



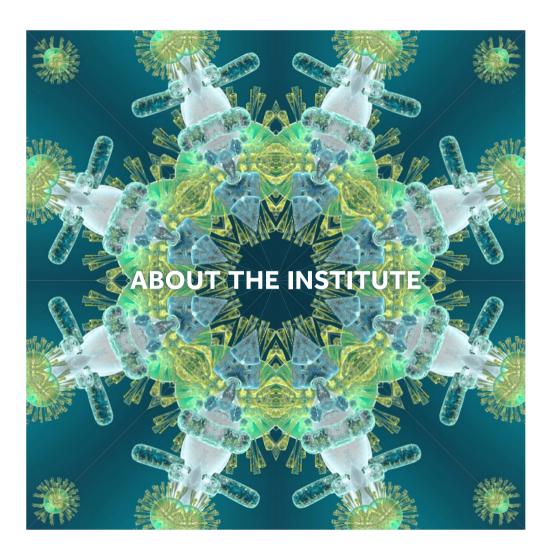
Lydia Becker Institute of Immunology and Inflammation



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"There are few examples in health and disease where the immune system is not important."



## Director: Professor Tracy Hussell

Division of Infection, Immunity & Respiratory Medicine School of Biological Sciences

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Institute Manager: Dr Fiona Foster

We have extensive immunology and inflammation experience at The University of Manchester. For the first time, this is being drawn together into a new, multidisciplinary research institute — The Lydia Becker Institute of Immunology and Inflammation.

The Lydia Becker Institute of Immunology and Inflammation is home to internationally renowned immunology and inflammation expertise in a vast array of basic and applied disciplines. We perform fundamental and translational exploratory science, applying the latest technologies to address the key new concepts in health and many areas of clinical unmet need. The great breadth and diversity of research in our Institute emphasises how immunology plays an everincreasing role in modern medicine.

The Institute is directed by Professor Tracy Hussell, who also directs the Manchester Collaborative Centre for Inflammation Research (MCCIR), a unique collaboration with industry in blue sky inflammation research.

The Institute is funded by the University of Manchester Research institute (UMRI).

An executive steering committee oversees the scientific direction of the Institute.

Tracy Hussell Director

Chris Griffiths Clinical immunology lead – Salford

TBC Clinical immunology lead – MFT

Fiona Thistlethwaite Clinical immunology lead – The Christie

Fiona Foster Institute manager

John Grainger Barrier immunology lead Robert Bristow Cancer immunology lead

Anthony Heagerty Cardiovascular and obesity immunology lead

Daniel Davis Cellular immunology lead Mark Travis Immune tolerance lead

Judi Allen Immuno-matrix lead

Peter Arkwright Life course immunology lead

David Brough Neuro-immunology lead

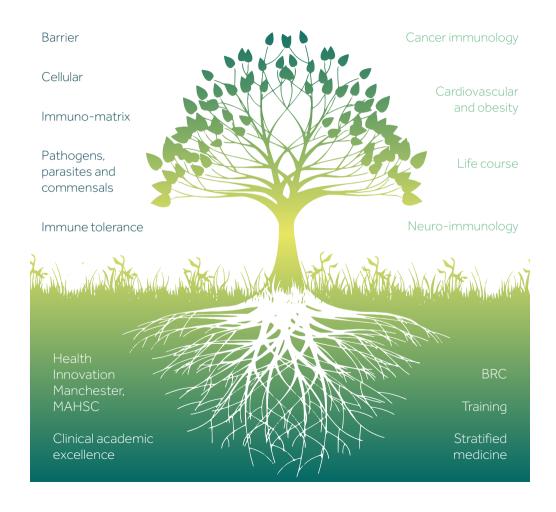
Richard Grencis Pathogens, parasites and commensals lead



Lydia Becker

The Institute is named after Manchester-born Lydia Ernestine Becker. Though better known for her pioneering work in the field of women's suffrage, she was also a celebrated natural scientist who conversed with Charles Darwin. She strongly believed that women were intellectually equal to men and deserved the same opportunities.

## Areas for development

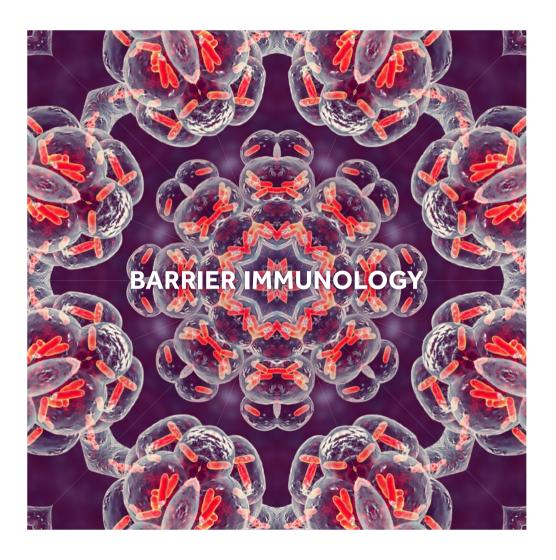


# We work across boundaries, harnessing complexity in tissues and disease to drive meaningful discovery.

### The Institute's strategic aims are:

- To promote the academic and clinical excellence in immunology and inflammation at The University of Manchester:
- To encompass a cross-disciplinary and collaborative approach in solving the most important problems;
- To discover new concepts in fundamental cell biology;
- To formulate and test new hypotheses in how the immune system works using appropriate infection and injury models;
- To understand how inflammation is prevented in health;

- To incorporate tissue and disease complexity in our research;
- To work with and learn from our patients to better understand their disease:
- To develop strategies to improve tissue repair pathways;
- To define the common processes underlying inflammatory diseases;
- · To take into account multi-morbidities;
- · To drive forward new ideas for medicine;
- To collaborate with clinicians and pharmaceutical companies for context and applications.



"We are advancing knowledge across the front lines of tissue immunity."



Lead: Dr John Grainger

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Deputy lead: Dr Joanne Konkel

Immune cells adapt to the needs of each tissue. Defining the molecular mechanisms influencing immune cell phenotype, function and persistence in health is critical for our understanding of disease and for the development of new medicines to treat them.

The barrier immunology community at The University of Manchester performs fundamental and applied research on every immune cell type in the lung, skin, oral cavity and gastrointestinal tract, taking into account tissue complexity across the life course.

Our research is underpinned by strong clinical collaborators within the National Institute for Health Research (NIHR)

Manchester Biomedical Research Centre's (BRC) themes relating to cancer, respiratory medicine and dermatology. With access to highly characterised patient cohorts and financial and scientific input from major pharmaceutical companies, we are ideally placed to ask the big questions.

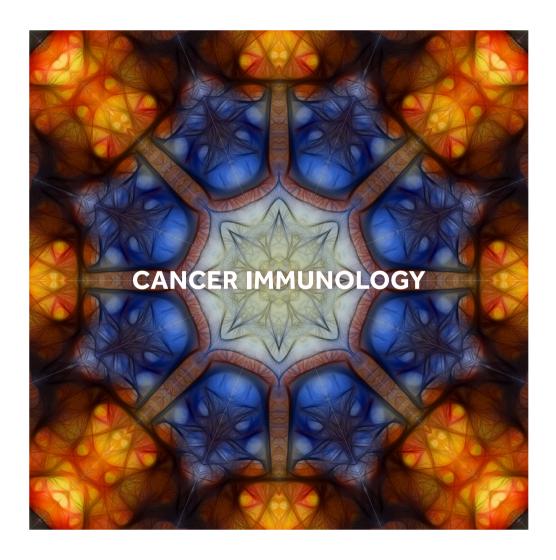
## Case study – Mapping the lungs: understanding the immune response to respiratory disease.

Principal Investigator: Professor Tracy Hussell

One area of intense immunological discovery is in the lung. Collaboration with cardiothoracic surgeons and respiratory clinical academics at the Manchester University NHS Foundation Trust (South) provides abundant human lung samples that enable many explorative hypotheses to be tested on the same patient including:

- the impact of the epithelium on innate immunity;
- the super-resolution structure of cells in health and disease;
- tissue-specific influences on innate immunity;
- matrix and fibroblast modifications across the life course:
- immunity and epithelial repair;
- rare immune cell types in health and disease.

By merging the results from multiple investigations we provide a personalised map of the patient's disease that will feed into the development of a stratified medical approach.



# "Cancer immunology is revolutionising the treatment of cancer."



## Lead: Professor Robert Bristow

Division of Cancer Sciences School of Medical Sciences

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Or via Christine Mullen, Executive Assistant to the MCRC Directors: christine.mullen@manchester.ac.uk At The University of Manchester, basic researchers and medical oncologists work closely together to expand our knowledge of the power of the immune system in fighting disease.

To combat immune recognition and elimination, tumours exhibit a plethora of evasive mechanisms.

However, the extent to which the immune system constitutes a natural barrier to cancer has been a long-lasting subject of debate. In the last few years, this notion has gained undisputable support following the clinical success of therapies aimed at harnessing cells from the immune system and limiting immune evasion by tumour cells. These unprecedented and outstanding outcomes – even in cancer types that were until recently considered as refractory to immune-based therapies – have fully reinvigorated the interest in the cancer immunology field.

But complete and durable responses have only been observed in a minority of patients and in selected cancer types. This highlights the need for basic, translational and clinical research to further uncover the mechanism of action of these treatments, and to identify novel immune pathways to target and increase the efficacy of cancer therapy.

# Case study – Understanding mechanisms of resistance to immunotherapy in head and neck/salivary gland cancer.

Principal Investigator: Dr Robert Metcalf

Dr Metcalf is a clinician scientist in medical oncology, based at The Christie NHS Foundation Trust, the Manchester Collaborative Centre for Inflammation Research, and the Cancer Research UK Manchester Institute.

Dr Metcalf and the team of expert immunologists at the Manchester Collaborative Centre for Inflammation Research are analysing the tumour and immune components within blood and tumour samples using flow cytometry, mass cytometry, proteomics and immunohistochemistry/immunofluorescence to understand the biology of anti-tumour immunity and develop newer and better cancer therapies.

#### The problem:

In his clinical practice he leads early phase clinical trials, testing the most recent drug therapies which stimulate the immune system to attack cancer. From this practice, although some patients are gaining long term tumour regressions (lasting years) unseen with previous therapies, the main clinical problem he is focusing on is that only a small proportion of patients (less than 20%) gain significant benefit from the newest immunotherapies.

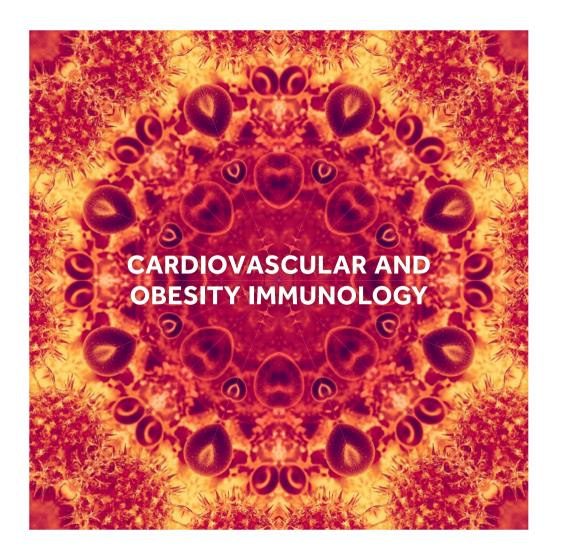
#### Our work:

His research seeks to identify mechanisms of response and resistance to immunotherapies and to use deep immune phenotyping to identify signatures which can be used to personalise current treatments.

Combining both his clinical and research expertise in the Hussell Lab, he is studying the interactions between tumour and immune cells in head and neck cancer.

Dr Metcalf brings together the clinical knowhow of the surgical team (led by Professor Homer), specialist histopathologists (led by Professor Thakker and Dr Betts) and the radiology and radiation oncologists through The Christie and Manchester University NHS Foundation Trust hospitals.

Patients consent to fresh tumour and blood collection during their routine treatment through the Manchester Cancer Research Centre Biobank (led by Jane Rogan).



"Inflammatory processes in perivascular fat in obesity play a role in arterial function, blood pressure and diabetes control."



 ${\sf Lead: Professor\, Anthony\, Heagerty}$ 

Division of Cardiovascular Sciences School of Medical Sciences

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# Cardiovascular researchers active within immunology are working on multi-morbidities, linking inflammation to obesity and coronary disease.

A key area of focus is on the role of perivascular adipose tissue and its influence on the structure and function of small arteries in both healthy and overweight people.

There is clear evidence that this fat depot is highly metabolically active and, in healthy individuals, releases vasodilator adipokines such as adiponectin. In obesity there is evidence of adipocyte hypertrophy and inflammation with the loss of the bioavailability of adiponectin with resultant vasoconstriction which can lead to a rise in blood pressure and a decrease of nutritive blood flow leading to insulin resistance and diabetes.

We have already published on the crucial role of the macrophage and its activation in this inflammatory process (Withers et al, ATVB 2016) and more recently in collaboration with the group led by Professor Else. We have also been exploring the role of the eosinophil in this process (Withers et al, Sci Rep 2017).

We now have funding from the British Heart Foundation to look at this in more detail, and a variety of animal models of obesity which are allowing us to look at the effects of influencing information and improving PVAT structure and function

# Case study – Investigating the role of inflammation in obesity and diabetes with particular focus on perivascular adipose tissue depots.

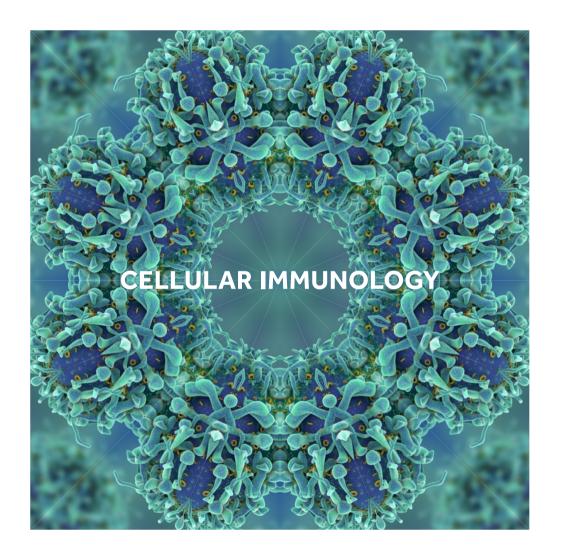
Principal Investigator: Professor Anthony Heagerty

The Division of Cardiovascular Sciences has a team looking directly at the role of macrophages and eosinophils in perivascular adipose tissue and how they influence the bioavailability of vasodilator adipokines which are reduced in overweight patients.

This leads to vasoconstriction and a loss of glucose uptake by skeletal muscle resulting in hypertension and glucose intolerance (diabetes).

Preventing or reversing inflammation is associated with an improvement with a reduction in blood pressure and an improvement in insulin resistance.

The aim is to develop novel therapies to prevent obesity related complications in the circulation.



"A huge array of blockbuster medicines – with uses from treating auto-immune diseases to combating cancer – stem directly from basic immune cell biology."



## Lead: Professor Daniel Davis

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Deputy lead: Dr Gloria Lopez-Castejon

# Understanding the immune system requires an in-depth knowledge about what each different type of immune cell does in the body.

We study many different types of immune cell, including T cells, B cells, natural killer cells, macrophages, monocytes and dendritic cells.

We also study how these different immune cells vary their behaviour in different organs of the body, as well as how and why their activity changes in old age, at different times of the day, and in different disease settings.

We study the ways in which these different immune cells work together to detect and deal with pathogens including bacteria, viruses, fungi or parasites, and in cancer.

We collaborate widely with academic scientists, clinicians and scientists in pharmaceutical companies.

Much of our success comes from our continuing use of state-of-the-art technology, from single cell analysis to super-resolution microscopy.

## Case study – Discovering how immune cells are able to talk to each other.

Principal Investigator: Professor Daniel M Davis

Using advanced microscopy, we have helped establish new concepts of how immune cells communicate with each other and how they detect signs of disease in other cells.

A new, emerging hypothesis is that immune responses are regulated, in part, by miniscule nanometre-scale changes to the organisation of immune cell surfaces. We are now testing how these changes in cell surfaces impact thresholds at which immune responses are switched on or off.

As well as understanding how immune cells work, we hope this will reveal new ways in which medicines could nudge immune activity up or down.

Specific topics include:

- understanding how genetic diversity impacts immune responses;
- studying how immune cells behave differently in states of health and disease;
- comparing the functions and activities of immune cells in different organs of the body.



"Determining how our immune system is regulated to prevent disease."



### Lead: Professor Mark Travis

Division of Infection, Immunity & Respiratory Medicine School of Biological Sciences

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Deputy lead: Dr Matt Hepworth

Our immune system has the difficult task of defending the body against potential threats while recognising and not attacking host molecules. In autoimmune diseases this tightly controlled system breaks down and the immune system targets the body's own organs and tissues.

Autoimmune diseases affect up to 3% of the population and examples include rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, psoriasis, myositis, systemic sclerosis, systemic lupus erythematosus and inflammatory bowel disease.

By working closely with basic scientists, immunologists and a variety of clinical disciplines, we aim to increase our understanding of how immune dysregulation causes disease so that scientific discoveries can be translated into the clinic to ultimately improve the management of these conditions.

## Case study – Understanding how genetic factors influence immune cells in patients with rheumatoid arthritis.

Principal Investigators: Professor Anne Barton and Dr Sebastien Viatte

### The problem:

Genetic predisposing factors account for roughly 60% of the causes of rheumatoid arthritis (RA). More than 100 RA susceptibility single nucleotide polymorphisms (SNPs) have currently been identified, yet for most of them, their mechanism of action remains uncertain.

### Our work:

Using clinical samples from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) consortium, we are trying to understand which immune cell types and functions are affected by genetic susceptibility factors and how these pathogenic cell types attack structures in the joints of patients with RA. Based on the outcome of genetic and functional studies on the causes of RA, we aim to develop clinical tests that will help clinicians to tailor treatment options to every individual patient based on their genetic make-up and individual immune profile.



"Discovering how immune cells and the extracellular matrix communicate is central to understanding the immune system itself."



### Lead: Professor Judi Allen

Division of Infection, Immunity & Respiratory Medicine School of Biological Sciences

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Deputy lead: Professor David Thornton

Research into matrix is a major strength at Manchester and immuno-matrix is a central theme of the University's Wellcome Centre for Cell Matrix Research as well as the Lydia Becker Institute of Immunology and Inflammation.

Matrix surrounds and supports our cells and accounts for one third of our body mass. Dysregulation of matrix is a central process in the pathogenesis of most human chronic diseases, and a critical factor in fibrosis (scarring). The extracellular matrix regulates and is regulated by the innate and adaptive immune system. We focus not only on collagen matrix but the mucus barrier that protects our tissues.

We study how matrix modulates the response of cells to immune signals and thus contributes to host protection. Conversely, we study how immune signals regulate matrix stiffness, quality and turnover, which is essential for the restoration of tissue homeostasis after injury or infection.

Our research is delivering new insights into the interconnectivity between matrix and immune function, with major implications for treatment of chronic diseases and understanding host–pathogen interactions.

# Case study – Rebuilding the lungs: investigating how respiratory tissue is remodelled after lung infection and injury.

Principal Investigators: Professor Judi Allen and Dr Tara Sutherland

We use models of lung migrating helminth infection and allergic asthma to understand how repair and tissue remodelling occurs in the lungs following infection and injury.

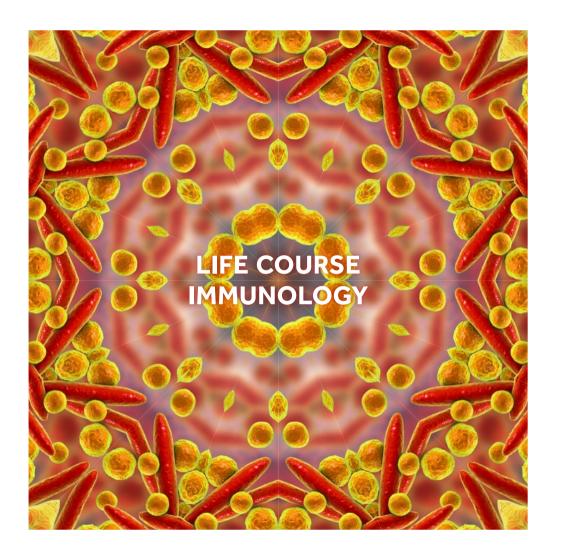
Working very closely with several investigators in the Wellcome Centre for Cell Matrix Research our research has an emphasis on the cellular dynamics of both immune and structural cells and their interplay with the extracellular matrix (ECM).

Collaboration with Wellcome Centre for Cell Matrix Research allows us to focus our research on the following questions:

- How does the early inflammatory response to infection and injury dictate subsequent tissue repair?
- How does the type 2 immune response that is induced by helminth infection and allergy regulate collagen deposition in the tissue?
- How does a family of sugar binding proteins (the chitinase-like binding protein) that are produced in enormous abundance in the lung during injury, interact with the ECM, and what are the consequences of this interaction?
- What is the contribution of the adaptive immune response to tissue remodelling in the lung?
- How do inflammatory events alter the epithelium and composition of the ECM in chronic pathology?

Our collaborations allow us to use exciting new research tools to visualise key changes in the lung ECM under different conditions and stages of injury and repair.

The underlying mechanisms we discover will have relevance to both healthy lung repair and regeneration, and to many common but severe chronic diseases of the lung such as asthma and COPD.



# "Exploring immune responsiveness from birth to old age."



Lead: Dr Peter Arkwright

Division of Infection, Immunity & Respiratory Medicine School of Biological Sciences

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Deputy lead: Dr Tracy Briggs

Infections, allergies, autoimmune and autoinflammatory diseases, as well as some cancers are increasingly recognised to have an immune basis.

The immune basis of disease is often due to specific underlying genetic mutations inherited at conception. Over 300 distinct genetic causes of immune disorders have now been identified and the list continues to expand rapidly.

Many patients present in childhood and are first seen after admission to children's hospitals, sometimes to intensive care. Other patients are identified because their brothers, sisters or other close family members have a disease.

Life course immunity in Manchester provides cutting-edge care for these children with the use of biologics, stem cell transplantation, and recently the potential for gene therapy. In addition it offers the power of modern genomic and cellular diagnostic techniques to provide both rapid and precise diagnosis, and the discovery of novel pathways and genes.

# Case study – Understanding the incomprehensible and treating the untreatable in allergic, infectious and immune diseases.

Principle Investigators: Dr Peter Arkwright, Dr Tracy Briggs, Dr Robert Wynn, Dr Stephen Hughes, Dr Bill Newman

Aimee Drew died over 20 years ago at the age of only five years old of glandular fever which developed into an aggressive and rapidly progressing lymphoma. Soon afterwards her parents Suzanne and lan formed the Aimee Drew Memorial Trust, and have worked tirelessly since then with family and friends — as well as clinicians at Royal Manchester Children's Hospital, The University of Manchester, and Hospital Trust Executives — to raise well over £100,000. The result is the establishment of a Clinical Academic Paediatric Allergy, Infectious Disease and Immunology Centre in Manchester which is second to none.

Turning tragedy into an internationally recognised, specialist healthcare service serving the wider community is what translational medicine is all about in its widest sense, with its far-reaching impact for the community at large. The genetic and biological basis of Aimee's disease has now been unravelled and at this stage is thought to be a disease unique to people living in the North West of England. CTPS1 deficiency occurs because immune cells give up their ability to protect against the Epstein-Barr and chickenpox viruses leading to devastating consequences (Martin E. et al, Nature, 2014). Other children have since been correctly diagnosed with this condition and completely cured by bone marrow transplantation.

Life course immunology has many more lessons to teach us, and many more allergic and immune diseases to unravel effectively and completely. CTPS1 deficiency has taught us that giving up is not an option. There is strength in working and pulling together: a reputation that Manchester is, and always will be, proud to expound and develop.



"Our goal is to understand how neuroimmune signalling contributes to multi-morbid states that affect the brain."



## Lead: Professor David Brough

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Deputy lead: Dr Kevin Couper

Interactions between the brain, innervation of peripheral tissues and organs, and local immune responses form the basis upon which patients experience symptoms in inflammatory diseases.

Neuronal activation may influence the nature of inflammatory responses and, in turn, inflammatory responses (caused by peripheral disease for example) can have profound effects on neuronal function.

We are combining expertise from clinical specialities with that from immunology and neuroscience to understand the bidirectional neuro-immune communication between the brain and peripheral systems that contributes to multi-morbidity.

To elucidate bidirectional immune and inflammatory mechanisms contributing to neuronal dysfunction and loss of tissue homeostasis, we will make use of:

- Unique disease cohorts and data sets, including studies where there has been an immune intervention, with study outcomes including measures of mental health;
- Pre-clinical models of multi-morbidity underpinning clinical cases, particularly around acute cerebrovascular disease where we have studies spanning basic research through to clinical trials;
- Expertise in molecular and cellular inflammation/immunology where we can dissect immune/inflammatory mechanisms contributing to brain disease.

This will enable us to:

- Understand how immune/inflammatory mechanisms operate across different and co-existing health conditions;
- Explore the relevance of known mechanisms in new disease areas;
- · Identify novel mechanisms and targets;
- Guide the development of new treatments.

## Case study – Brain attack: determining the role of neuroinflammation in stroke

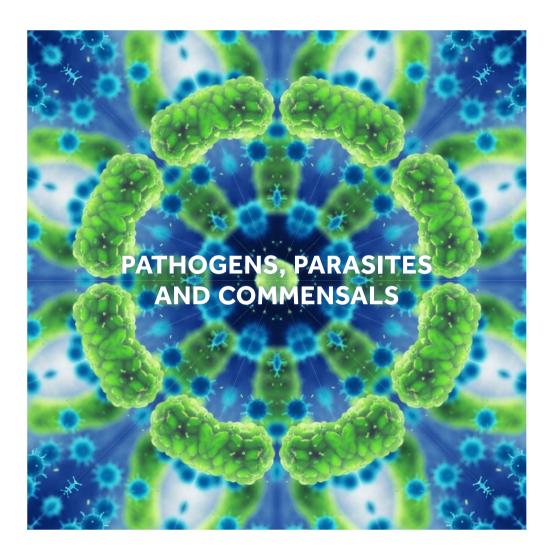
Principal Investigators: Professor Stuart Allan and Professor David Brough

Driven by basic science at the University and clinical academics at Salford Royal Foundation NHS Trust, we aim to understand the impact of systemic and local inflammation on progression and outcome of acute cerebrovascular disease such as ischaemic and haemorrhagic stroke.

This interaction allows us to deliver transformative research and investigate the following highlight areas:

- the impact of chronic inflammatory disease on patient outcome after an acute cerebrovascular event;
- the effects of immune interventions on brain injury and repair in people and animal models;
- inflammatory pathways contributing to tissue injury;
- the influence of matrix changes on inflammatory and vascular responses;
- the temporal and cellular profile of immune changes in the brain during disease;
- the link between post-stroke depression and altered immune homeostasis:
- how brain injury impacts upon peripheral immune cell function and increases susceptibility to infection.

Our iterative research approach between the lab and the clinic, with access to patient samples, allows unique opportunities to make new insights into disease processes and to develop new therapies.



"Defining immunity in the context of the microbiota underpins health and therapeutic control."



### Lead: Professor Richard Grencis

Division of Infection, Immunity & Respiratory Medicine School of Biological Sciences

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Deputy lead: Dr Lizzie Mann

Infectious disease continues to be a major threat to health in man and animals worldwide. Our immune system has evolved to recognise, respond to and remove the myriad of pathogens we are exposed to.

Harnessing the immune system effectively to control infection (by vaccination for example) has saved hundreds of millions of lives, but for the majority of pathogens there are no vaccines available and the drugs to remove them often have limited efficacy. Thus, understanding and exploiting our immune system will ultimately be our best protection against them. Moreover, it is now clear that the interplay between pathogen, immune system and our commensal microbiota underpins protective immunity, chronic infection and ultimately overall health.

Parasitic infection is ubiquitous across the globe affecting billions of individuals. Parasites present a complex antigenic challenge and have evolved effective immune evasion strategies. We work with Plasmodium exploring mechanisms of immunity and immunopathology in malaria, and utilise Toxoplasma as a model proinflammatory pathogen. We have one of the strongest groups in the world defining immunity to helminths or parasitic worms, including schistosomes, gastrointestinal and filarial nematodes and cestodes that is not. only defining new mechanisms of protective immunity and immunomodulation, but also generating new information on fundamental immunity and tissue repair.

Trillions of bacteria live within and on our bodies and play an essential role in educating our immune system. Defining the balance between commensals, pathobionts and pathogens and their role in progression to immune and inflammatory disease is a major focus and facilitated by our gnotobiotic animal facility. We are actively using metagenomic approaches to study host intestinal microbiota and to decipher the interactions between commensal organisms and pathogens in the onset and development of disease.

We are recognised as a centre of international excellence for fundamental and applied research into fungal diseases, particularly aspergilosis. The link with experimental immunologists has enabled ground-breaking work on the contribution of Aspergillus to allergic lung disease and asthma and the underlying immune basis.

# Case study – Environment versus genes: understanding the causes of variable immune responses to infection.

Principal Investigators: Professor Kathryn Else, with Professor Jan Bradley (University of Nottingham)

#### The problem:

There is enormous variation in the way individuals respond to infection.
Understanding the causes of this variation underpins our knowledge of disease susceptibility and control of infectious diseases. Remarkably, the main contributors to immune variation are poorly defined.

To minimise variation, conditions are carefully controlled within the laboratory. However, outside of the laboratory, multiple forces, both heritable and environmental, including parasite exposure, combine to shape the ultimate immune response.

Understanding the main drivers of immune variation in the wild will inform strategies to increase resistance to diseases in humans and domestic animals.

#### Our work:

Together with a team of researchers at the University of Nottingham, we are defining the relative contributions of host genetics and pathogen exposure to variation in immune responses in the wild. We study a highly tractable wild mouse population on the Isle of May and use a 'mark-release-recapture' approach to test three hypotheses:

- variability in immune responses is driven more by environmental factors than host genetics;
- the main environmental factor driving variability in immune responses is infection;
- variability in immune responses will increase with age.

The collaboration with the University of Nottingham brings an interdisciplinary approach to answer fundamental questions in immunology. It takes full advantage of our state-of-the-art flow cytometry environment and cutting-edge cell biology tools available at Manchester.



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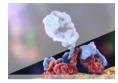
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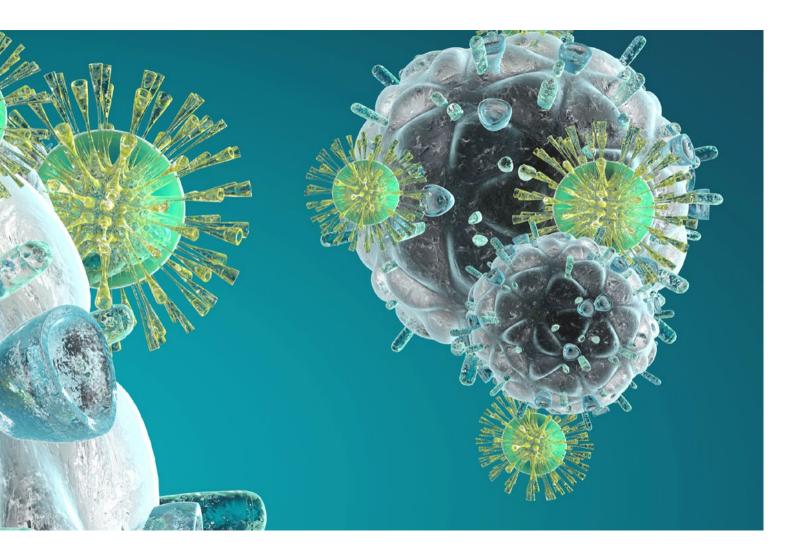
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### Visualising the ethos of the Institute

Using a repeated reflection of one section of an immunology image presents it from multiple angles or viewpoints in one, and conveys both a sense of challenging complexity and the opportunities of collaboration: a kaleidoscope representing an approach with infinite possibilities.



Lydia Becker Institute of Immunology and Inflammation

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www.manchester.ac.uk/lydia-becker-institute