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 five fully-funded studentships available that will commence in June 2025.

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 £14,825)
- 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 2028, or if this was not permitted, consider completing their medical training at the University of Birmingham from 2028 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/research/inflammation-ageing/ageing-and-frailty.aspx

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

Inflammatory gut and liver disease
https://www.birmingham.ac.uk/research/immunology-immunotherapy/gut-and-liver-inflammation.aspx

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/research/inflammation-ageing/acute-care-research.aspx

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

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, multi-modal single cell characterisation and spatial imaging technologies to understand tissue pathology and identify the cellular and molecular drivers of disease persistence and tissue inflammation in adult and paediatric immune mediated inflammatory diseases. We are now employing cellular and molecular technologies to specifically target these pathways and modulate fibroblast function in disease. Furthermore, we are developing engineered T cells to selectively deplete pathogenic fibroblasts from the inflamed tissue microenvironments to promote the resolution of tissue inflammation. Furthermore, we are exploring the cross-talk between macrophages and fibroblasts in the tissue and how this impacts on the outcome of the disease using novel co-culture techniques, tissue organoid models with functional readouts, and inducible pluripotent stem cells to model diseased tissues.

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 create the first comprehensive 3D atlas of the bone cell network, revealing how osteocytes and blood vessels communicate to maintain skeletal health in ageing and inflammation. We will utilise cutting-edge 3D microscopy imaging technologies to visualise 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 quantitative preference-based methods to inform decision-making in the context of therapies for inflammatory conditions. Building on research funded by the EU and Versus Arthritis, 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: We combine multi-cellular in vitro models, with ex vivo patient sample analysis, preclinical models of disease and big data to investigate 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.

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 antibody molecules 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.

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:

Prof Leigh Breen: Mechanisms and countermeasures to inflammation-induced muscle anabolic resistance in obesity. This project builds on *in vivo* human work demonstrating that muscle anabolic resistance in older individuals is closely linked to their inflammatory profile.

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: Targeting steroid metabolism to prevent inflammatory muscle wasting and bone loss in chronic inflammatory diseases. We have identified unique changes in myeloid steroid metabolism that shape the local immune-microenvironment. This project utilises primary co-culture, ex vivo tissue culture and in vivo models to examine interventions that suppress inflammation and prevent muscle wasting and bone loss in diseases such as rheumatoid arthritis and chronic kidney 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 Versus Arthritis exploring the role of a distinct synovial fibroblast population in mediating inflammation and pain in patients with OA.

Dr Yu-Chiang Lai: Investigating the molecular mechanisms of inflammatory disease-induced sarcopenia. This project will address how inflammation causes muscle loss with a focus on signalling mechanisms and mitochondrial dysfunction

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:

Dr Sarah Dimeloe: Interrogating T cell metabolic dysfunction in chronic inflammatory disease. This project builds on research exploring how disease-associated dysregulation of T cell metabolic phenotypes determines their immune 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).

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.

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.

Prof Claudio Mauro, 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.

Dr Prasad Nagakumar, Dr Aaron Scott: Vaping has become very common in teenagers. Active/passive smoke exposure is an important risk factor for poor asthma control/asthma attacks in children. The immunological mechanisms of e-cigarettes promoting inflammation through alveolar macrophage pathway in adults is well described. However, there are no data in children. In this project we will evaluate the mechanisms by which alveolar macrophages promote airway inflammation in children with asthma.

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, Prof David Thickett, Dr Dhruv Parekh: Establishing the importance of intermittent hypoxia in the progression of idiopathic pulmonary fibrosis (IPF). This work will use primary lung tissue to study whether intermittent hypoxia exaggerates the progression of fibrosis. In addition, clinical samples from the HYBRID cohort study in IPF will be used to determine if correcting intermittent hypoxia reduces novel biomarkers of collagen turnover and lung epithelial dysfunction.

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:

Dr 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). This multi-disciplined collaborative project is led out of the University of Birmingham with input and co-supervision from clinical experts in Clinical Ophthalmology and Imaging (Prof Alastair Denniston, UHB & Prof Andrew Dick, University of Bristol/Moorfields).

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: Elucidating novel therapies to rescue mitochondrial quality control in inflammatory eye. This will explore approaches to protecting tissues from stress-induced mitochondrial damage and evaluate translational relevance, using in vivo and cellular models of retinopathy and other forms of inflammatory eye disease.

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.

Dr 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.

Prof Krish Nirantharakumar: Treatment effectiveness of DMARDS in the presence of comorbidities; repurposing medications prescribed for other health conditions towards rheumatoid arthritis; comparative analysis of electronic health record data against trial data for treatment effectiveness; predictive modelling for RA: analysis of electronic health records and UK Biobank data; automated clinical epidemiology for rheumatoid arthritis; and artificial intelligence in the management of rheumatoid arthritis and multimorbidity. Projects builds on innovative methodological work to develop predictive analytics and advanced epidemiological designs for early identification and management of patients with RA.

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, 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 Alex Sinclair, Dr Lisa Hill: Identifying biomarkers of neuroinflammation after concussion. mTBI-PREDICT is a long-term study that aims to identify the most accurate, reproducible and clinically practical biomarkers to better identify those at risk of long-term health issues after a head injury. This will be achieved through a harmonised program of detailed clinical phenotyping of patients after concussion coupled with state-of-the-art multimodal biomarker evaluation within the laboratory, including measures of inflammatory markers within various biofluids. As part of the wider clinical study, in this project we are seeking to understand how and why neuroinflammation exacerbates outcomes for patients after concussion. Our vision is to deliver a step change in the care of patients with mTBI and bring much needed advances in patient rehabilitation by revealing ground-breaking evidence to justify which biomarkers should be used to inform the diagnosis and early management of concussion [https://www.youtube.com/watch?v=ME9aW4uwxcY].

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: Neuroinflammation-mediated myelin damage. Myelin, the structure that enwraps axons and promotes normal conduction of the action potential, is susceptible to damage by inflammation. For example, multiple sclerosis is a disease where inflammation attacks the white matter axons, causing damage to axons, neuropathic pain, spasticity, tremors and eventual paralysis. Our work identifies ways of preventing this immune attack, preserving myelin and eventually promoting its repair to improves alleviate pain and improve functional outcomes for patients.

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.
- Three national Centres of Excellence with a focus on musculoskeletal disease and inflammation – The NIHR Birmingham Biomedical Research Centre, The MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research and the Versus Arthritis Centre for Rheumatoid Pathogenesis.

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-Versus Arthritis) and RACE (Versus Arthritis) 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.