training opportunities and input.

The supervisor team have established themselves as an effective co-supervisory team, with strong collaborative and productive interactions, significant external research funding, as well as an established excellent track-record of multidisciplinary training of postgraduate students, with many accolades to our students including award of local and national prizes, high-impact publications, invited plenary talks, PDS scholarships and laboratory experimental commercial sponsorship.

Supervision and lab culture We meet regularly as an overall group twice a month (with all group members), once a week with our students (formally) and informally anytime when required. We foster a collaborative, supportive and rigorous research culture within our group. See above under team for further details.

Exploring how inflammation influences circadian disruption in critical care

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Supervisor 2: Prof. Andrew Hazel.

Division and School: School of Mathematics

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Primary location(s) where student will undertake work: AV Hill

Project Description

The circadian clock is an evolutionarily conserved internal timing system that regulates physiological processes based on the time of day. Our research group has recently found that inflammation during hospitalisation can disrupt this clock, potentially leading to increased mortality rates and complications. Further investigation of the circadian clock in the clinic is limited by the absence of suitable mathematical methods capable of detecting circadian disruption from 1 or 2 blood samples. Development of such models will determine both the significance of circadian disruption and if it is driven by inflammation.

Hypothesis: Inflammation disrupts circadian rhythms in the hospital setting, altering patient mortality.

Aim 1: Develop and validate a mathematical method to identify circadian disruption from one or two blood samples.

Our research groups have developed several promising methods that can potentially identify circadian disruption using 1 or 2 blood samples. These methods are based on partial least squares regression but combine it with the power of machine learning to determine the presence or absence of circadian disruption. They have already been validated using simulated and experimental data, however the student will complete validation by investigating their accuracy in the clinic. Specifically the student will compare each method against the current gold standard, ClinCirc, using a ROC curve. Samples have already been obtained from critical care patients for this analysis to be performed.

Aim 2: Identify which metabolites cause circadian disruption.

Previous research from our laboratories has linked circadian disruption to 19 inflammatory mediators. The student will now characterise differentially expressed metabolites using both liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) on existing clinical samples (n=73 patients). The function of these metabolites will then be inferred in a prospective clinical study of cardiac surgery patients (n=20) where samples are taken at baseline (circadian clock intact), post-surgery (circadian clock intact or disrupted), and during recovery (circadian clock intact). The potential role of key differentially expressed metabolites in causing circadian disruption will then be investigated high throughput screen of cultured human monocytes *in vitro*.

Aim 3: Determine the effects of circadian disruption in a large patient cohort.

The student will analyse our existing database to identify non-invasive markers of circadian disruption and its potential effects. Potential markers will be selected from routinely collected physiological data e.g. ventilation parameters, cardiovascular state, and gastrointestinal function. Their performance will then be compared against the presence/ absence of circadian disruption identified from the blood of patients collected for aims 1 and 2. Validated surrogate markers of circadian disruption will then be used to interrogate the effects of circadian disruption using an international databases we have access to. It is anticipated that this analysis will not only determine how circadian disruption affects patient outcomes but also identify potential treatments for this condition.

Background to research of supervisory team

The student will become part of a multidisciplinary team specialising in circadian biology, applied mathematics, and mass spectrometry. They will benefit from well-established patient recruitment and sampling systems in our groups, as well as access to cutting-edge equipment and expertise at the Manchester Institute of Biotechnology, and strong links with the Centre for Biological Timing. This project builds upon previous research within our groups, which has already produced high-impact publications, visible at these links: JCI and The Lancet Respiratory Medicine.

Currently, translating the insights from circadian biology into practical applications is a major focus for our research groups. The foundational mathematics for this project has been established by Hazel, significantly reducing the project's risk. Additionally, Blaikley is supported by several clinical fellows who are investigating the effects of circadian disruption. This will ensure that the prospective student will benefit from an existing network of scientists who are already working in the area and also develop contacts with other academic clinicians which will enhance their clinical training.

Supervision and lab culture

Both of our groups are compact (2 to 5 people) but also operate as part of a bigger collection of people. Therefore, the student will have access to the benefits which come from both small and large groupings of scientists. Blaikley is affiliated with the Centre for Biological Timing, which regularly organises symposia and 'Clock Club' meetings. Additionally, several chronobiologists research groups meet together one day a week to share their lab's progress and support each other's objectives. Hazel belongs to an active mathematics group that meets frequently to discuss how innovative mathematical techniques can provide novel insights into scientific problems. This will provide the student with access to an extensive group of mathematicians, allowing them to quickly get up to speed in the field of mathematics.

We will have a formal joint meeting with the student once a week initially at least for the first year. Following this we will give the student the option to continue to attend this meeting or make it less regular. In addition both Hazel and Blaikley have an open door policy and it is not unusual for us to meet our PhD students multiple times a week if the project demands it. Since the PhD student is working across schools they will be able to access formal training from both schools

specifically in the handling of data.

Enabling the MB-PhD student to investigate this area will establish them in this exciting field which is likely to be under active investigation for a least the next decade. This will establish them in both research but also generate a clinical interest which they can then pursue for the rest of their career. This approach has already been adopted by one of their supervisors who began his PhD in 2007 and is still working in the field. Specifically, he combines his academic interest with his clinical interests in critical care, discovering how circadian biology affects the patients he treats.

The student will also benefit from the supervisory team's extensive network within relevant fields. This support may include placements with collaborators following completion of the PhD, should the student wish to pursue them. Additionally, Dr. Blaikley has strong connections within the ICAT Network, which will allow the student to engage with clinician scientists across the country. It is anticipated that this support will continue at least through the student's foundation years.

Both supervisors regularly maintain contact with former students, providing mentorship and supporting them in their career objectives. Both supervisors of this project hold tenured positions, ensuring stability and ongoing guidance for the student's formative years.