MANCHESTER 1824 The University of Manchester

Inflammation IMPACT Programme

Innovation in MB-PhD and Academic Clinical Training

MB-PhD Supervisor Profiles – Summer Placement Opportunity

1. Prof. Anne Barton
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To give 1st and 2nd year University of Manchester & St Andrews-Manchester Pathway Medical School students a taste of academic research and our MB-PhD inflammation programme, some of our supervisors are offering summer placements of up to a week with various supervisory teams/lab groups where you will get a valuable insight into the real world of academic research. If you have been considering applying for the programme now or in the future this is a brilliant opportunity to meet the team and to find out if this is the right path for you.

Details of the placements available and the supervisory styles can be found on our website http://uom.link/impact-phd

Students who are interested in this opportunity should return the below details as soon as possible via email to jemma.fielding@manchester.ac.uk

- Name
- Current Year of MBChB Study
- Intending to apply for an MB-PhD programme in future – Yes/No
- AND/OR applying for this opportunity due to a general interest in academic research – Yes/No
- 200 words maximum on why you have submitted an Expression of Interest
- Lab preference/s

Depending on interest shown, preference may be given to students who are eligible to apply to the MB-PhD in the 2024-25 recruitment round.

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Expressions of interest should be returned by **1st March 2024**

Placement weeks will be arranged between students and supervisors at the end of the summer term **(w/b 17th and 24rd June)** or the beginning of the new academic year **(2nd– 6th September).**

MB-PhD details and student eligibility criteria can be found on IMPACT Inflammation MB-PhD. Applications for 2024/25 will open on the 1 October 2024.

For any queries, please contact Jemma.fielding@manchester.ac.uk IMPACT MB-PhD administrator.

Professor Anne Barton

Lead Staff Member: Professor Anne Barton

Co-Supervisors: Professor Kimme Hyrich, Professor Stephen Eyre, Professor Maya Buch, Dr Jennifer Humphreys, Dr Darren Plant

Project: Investigating the studies performed in the Centre for Musculoskeletal Research to find the genes that predispose to arthritis and factors that influence how patients respond to treatment.

Background to lab: The Centre for Musculoskeletal Research (CfMR) comprises ~100 staff and students (a mixture of scientists and clinicians) studying osteoarthritis, rheumatoid arthritis, psoriatic arthritis and childhood arthritis. We look for the genes that predispose to these conditions and try to understand how they increase the risk of disease. We also investigate what factors influence why some patients respond to a particular therapy whilst others don't (precision medicine – ideally we would like to target the right treatments to the right patients). Some researchers perform lab-based studies; some perform statistical analysis of data we have collected over many years, whilst others interact directly with patients to deliver clinical studies.

Supervision: Placement students will be offered taster sessions across a range of research areas to provide a flavour of the work undertaken. Priority will be given to students considering an academic career, especially if considering the MBPhD programme option. Placement students will have the opportunity of talking to our current PhD students, post-doctoral researchers and senior clinical academics to understand more about what a clinical academic career entails. We will show you how to pipette, perform ELISAs and do some basic statistical analysis in dedicated software.

Lab culture: We are a very diverse research group and encourage an inclusive approach to staff, students and our research participants. The atmosphere is welcoming and vibrant with lots of discussion about new research to meet the needs of patients.

Career Development: Placement students will have a chance to experience working in an internationally recognised Centre of Research Excellence. Whilst our work focusses on rheumatology, inflammation underpins many systemic diseases and the skills students

can learn are widely applicable across medicine. We host clinical and non-clinical PhD students and many of the past clinical PhD students have gone on to be Professors in our department!

Dr Kieron South

Lead Staff Member:

Dr Kieron South, Stroke Association lecturer, Division of Neuroscience

Co-Supervisors:

Prof Stuart Allan, Professor of Neuroscience, Division of Neuroscience

Prof Craig Smith, Professor of Stroke Medicine, Division of Cardiovascular Sciences

Dr Matthew Gittins, Senior Lecturer in Biostatistics , Division of Population Health

Project:

Approximately a third of stokes, and as many as half of those occurring in adults aged under 49 years of age, cannot be explained by common aetiologies or cardiovascular risk factors. Inflammatory diseases of the peripheral organs (e.g. rheumatoid arthritis and inflammatory bowel disease), which affect around 10% of the UK population, may represent an under-researched but clinically relevant stroke risk factor. Our hypothesis is that these pathologies may cause an increase in stroke incidence and/or severity through von Willebrand factor (VWF)-driven systemic thromboinflammation, similar to that observed during peripheral infection (e.g. bacterial pneumonia, COVID-19 etc). We have devised a programme of work focussed on epidemiological analysis, to define the potential link between inflammatory disease and incident stroke, and analysis of patient samples to substantiate a possible causal role of VWF in this context. Additional experiments, in animal models of inflammatory diseases, will be utilised to provide mechanistic insight and to provide a platform for testing novel imaging techniques and interventions to identify and reduce stroke risk. Establishing a causal mechanism linking inflammatory disease and stroke would provide rationale for prospective studies of these patient populations providing a meaningful contribution to the prevention/treatment of stroke and benefit to patients.

Background to lab:

All the proposed work will be undertaken in the Brain Inflammation Group, headed by Prof Stuart Allan at the University of Manchester (https://www.braininflamelab.org/). The BIG sits within the Stroke and Dementia Research Theme of the Geoffrey Jefferson Brain Research Centre (GJBRC) (https://gjbrainresearch.org/our-research/stroke-and-dementia/). The Stroke Research theme uniquely covers the spectrum of research from basic life sciences right across the clinical stroke pathway addressing both knowledge translation gaps: bench to bedside and implementation into clinical services. Almost uniquely, our research combines life sciences and interdisciplinary clinical research, covers all clinical subtypes of stroke (including ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage) and all stages of clinical care and service organisation. The University of Manchester maintains close links with the Manchester Centre for Clinical Neurosciences (MCCN) at Salford Royal NHS Foundation Trust (SRFT) which is the Comprehensive Stroke Centre for Greater Manchester, the Regional centre for neurosurgery and interventional neuroradiology and hosts the NIHR GM Hyperacute Stroke Research Centre. This allows for rapid translation of basic research to the stroke clinic.

Supervision:

The principal investigator, Dr Kieron South, is a mid-career researcher with ten years post-doctoral experience who has recently started a lectureship, with funding from the Stroke Association. This funding will be used to develop an independent research programme on thromboinflammation, an important and previously overlooked aspect of stroke research, with a particular focus on causes of stroke in young adults.

Dr South's supervision of the proposed project will be supported by the continued mentorship of University of Manchester colleagues Professors Stuart Allan and Craig Smith, who have a long track-record of translational research in the field of infection and inflammation in stroke, and Dr Matthew Gittins who brings biostatistics expertise.

Lab culture:

The Brain Inflammation lab at University of Manchester consists of 11 principle investigators, at varying stages of their academic careers, 5 post-docs, 5 fellows, 1 research technician and 16 PhD students. The lab prides itself on having a highly collaborative research environment with all PhD students given the freedom and encouragement to develop research collaborations within the group and beyond.

The lab has a long successful track record of running innovative (and award winning) public engagement events which all PhD candidates are encouraged to participate in to disseminate their research to stroke survivors and the wider public.

Career Development:

PhD candidates will benefit from being part of the GJBRC, a unique network of basic and clinical scientists from UoM, the MCCN and the Manchester Academic Health Science Centre and will be associated with the Stroke IMPACT transatlantic Leducq network being led by the stroke research group at UoM. This will provide opportunities for networking with a worldwide network of the top stroke researchers, to apply for ECR grants to build independent collaborations within these networks and to receive additional training outside of their host lab.

Gisela Orozco

Lead Staff Member: Gisela Orozco (Functional Genomics)

Co-Supervisors: Anne Barton (clinical academic - Rheumatology), Andrew Morris (Genetics), Steve Eyre (Genome Editing), Stefano Rossi (Immunology)

Project:

Autoimmune diseases such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) or Juvenile Idiopathic Arthritis (JIA) have 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 susceptibility is genetics. Through the application of genome wide association studies (GWAS), our group has identified hundreds of genetic variants that are associated with disease 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 are cell type specific, and 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 determine the genes, biological pathways, and mechanisms by which these variants act in patients' immune cells to increase the risk of disease. This knowledge can then be used to identify novel therapeutic targets and aid personalized medicine and risk prediction.

Background to lab:

The Centre for Genetics and Genomics (CfGG) is a vibrant, 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**.**

Supervision:

Students will have the opportunity to work with different members of the team on different days, getting an overview of the range of research areas and techniques at the CfGG. They will also attend lab meetings, have one-to-one discussions with team members and will have the opportunity of talking to PhD students, post-doctoral researchers and clinical academics to understand more about what a clinical academic career involves. Some experience of wet-lab techniques will be provided. Priority will be given to students considering an academic career, especially if considering the MBPhD programme option.

Lab culture:

The CfGG prides itself on being a very diverse, inclusive and vibrant research group. The atmosphere is welcoming, and we encourage a lot of discussion from all members of the team.

Career Development:

Students will have the chance to experience working in an internationally leading research Centre. They will learn interdisciplinary skills that can be applied to a wide range of areas across medicine. The CfGG has a strong track record of mentoring students and trainees along the clinical academic pathway.

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Dr John Grainger

Lead Staff Member: Dr John Grainger (Scientist – Immunology)

Co-Supervisors: Prof. Craig Smith (Clinical academic – Stroke); Prof. Stuart Allan (Scientist – Neuroinflammation)

Project: The student will get to experience one week working alongside clinical academics and scientists that form the Stroke-IMPaCT (Immune Pathways and Cognitive Trajectory) team at The University of Manchester. The aim of the week will be to gain a broad understanding of how scientific research works on a project that bridges fundamental science and the clinic.

Background to lab: Stroke-IMPaCT is a collaborative network of clinicians and scientists across Europe and North America that are working together to understand how the immune system leads to post-stroke cognitive decline, a common and distressing complication for stroke survivors. The team at The University of Manchester are based in Lydia Becker Institute of Immunology and Inflammation, Geoffrey Jefferson Brain Research Centre and Manchester Centre for Clinical Neurosciences, Salford Royal Hospital. The researchers on the team have a variety of different roles that allow the research topic to be addressed including establishing prospective cohort studies of patients with stroke, clinical and cognitive assessments, lab-based studies of human samples (e.g. high dimensional flow cytometry), computational and statistical analysis.

Supervision: Placement students will be offered the opportunity to work on different days with different members of the team to get a good overview of the research environment. They will also attend lab meetings and have one-to-one discussions with team members. Priority will be given to students considering an academic career, especially if considering the MB-PhD programme option. We will give you some experience of wet-lab techniques including methods of blood processing and analysis of immune cell profiles.

Lab culture: The research team is very diverse and made up of technicians, students, post-docs and clinicians. We encourage a lot of discussion from all members of the team and meet regularly for project updates.

Career Development: Placement students will have a chance to experience what it is like to work on an international project in the field of neuroinflammation and cognition. Although our work is focussed on the immune system in stroke the skills acquired would be relevant to research in diverse areas of medicine as immune system dysregulation underpins inflammatory diseases. Within our institutes we have experience of hosting both clinical and non-clinical PhD students and many have moved on to successful to academic careers.

Dr Sebastien Viatte

Lead Staff Member:

Dr Sebastien Viatte (basic clinical/science researcher)

Co-Supervisors:

Prof. Anne Barton (clinical academic)

Dr. John Grainger (basic science researcher)

Project:

Immunology of treatment response in rheumatoid arthritis

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 400 patients has already been biobanked. Demographic and clinical patients' characteristics have been collected before and after treatment to determine treatment response. Two mass 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 mass 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 lab:

Sebastien Viatte is a physician and an immunologist by training and was appointed as a Lecturer in Genetics at the Centre for Musculoskeletal Research (CfMR) in March 2016. His main focus of research has been the role of HLA-DRB1 polymorphisms in RA severity and response to treatment [Viatte,S., [...], S.Raychaudhuri, and A.Barton. 2015. JAMA 313:1645-1656.]. He demonstrated, for the first time in the field of complex autoimmune disease genetics, that HLA-DRB1 polymorphisms are shared genetic predictors between disease susceptibility, severity and treatment response, suggesting a likely role for antigen presentation at every stage of RA progression. Since then, he has established various biobanks of clinical samples (blood, synovial fluid cells, synovial biopsies) in the CfMR and developed a programme of work using deep immune phenotyping with mass cytometry (CyTOF) to follow up on HLA-DRB1 genetic associations with functional studies.

The Viatte lab is currently located within the Lydia Becker Institute for Immunology and within the Centre for Genetics and Genomics (CfGG) in the CfMR. The CfMR is internationally recognized as a centre of excellence for genetic epidemiology and functional genomics and has over 20 years of research experience in the field with over 250 peer reviewed publications between 2017 - 2022 alone.

The Viatte lab is a multi-disciplinary laboratory comprising immunologists, clinicians and bioinformaticians at all stages of their career, with a main focus of translational research, in order to bridge the gap between basic science and clinical research. The main current area of research is the investigation of immune cell types under the genetic control of rheumatoid arthritis (RA) susceptibility polymorphisms with the aim to identify genetic, clinical and immunological biomarkers of RA outcome to guide clinical decision making for stratified / personalized / precision medicine.

Supervision:

All members of the supervisory team are longstanding collaborators. Both the CfMR and the 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. Regular monthly meetings with every member of the supervisory team.

Lab culture:

The Viatte lab represents 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 provide a multidisciplinary training to PhD students. Second, the Centre 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 several branches of the Lydia Becker Institute for Immunology (Immune Tolerance, Immuno-informatics, Cellular Immunology). Forth, the Viatte lab consists of PhD students and postdoc from both clinical and basic science background, including dry and wet lab scientists.

Professor Tao Wang

Lead Staff Member: Professor Tao Wang

Co-Supervisors: Professor Craig J Smith, Professor Stuart Allen

Project: The focus of this project is about microglia, the brain immune cell type responsible for brain inflammation.

Background to lab: Tao Wang is Professor of Molecular Medicine and a previous Cardiologist. Her research interest is on genetic small vessel disease and vascular dementia and uses extensively the iPSCs and CRISPR/Cas9 gene editing technology as a disease modelling platform to understand disease mechanisms and identify drug targets. She is the recent winner of the AstraZeneca 2023 CoSolve program challenge on innovative *in vitro* model systems to better understand neurovascular conditions.

Craig Smith is Professor of Stroke Medicine and Consultant in Stroke Medicine. Prof Smith is the Stroke Research Lead of the Geoffrey Jefferson Brain Research Centre and the Stroke Research Lead for the Greater Manchester Local Comprehensive Research Network. His research is focused on the translational, inter-disciplinary theme of inflammation, immunity and infection in cerebrovascular disease and he is one of the PIs in the Brain Inflammation Group. The scope of his research and clinical practice includes ischaemic stroke, cSVD and post-stroke cognition. He leads the Stroke-IMPaCT clinical cohort study and MRC B-cell cohort study at Manchester Centre for Clinical Neurosciences and also the multicentre CHOSEN trial.

Stuart Allan is Professor of Neuroscience, the Academic Lead for the Neuroscience Domain in the Manchester Academic Health Science Centre and Co-director of the Geoffrey Jefferson Brain Research Centre. Prof Allan is one of the Principal Investigators (PIs) in the Brain Inflammation Group (BIG), aiming to understand the inflammatory mechanisms in the healthy and diseased brain to reveal novel therapeutic targets. He 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.

Supervision: The main research work will be carried out at Prof Wang's lab at Michael Smith Building, where we have collaboration with various research groups working on iPSC disease modelling. All the core facilities used for the project are also in the Smith building and the interlinked AV Hill building, including the Bioimaging facility, the gene editing facility, and genomic facility etc. We have regular lab meetings held on Thursday mornings, where each member updates their lab work and raises issues encountered during the week for discussions and exchange ideas to solve problems. The lab meeting also includes a formal research presentation each week and a journal club fortnightly. Meetings with Co-supervisors usually held monthly.