University of Birmingham

Kennedy Trust for Rheumatology Research

MB-PhD Programme

We have a fantastic opportunity for medical students to complete a three-year intercalating PhD in the area of Immune mediated inflammatory or musculoskeletal diseases. This programme will develop the next generation of clinical academics and provides an outstanding opportunity for early career training in a dynamic, multidisciplinary, nurturing and supported environment.

The Kennedy Trust for Rheumatology Research was founded in 1965, with a mission to achieve a meaningful impact in the development of cures and preventative treatments for musculoskeletal and related inflammatory diseases. Mindful of the importance of clinician scientists and the key role they play in translating discovery into clinical benefit, the Trust launched its MB-PhD scheme in 2020.

We have four fully-funded studentships available that will commence in June 2026.

Applications are invited for three Intercalating PhD studentships (MB-PhDs) in musculoskeletal diseases and other inflammatory diseases. These three-year studentships provide:

- A living stipend (£23,000 in year 1, £24,759 in year 2, £26,000 in year 3)
- PhD tuition fee costs (up to £16,039.36)
- Laboratory consumables (£5,000 per year) and training allowance

Eligibility

Current University of Birmingham students

To be eligible you must be a current UK medical student at the University of Birmingham and:

- Have completed three or four years of your MBChB, or three years if you are on the Graduate Entry Course (GEC)
- Have completed or be completing an intercalating degree OR have completed an undergraduate degree in a relevant subject (for GEC students only)

Current students from other UK universities

The programme is also open to current year 3 or year 4 UK medical students from other UK universities, who have completed or are in the process of completing an intercalated degree.

Non-University of Birmingham students would need an agreement from their current university to allow them to return to their medicine programme in 2029, or if this was not permitted, consider completing their medical training at the University of Birmingham from 2029 onwards.

Our Research:

We have a strong international research reputation in immune mediated inflammatory diseases and musculoskeletal diseases, focused within the following broad themes:

Inflammatory musculoskeletal diseases
https://www.birmingham.ac.uk/research/inflammation-ageing/research/rheumatology-research-group/index.aspx

Musculoskeletal ageing
https://www.birmingham.ac.uk/about/college-of-medicine-and-health/inflammation-and-ageing/ageing-and-frailty

Immunometabolism
https://www.birmingham.ac.uk/research/metabolism-systems/metabolism.aspx

Inflammatory gut and liver disease
https://www.birmingham.ac.uk/about/college-of-medicine-and-health/immunology-and-immunotherapy/gut-and-liver-inflammation

Inflammation and the cardiovascular system
https://www.birmingham.ac.uk/research/cardiovascular-sciences/index.aspx

Birmingham Acute Care Research (BACR)
https://www.birmingham.ac.uk/about/college-of-medicine-and-health/inflammation-and-ageing/acute-care-research

Inflammatory eye disease
https://www.birmingham.ac.uk/research/inflammation-ageing/research/academic-unit-of-ophthalmology

Applied health science: Data science & informatics, Clinical trial design, Patient reported outcome & Regulatory Science
https://www.birmingham.ac.uk/research/applied-health/research/methodological-innovations.aspx

Neuroinflammation
https://www.birmingham.ac.uk/research/inflammation-ageing/neuroscience-and-ophthalmology

This brochure describes the research that we conduct in each of these themes, and outlines potential PhD projects that may be available. However, this project list is not exhaustive and there are opportunities for other projects to be developed within these research themes.

The specific project that an individual student undertakes will be supervised by a team with subject specific expertise (including a clinical supervisor) and, in addition, clinical expertise to facilitate students maintaining and developing relevant clinical skills during their PhD training.

To discuss any of these projects, or other opportunities within these areas, in the first instance please contact Prof Adam Croft, Professor of Translational Rheumatology (a.p.croft@bham.ac.uk). If you have any other questions about the scheme, please contact Rebecca Birch (r.birch@bham.ac.uk) for more information.

Our Research Themes:

Inflammatory musculoskeletal diseases

The overarching objective of this theme is to improve clinical outcomes for those at risk of, and living with, rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE), including those with diseases refractory to current treatments. Important areas of research include:

- Studying pathobiology and comorbidity associated with RA, JIA, SS and SLE, as well as their epidemiology and clinical management;
- Exploring the therapeutic targeting of the tissue microenvironment and comparing and contrasting the biological processes underpinning the development, maintenance and resolution of inflammation;
- Comparing shared biological mechanisms in different tissues in order to develop process-driven links to other disease areas in inflammation biology;
- Studying patient perspectives on the acceptability of interventions, and the incorporation of relevant patient outcome measures into clinical trial endpoints, to ensure that the results we generate are clinically meaningful and broadly applicable across diverse clinical settings.

Examples of potential projects:

Prof Adam Croft: We use functional genomics, human tissue organoids, multi-modal single cell characterisation and multi-dimensional spatial imaging anlaysis to understand inflamed tissue ecosystems and identify the cellular and molecular drivers of disease persistence that operate within the target tissues of immune mediated inflammatory diseases. We are employing state of the art technologies to specially modulate these disease patwhays and deplete pathogenic cell populations to rest these diseased tissue microenvironements to a state of health. For example, we are developing engineered T cells to selectively deplete pathogenic fibroblasts from the inflamed tissue microenvironments to promote the resolution of tissue inflammation and re-esatblish key cellular checkpoints between fibroblasts and macropahges that promote long-term freedom from disease.

Prof Adam Croft, Dr Saba Nayar: Chronic inflammation in immune-mediated inflammatory diseases (IMIDs) often leads to the formation of tertiary lymphoid structures (TLS), which support immune cell function and can foster autoimmunity. These structures can also pose challenges in treatment, as they create a protective environment for immune cells. Non-immune stromal cells within TLS are crucial for maintaining local immunity. Recent studies suggest that modulating peripheral nerves, can reduce inflammation in IMIDs, highlighting the significant interplay between the nervous and immune systems in IMIDs, yet the cellular and molecular mechanisms remain poorly understood. This project aims to investigate how nerves regulate TLS formation and pathology. We will utilize preclinical disease models, ex vivo patient sample analysis and multi-omic approaches to explore the cellular and molecular relationships between the peripheral nervous system and the immune-stromal niche in TLS development during inflammation.

Dr Georgiana Neag, Prof Adam Croft: Our team aims to study how chronic inflammation in the joint leads to bone loss and osteoporosis. We will utilise cutting-edge multi-omics and 3D microscopy imaging technologies to study bone architecture at unprecedented resolution. These advanced techniques allow mapping of protein expression patterns directly onto 3D cellular structures. Our image analysis methodology relies on artificial intelligence-based quantitative histocytometric analysis, including automated segmentation algorithms and deep learning-based approaches. This innovative approach will allow exploration of the intricate relationships between cells in the bone and will inform development of novel interventions to preserve bone health throughout the lifespan.

Dr Paola de Pablo: Predictors and comorbidities in autoimmune rheumatic conditions. This project builds on work exploring the role of periodontal disease as a predictor of outcome in rheumatoid arthritis.

Dr Marie Falahee: Use of qualitative and quantitative preference-based methods to inform decision-making in the context of therapies for inflammatory conditions. Building on research funded by the EU and Arthritis UK, this project will explore patient preferences, for example in the context of intervention and relevant outcomes, and will include an assessment of preference heterogeneity in risk tolerances, minimum clinically important differences and outcome prioritization.

Prof Ben Fisher: Validating anti-IL22 as a treatment for Sjögren's syndrome. This project builds on high impact publications suggesting IL-22 as a therapeutic target.

Prof Helen McGettrick: : Our team are interested in understanding the cellular and molecular mechanisms underpinning inflammation and tissue repair in health, with age and in disease (e.g., RA, PsA, JIA and osteoporosis), with the view of translating these finding for patient benefit. We combine multi-cellular in vitro models, with ex vivo patient sample analysis, preclinical models of disease and big data. Specifically, we are developing novel peptide (PEPITEM)-based therapies that act to limit inflammatory processes and/or promote bone formation to reset tissue homeostasis.

Dr Amy Naylor: Osteoblast bone-forming activity is perturbed in immune mediated inflammatory diseases. This leads to pain, loss of joint function and permanent disability for patients. Understanding the role of endothelial cells and synovial fibroblasts in controlling osteoblast activity in disease states is a central theme of my group's research. This project uses bespoke in vitro models of the bone and synovium in combination with patient tissue to uncover the regulatory mechanisms that can be harnessed therapeutically.

Dr John Reynolds: Understanding the drivers of inflammation in cutaneous lupus. This work builds on our programme of single cell -omics and histology to understand why lupus inflammation occurs in the skin and to identify new personalised therapeutic targets.

Prof Dagmar Scheel-Toellner: Each plasma cell can produce about 10.000 antibodies per second over many years. Within a global network of collaborators, we are exploring the metabolic processes which allow plasma cells to maintain the energy supply needed to support their continuously high protein output. We use state-of-the-art technologies to image the interaction of plasma cells with the feeder cells in their direct environment.

Musculoskeletal ageing

This aim of this research area is to understand the mechanisms underlying the age-related decline of the musculoskeletal system, including muscle, bone and cartilage that ultimately predisposes the individual to musculoskeletal disease and frailty (http://cmar.online/). Considerable emphasis is placed on the role of the age-related increase in systemic inflammation (inflammaging) and the remodelling of the immune system with age (immunesenescence). Important areas of research include:

- The basis of age-related musculoskeletal decline and progression to disease and the factors modulating this trajectory, including cell senescence, immunesenescence, inflammation, metabolism, physical inactivity, obesity and the gut microbiome;
- Mechanisms driving the development of osteoarthritis and inflammatory disease-related sarcopenia;
- Pharmacological and lifestyle interventions in healthy, frail and disease populations to improve musculoskeletal health.

Examples of potential projects:

Dr Niharika Duggal: A gut-centric view of immunesenescence: unravelling host gut epithelial-immune cell cross-talk in ageing and multimorbidity. Dissecting the role of immunesenescence in a gut microenvironment to identify cellular and molecular drivers of loss of intestinal barrier function in healthy ageing and older adults with underlying co-morbidities by employing spatial imaging technologies and a 3D in-vitro colonic model that mimics the key features of the intestinal mucosa and immune interactions. We will also investigate the possibility of therapeutically targeting pro-inflammatory senescent T and B cells as an approach for restoring gut homeostasis and evaluate translational relevance.

Dr Rowan Hardy: Harnessing novel injectable hydrogels to modulate local steroid signalling and inflammation in musculoskeletal disease. In collaboration with leaders from the School of Chemical Engineering, this project will investigate innovative fluid gel-based hydrogels that provide sustained drug delivery and unique viscoelastic properties suited for the joint environment. Using primary co-culture, ex vivo tissue culture and in vivo models, the student will define how these materials influence joint function, cartilage preservation and muscle integrity. This interdisciplinary approach will link biomaterials engineering with endocrinology and immunology, advancing new strategies to protect joint and musculoskeletal health in chronic inflammatory disease.

Prof Simon Jones, Prof Zubair Ahmed: Development of novel approaches to modulate the synovial fibroblast phenotype and reduce pain in patients with OA. This project builds on work funded by Arthritis UK exploring the role of a distinct synovial fibroblast population in mediating inflammation and pain in patients with OA.

Prof Thomas Jackson, Prof Helen McGettrick: We use multi-modal physiological, biological and psychological measurements to understand the chronological age of an individual. In particular, we are interested in answering the question as to why some individuals bounce back (rebound) from a stress event (e.g., surgery, infection) and why others do become frailer than before the episode. Our aim is to identify the cellular/molecular signature that could predict a person's dynamic resilience to a stress event that could alter the clinical management of these individuals.

Immunometabolism

The field of immunometabolism is one of the fastest growing areas of biomedical research, focused around the interaction between immune cells and their metabolic environment. This relationship is reciprocal – while diet can influence both response to infection and inflammatory signals, the change in local metabolism caused by chronic inflammation can alter the structure of the tissue itself. Potential disease areas of interest include chronic inflammatory diseases such as rheumatoid arthritis and non-alcoholic fatty liver disease, response to infection, ageing, neurodegeneration and delirium. Examples of research questions include:

- How does the metabolic environment alter T cell function?
- Does the role of lactate on immune cells vary with the disease environment?
- What is the influence of tissue hypoxia on infiltration and function of immune cells?
- What are the implications of inflammatory immune cell metabolism on the function of the local tissue?

Examples of potential projects:

Prof Sarah Dimeloe: The team have previously identified that T cells exhibit heightened metabolism in chronic inflammatory disease, which may underpin their dysregulated activity. Future projects will further interrogate the mechanistic basis for this, and potential for therapeutic targeting to restore normal T cell function.

Dr Ilse Pienaar: Integration of multi-omic sequencing data derived from single cell cholinergic neurons taken from post-mortem brains of patients diagnosed with Parkinson's disease (PD) to discern how inflammatory pathway activation intersects with anti-inflammatory cholinergic signalling and mitochondrial DNA responses to drive PD processes. This detailed approach promises to identify intervention nodes using synergistic anti-inflammatory and mitochondrial restorative strategies to prevent cholinergic degeneration in PD. This project builds on work funded by the Alzheimer's and Royal Society, investigating mechanisms of cholinergic neuronal death in PD and to offer new preventative and restorative therapies.

Prof Dan Tennant: Investigating the effects of cellular metabolism on chronic inflammatory processes. This project builds on work investigating the role physiologically-relevant metabolism of inflammatory and nearby stromal cells on their environment and disease pathology.

Inflammatory gut and liver disease

The overarching objective of this theme is to improve clinical outcomes for those with inflammatory liver disease. This includes patients with immune-mediated liver disease such as autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis as well as other conditions such as non-alcoholic fatty liver disease and alcoholic hepatitis. Important areas of research include:

- The role of specific adhesion molecules and chemokines in the regulation of lymphocyte recruitment to the liver and gut;
- The role of dendritic cells in regulating local immune responses in the liver;
- The relationship between hepatic inflammation and the development and progression of injury;
- The role of cellular therapies to ameliorate the pro-inflammatory environment.

Examples of potential projects:

Prof Trish Lalor: Investigating the molecular pathophysiology of human metabolic liver disease (MASLD). This project will investigate how key cell populations such as platelets and sinusoidal endothelial cells contribute to progression of steatosis to inflammation, fibrosis and cancer in metabolic liver disease and builds on previous work funded by UKRI and pharmaceutical partners. The project will utilize human cell samples, data and tissue to understand pathophysiology.

Dr Chris Weston: Chronic liver disease and malignancy develops on the background of inflammation, fibrosis and metabolic perturbation. However, our understanding of the mechanisms that drive disease are incomplete. This project will use recent transcriptomic data to investigate how cross-talk between specialised liver cells such as endothelium, fibroblasts, neurones and immune cells contributes to disease pathophysiology, and explore the impact of cellular heterogeneity on these processes. This project builds on previous work supported by pharmaceutical collaborators and UKRI, and our experience of developing and exploiting therapeutic agents not only in human and murine models, but also an early phase clinical trial of a molecule implicated in inflammation and fibrosis (BUTEO trial).

Prof Ye Htun Oo, Dr Amber Bozward: Regulatory T cells (Tregs) are crucial in preventing autoimmune liver diseases, AILD (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis and inflammatory bowel diseases). We explore fundamental basic biology of human Treg with explant livers, bloods from patients with AILD, their tissue gene signatures, immunological function, stability and cross talk of Tregs in the liver and gut microenvironment and translate these findings towards GMP Treg trials: AUTUMN and SPRING for patients with unmet clinical need. This project will build on established discovery to GMP Treg translational cell therapy programme funded by Sir Jules Thorn Trust.

Prof Shishir Shetty: Liver cancer is a global killer, with cases rising dramatically in the UK. Immunotherapy has been a major breakthrough in the field, yet many patients remain resistant to this therapy. We study the liver microenvironment surrounding the cancer. Understanding the cellular cross talk in this microenvironment could lead to new treatments that boost the success of current immunotherapy. We focus on macrophages and endothelial populations which play a critical in this process and this project builds on our long standing interest in the scavenger family of receptors, recently funded by CRUK, the Wellcome Trust and the MRC and building on the early phase clinical trial of anti-scavenger receptor therapy (MATINS).

Prof Asif Iqbal, Prof Helen McGettrick: We use functional genomics, multi-modal single cell characterisation and 3D organoid cultures to understand tissue pathology and identify the cellular and molecular drivers of disease persistence and tissue inflammation in adult inflammatory bowel disease (IBD). We are now employing prokaryotic cell therapy to specifically target the gut microbiome and modulate prokaryotic-eukaryotic cell interactions. Furthermore, we are exploring the cross-talk between oral inflammation and gut inflammation, examining the cellular and molecular mechanisms driving persistent disease in these sites. Additionally, we are investigating the bioactivity of the adiponectin-PEPITEM pathway in IBD and whether this becomes dysfunctional leading to aberrant leukocyte infiltration into the gut.

Inflammation and the cardiovascular system

This theme addresses the role of the vascular system and its components in the initiation and maintenance of chronic inflammation. Specific areas of research interest include:

- Platelet biology: platelets are now recognised as important players in chronic inflammatory disease through their interaction with other vascular cells and coagulation factors. Platelets maintain vascular integrity through regulation of neutrophils and undergo cross-talk with endothelial cells, monocytes and tissue-based macrophages, and mast cells;
- Leukocyte trafficking and vascular biology: this investigates the process of leukocyte recruitment, how it is dysregulated in disease and the fate of the inflammatory infiltrate in acute inflammation and inflammatory mediated immune diseases, including atherosclerosis. Furthermore, we have pioneered complex co-culture adhesion assays which use tissue engineering principles to reconstruct disease microenvironments, allowing pathways of inflammatory cross-talk between the tissue stroma and the vasculature to be defined;
- Regulatory mechanisms of angiogenesis: we have applied endothelial genomics and Ingenuity pathway analysis to discover new shear-regulated genes which influence thrombotic as well as angiogenic responses;
- Exploring the therapeutic targeting of the tissue microenvironment and comparing and contrasting the biological processes underpinning the development, maintenance and resolution of inflammation;
- Comparing shared biological mechanisms in different tissues in order to develop process-driven links to other disease areas in inflammation biology.

Examples of potential projects:

Dr Alex Brill: Exploring the role of mast cells in DVT. We have demonstrated severe hypoxia as a driving force of venous thrombosis and anticipate mast cells as a first responder to this in the setting of venous stasis. We will investigate the possibility of targeting mast cell degranulation and their pro-inflammatory agents as an approach to prevent venous thrombosis.

Dr Ingrid Dumitriu: Exploring the role of T cells in cardiovascular risk in rheumatoid arthritis (RA). Patients with RA have accelerated atherosclerosis and increased risk for severe cardiovascular events, but the precise mechanisms remain poorly understood. This project builds on BHF-funded work on a T-cell subset (CD4+CD28null T cells) that expands both in acute coronary syndrome (ACS) and in RA patients and predisposes to severe disease progression and unfavourable prognosis. This research seeks to identify novel targets and therapeutic strategies to tackle inflammation to improve patient management and outcomes.

Prof Asif Iqbal: Monocytes/macrophages play a major role in driving the progression of atherosclerosis through foam cell formation and pro-inflammatory cytokine production. Slowing or stabilising this process could help reduce the risk of secondary cardiovascular complications. This project will address the effects of Galectin-9 on monocyte recruitment and macrophage function in the context on cardiovascular inflammation.

Prof Ed Rainger: We work on a novel peptide hormone, PEPITEM, which we discovered several years ago. We now know that PEPITEM has two smaller tripeptide sequences (pharmacophores) that are independently active in regulating inflammation. In this project we will identify how the tripeptides regulate cellular function in leukocytes and endothelial cells, identify their counter receptors using novel probes developed in collaboration with the School of Chemistry and determine whether the tripeptides have the same, overlapping or discrete molecular targets in the immune and inflammatory systems. These studies will help translate the tripeptides into the clinic for patient benefit.

Dr Julie Rayes: Platelet activation potentiates acute and chronic inflammation directly through the secretion of immunoregulator molecules and through interacting with immune cells. In particular, the interaction of platelets with monocytes-derived and tissue resident macrophages regulates tissue inflammation. My team is interested in novel mechanism of platelet activation by DAMPs (including haem) which differentially regulates their interaction with macrophages. This project will explore the mechanisms by which haem interaction with platelets regulates immune cell phenotype in chronic inflammation using *in vitro, ex vivo* and experimental *in vivo* models and intravital microscopy.

Dr Jose M Romero, Prof Parth Narendran, Prof Fabian Spill: Mitochondria-Targeted Therapeutics for Multisystem Management of Diabetes. This project aims to develop innovative mitochondria-targeted therapies to prevent and treat multisystem complications of diabetes. Our team has recently identified novel drug candidates with the potential to repair mitochondrial dysfunction and alleviate pathology across multiple tissues. The project is highly translational, combining state-of-the-art approaches including in vivo models, mitophagy reporters, bioenergetic and metabolic assays, molecular techniques, and metabolic immunophenotyping. It also provides training in computational modelling to understand and predict mitochondrial network dysfunction, complemented by clinical collaborations with local diabetic cohorts to integrate preclinical findings with patient-relevant data. Together, these studies aim to advance mitochondria-based therapies toward real-world impact for people living with diabetes.

Prof Zubair Ahmed: Understanding the contribution of inflammasome-mediated inflammation in eye disease such as age-related macular degeneration (AMD). This project will elucidate the role of the inflammasome pathway in mediating inflammation in the eye and will test various tool inhibitors of the inflammasome pathway to alleviate the neurodegenerative consequences of inflammation.

Prof Zubair Ahmed: Development of “red-light” therapy, or photobiomodulation (PBM), towards alleviating inflammatory eye diseases. Our interdisciplinary team (Prof Will Palin, Dr Mohammed Hadis, Dr Andrew Stevens and Dr David Davies) has already shown that a precisely-tuned dose of PBM, delivered non-invasively to either the spinal cord or brain after injury, alleviates neuroinflammation and as a consequence protects neurons from inflammation-mediated damage. We now wish to use the optic nerve crush injury model to determine a precisely-tuned dose of PBM and use this non-invasively to reduce inflammation in the eye and thus promote visual function. This is a first step towards evaluating the potential of PBM to treat inflammatory eye diseases.

Birmingham Acute Care Research (BACR)

Acute care is any unplanned health care contact or care escalation (from a hospital ward to intensive care). Each year, the NHS provides approximately 110 million urgent same-day patient contacts, with the numbers rising year on year, at a cost of £17billion pounds. Acute illnesses place a huge burden on the individual, with long-term consequences noted with even short admissions. Patients are increasingly complex, with >70% of people presenting to hospital having 2 or more long term medical conditions (LTMC- termed multi-morbidity) and 60% having 3 or more LTMC. Despite this, our treatment pathways and approaches to disease remain focused on a single organ or disease spectrum. The old "ology" approach can be harmful, with medications used for one acute condition harming or exacerbating another disease. There are also opportunities lost, with poor use of potentially synergistic treatments (one drug targeting many diseases through shared mechanisms).

Acute care is focused on the person holistically, with multi-morbidity, ageing and inflammation a central theme.

Our multi-disciplinary and clinically focused experimental science is supplemented with access to highly detailed health data through the National Data Hub in acute care, PIONEER. We also offer the opportunity to meet patients, mix with clinical academics of all grades, in a supportive and friendly environment.

We offer specific training in:

- Acute, Respiratory, Perioperative and Critical care medicine with a major focus on inflammation in both adults and children;
- The impact of ageing and multi-morbidity;
- Support in accessing our curated health data and statistical analytical support;
- Deep phenotyping of patients, from epidemiology to cutting edge bench science;
- Utilising clinical cohorts and animal models of injury, infection and inflammation;
- Neutrophil and macrophage biology and lung epithelial repair;
- The lung microbiome;
- Host/pathogen interactions.

Examples of potential projects:

Prof Helen McGettrick, Prof Fang Gao-Smith and Dr Ali Mazaheri: Dissecting the cellular and molecular signature that defines opioid addiction. This project will interrogate the phenotype and functional responsiveness of the immune system, in conjunction with neurobiology and cognition in patients before and after opioid prescription to identify a molecular signature that predicts addiction to enable prescription of alternative pain relief.

Dr Suzy Gallier, Prof Elizabeth Sapey: Health data from regional hospitals, the ambulance service and primary care is available from the Health Data UK Hub in acute care, PIONEER, and can be used to understand healthcare systems, assess patient outcomes and build new systems such as clinical decision support tools. In this PhD, you will be taught how to use health data to answer questions about health care and health care services using advanced statistical techniques and machine learning. You can also build tools for use in electronic health records to help understand and improve health care, working alongside a team of

supportive data scientists, analysts and clinicians. Projects will be developed to suit your interests including any surgical and medical emergency, common or rare presentations of disease and medical challenges such as multimorbidity and polypharmacy. This PhD is affiliated with the NIHR Midlands Patient Safety Research Collaboration, and is aimed at improving patient safety and experience in health care.

Dr Michael J Cox, Dr Aaron Scott, Prof Elizabeth Sapey: Characterising host-pathogen interactions in acute infections and the impact of antibiotic stewardship. Anti-microbial resistance is increasing and is a significant global challenge. Currently, broad spectrum antibiotics are used frequently in acute care, which can result in resistance, the onset of hospital-acquired infections and poor outcomes for patients – but this does not occur in all patients, so why are some more susceptible? In this project, you will assess host factors (age, co-morbidities, immune system function, other medications, microbiome) and pathogen factors (what bacteria, which strain, what antimicrobial resistance genes) in patients on broad spectrum antibiotics, to determine the long-term impact of antibiotic choice.

Dr Rahul Mahida, Dr Aaron Scott, Dr Dhruv Parekh: Extracellular vesicles (EVs) and their cargo in the pathogenesis of progressive pulmonary fibrosis (PPF). PPF describes scarring lung diseases with common pathogenic mechanisms which cause declining lung function and early mortality. Alveolar macrophages co-ordinate the immune response within the lungs; alveolar macrophages from patients with lung fibrosis promote fibroblast activation. In mouse models of lung fibrosis, alveolar macrophage metabolic profiles are re-programmed towards glycolysis, which is associated with a pro-fibrotic phenotype. Extracellular vesicles (EVs) are membrane-bound anuclear structures which transfer biologic cargo including organelles, mRNA, microRNA and proteins between cells EV-mediated cargo transfer is implicated in the development of a pro-fibrotic phenotype in alveolar macrophages. This project will elucidate the role EVs play in PPF pathogenesis, in particular their impact on alveolar macrophage metabolic profile and function and determine whether inhibiting these EVs could slow or halt progression of fibrosis in PPF.

Prof Adel Mansur, Dr Michael J Cox: People with Severe Asthma with Fungal Sensitisation (SAFS) represent a significant subset of asthmatics with severe, persistent asthma, with fungal sensitisation by skin prick test or specific IgE. There have been relatively few prospective studies, but there is evidence that antifungal treatment alleviates respiratory and nasal symptoms in these patients. Identifying which patients will most benefit from anti-fungal treatment relies on multiple parameters and here we aim to use molecular diagnostics of fungi in the airways to develop a rapid, sensitive and reliable method for stratifying patients and improving patient outcomes.

Dr Alba Llibre Serradell: Investigating the immune and metabolic host response in tuberculosis disease. Mycobacterium tuberculosis (M.tb) is the number one infectious disease killer worldwide, despite vaccination and available treatments. We need new drugs to treat TB and host-directed therapies (HDTs) are a promising strategy. To design effective HDTs against M.tb, we need a comprehensive understanding of the host response to infection. Through an interdisciplinary approach, combining the fields of clinical microbiology, immunology, metabolism and big data, our research focuses on answering the urgent question of how immune-metabolic responses impact the host's ability to resolve M.tb infection. This knowledge has the potential to reveal new host immune-metabolic therapeutic targets for TB disease, which are urgently needed.

Dr Dhruv Parekh, Dr Mansoor Bangash, Dr Alba Llibre Serradell: Investigating the impact of lactate in acute disease states on cellular immune-metabolic phenotype. Clinically, hyperlactatemia can be observed in patients who are critically ill with a variety of aetiologies and is strongly associated with adverse outcome in sepsis. Discovery of lactate's signalling and immunomodulatory roles challenges the putative theory that lactate is a bystander molecule and implies tissue malperfusion or mitochondrial dysfunction: instead hyperlactataemia itself may induce multisystem immunomodulation with maladaptive consequences in critical illness. A better understanding of the pathophysiology associated with (or perhaps induced by) abnormal circulating lactate level may allow novel therapeutic approaches for patients in certain shocked states, focussing on abnormal inflammation alongside haemodynamic & oxygenation optimisation. The deep metabolic and immune phenotyping this project involves may uncover an immunometabolic 'signature' implying different subtypes of hyperlactataemia, allowing treatments to be targeted and personalised. This also links with the Immunometabolism theme.

Prof Babu Naidu, Prof David Thickett, Dr Aaron Scott : How does cigarette smoking modulate alveolar macrophage function in patients undergoing thoracic surgery? This study will evaluate the importance of changes in SIRP alpha on alveolar macrophages from lung cancer patients undergoing thoracic surgery. Current smokers' macrophages have defective efferocytosis, so don't clear pulmonary inflammation adequately that leads to increased post-operative complications. This project will look at the mechanisms behind this effect.

Dr Aaron Scott, Louise Crowley, Prof David Thickett, Dr Dhruv Parekh: Neutrophils are abundant in the airspaces of idiopathic pulmonary fibrosis (IPF) and related progressive pulmonary fibrosis (PPF), and they are increasingly implicated as effectors that couple repetitive epithelial injury to maladaptive repair. Our previous clinical data showed that IPF patients experience intermittent daytime and overnight hypoxaemia, even early in the disease process, with the impact of hypoxia on neutrophil function in this context still unclear (10.3389/fimmu.2020.02190). Our ex vivo work, has demonstrated that TGFβ1 exposure induces neutrophil chemokinesis and IPF-derived neutrophils appear to move less directly upon exposure to this pro-fibrotic cytokine. Multiplex immunofluorescence places neutrophil proteinases and NET associated citrullinated histone in close proximity to hyperplastic epithelium. Furthermore, data from our novel in vitro model suggests that the alveolar microenvironment promotes neutrophil priming/activation.

This project will build on these findings through the HYBRID cohort study with longitudinal, multi-compartment study of IPF and PPF linking clinical hypoxaemia and disease trajectory to neutrophil phenotype and function and the consequences for cells critical in lung fibrosis; epithelial cells and fibroblasts. This project will test the hypothesis; In IPF/PPF, a TGFβ1 rich and intermittently hypoxic microenvironment reprograms neutrophil maturation and motility, leading to dysregulated, persistent neutrophil activity. NET and proteinase release amplify epithelial injury and remodelling and drive fibroblast activation.

Training elements for the candidate: Primary cell isolation and culture: neutrophil, epithelial cells, fibroblasts. Expansion of our in vitro model of the alveolar space including a transwell epithelial migration model utilising IPF and control derived neutrophils and bronchoalveolar lavage fluid samples (BALF) from the HYBRID study. TGFb1 activation assay - in collaboration with Amanda Tatler from Nottingham University. High parameter flow cytometry, molecular biology techniques including QPCR, Western blotting. Transcriptomic analysis, bulk and single-cell RNAseq. The student will gain experience of clinical research through the HYBRID study

including participant recruitment, clinical assessments; 6MWT, daytime and overnight oximetry, phlebotomy, and observe flexible bronchoscopy + bronchoalveolar lavage.

Dr Dhruv Parekh, Prof Adam Croft, Dr Aaron Scott; Chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis (PF), represent opposite ends of the disease spectrum but are both characterised by a dysregulated wound healing response. Both conditions are characterised to some degree, by development of small airways disease (SAD) – thickening/fibrosis of small bronchioles and emphysema - destruction of alveolar walls, leading to airspace enlargement and compromised lung function. Despite their paradoxical nature, both pathologies coexist in COPD and PF patients, highlighting the need to understand their common underlying mechanisms. This project aims to elucidate the common drivers of dysfunction in airway remodelling and excessive/dysregulated repair in fibrosis using ex vivo and in vivo modelling.

Inflammatory eye disease

Major clinical and research interests are based around the theme of '*Inflammatory Mechanisms in the Ocular Microenvironment*'. The focus of our research is the regulation of ocular immunity, in particular immunologically-driven ocular surface diseases (*OSD*) and mitochondrial exhaustion in inflammatory eye disease. Our specific interests range from discovery science and how novel biomaterials or drugs impact upon wound healing and scarring, to the development of patient-driven health-related technologies to robustly quantify disease. Our multifaceted research portfolio includes:

- Inflammatory mechanisms driving the ocular microenvironment in health and disease using molecular, cellular, *ex vivo* and *in vivo* modelling systems;
- Identification of innovative approaches to diagnostics and therapeutics including ocular drug delivery, medical devices, biomarkers and imaging;
- Improving and standardising clinical, patient and automated imaging outcome measurements for activity and damage reporting in early phase clinical trials and observational studies.

Examples of potential projects:

Prof Lisa Hill: Developing and translating immunotherapies and drug delivery technologies to treat chronic inflammation and oxidative stress in retinal neurodegenerative diseases. This project aims to develop non-invasive topical therapies to treat retinal disease (including glaucoma and age-related macular degeneration).

Prof Saaeha Rauz: Development of drugs and devices for the prevention and reversal of progressive ocular surface scarring. This project is underpinned by an assembly of multi-disciplinary expertise exploring chemically engineered biomaterials (Prof Liam Grover) and novel drugs (Prof Nicholas Barnes) across the full breadth of the translational pathway, from bench to bedside phase I/II clinical trials.

Dr Jose Romero: Mitochondria-Based Therapies for Inflammatory and Scarring Eye Diseases. This project aims to develop innovative therapies to protect and restore mitochondrial function in ocular tissues affected by stress-induced damage. The team has recently identified novel mitochondria-protective drugs with unprecedented capacity to repair and reverse disease across multiple eye conditions. The project is highly translational, combining state-of-the-art approaches including in vivo models of ocular disease, cellular assays, metabolic profiling, drug screening platforms, and spatial proteomics to uncover pathways that improve mitochondrial function. This multidisciplinary approach is complemented by clinical collaboration at the Birmingham and Midland Eye Centre (Prof Saaeha Rauz, Dr Yu Jeat Chong) to assess retinal mitochondrial function non-invasively using next-generation imaging technologies, alongside systemic metabolic profiling of peripheral blood populations. The vision is to integrate experimental and clinical studies to maximize the translational potential of these therapeutic strategies for patients.

Applied health science: Data science & informatics, Clinical trial design, Patient reported outcomes & Regulatory science

The Institute for Applied Health Research is focussed on advancing understanding of disease aetiology, identifying modifiable prognostic factors, developing, evaluating and implementing interventions that improve health management and outcomes. Relevant areas of research interest include:

- The Centre for Patient Reported Outcomes Research. This Centre, the only one of its kind in the UK, has over 80 interdisciplinary members and has led international guidance for the use of patient reported outcomes in clinical trials, informing EMA, FDA and NICE guidance;
- The Birmingham Clinical Trials Unit has particular expertise in early phase trials design and the development of novel methodologies which are being deployed in our inflammation focussed trials unit I-ACT;
- Our Health Informatics portfolio includes work with Health Data Research UK and the THIN database to answer questions around disease aetiology and management. We were the first in the UK to innovate an Automated Clinical Epidemiology Studies platform enabling reproducible and transparent research which has attracted over 10 doctoral students in the last two years.

Examples of potential projects:

Prof Alastair Denniston, Dr Xiaoxuan Liu: Improving the evaluation and regulation of AI health technologies; bringing regulatory science approaches to ensure that products that are approved for use in patients are safe, effective, equitable and sustainable.Improving the evaluation and regulation of AI health technologies; bringing regulatory science approaches to ensure that products that are approved for use in patients are safe, effective, equitable and sustainable.

Prof Thomas Jackson: Artificial intelligence (AI) and multi-morbidity. This project builds on UKRI funded research to apply AI techniques to identify multi-morbidity clusters and to determine underlying mechanisms.

Neuroinflammation

Major clinical and research interests are based around the theme of '*Inflammatory Mechanisms in the CNS Microenvironment after Neurotrauma*'. Our focus is understanding the pathophysiology of acute and chronic neuroinflammation, providing insight into factors that influence the acute clinical course and later functional outcomes. Neuroinflammation, if left unregulated, leads to dysregulated wound healing, scarring, loss of function and the development of neuropathic pain. We strive to develop potential therapies to control or treat neuroinflammation and neuropathic pain, thereby improving functional outcomes after CNS trauma and disease. Our specific interests range from discovery science to how novel biomaterials or drugs can be used to impact upon wound healing, scarring and pain triggered by inflammation, to the development of drugs and devices to target these processes. Our multifaceted research portfolio includes:

- Understanding the inflammatory mechanisms driving the microenvironment of the damaged brain, spinal cord and peripheral nerve in health and disease using molecular, cellular, *ex vivo* and *in vivo* modelling systems.
- Understanding the contribution of inflammation to the development of neuropathic pain using translational *in vitro*, *ex vivo* and *in vivo* models.
- Identification of novel genes and drugs for the treatment of neuroinflammatory disorders of the brain, spinal cord and peripheral nerve.
- Identification of innovative approaches to diagnostics and therapeutics including drug delivery, gene therapy, medical devices, biomarkers and imaging to restore lost function and alleviate neuropathic pain.

Examples of potential projects:

Prof Zubair Ahmed: Elucidating the neuroinflammatory differences between spinal cord injury (SCI) in the rat versus the mouse. To date there are no reparative treatments for SCI and both rat and mouse models of SCI are used interchangeably to model preclinical SCI. However, despite the recognition of fundamental differences between mouse and rat SCI responses for decades, these differences have largely been ignored. For example, it is well established that in the rat SCI site, cavitation results just like in humans, yet cavitation is largely absent in mouse SCI sites. Genome-wide expression studies by us show that there are only 31 common gene changes after SCI in mouse versus rat, and preliminary experiments indicate that the most significant differences are in genes related to inflammation. We therefore wish to understand what the differences in inflammation are between mouse versus rat SCI and whether these differences could explain the lack of a clinical therapy.

Prof Zubair Ahmed: The role of the DNA damage response pathway in microglial-mediated neuroinflammation after CNS injury. Previous work by us has shown that aberrant activation of the DNA damage response pathway, such as that seen after CNS injury, mediates neuroinflammation. Preliminary studies by us shows that pretreatment of primary microglia in vitro, with an inhibitor (AZD1390) to one components of the DNA damage pathway, ataxia telangiectasia mutated (ATM) ameliorated LPS-induced inflammation. We now wish to test if the negative consequences of DNA damage-mediated inflammation in CNS injury models can be reversed using AZD1390, which is a brain penetrant ATM inhibitor, that is currently being assessed in Phase 2 clinical trials for cancer therapy.

Prof Zubair Ahmed, Dr Claire Palles, Dr Richard Tuxworth: Injury-induced neuropathic pain. Spinal cord injury leads to debilitating chronic neuropathic pain. We are using state-of-the-art

technologies such as single cell RNAseq and spatial transcriptomics to understand which neurons respond to pain signals originating from the damaged site. Initial experiments suggest that different neurons respond to, for example, an injury- as opposed to chemotherapy-induced neuropathic pain and hence there is an exciting opportunity to target specific populations of neurons to develop "tailored" pain alleviating therapies for different indications.

Prof Lisa Hill, Prof Alex Sinclair, and Lt Col James Mitchell are leading cutting-edge research to identify biomarkers and develop effective treatments for neuroinflammation following concussion and traumatic brain injury (TBI).

Our flagship initiative, mTBI-PREDICT, is a long-term, multidisciplinary study designed to identify the most accurate, reproducible, and clinically viable biomarkers for predicting long-term health outcomes after head injury. This ambitious project combines detailed clinical phenotyping of patients post-concussion with state-of-the-art, multimodal biomarker analysis in the lab, including the investigation of inflammatory markers across a range of biofluids.

A key focus of the project is to understand how and why neuroinflammation worsens recovery outcomes after concussion and brain injury. Through this integrated approach, our vision is to drive a step change in the clinical care and rehabilitation of patients with mild TBI. By generating robust evidence to support the use of specific biomarkers in early diagnosis and management, we aim to transform clinical practice and improve long-term recovery for those affected by concussion.

Prof Antonio Belli, Dr Valentina Di Pietro: Concussion and inflammation. The link between concussion or brain injury has long been established and key cytokines are elevated for 2-6 days after head injury, including those related to neuropathic pain. Blood tests have been used in athletes to test for concussion-related biomarkers of inflammation, but more research is needed to establish the links between blood-based markers, neuropathic pain and other outcomes after concussion.

Dr Daniel Fulton, Felix Chan: Dysregulation of the complement system is increasingly recognised as a key driver of neuroinflammation and neurodegeneration in progressive CNS disorders, including multiple sclerosis and epilepsy. Metabolic pathways appear to be connected to these events with recent findings identifying complement activation in tuberous sclerosis complex (TSC)—a rare genetic disorder caused by mutations in TSC1 or TSC2, leading to hyperactivation of the mTOR pathway and a spectrum of neurological symptoms. However, the extent to which the mTOR / complement axis contributes to the injury of specific neural components such as synapses and myelin remain unknown. Answering this question will improve understanding of neuroinflammatory disease mechanisms and potentially identify therapeutic targets for neuroinflammatory conditions marked by synaptic and myelin pathology.

To explore this question, this project will examine the relationship between mTOR dysregulation, glial-driven complement activation, and the resulting injury to synapses, myelin, and the neural circuits these elements support. These aims will be pursued in mouse organotypic brain slice cultures transduced with recombinant viral vectors designed to modulate relevant mTOR pathway components. Molecular, structural and functional changes to CNS structures will then be exploring using a combination of immune-metabolic profiling, molecular and biochemical assays, electrophysiology and cellular imaging. The project will also incorporate human post-mortem tissue analysis to validate findings in a clinically relevant context.

Our Facilities

We are proud to host a wide range of world-class facilities at the University, which are critical for our ambitious inflammation research programmes. You can find out more about them here:

https://www.birmingham.ac.uk/university/colleges/mds/facilities

These include:

- State of the art genomics capability including Illumina, single cell and nanopore sequencing platforms, a CyTOF facility and molecular histology (NanoString).
- A £10M imaging suite equipped with single molecule, single cell and whole animal imaging equipment in the cross institutional COMPARE initiative with the University of Nottingham to enhance biological imaging capability.
- The Phenome Centre Birmingham, Steroid Metabolome Analysis Core and Metabolic Tracer Analysis Core represent a unique array of interlinked technology platforms supporting all aspects of metabolome and metabolic analyses in health and disease.
- The Henry Wellcome Building for Biomolecular NMR Spectroscopy is the largest open access high and ultra-high field NMR facility in the UK.
- The NIHR Wellcome Clinical Research Facility (CRF) that provides high-quality clinical environments for experimental medicine, complex research studies, and early phase clinical trials, including an Advanced Therapies Facility.
- Birmingham CRUK Clinical Trials Unit established the I-ACT (Inflammation & Advanced Cell Therapies) team, which delivers an academic-led trials portfolio focussed on early phase clinical trials in inflammatory diseases.
- The Birmingham NIHR Bioresource for Common and Rare Diseases Hub, the 2nd highest recruiter to UK rare disease cohorts. The work of the CRF covers high profile studies (e.g. gene therapy for haemophilia A) with implementation in healthcare (therapy for chronic HepC infection in children).
- The Healthcare Technologies Institute, that brings together leading experts from chemical engineering, biomedical science, computer science, applied mathematics, chemistry and physics to develop new technologies that will transform healthcare.
- The Microbiome Treatment Centre (MTC), pioneered by Birmingham. This is the only MHRA approved provider of FMT for clinical treatment in the UK and provides transplants to all UK NHS Trusts.
- The Genomic Medicine Centre links 17 regional NHS Trusts together through shared academic and clinical leadership, accelerating both service innovation and our capabilities to deliver transformative research.
- The Centre for Computational Biology (CCB) has played a vital role in massive expansion of data science within genomics and high-throughput technologies as the basis of stratified medicine approaches.
- Four national Centres of Excellence with a focus on musculoskeletal disease and inflammation – The NIHR Birmingham Biomedical Research Centre, The MRC- Arthritis UK Centre for Musculoskeletal Ageing Research ,the Arthritis UK Centre for Rheumatoid Pathogenesis and the Arthritis UK Research Consortium: ARCADIA (MoleculAR And CellulAr Definition Of Remission In Childhood And Adult Inflammatory Arthritis).
- Access to established patient and public involvement networks, including the Rheumatology Research Patient Partnership (R2P2) and other groups affiliated with the NIHR Birmingham Biomedical Research Centre. These networks support meaningful involvement of patients and the public across the research process.

Training

The scheme for Kennedy Trust MB-PhD students will build on the well-developed mentorship programme for PhD students at the University of Birmingham, with additional refinements as follows:

- Ensuring that PhD students always have a clinical supervisor and non-clinical supervisor.
- Facilitating quarterly clinical 'keeping in touch' days through which the PhD student will maintain clinical contact and exposure, enabling them to maintain their skills.
- Linking each PhD student with two Patient Research Partners via our innovative Student-Patient Alliance. Patient Research Partners will support the development of the students' skills in PPIE and will facilitate their understanding of the clinical relevance of their research.
- Integrating Kennedy Trust students with MB-PhD students on related schemes via annual networking meetings.

In addition to normal supervision and mentoring, a range of training opportunities, both project specific and generic, will be available to equip Kennedy Trust students to undertake their research successfully and to enhance their personal development. Each academic year, the students will complete, a Development Needs Analysis that assesses training needs, aligned to the Vitae Researcher Development Framework. Identified needs will be supported through formal training programmes. There is extensive training in transferable skills such as communication, publishing and thesis preparation. In addition, there are practical opportunities to gain an understanding of business and develop entrepreneurial flair at our Enterprise Summer School, and opportunities to undertake outreach media activity (mock TV and radio interviews).

The Medical School provides a vibrant environment for postgraduate students which the Kennedy Trust students would join. There are currently 158 postgraduate research registrations in 'Clinical Medicine' at UoB. A collaborative environment is enriched by the Doctoral Training Programme (DTP) symposia (including students from IMPACT (MRC), MIBTP (BBSRC), CRUK Centre Birmingham (CRUK), MIDAS (Wellcome Trust), AAMR (Wellcome Trust), CMAR (MRC-Arthritis UK) and RACE (Arthritis UK) DTP schemes), the annual PhD Research Festival and PGR-led journal clubs, which encourage open scientific discussion in a safe and nurturing environment. Kennedy Trust students will also have access to the innovative and sector-leading training programme led from Birmingham's MRC-funded DTP.