Biomedical Vacation Scholarship – Undergraduate Placements 2021/22

Supervisor	Project Title (further details below)
Professor David Brough & Dr Kevin Couper	Understanding brain inflammation in disease
Professor Tracy Hussell	Inflammation in the lung
Professor Mark Travis	Determining how immune responses at barrier sites are regulated by cytokines
Professor Martin Humphries	How do pancreatic tumour cells sense rigidity?
Dr Rachel Lennon (PI), Maryline Frequest (research assistant), Bernard Davenport (technician)	Characterising the basement membrane in membranous nephropathy by three-dimensional electron microscopy
Professor Silvia Bulfone Paus	The role of extracellular matrix components in the modulation of human mast cells activities
Dr Matthew Hepworth	Keeping the peace: Immune cells and microbes in the gut
Professor Anthony J Day	Towards understanding the molecular basis of TSG-6's anti-inflammatory effect on leukocytes
Professor David Thornton	Understanding mucus barrier function in health and disease
Dr Amy Saunders	Regulators of skin inflammation
Dr Patrick Caswell	How do inflammatory cytokines promote formation of the metastatic niche for ovarian cancer?
Dr Gloria Lopez Castejon	How immune cells and the extracellular matrix interact during inflammation?
Professor Andrew MacDonald	Defining the relationship between fibrosis and immune cell infiltration in tumours
Dr Tara Sutherland	Regulation of the airway epithelium during chronic allergic inflammation

Supervisor Details	***Professor David Brough & Dr Kevin Couper*** **Enquiries:** David.Brough@manchester.ac.uk; kevin.couper@manchester.ac.uk https://www.research.manchester.ac.uk/portal/david.brough.html https://www.research.manchester.ac.uk/portal/kevin.couper.html
Project Title	**Understanding brain inflammation in disease**
Project outline	Devastating diseases and injury of the brain such as Alzheimer's disease, or cerebral malaria, or stroke, cause an inappropriate activation of the immune system driving a process called inflammation. Our immune systems protect us against infection, but when activated inappropriately, the immune system can make diseases worse, and this is the case in the brain. Understanding brain inflammation thus allows us to understand how diseases of the brain progress. Understanding brain inflammation will also allow us to develop new medicines to treat brain disease. This project uses immune cells from the brain to understand mechanisms and signals that cause an inflammatory response. The project will involve learning cell culture methods and protocols, and also methods used to analyse and quantify levels of inflammation. These include western blots and ELISA which use antibodies to detect specific inflammatory molecules. We will be using disease specific signals to trigger inflammation and to analyse the specific responses.

Supervisor Details	***Professor Tracy Hussell*** **Enquiries:** tracy.hussell@manchester.ac.uk https://www.research.manchester.ac.uk/portal/tracy.hussell.html
Project Title	**Inflammation in the lung**
Project outline	The lungs are necessary to transport oxygen into the body. This is difficult, however, when they are inflamed as inflammatory cells prevent the normal contraction and relaxation process required to inhale air. In our laboratory we are studying ways to reduce inflammation, which involves studying which immune cells are there and what they are doing. The student will join a fun and lively team at the University of Manchester and gain experience of sterile cell culture, how to identify different immune cells and measurement of inflammatory products they produce. Full supervision will be provided. Students will be encouraged to appreciate the wider implications of the research by spending time with clinicians whose patients experience respiratory diseases such as asthma, Chronic obstructive Pulmonary Disease or infection.

Supervisor Details	***Professor Mark Travis*** **Enquiries:** mark.travis@manchester.ac.uk https://www.research.manchester.ac.uk/portal/mark.travis-2.html
Project Title	**Determining how immune responses at barrier sites are regulated by cytokines**
Project outline	Our body has a number of so-called 'barrier sites' that are exposed to the outside environment. These include the lung, which is exposed to everything we breathe in every day, and the intestine which is exposed to all food and other substances we swallow daily. The immune system at these sites has a tricky job- it must deal with any harmful bacteria, viruses or other infection-causing organisms that we breathe in or swallow, but at the same time remain silent against all the harmless substances we are exposed to. We are interested in the cells and molecules that regulate these reactions, and how these go wrong in certain diseases. Particular, we focus on specific molecules called cytokines and how these control the immune system at barrier sites. My lab has focussed on a particular cytokine, called TGF-beta, and how it is regulated to control the immune system, at barrier sites. This project will aim to study how TGF-beta is such a crucial regulator of the immunity, and how this goes wrong in certain diseases to cause unwanted inflammation.

Supervisor Details	***Professor Martin Humphries*** **Enquiries:** Martin.Humphries@manchester.ac.uk https://www.research.manchester.ac.uk/portal/martin.humphries.html
Project Title	**How do pancreatic tumour cells sense rigidity?**
Project outline	Pancreatic tumours, like many other cancers, are rock-hard. We know that this rigidity is caused by an over-production of collagen fibres, which form a net-like matrix that envelopes the tumour cells and compresses them. We also know that there is a link between the hardness of the matrix and poor outcomes for patients, but we don't understand the reasons why rigidity is bad. There are suggestions that tumour cells grow more rapidly in a hard environment, and that they can grip better and therefore spread to other parts of the body more quickly, but how rigidity causes these behavioural changes isn't clear. We are focusing our research on the sites at which tumour cells stick to the collagen matrix and identifying the proteins that are found at these sites. If we can decipher how cells sense the difference between a soft and a stiff external environment by recruiting different proteins, we can hopefully find ways to interfere in the process and stop the rigid matrix from stimulating the tumour.

Supervisor Details	***Rachel Lennon (PI), Maryline Frequest (research assistant), Bernard Davenport (technician)*** **Enquiries:** Rachel.Lennon@manchester.ac.uk; Maryline.Fresquet@manchester.ac.uk; Bernard.Davenport@manchester.ac.uk https://www.research.manchester.ac.uk/portal/rachel.lennon.html https://www.research.manchester.ac.uk/portal/maryline.fresquet.html
Project Title	**Characterising the basement membrane in membranous nephropathy by three-dimensional electron microscopy**
Project outline	Membranous nephropathy (MN) is an auto-immune disease causing kidney damage, affecting around 700 new patients a year in UK with 8000 currently with the disease. 80% of patients with MN have a harmful antibody in their blood that binds to a protein called phospholipase A2 receptor or PLA2R. These antibodies form immune complexes which get deposited in specialised scaffolds in the kidney called glomerular basement membranes (GBM). This basement membrane in MN is very abnormal, and is characterised by a dramatic thickening affecting its function. We currently have limited understanding about the consequences of PLA2R antibody accumulation in the GBM. This research project is seeking to characterise in detail features of the basement membrane in MN using an imaging technique called three-dimensional electron microscopy. Kidney samples obtained from patient biopsies and our MN mouse model will be stained and analysed using serial block face scanning electron microscopy. The acquired images will then be used to generate 3D reconstructions of the GBM by drawing contour around the features of interest. These analyses will allow unique 3D modelling of the affected region of the kidney in MN with the potential to discover new features of the disease and help us understand how the immune mechanism causes the structural and functional changes in the GBM.

Supervisor Details	***Professor Silvia Bulfone Paus*** **Enquiries:** silvia.bulfone-paus@manchester.ac.uk https://www.research.manchester.ac.uk/portal/silvia.bulfone-paus.html
Project Title	**The role of extracellular matrix components in the modulation of human mast cells activities**
Project outline	Interactions between tissue-resident immune cell and extracellular matrix regulate tissue homeostasis. A disruption and modification of such interactions promote the onset and progression of inflammatory diseases by inducing the release of reactive oxygen species, cytokines and chemokines. These mediators are vital in regulating the recruitment of leukocytes into the tissue. Mast cells are tissue immune resident cells in the lung, strategically located at the host-environment interphase. They contribute to innate immunity through the release of a great variety of pro- and anti-inflammatory pre-stored and de novo synthesized molecules. The project proposes to investigate the effect of two extracellular matrix components that are increased in lung diseases, versican and hyaluronan, on mast cell activation. Understanding the impact of these components on mast cell activities will indicate the role of these cells in the disruption of lung architecture and function.

Supervisor Details	***Dr Matthew Hepworth*** **Enquiries:** matthew.hepworth@manchester.ac.uk https://www.research.manchester.ac.uk/portal/matthew.hepworth.html
Project Title	**Keeping the peace: Immune cells and microbes in the gut**
Project outline	Our guts are home to trillions of "good bacteria" (known as the commensal microbiota), that help us to get nutrients from our diet and to keep us healthy. While these bacteria are helpful, they need to be carefully contained to stop them from invading the body and causing disease. These bacteria are kept in check by a network of immune cells that produce molecules that keep the bacteria within the intestine and stop them from entering our tissues and blood stream. In the lab we study the different pathways through which the immune system maintains a healthy interaction with our commensal microbiota, and how disruption of these immune responses can result in inflammation and disease, such as Inflammatory Bowel Disease (IBD).

Supervisor Details	***Professor Anthony J Day*** Enquiries: anthony.day@manchester.ac.uk https://www.research.manchester.ac.uk/portal/anthony.day.html
Project Title	**Towards understanding the molecular basis of TSG-6's anti-inflammatory effect on leukocytes**
Project outline	TSG-6 is a protein that is made by various cell types in response to pro-inflammatory mediators with an emerging role of protecting tissues from the damaging effects of inflammation. While it is well established that TSG-6 can inhibit the migration of white blood cells (leukocytes) during inflammation, e.g. by interacting with chemokines, its effects on anti-inflammatory cell signalling in leukocytes are less well understood. For example, TSG-6 has been shown to regulate macrophages (an important type of leukocyte associated with chronic inflammation and fibrosis) by suppressing their expression of pro-inflammatory cytokines and by switching macrophages into an anti-inflammatory (M2) state. However, the mechanistic basis of this is not clear. Here we will test the hypothesis that TSG-6 mediates its effects on macrophages by interacting with polysaccharides and proteoglycans that form a sugar coat (glycocalyx) on the surface of leukocytes. This will involve techniques such as the isolation and culture of macrophages, flow cytometry and biophysical analyses. The outcomes of this work will contribute to our understanding of TSG-6's therapeutic effects in models of disease, such as atherosclerosis, arthritis and diabetes, and support our development of this protein as a new class of biological drug.

Supervisor Details	***Professor David Thornton*** **Enquiries:** dave.thornton@manchester.ac.uk https://www.research.manchester.ac.uk/portal/dave.thornton.html
Project Title	**Understanding mucus barrier function in health and disease**
Project outline	Mucus is a critically important defensive barrier that provides the first line of protection for the gut and lung against attack from a range of external agents (e.g. noxious gases, particulates and microbes). Barrier dysfunction, for example in lung diseases such as cystic fibrosis and chronic bronchitis, is an important aspect of morbidity and mortality associated with these conditions. A family of large glycoproteins (known as mucins) dictate the functional properties of the mucus matrix. It is becoming increasingly clear that mucin biology is mediated by infection and the body's immune system and changes in mucins can impact human health. Students on the summer placement will contribute to on-going projects in the Thornton lab that are deciphering the dynamic interplay between mucins, the immune system and infectious challenges (bacterial, fungal and parasitic worms).

Supervisor Details	***Dr Amy Saunders*** **Enquiries:** amy.saunders@manchester.ac.uk https://www.research.manchester.ac.uk/portal/amy.saunders.html
Project Title	**Regulators of skin inflammation**
Project outline	Barrier sites such as the skin, gut and lung are home to harmless microbes, whilst also being the sites where infection commonly occurs. Therefore, the immune cells at these sites must be ready to respond to an infection whilst ignoring the harmless microbes which reside there. The skin is a highly organised tissue comprising cells which are embedded in extracellular matrix. This matrix consists of proteins and polysaccharides which form an organised meshwork throughout the tissue. The fibrous structural proteins present in the matrix confer strength and resilience, but extracellular matrix does not merely fulfil a structural role. It also regulates key cell processes such as proliferation, shape, survival, migration and differentiation. Despite the known importance of immune cells and extracellular matrix to skin health, interactions between the two, and how they regulate one another, is poorly understood. This project will examine the levels, and the spatial organisation of immune cells and extracellular matrix proteins in healthy skin, and in inflammatory skin disease. This will provide insight into the interplay between matrix components.

Supervisor Details	***Dr Patrick Caswell*** **Enquiries:** patrick.caswell@manchester.ac.uk https://www.research.manchester.ac.uk/portal/patrick.caswell.html
Project Title	**How do inflammatory cytokines promote formation of the metastatic niche for ovarian cancer?**
Project outline	Cell within the niche provide the microenvironment that promotes growth of metastases. Extracellular matrix is a key factor in determining this niche, and supports proliferation, invasion and resistance to therapy. Inflammatory cytokines play a key role in matrix assembly in a range of pathologies, but their role in metastatic niche formation in ovarian cancer metastasis is unclear. This project aims to determine the effect of IL-4 and IL-13 on matrix assembly by cancer-associated fibroblasts (CAFs) isolated from ovarian cancer metastases. By co-culturing CAFs, cancer cells and immune cells, we will determine which cells are cytokine-responsive, and reveal the complex interplay between cells generating the metastatic niche.

Supervisor Details	***Dr Gloria Lopez Castejon*** **Enquiries:** Gloria.Lopez-Castejon@manchester.ac.uk https://www.research.manchester.ac.uk/portal/gloria.lopez-castejon.html
Project Title	**How immune cells and the extracellular matrix interact during inflammation?**
Project outline	Our immune systems are able to sense when the body is in danger. When cells are damaged or infected with pathogens, they release 'signals' that alert our immune system. The first immune cells that encounter these signals are macrophages and their main job is to destroy the threat and call for back up to achieve repair and restore health. However when the immune system fails this otbeneficial response becomes damaging leading to inflammatory disease such as arthritis, cancer or lung diseases such as COPD (Chronic Obstructive Pulmonary Disorders). The extracellular matrix (ECM) is meshwork of molecules that provide essential structural and biochemical support to cells and which composition is altered during inflammatory disease. How changes in the ECM affect the ability of macrophages to respond to danger is not understood. This project will investigate how this happens. We will use different cellular and molecular approaches as well as *in vitro* macrophage activating models to determine how the ECM affects the ability of macrophages to secrete pro-inflammatory molecules using techniques such as ELISA or western blot.

Supervisor Details	***Professor Andrew MacDonald*** Enquiries: andrew.macdonald@manchester.ac.uk https://www.research.manchester.ac.uk/portal/andrew.macdonald.html
Project Title	**Defining the relationship between fibrosis and immune cell infiltration in tumours**

Project outline	Cancer is the second leading cause of death worldwide, causing approximately 9.6 million deaths in 2018. Cancer growth and progression are associated with the suppression of the immune system. In particular, in many cancers immune cells lose their ability to invade tumours and kill cancerous cells. As such, drugs that activate immune cells – immunotherapies – have revolutionised cancer treatment. However, not all cancer patients benefit from immunotherapy, so a better understanding of how immune cells are regulated during cancer is urgently needed. One known factor regulating immune cells during cancer is the tumour microenvironment. A major component of this environment is the structural protein collagen, which has been shown to form dense fibrotic regions within the tumour and support cancer progression. Importantly, collagen can affect the ability of immune cells to enter the tumour and kill cancerous cells. However, it's unclear how different levels of fibrosis relate to immune cell infiltration into tumours. This project will investigate how fibrosis affects the ability of cancer fighting immune cells (T cells) to invade tumours. Using histological and molecular techniques, we will visualise and quantify how tumour fibrosis changes over time or following immunological intervention, and define how this relates to T cell localisation within the tumour. This will inform future development of more effective immunotherapies for cancer treatment.

Supervisor Details	***Dr Tara Sutherland*** **Enquiries:** tara.sutherland@manchester.ac.uk https://www.research.manchester.ac.uk/portal/tara.sutherland.html
Project Title	**Regulation of the airway epithelium during chronic allergic inflammation**
Project outline	The airway epithelium can repair itself quickly after injury. However, in some instances like in asthmatic airway disease, chronic insult from allergens, pollutants inflammatory cells etc. limits the ability of the epithelial layer to regenerate. These damaged epithelial cells can undergo multiple biochemical changes that cause them to differentiate into a mesenchymal fibroblast-like cell, a process known as the epithelial-mesenchymal transition (EMT). Once EMT has occurred, these mesenchymal cells can secrete excessive amounts of matrix proteins like collagen, contributing to structural changes in the lung architecture which leads to stiffening of the airways and reduced lung function. It has been suggested that a family of proteins, the chitinase-like proteins (CLPs) can regulate EMT during tumour progression, but no studies have explored whether CLPs influence epithelial cells in the lung. Considering, CLPs are abundantly expressed during chronic inflammatory lung diseases like asthma, we want to investigate whether CLPs play a role in EMT during asthma. Techniques include visualising whether lung epithelial cells express markers of EMT in the lung via microscopy.