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THE UNIVERSITY OF MANCHESTER
OFFICIAL OPENING
OF

The Manchester Collaborative Centre for Inflammation Research (MCCIR)

Monday 11th March 2013

Programme of Events

gsk GlaxoSmithKline

AstraZeneca

The MCCIR

The Manchester Collaborative Centre for Inflammation Research (MCCIR) is a unique partnership between academia and industry, including two major pharmaceutical companies, to establish a world-leading centre for basic and translational research into inflammation and inflammatory disease.

The MCCIR Vision

The University of Manchester (UoM), GlaxoSmithKline (GSK) and AstraZeneca (AZ) have together created the Manchester Collaborative Centre for Inflammation Research (MCCIR).

The aim of the Centre is to operate at the cutting edge of inflammation research and to make a substantial impact on our understanding of inflammatory disease processes that can be translated effectively into the identification and exploitation of novel therapeutic targets.

The MCCIR, directed by Professor Tracy Hussell, is built around strategic appointments of world leading research scientists. The Centre will embrace scientific strengths and key personnel from the UoM, GSK and AZ.

"The translation of basic research discoveries into new medicines is challenging, but we believe we improve our chances of success through collaborative science. The MCCIR will embody this approach, and I am delighted that GSK has been able to contribute to its development."

Dave Allen, Senior Vice-President of Respiratory Research at GSK

"Inflammatory processes underpin many of our priority areas of research and this is a ground-breaking collaboration. The creation of the new centre is indicative of a new era of pre-competitive sharing within the pharmaceutical sector and with academic scientists, to bring our learning together to ensure the faster delivery of effective medicines to patients."

Dr Menelas Pangalos, Executive Vice-President Innovative Medicines at AZ

"The University of Manchester welcomes greatly this opportunity to ensure that some of its fundamental biomedical research will become more closely aligned with the need to develop new therapies for inflammatory diseases. This collaboration builds on the mutual understanding developed between the University and both GSK and AstraZeneca over recent years, and will bring together expertise in biomedical research from the University with the resources and drug discovery expertise from GSK and AstraZeneca to create true partnership and synergy. It firmly establishes the UK and The University of Manchester at the forefront of innovative and enterprising research into inflammatory disease."

Professor Ian Jacobs, Vice-President of The University of Manchester and Dean of the Faculty of Medical and Human Sciences

"There is no better way to exploit serendipitous discovery than to co-locate researchers from academia and industry in the same physical space. This co-location will optimally facilitate the bi-directional osmosis of ideas, shaped through differing priorities, and the definition of a critical path to improved health and wealth. The establishment of the MCCIR is therefore an exciting example of a new approach to academe-industry collaboration, and the University is delighted to be hosting it."

Professor Martin Humphries, Vice-President of The University of Manchester and Dean of the Faculty of Life Sciences

"The announcement made today by The University of Manchester, GlaxoSmithKline and AstraZeneca is a fantastic example of partnership working and its potential to translate cutting-edge science into health and commercial benefits. It is a clear vote of confidence in the UK's world-class academic research base by our leading pharmaceutical companies and is an exciting development."

Minister for Universities and Science, David Willetts

"This new centre provides a unique opportunity to translate cutting edge hypotheses in inflammation research into critical patient cohorts working not only with the academic and medical resources of Manchester University, but also with pharmaceutical industry. We have been working hard to build the centre by recruiting the best investigative scientists at all levels, forging links with our translational and industrial colleagues and gathering interest from other potential partners in the future. I am hugely excited by the prospect of guiding it into a world leading institution for translational research and innovation".

Professor Tracy Hussell, Director of MCCIR

Research Abstracts

Professor Tracy Hussell
Changing expectations for inflammatory lung disease: take a deep breath

The newly formed Manchester Collaborative Centre for Inflammation Research is a unique venture combining the expertise of senior academics with expertise on fundamental pathways in inflammation, clinicians with defined patient cohorts in asthma, COPD and inflammatory bowel disease and two major pharmaceutical companies, GlaxoSmithKline and AstraZenecca. Both industrial partners and the University of Manchester have invested £5M each to create state-of-the art facilities and enable the recruitment of investigators with agenda-setting research portfolios. Many of the pathways identified require translation from in vivo models into humans. For example, the work of Professor Tracy Hussell (MCCIR Director) has shown that inflammation in mucosal tissues does not rely on the presence of antigen alone, but that a loss of structural integrity is also necessary. The group has identified the signals provided by epithelia and other structural components to dampen innate immunity in the absence of structural damage. These include CD200 that transmits a suppressive signal to airway macrophages via CD200R, TREM 2 that sequesters the Toll like receptor adapter MyD88 and TAM receptors that facilitate macrophage efferocytosis of apoptotic cells leading to macrophage de-sensitisation. Following chronic inflammation, these pathways are over-expressed and contribute to future exacerbation of disease by bacteria. All of these pathways are conserved in humans, but are yet to be investigated in defined patient cohorts with inflammatory lung disease. We will test the hypothesis that the remodelled epithelium over-regulates airway macrophages in patients with COPD or Asthma. Therapeutic manipulation of such regulatory pathways would re-set the inflammatory tone in the lung and prevent exacerbation of chronic disease.

Dr James Fildes
Passenger monocytes, lung inflammation and transplantation: The next generation for targeted immunomodulation

Monocytes, macrophages and dendritic cells (DCs) are a heterogeneous population of blood and tissue phagocytes that have been classified as the mononuclear phagocyte system (MPS). One of the critical roles of the MPS is in tissue surveillance and orchestration of immunity, particularly within the transplanted lung, as it is continually exposed to stimuli from the external and recipient environment. We have identified a large reservoir of non-classical monocytes within the human donor lung which mobilise and traffic into the recipient circulation in response to inflammation. This cell type rapidly differentiates to an inflammatory DC, which polarises naïve recipient CD4+ T cells to mature Th1 T cells with donor antigen specificity, a process termed direct allorecognition. Direct allorecognition, and the generation of mature alloreactive Th1 T cells is considered the central nexus of graft rejection, and requires permanent and continuous immunosuppression. Using a novel approach, we have identified endogenous proteins that modify the differentiation pattern of non-classical monocytes from inflammatory DC to 'regulatory' IL-10+ DC, which generate regulatory T cells, rather than Th1 T cells. We are now attempting to reduce graft immunogenicity via gene transfer of endogenous proteins into the human lung prior to transplantation, using viral vectors and ex-vivo lung perfusion. As monocyte differentiation is dictated by the local tissue environment, we are also attempting to reverse donor associated lung injury using gene transfer of anti-apoptotic molecules, and assessing the effects of mechanical unloading of the lungs (via extra-corporeal membrane oxygenation) using a systems biology approach.

Professor Daniel Davis
Using super-resolution microscopy to watch immune cells kill

Cell-contact dependent regulation of immune cell responses plays a vital role in balancing the need for rapid and efficient responses to a wide variety of pathological challenges, while at the same time maintaining self-tolerance. Over the last decade, our imaging studies – and those of other teams - have helped establish the emerging new paradigm that immune cell activation and inhibition is controlled by transient interactions between supramolecular assemblies of receptors, kinases and adaptors. This is a significantly different concept from a linear cascade of individual protein-protein interactions depicted in textbook diagrams of immune receptor signaling pathways. The new challenge is to assess the heterogeneity and single-molecule level organisation of protein clusters and understand how this influences signal integration and downstream effector functions. Here, I will present new data using high- and super-resolution imaging techniques that reveal novel insights into molecular recognition by human Natural Killer cells and T cells - and how specific effector functions are realized. Our data reveal, for example, that remodelling of the cortical actin mesh occurs at the central region of the NK cell immune synapse during a cytolytic response. This is likely to occur for other types of cell secretion and emphasises the importance of emerging super-resolution imaging technology for revealing new biology. The application of new imaging technology also reveals unexpected phenomena: here, I will present unpublished data indicating that transfer of small RNAs from immune cells into cancer cells can serve as a new kind of immune defence.

Professor Mark Exley
Anti-tumour, anti-viral, and immuno-metabolic NKT cell populations

We functionally defined 2 distinct human CD1d-reactive 'NKT' (bearing NK and T cell characteristics) populations, invariant and 'non-invariant', from blood and tissues. NKT produce high levels of various cytokines/chemokines and potent CD1d-specfic cytotoxicity. NKT have physiological roles in anti-tumor and anti-viral responses. Reversible defects of NKT from cancer and hepatitis patients have led to promising translational observations. Our anti-NKT mAb is in clinical trials ex vivo, has been humanized for in vivo use, and is widely used in research. NKT can positively or negatively regulate anti-tumor and anti-pathogen immunity via NK and dendritic cells (DC). In mice, we found that interactions between NKT and CD1d+ DC augment Th1-type immunity, promising for therapy directly and with DC-based and other vaccines. NKT from tumour-bearing mice had reversible defects, similar to those we first identified of cancer patients. In humans, NKT appear to contribute to protective responses against cancers and viruses. Cancer patient survival is associated with Th1-biassed NKT. A clinical trial of expanded autologous NKT completed treating 8 melanoma patients, producing grade 1-2 toxicity. IFNgamma production was restored in vitro, suggesting potential for improved anti-tumour activity, and there was systemic CD8 T cell and CD1d+ APC activation in vivo. Half these highly-selected patients remained with no evidence of disease long-term, half had (mostly slow) treatment-responsive progression. Finally, we are monitoring contrasting NKT populations in adipose and liver, where they can respectively suppress or contribute to inflammation (including Type 2 Diabetes) and eventual fibrosis. NKT cells represent a unique and potentially therapeutic population.

Dr Mark Travis
Gut reactions: how dendritic cells control intestinal immunity

The intestine is a challenging environment for the immune system, which must remain silent against the trillions of bacteria that line the gut but mount rapid responses against pathogens. Specific mechanisms are therefore required to control intestinal immunity, with breakdown in these mechanisms leading to inflammatory bowel disease.
Work in our laboratory focuses on how immunity is regulated in the gut to prevent harmful inflammation. Here, I will describe our recent work identifying a crucial pathway by which specialised dendritic cells (DCs) in the gut promote immune tolerance. These tolerogenic DCs express high levels of the integrin αvβ8, which enables them to activate high levels of the cytokine TGFβ. Enhanced TGFβ activation enables the DCs to induce regulatory T-cells (Tregs), a specialised subset of T-cells that suppress self-harmful immune responses. Disruption of this pathway results in inflammatory bowel disease in animal models, highlighting a vital anti-inflammatory pathway in the intestine.
We have also found that this integrin-mediated activation of TGFβ by DCs is important in regulating type 2 immune responses during infection, and also driving autoimmune response by inducing Th17 cells. Thus, this pathway appears central to the control of both pro- and anti-inflammatory immune responses in the intestine during health and infection. Our future work aims to determine how this, and novel DC pathways control and are controlled by the intestinal environment. We therefore hope to build a detailed cellular and molecular understanding of how DCs control T-cell responses in the gut to control gut inflammation.

Professor Andrew MacDonald
Dendritic cells: central players in orchestration of Type 2 inflammation

Dendritic cells (DCs) are specialised innate immune cells that play a key role in initiation and direction of adaptive immunity against diverse immune challenges. However, relatively little is known about precisely how DCs become activated and function in Type 2 settings, either during parasitic helminth infection or following exposure to allergens. Using a combination of in vitro and in vivo model systems, we have shown that DCs responding to helminths display an unusual, low level, activation phenotype distinct from that ordinarily seen during viral or bacterial infection. Irrespective of this, we have demonstrated that DCs are both sufficient and necessary for induction of Type 2 immunity against several helminth species. More surprisingly, we have also found that DCs can also be critical for maintenance of the Type 2 response and for survival during chronic infection with the medically important helminth Schistosoma mansoni. Although DCs are clearly centrally involved in coordination of the immune response during Type 2 inflammation, the specific mechanism(s) by which they direct Th2 polarisation remain poorly understood. We have recently discovered that epigenetic regulation of DCs, via the action of the methyl-binding protein Mbd2, is vital for optimal induction and development of Type 2 inflammation against either helminths or allergens. This reveals that epigenetic mechanisms can play an essential role in controlling DC activation and function, and identifies methyl-binding proteins and/or the genes that they regulate as exciting new targets for therapeutic modulation of Type 2 immunity.

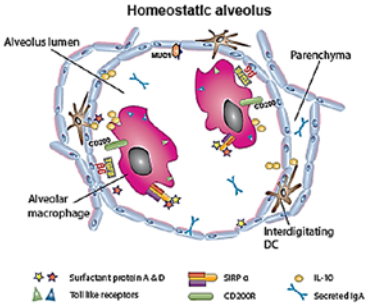
MCCIR Investigators

Senior Investigators

Professor Tracy Hussell – *Director of MCCIR*

Identification of methods that reduce inflammatory disease often arise from studying the inflamed organ in question to see what is in excess compared to healthy tissue. However, several opportunities may be missed using this strategy. It is now recognised that inflammatory cells are ready to activate at any time but are restricted by regulatory signals from the surrounding microenvironment. Proof of this concept came from studies that removed certain regulatory proteins from the cells lining the lung. In this case nearby immune cells became activated even in sterile conditions. Understanding the signals that maintain immune health can therefore provide novel strategies to restore it in inflammatory disease.

Recently we have observed that upon resolution of inflammation local immune cells behave differently to those that were present at the start. We call this condition "altered health" that in some (those with asthma, chronic obstructive pulmonary disease, fibrosis etc) leads to complications later in life. Understanding the difference between immune health and altered heath at the molecular level is also likely to reveal new therapeutics. The MCCIR provides the ideal conduit to translate these new concepts into patients with inflammatory disease with the assistance of our industrial partners.



Selected Publications

Habibzay M, Saldana JI, Goulding J, Lloyd CM, Hussell T.(2012) *Altered regulation of Toll-like receptor responses impairs antibacterial immunity in the allergic lung.* **Mucosal Immunol.** 5(5):524-34.

Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Kinloch A, Gaggar A, Shastry S, Rowe SM, Shim YM, Hussell T, Blalock JE (2010). *A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation.* **Science**. 330(6000):90-4.

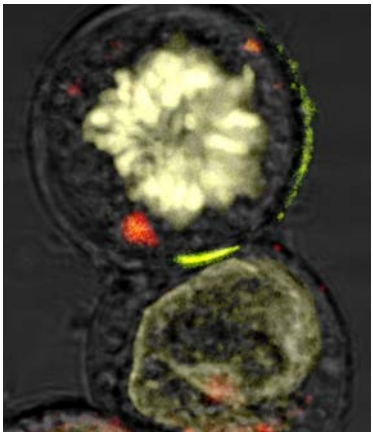
Snelgrove RJ, Goulding J, Didierlaurent AM, Lyonga D, Vekaria S, Edwards L, Gwyer E, Sedgwick JD, Barclay AN**,** Hussell T (2008)**.** A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. **Nat Immunol**. 9(9):1074-83..

Didierlaurent A, Goulding J, Patel S, Snelgrove R, Low L, Bebien M, Lawrence T, van Rijt LS, Lambrecht BN, Sirard JC, Hussell T(2008). *Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection.J* **Exp Med**. 205(2):323-9

Professor Daniel Davis – *Director of Research, MCCIR*

We have given names to nearly all the different protein molecules that mediate communication between human cells. Now, the audacious goal of contemporary cell biology is to understand how the billion proteins in an average cell allow them to move, multiply, create a brain or defend us against viruses and bacteria. Imaging where and when proteins interact with each other has a major role to play at this frontier. Recent imaging of just a few types of proteins has already led to important new concepts in how immune cells communicate with each other and how they recognize signs of disease. Images of immune cells contacting other cells have revealed temporary membrane structures, often called immune synapses, similar to the synapses that nerve cells make with one another for communication. Exploring how such changing arrangements of proteins occur and how they control immune cell communication is the new science opened up by the immune synapse concept.

My research team and others have also very recently observed that long tubes, made of cell membrane, readily form between immune cells. We called these connections membrane nanotubes and they could constitute a new mechanism for communication between cells that are far apart. A cost, however, is that viruses such as HIV may use these connections to efficiently spread between cells. Thus, we aim to determine how these connections form and what functional consequences they have for the human immune system. We have also observed that RNA can traffic between cells suggesting a new and unexpected mechanism by which cells interact with each other. Specifically, we have found that immune cells can deliver small RNAs into cancer cells to stop them multiplying. Excitingly, high-resolution microscopy of immune cell interactions is still a very young field and more surprises are surely in store.



Selected Publications

Davis DM, The Compatibility Gene, **Penguin Books**, (2013)

Brown A, Oddos S, Dobbie I, Alakoskela, J, Parton R, Eissmann P, Neil M, Dunsby C, French P, Davis I, Davis DM (2011). *Remodelling of cortical actin where lytic granules dock at natural killer cell immune synapses revealed by super-resolution microscopy.* **PLoS Biology**, 9(9),

Chauveau A, Aucher A, Eissmann P., Vivier E, Davis DM (2010). *Membrane nanotubes facilitate long-distance interactions between natural killer cells and target cells.* **Proc Natl Acad Sci U S A**, 107(12), 5545-50.

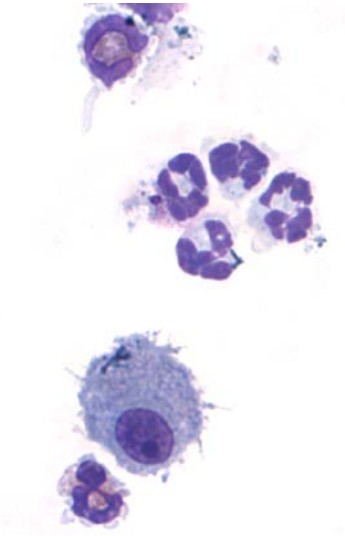
Sowinski S, Jolly C, Berninghausen O, Purbhoo, M, Chauveau, A, Köhler, K, Oddos, S, Eissmann, P, Brodsky, F, Hopkins, C, Onfelt, B, Sattentau, Q, Davis, DM (2008). *Membrane nanotubes physically connect T cells over long distances presenting a novel route for HIV-1 transmission.* **Nature Cell Biology**, 10(2), 211-9.

Professor Andrew MacDonald

The research in my laboratory investigates how pathogen interaction with the innate immune system influences the development of adaptive immunity and inflammation. My particular interest is Type 2 inflammation, which is responsible for widespread suffering in allergy, as well as being a hallmark of infection with parasitic worms (helminths). Our work addresses some outstanding fundamental questions about the role of a specialised type of immune cell – the dendritic cell (DC) – in orchestration of Type 2 inflammation. DCs are centrally involved in initiation of immune responses in most settings, but the precise mechanisms by which they direct Type 2 inflammation are currently not known.

The main questions we are addressing at the moment are:

How do DCs become activated in Type 2 settings?
How necessary are DCs for induction and coordination of Type 2 inflammation?
By what mechanism do DCs initiate Type 2 inflammation?



Our research uses a combination of in vivo and in vitro model systems, focussing on the Type 2 response to the medically important parasitic helminth Schistosoma mansoni. Models of infection with this parasite provide a relevant experimental model of Type 2 inflammation that has been used extensively by my laboratory and others to reveal important cellular and molecular players and processes during hepatic, intestinal and pulmonary inflammation. The overarching aim of our research is to determine how Type 2 immunity is initiated, maintained and regulated, with the ultimate goal being identification of cellular and molecular targets for rational development of therapeutics.

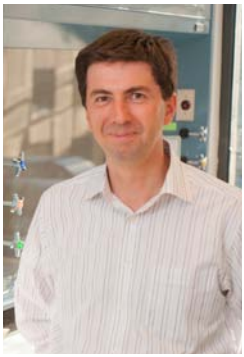
Selected Publications

Cook P.C., Lucy H. Jones, Stephen J. Jenkins, Thomas A. Wynn, Judith E. Allen and Andrew S. MacDonald (2012). *Alternatively activated dendritic cells regulate CD4⁺ T cell polarization in vitro and in vivo*. **P.N.A.S**. 109: 9977-9982.

Stephen J. Jenkins, Dominik Ruckerl, Peter C. Cook, Lucy H. Jones, Fred D. Finkelman, Nico van Rooijen, Andrew S. MacDonald and Judith E. Allen. (2011). *Local macrophage proliferation, rather than recruitment from the blood, is a signature of Th2 inflammation*. **Science**. 332: 1284-1288.

Alexander T. Phythian-Adams, Peter C. Cook, Rachel J. Lundie, Lucy H. Jones, Katherine A. Smith, Tom A. Barr, Kristin Hochweller, Gunter J. Hammerling, Stephen M. Anderton, Rick M. Maizels and Andrew S. MacDonald. (2010). *CD11c depletion severely disrupts Th2 induction and development in vivo*. **Journal of Experimental Medicine**. 207: 2089-2096.

Professor Mark Exley



We functionally defined 2 distinct human 'NKT' cell populations (bearing both NK cell and T cell characteristics) from blood and tissues. NKT produce high levels of various immune controlling factors as well as being able to kill cells expressing their target molecule. NKT have physiological roles in anti-tumour and anti-pathogen responses and can positively or negatively regulate immunity via NK and other cells. In immune models, we found that interactions between NKT and their target cells augment cellular immunity, which is promising for therapy both directly and with various vaccines. NKT from tumour-bearing mice had reversible defects, similar to those we first identified of cancer patients. In humans, NKT cells also appear to contribute to protective responses against cancers and infections. Reversible defects of NKT from cancer and hepatitis patients have led to promising translational observations. Cancer patient survival is associated with NKT cell activity.

Our NKT cell monoclonal antibody has begun both cell therapy and direct use clinical trials, as well as being widely used in research. A clinical trial for melanoma using the antibody to expand NKT in the lab. before infusing them has completed, producing only minimal toxicity. NKT activity assayed in the lab. was restored, suggesting potential for improved anti-tumour activity, and systemic immune cell activation was seen. Half of these highly-selected patients remained with no evidence of disease long-term, half had (mostly slow) treatment-responsive progression. Finally, we are monitoring contrasting NKT populations in adipose and liver, where they can respectively suppress or contribute to inflammation (including Type 2 Diabetes) and eventual fibrosis. NKT cells represent a unique potentially therapeutic population.

Selected Publications

Lynch L, Nowak M, Varghese B, Clark J, Hogan A, Toxavidis V, Balk S, O'Shea D, O'Farrelly C, Exley MA (2012). *Unique Adipose Tissue Invariant Natural Killer T Cells Protect Against Diet-Induced Obesity and Metabolic Disorder Through Regulatory Cytokine Production*. **Immunity**. 37:574-87.

Li S, Vriend LE, Nasser IA, Popov Y, Afdhal NH, Koziel MJ, Schuppan D, Exley MA, Alatrakchi N (2012). *Hepatitis C virus-specific T cell-derived transforming growth factor beta is associated with slow hepatic fibrogenesis*. **Hepatology**. 56(6):2094-105.

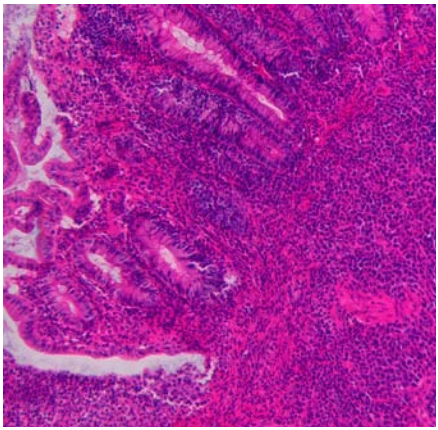
Yue SC, Shaulov A, Wang R, Balk SP, Exley MA (2005). *CD1d ligation on human monocytes directly signals rapid NF-kappaB activation and production of bioactive IL-12.* **Proc Natl Acad Sci U S A**. 102(33):11811-6.

Principal Investigators

Dr Mark Travis

Immune responses need to be activated quickly when we get infected with pathogens, but must be tightly regulated when we are healthy so that our own tissues are not attacked. An area of the body where immune regulation is especially important is the intestine. The intestine is lined by trillions of bacteria (called commensal bacteria) that are important in human health, but that can potentially trigger inflammation in the gut. Also, we ingest a wide variety of different foods that can potentially trigger immune reactions in the intestine resulting in food allergy. The intestinal immune system must therefore be controlled to prevent unwanted responses against commensal bacteria and food, but still be capable of responding to any pathogens that enter the intestine.

Our group aims to identify cells and molecules of the immune system that control immune responses in the intestine. We focus on dendritic cells, which are crucial in controlling T-cell responses. Dendritic cells instruct T-cells to either become activated to trigger an immune response, or else ignore harmless substances to prevent unwanted inflammation. We have a particular interest in regulatory T-cells, which can actively dampen inflammation and are highly prevalent in the intestine. Thus, our work aims to uncover how the intestinal immune system is keeping us healthy. Such work will be vital in identifying potential therapeutic targets for immune disorders of the intestine, such as inflammatory bowel disease and food allergy.



Selected Publications

Worthington JJ, Czajkowska BI, Melton AC, Travis MA (2011). *Intestinal dendritic cells specialize to activate transforming growth factor-β and induce Foxp3+ regulatory T cells via integrin αvβ8.* **Gastroenterology**. 141(5):1802-12.

Melton AC, Bailey-Bucktrout SL, Travis MA, Fife BT, Bluestone JA, Sheppard D (2010). *Expression of αvβ8 integrin on dendritic cells regulates Th17 cell development and experimental autoimmune encephalomyelitis in mice***. J Clin Invest**. 120(12):4436-44.

Travis MA, Reizis B, Melton AC, Masteller E, Tang Q, Proctor JM, Wang Y, Bernstein X, Huang X, Reichardt LF, Bluestone JA, Sheppard D (2007). *Loss of integrin alpha(v)beta8 on dendritic cells causes autoimmunity and colitis in mice*. **Nature**. 20;449(7160):361-5.

Dr James Fildes

Our group studies how the human immune system contributes to the repair of injured tissue, primarily in the heart and lungs, and how errors in this process can develop into chronic diseases (such as allergy, chronic heart failure or asthma).

We work on the principle that the main task of the immune system might not be in discriminating self from non-self, but in surveying our own tissues for stress or injury. Simple classroom facts suggest this is likely, only 10% of our entire cellular content is human (the other 90% is made up mainly of potentially dangerous bacteria and fungus), our immune system removes between 20-70 billion self cells each day because they are damaged or dying, and another 20-50 million cells are removed because they have become cancerous. Yet all of these daily occurrences fail to trigger an inflammatory response.

Clearly the immunologic 'machinery' required to maintain this process is very complex, and when errors occur the effects can result in inflammation and eventually, chronic disease. We know that when an acute injury occurs to the heart or lungs, an immune cell called a monocyte rapidly moves to the organ and surveys for damage. The injured cells provide signals to the monocyte, which then orchestrates the type of immune response that ensues. We are trying to understand this process, as unraveling how injured/diseased cells cause the immune system to activate and respond is essential for us to develop specific therapies.

We use artificial human heart and lung culture models, and confirm our laboratory findings by performing observational studies in patients, and finally intervention studies using organs assessed for transplantation.

Selected Publications

Fildes JE, Archer LD, Reagan S, Sjöberg T, Steen S, Yonan N, *Improved clinical outcome of patients transplanted marginal donor lungs using ex-vivo lung perfusion*. ***Transplantation.*** *In Press*

Archer LD, Langford-Smith K, Critchley WR, Bigger B, Fildes JE (2012).*Characterisation of the T cell and Dendritic Cell Repertoire in a Murine Model of Mucopolysaccharidosis I (MPS I).* **Journal of Inherited Metabolic Disease**. Jul (ePub).

Khan AU, Davidson JA, Poulton KV, Wynn RF, Fildes JE (2011). *Activated NK cells have a therapeutic role in sustaining donor engraftment following paediatric haematopoietic stem cell transplantation for non-malignant disease*. **British Journal of Haematology** 2011 154(4):527-9.

Post-doctoral Prize Fellows

Dr Gloria Lopez-Castejon

Inflammation is the response of the body to infection or injury, initiated when immune cells sense the presence of danger signals. The nature of these danger signals can be really diverse. They can have a pathogenic origin such as bacterial infections. However, in many other occasions these signals come from within the body and are constituted by molecules that in healthy condition should not be present outside the cells, such as ATP or monosodium urate crystals. Macrophages are one of the first immune cells to sense the presence of danger signals. They respond to this by removing the threat and by releasing pro-inflammatory molecules, such as cytokines, that alert other immune cells about this dangerand thus trigger an inflammatory response.

I am interested in identifying new endogenous danger signals that activate macrophages and studying how these contribute to the progression of inflammatory diseases. My research focuses on the study of the mechanisms by which deubiquitinase enzymes (DUB) contribute to the release of pro-inflammatory mediators, in macrophages, in response to danger signals as well as on the characterization of some of these endogenous mediators, such as actin, to understand their role in shaping the inflammatory response.

The incidence of chronic inflammatory diseases, such as atherosclerosis, arthritis or cancer has seriously increased in recent years meaning that new or improved treatments are necessary. With this research I aim to identify new points of intervention in the inflammatory response that will contribute to the development of new and improved therapeutical treatments for inflammatory disorders.

Selected Publications

Lopez-Castejon G, Luheshi NM, Compan V, High S, Whitehead RC, Flitsch S, Kirov A, Prudovsky I, Swanton E, Brough D (2013). *Deubiquitinases Regulate the Activity of Caspase-1 and Interleukin-1β Secretion via Assembly of the Inflammasome.* **J Biol Chem.** 288(4):2721-33.

Compan V, Baroja-Mazo A, López-Castejón G, Gomez AI, Martínez CM, Angosto D, Montero MT, Herranz AS, Bazán E, Reimers D, Mulero V, Pelegrín P (2012). *Cell volume regulation modulates NLRP3 inflammasome activation.* **Immunity**. 37(3):487-500.

Lopez-Castejón G, Baroja-Mazo A, Pelegrín P (2011). *Novel macrophage polarization model: from gene expression to identification of new anti-inflammatory molecules*. **Cell Mol Life Sci**. 68(18):3095-107.

Dr Amy Saunders

The skin is the largest organ of the body and acts as a barrier to the environment. There are many immune cells present in the skin which prevent the invasion of microorganisms. The outer epidermal layers of the skin are colonised with a plethora of microorganisms which make up the microflora. These organisms can be pathogenic or can be commensals which do not harm the host. The skin immune system must remain tolerant to the commensal microbes to avoid constant activation and inflammation, but must also remain sensitive to invading pathogens so that infection and tissue damage can be avoided. Therefore the immune system has to be finely balanced to remain effective but avoid inappropriate activation and inflammation.

There are a variety of inflammatory skin diseases which are caused or exacerbated by chronic activation of the immune system. Psoriasis is an inflammatory skin disease which affects 2-3% of the population worldwide and has a profound impact on the quality of life of a great many of those affected. It is characterized by scaly plaques which are caused by chronic immune cell activation and the overproduction of skin cells called keratinocytes.

My research is examining the mechanisms which actively maintain the homeostasis of the skin immune system and preserve the impassivity to microflora. In addition to this I am investigating the dysregulation of these mechanisms in the chronic inflammatory disease, psoriasis. The type of homeostatic mechanisms I am particularly interested in is those involving communication between cells. I hypothesize that these signals are constantly required to ensure non-responsiveness of the immune system and will become perturbed when tissue becomes damaged thus allowing a immune response to be generated. The ultimate aim of this work is to determine novel pathways involved in regulating the skin immune system which may uncover potential therapeutic targets for the treatment of inflammatory skin diseases such as psoriasis.

Selected Publications

Saunders A, Webb LM, Janas ML, Hutchings A, Pascall J, Carter C, Pugh N, Morgan G, Turner M, Butcher GW (2010). *Putative GTPase GIMAP1 is critical for the development of mature B and T lymphocytes*. **Blood**. 115(16):3249-57.

Saunders AE, Johnson P (2010). *Modulation of immune cell signalling by the leukocyte common tyrosine phosphatase, CD45.* **Cellular Signalling**. 22(3):339-48.

Saunders A, Lamb T, Pascall J, Hutchings A, Dion C, Carter C, Hepburn L, Langhorne J, Butcher GW (2009). *Expression of GIMAP1, a GTPase of the immunity-associated protein family, is not up-regulated in malaria*. **Malaria Journal**. 8:53.

Notes

MCCIR Official Launch - Monday 11th March 2013

Schedule of Events

10.30am -11.30am: **Registration with Coffee and Croissants**

All talks will take place in the Alexandra Suite, The Midland Hotel

Chair: Professor Ian Jacobs

11.30am - 11.35am: Professor Ian Jacobs, Vice-President and Dean of the Faculty of Medicine and Human Sciences, the University of Manchester
Opening address and introduction

11.35am - 12.05pm: Professor Tracy Hussell, Director of the MCCIR
'Changing expectations for inflammatory lung disease: take a deep breath'

Chair: Professor Chris Griffiths

12.05pm - 12.15pm: Dr James Fildes, Senior Lecturer in Translational Immunology, MCCIR, Principal Research Scientist (UHSM)
'Passenger monocytes, lung inflammation and transplantation: The next generation for targeted immunomodulation'

12.15pm - 12.30pm: Dr David Allen Senior Vice-President of Respiratory Research, GlaxoSmithKline
'Bridging between academia and industry through inflammation research'

12.30pm - 12.45pm: Dr Maarten Kraan, Vice-President and Head of Respiratory and Inflammation, AstraZeneca
'Inspiring Open Innovation'

12.45pm - 2.15pm: **Lunch - Colony Restaurant, The Midland Hotel**

Chair: Professor Tracy Hussell

2.15pm - 2.45pm: Professor Daniel Davis, Director of Research, MCCIR
'Watching immune cells kill'

2.45pm - 3.15pm: Professor Mark Exley, Professor of Immunology, MCCIR
'Anti-tumour, anti-viral, and immuno-metabolic NKT cell populations'

3.15pm – 3.50pm: **Coffee break**

Chair: Professor Martin Humphries

3.50pm – 4.00pm: Dr Mark Travis, Principal Investigator, MCCIR
'Gut reactions: how dendritic cells control intestinal immunity'

4.00pm – 4.30pm: Professor Andrew MacDonald Professor of Immunology, MCCIR
'Dendritic cells: central players in orchestration of Type 2 inflammation'

4.30pm – 5.00pm: Sir John O'Reilly, Director General of Knowledge and Innovation, Department for Business, Innovation and Skills (BIS)
Keynote address: 'Research and Innovation: A shared endeavour'

5.00pm – 6.00pm: Official Opening of MCCIR by Professor Dame Nancy Rothwell, President and Vice-chancellor University of Manchester
Followed by a champagne and canapés reception