Theme 1
Molecules, Cells and the Basis for Disease

2018/2019
Molecules, Cells and the Basis for Disease

This theme brings together stem cells and regenerative medicine (inc. cellular therapies), immunology, genetics, cellular biology (particularly relating to cancer), and biophysics. These areas – and particularly the interfaces between them – are current strengths and priorities for King’s.

Lead: Professor Rebecca Oakey

When choosing a project from this catalogue in the funding section & research proposal section of the online application form please enter MRCDTP2018_Theme1

Deadline for application: Sunday 26th November 2017

Shortlisted candidates will be contacted in early January.

Interviews: 31st January & 1st February 2018

The 2018/19 studentships will commence in September 2018.

For further Information or queries relating to the application process please contact mrc-dtp@kcl.ac.uk

Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.
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1.1 Targeting Wnt signaling for therapy in human prostate cancer (PCa) stem like cells

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Project Description:

PCa is the most frequently diagnosed cancer in men and in the UK kills about 10,000 men every year. It has been proposed that cells in aggressive PCa acquire properties and expression profile resembling embryonic stem cells (ESC). Self-renewal, a key property of stem cells, is regulated by the Wnt signaling cascade for which Ca2+ and β-catenin transcription factor co-activators are intracellular transducers. We have shown that Wnt signaling is important in PCa but its role in PCa stem like cells has not been characterized. Targeting Wnt signalling in PCa stem cells with our novel membrane potential regulating compound (MPRC) inhibitors (International Patent Application PCT/GB2014/053138) could provide an effective treatment for this disease. The key objective will be to investigate the role of Wnt signaling and potential for MPRC to inhibit Wnt signaling regulated self renewal in human PCa stem like cells using the following techniques:

1. Quantitative multilabel immunochemistry for stem cell, Wnt, PCa and ESC signature markers to identify stem cells in situ using confocal and super resolution microscopy (Year 1)
2. Magnetic and fluorescence activated cell sorting, using markers such as Trop2 and CD49f to isolate human PCa stem like cells (Year 1)
3. Cell culture characterization and knockdown for Wnt signaling genes in PCa derived cells using CRISPR/Cas9 (Years 1/2)
4. Patch clamp, live calcium imaging and immunocytochemistry for β-catenin ± MPRCs to investigate functional activity of Wnt signaling (Years 2/3)
5. Serial transplantation of PCa stem like cells in in vivo mouse models (Year 3)

One representative publication from each co-supervisor:


2.1 Using exosomal delivery to gene-edit pancreatic cancer cells for therapy

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Project Description:

Pancreatic cancer (PC) currently has no effective treatment. The development of exosomes as delivery systems for biologics is an emerging topic in the field of cancer therapy. An attractive target is the PAK family kinases (PAK1-6) many of which are overexpressed in pancreatic cancer and have previously been shown to drive both proliferation and cell invasion.  
This 3+1-year project aims to validate the role of PAK family in PC progression using a combination of gene-editing approach and exosomal delivery (nanomedicines).

In the rotation project, the candidate will learn techniques such as culturing PC cells, isolation and characterisation of exosomes: size and surface markers (CD81/CD9) by nanoparticle tracking analysis and flow cytometry, respectively. Exosomes will be fluorescently labelled and uptake in cancer cells will be studied by flow cytometry.

Plans for Years 1-3 are as follows:

Year 1: Target validation and engineering of exosomes

Initially, the role of PAK family genes will be studied by siRNA technology using commercial transfecting reagents. The two most effective genes will be picked up for subsequent CRISPR-gene-editing studies. Exosomes (as carriers) will be engineered to carry Cas9/gRNA complex (therapeutic cargo).

Year 2: In vitro efficacy studies

The ability of exosomes to deliver Cas9/gRNA complexes into pancreatic cancer cells will be studied by flow cytometry. Gene-editing and effect on cell proliferation will be studied by molecular biology techniques (PCR, Western Blotting, T7 assay) and cell proliferation assay, respectively.

Year 3: In vivo biodistribution and therapy studies

Quantitative uptake of exosomes will be assessed in orthotopic pancreatic cancer mouse model by ex vivo gamma counting. Therapeutic effect will be monitored by measuring tumour size by live animal bioluminescence imaging.

Year 3: In vivo biodistribution and therapy studies

Quantitative uptake of exosomes will be assessed in orthotopic pancreatic cancer mouse model by ex vivo gamma counting. Therapeutic effect will be monitored by measuring tumour size by live animal bioluminescence imaging.
**One representative publication from each co-supervisor:**

3.1 Autoimmune pain

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Project Description:

About 10% of adults in the UK suffer from chronic pain, with about half of this group experiencing depression and 25% losing their jobs because of pain (Chief Medical Officer). The available therapies are ineffective in many patients and for several important disorders the cause of pain is unknown.

We have discovered that Complex Regional Pain Syndrome (CRPS) is an autoimmune condition, where autoantibodies cause pain by stimulating pain-sensing nerves. CRPS can be studied in a “passive transfer” model, where antibodies purified from patients produce a CRPS-like condition in mice. The identification of CRPS as an autoimmune condition will lead to new opportunities for development of treatments and diagnostic tools.

Very recently we have discovered that a second, far more common, musculoskeletal pain disorder can be transferred from patients to mice using passive transfer. During this studentship, the student will have an opportunity to identify the cause of this common chronic pain disorder.

In the first 12-18 months, the PhD student will determine the effects of patient antibodies on the function of mouse sensory nerves using electrophysiology (skin-nerve preparations).

During the remainder of years 2-3, the effect of patient antibodies on neurons isolated from mice will be studied to identify the mechanisms responsible for pain.

Throughout the project, the student will use histochemical, biochemical and proteomic approaches to identify molecules targeted by autoantibodies.

Year 4 will be spent completing experiments, writing manuscripts, thesis and fellowship applications. The student will be encouraged to present findings at national and international meeting.

One representative publication from each co-supervisor:


4.1 Manipulating the pituitary stem cell compartment during development and disease

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Project Description:

Background  
This project will study the function of novel determinants that regulate stem cell potential during development and disease. The Hippo kinase cascade is a signaling pathway regulating organ size, proliferation and apoptosis and we have found this to be active in pituitary stem cells (Lodge et al 2016). We have recently established that deregulation of this cascade in the pituitary leads to neoplasia, where stem cells undergo uncontrollable rounds of symmetric divisions. This project will explore the molecular mechanisms underlying this process and aim to restore normal stem cell behaviour through pharmacological targeting of the Hippo pathway. This research ultimately aims to open new avenues for safer and better treatments for human conditions and the findings will additionally be of relevance to regenerative medicine approaches.

Objectives for 3mo rotation  
The student will use in vitro approaches on stem cell cultures and ex vivo on whole pituitaries, to assess the effects of pharmacological manipulation of the Hippo pathway on pituitary stem cell behaviour and potential.

Objectives for 3y PhD  
1. To test the action of pharmacological manipulation of the Hippo pathway in vivo, on genetic models of pituitary tumours and in zebrafish xenograft models.  
2. To understand the molecular mechanisms regulating cell fate decisions via Hippo signalling, through mouse genetics and molecular biology approaches.

Laboratory skills training provided  
Mouse genetics, zebrafish injections, developmental biology, dissection, immunofluorescence, ex vivo/in vitro culture, microscopy, molecular biology, RNAscope in situ hybridisation.

One representative publication from each co-supervisor:  

5.1 Exploring the impact of defects in DNA repair and DNA tolerance pathways on DNA damage and mutations induced by human carcinogens using next generation sequencing

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Project Description:

Modern life involves unavoidable exposure to environmental carcinogens. These can damage cellular DNA and cause mutations that make key contributions to various human diseases including cancer. To ensure genome integrity, DNA damage response (DDR), DNA repair and DNA damage tolerance pathways act as fail-safe mechanisms. Mutations in DNA repair genes have been linked to tumour development but the underlying role of DNA repair defects in mutagenesis is less well characterised. In addition, certain types of DNA damage are substrates for DNA damage tolerance pathways. Translesion synthesis (TLS) polymerases can bypass the damage to enable replication to continue. However, error-prone TLS can lead to mutations.

The project aims to determine the mutational patterns induced by DNA damaging agents (i.e. environmental carcinogens or chemotherapeutic drugs) in human induced pluripotent stem cells by next generating sequencing.

Objectives are:
- to investigate cellular responses in normal and DNA repair- or TLS polymerase-defective cells (YEAR 1+2).
- to use whole genome sequencing to gain insights into how DNA repair or DNA damage tolerance pathways prevent or promote mutagenesis (YEAR 3+4).

Correlation between mutagenesis linked to gene-environmental interactions and reduced cellular viability, activation of DDR pathways and induced DNA damage will be sought. Mutation patterns obtained by whole genome sequencing will be compared with mutational signatures in human cancer genomes in the COSMIC database (Catalogue Of Somatic Mutations In Cancer; http://cancer.sanger.ac.uk/cosmic) database. Bioinformatics analysis will reveal conserved mutation patterns and illuminate how deficiencies in DNA repair or DNA tolerance pathway prevent or promote mutagenesis induced in human cells.

One representative publication from each co-supervisor:

6.1 Investigation into novel immunotherapeutics which target the development of tumour associated macrophages in cancer

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Project Description:

The tumour microenvironment and facilitate cancer progression. Macrophages get hijacked by the tumour to help support angiogenesis, immune and chemotherapeutic suppression, and tumour cell migration which results in metastasis. Our laboratory has characterised a subpopulation of TAMs which have potent immune suppressive functions in the tumour microenvironment. However, little is currently known about the environmental signals which these cells receive to direct their generation within the tumour. Macrophages are a highly plastic cell type and their phenotype is acutely defined by the microenvironment in which they differentiate. By understanding the key environmental cues that these cells are responding to will allow for us to further understand the response pathways being utilised by these cells. Also, this investigation will allow for us to identify novel targets for therapeutic intervention, and even potentially uncover the key to preventing these cells from adopting the phenotype altogether.

The proposed project will utilise spontaneous in vivo models of breast cancer and a novel transgenic model that has been developed by the laboratory, alongside transcriptomic microarray analyses and gene knockdown studies to try to gain insight into the key signals directing the TAM’s pro-tumoural phenotype. Once the targets of interest have been identified they will be investigated in detail for their role in macrophage differentiation. The findings will be validated in human breast cancer, utilising in vitro macrophage culture, tumour sections and online patient survival and expression databases.

This project will utilise the following techniques: Transcriptomic microarray and associated software analysis, flow cytometry, confocal microscopy, quantitative reverse transcriptase PCR, Western blot, In vivo and ex vivo models, cell culture (primary and cell line), co-culture, and therapeutic interventions (small molecule inhibitors, neutralising antibodies).

Objectives

Year 1 Target identification/establishment of assays

Year 2 In vivo and in vitro characterisation of targets in TAM development

Year 3 Identification and validation of a strategy to therapeutically exploit the target using in vivo models

One representative publication from each co-supervisor:


7.1 Exploring epigenetic alterations to elucidate the role of smoking in inflammatory bowel disease: implications for therapy

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Project Description:

Inflammatory bowel disease (IBD) represents a group of autoimmune diseases that affect the gastrointestinal tract, with two primary disease subtypes - Crohn’s Disease (CD) and Ulcerative Colitis (UC). It is well established that smoking has a strong influence on IBD, but with striking divergent risk effects between CD and UC: while smoking is a risk factor in CD with detrimental effects on its clinical course, smoking has protective effects in UC with a beneficial influence on progression. Much research has explored the differential smoking effects in IBD subtypes, but the molecular mechanisms involved are poorly understood.

Epigenetic mechanisms, including DNA methylation, are key regulators of gene expression and can mediate environmental disease risk. Many studies have identified a strong influence of smoking on methylation, with distinct methylome signatures at many genomic loci, which can persist for decades after quitting smoking.

Our hypothesis is that epigenetic alterations mediate the differential effects of smoking on CD and UC. The project will investigate this in a cohort of IBD patients and healthy controls (TwinsUK) using genome-wide DNA methylation profiles in multiple tissues including intestinal biopsies from smokers and non-smokers.

Aim 1. Identify epigenetic changes in the gut and blood that mediate the contrasting risk effects of smoking on CD and UC.
Aim 2. Explore gene expression profiles in biopsies from patients and controls to identify functional impacts of these epigenetic changes.
Aim 3. Harness combined smoking, metabolomic, epigenetic and expression data to dissect how components of tobacco smoke affect IBD risk and progression.

One representative publication from each co-supervisor:


A characterisation of IL-36 signalling as a therapeutic target in psoriasis

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Project Description:

Psoriasis is a chronic inflammatory skin disorder that affects more than a million people in the UK alone. In recent years our group has carried out gene identification and transcriptional profiling studies, which have demonstrated a pathogenic role for the de-regulation of IL-36 signalling. While these findings point to IL-36 blockade as an attractive therapeutic strategy, the physiological function of IL-36 is not fully understood so that cytokine inhibition may have unexpected adverse consequences.

The aim of this project is to characterise the systemic effects of IL-36 and the consequences of IL-36 blockade on immune function.

During their rotation project, the student will carry out IL-36 stimulations in purified immune populations, with a view to identifying the leukocyte subsets that respond to IL-36 and the consequences of IL-36 treatment on their activation status.

In subsequent years, the student will:

- Identify IL-36 driven transcriptional networks by carrying out RNA sequencing in the cell populations identified during the rotation project (Year-1).
- Experimentally validate the newly identified networks through in-vitro studies (e.g. by CRISPR-mediated gene silencing of key transcriptional regulators) (Year-2)
- Investigate the consequences of IL-36 blockade on the newly identified networks through ex-vivo studies of purified cell populations obtained from patients and controls (Year-3)

The student will be monitored by two experienced supervisors with complementary expertise in functional genomics (FC) and clinical dermatology (JNB). Training will be provided in the use of computational tools (differential expression and network analysis) and experimental techniques (isolation, culture and manipulation of primary cells).

One representative publication from each co-supervisor:


9.1 Investigating developmental and epigenetic mechanisms of adipose tissue homeostasis.

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Project Description:

Obesity involves the expansion of white adipose tissue (WAT). This occurs through increased lipid filling within existing adipocytes to increase adipocyte size (hypertrophy), OR increased differentiation of adipocyte precursor cells (APCs) to increase adipocyte number (hyperplasia). The size of adipocytes is important – large cells are pro-inflammatory and associated with insulin resistance, especially if this occurs in the visceral compared to the subcutaneous WAT depot. Therefore, the availability of APCs, which is determined in early development, is a critical factor in how WAT behaves.

In this project, we will use a mouse model to determine how perinatal nutrition, a risk factor for later life metabolic disease, influences the APC store. This will involve assessing the number, distribution and differentiation capacity of APCs both in vivo and ex vivo. Additionally, we will examine gene expression and the role of the mRNA epitranscriptomic modification, N-6-methyladenosine (m6A). A role for m6A in obesity is suggested by genome-wide association studies in humans and this will provide an exciting opportunity to examine its function in a disease relevant cell type.

Aim 1 (Years 1-2): To determine if maternal protein restriction changes APC numbers and differentiation capacity in neonatal mice (animal models, microdissection, FACS, cell culture).

Aim 2 (Years 1-2): To examine if maternal protein restriction alters m6A levels, distribution and the transcriptome of APCs (molecular biology, high throughput sequencing, bioinformatics).

Aim 3: (Years 2-3): To examine how maternal protein restriction influences the WAT response to a high fat diet in adulthood (microscopy).

One representative publication from each co-supervisor:


10.1 Defining cellular and molecular mechanisms underlying cancer immunotherapy-induced auto-inflammatory syndromes

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Project Description:

Cancer therapy with immune checkpoint inhibitors is transforming the treatment of solid tumours such as melanoma. The rationale is based on breaking immune tolerance to tumour antigens, unleashing effector T cells to kill tumour antigen expressing cells. This is accomplished by inhibiting the function of the immune system’s own immunosuppressive “checkpoint” molecules, the best characterised being CTLA4 and PD-1. In spite of these breakthroughs, response rates to cancer immunotherapy are well below 50% across indication, highlighting a need to better understand responders and non-responder states. These therapies, at the same time, break tolerance to self antigens leading to an emerging group of auto-inflammatory syndromes comprising rapid onset (6-8 weeks), and often severe inflammatory disease targeting skin, gut, joint or endocrine organs. Being one of the largest cancer immunotherapy centres in the UK offers an unparalleled opportunity to understand the delicate balance between tumour immunity and autoimmunity in cancer patients, with the explicit intention of preventing adverse immune reactions on the one hand, and uncovering new insights into the pathogenesis of autoimmunity on the other. In this project the student will undertake deep immune phenotyping of peripheral blood and tissues from cancer patients before and after receiving checkpoint inhibitor therapy (Year 1), exploiting high-end flow and mass cytometry to map the very earliest events associated with the onset of immune mediated inflammatory syndromes. This will be complemented by analysis of blood transcriptomes (Year 2), seeking to understand the relationship between cellular and molecular signatures and specific disease phenotype (Years 1-3).

One representative publication from each co-supervisor:


11.1 Allergic Disease: To Nip in the Bud

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Clinical Supervisor: Dr Stephen Till
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Project Description:

IgE antibodies play a key role in allergic disease by sensitizing mast cells for allergen triggering. Allergen-specific IgE antibodies are produced by the interaction between allergen and the B cell receptor (BCR) on cells that have switched to the expression of membrane IgE (mIgE). While studies of antigen recognition by the IgM- and IgG-BCRs have elucidated aspects of antigen uptake and signaling, it is now clear that the outcomes for the IgE-BCR are fundamentally different. This means the IgE-BCR signalling pathway could be a unique target for intervention in allergic disease. As demonstrated in studies of the IgM and IgG-BCR, high-resolution imaging is a powerful approach to elucidate the pathways of BCR signaling. The Cox group develops super-resolution localisation microscopy techniques, specialising in live cell measurements.

This project uses an innovative method which allows simultaneous imaging of a single fluorophore in two colour channels to track both single molecules and global structures of various proteins, including the IgE-BCRs, membrane proteins, cytoskeleton components and signalling molecules. The dynamics of these proteins will be followed through the processes of allergen uptake, endocytosis and the subsequent fate of the cell. The student will image live human B cells transformed to express allergen-specific recombinant mlgEs, derived from allergy patients. In year 1 the student will be introduced to imaging and will construct vectors for expression of the different antibody classes, with the imaging technique being adapted to the specific problem in year 2 and acquisition of data in years 2 and 3.

One representative publication from each co-supervisor:


12.1 Integrative analysis of multi-omics datasets for the identification and validation of immune biomarkers in psoriasis

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Project Description:

Psoriasis is a chronic inflammatory skin disease affecting at least 1 million people in the UK, with a severe impact on patient quality of life. Monoclonal antibodies targeting key pro-inflammatory molecules (“biologics”), are effective, but not in every patient, and there is an unmet need to identify biomarkers that predicts patient response to therapy. As part of the MRC-funded PSORT (Psoriasis Stratification to Optimise Relevant Therapy) Consortium, we are employing high-throughput ‘omics’ platforms to interrogate relevant immune pathways in patients treated with biologics, and identify predictive immune biomarkers.

Using phospho-flow cytometry, we have measured the phosphorylation status of key transcription factors in peripheral blood mononuclear cells of patient receiving biologics. Independent cohorts for replication studies, as well as additional datasets for multi-omics data integration are also available. The objectives of this project are: rotation & Year1) to develop Exploratory Data Analysis (EDA) strategies, underpinned by principles of immunology, bioinformatics and system biology, for the selection of putative phospho-biomarkers in existing datasets; Year2) to experimentally replicate putative biomarkers in an independent patient cohort; Year3) to develop innovative analysis strategies for the bioinformatic integration of multi-omics datasets and the identification of predictive immune biomarkers in psoriasis.

The student will benefit from the co-supervision model of the DTP Studentship being fully integrated in an immunology and a bioinformatics group, with clinical inputs from an academic dermatologist. He/she will receive extensive training in both disciplines, ultimately developing a highly distinctive skillset, spanning from the generation to the analysis of high-dimension complex biomedical data.

One representative publication from each co-supervisor:


C. Ainali, N. Valeev, G. Perera, A. Williams, J.E. Gudjonsson, C.A. Ouzounis, F.O Nestle, S. Tsoka,  

13.1 Broadly neutralizing antibody responses in HIV infection

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Project Description:

An HIV vaccine is desperately needed to prevent new HIV infections worldwide. Approximately 10-30% of HIV infected individuals generate antibodies that are capable of neutralizing a broad range of HIV isolates and these antibodies have been shown to protect against SHIV challenge in Macaque models. Isolation and characterisation of these antibodies has revealed regions of the HIV envelope glycoprotein, gp120/gp41, that are susceptible to antibody binding and re-eliciting these antibodies may be a key step for a successful HIV vaccine. Gp120 is heavily glycosylated with host-derived N-linked glycans and it was previously thought that these glycans shield conserved protein regions from the immune system. However, we have recently shown that many of the most broad and potent HIV neutralizing antibodies bind directly to these glycans highlighting them as potential targets for HIV vaccine design.

Using unique longitudinal patient samples from acutely HIV infected individuals in the SPARTAC study (N Engl J Med 2013;368:207-17) we will investigate the development of HIV broadly neutralizing antibodies (bnAbs) in vivo using in vitro neutralization assays, antigen-specific B cell sorting and antibody cloning, next generation sequencing of antibody genes and viral Envelope single genome amplification. We will determine how the viral Envelope evolution guides and directs bnAb development in these HIV-infected individuals. Ultimately these studies will be used to design immunogens and immunization strategies aimed at re-eliciting these bnAbs through vaccination.

One representative publication from each co-supervisor:


14.1 Cell Death for Regeneration: Mesenchymal Stromal Cells and Myocardial Repair

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Project Description:

Myocardial infarction (MI) is damage/death to the heart muscle. Immediately after MI, cardiac wound repair is initiated, starting with a strong infiltration of immune cells and inflammatory response. Recent data shows that mesenchymal stromal cells (MSCs) can facilitate myocardial tissue repair. However, the therapeutic activity is dependent on exposure of MSC to the correct setting of microenvironment, also known as MSC ‘licensing’. A better understanding of the licensing mechanisms will shed light on key signals that stimulate endogenous tissue repair mechanisms and provide crucial steps for clinical development.

The Dazzi lab has recently shown that injected MSCs are induced to undergo apoptosis by the recipient cytotoxic T cells and natural killer (NK) cells. Apoptotic MSCs are then engulfed by host phagocytes that become immunosuppressive (Galleu et al. 2017). This activity could prove fundamental also for stimulating spontaneous myocardial tissue repair and facilitate engraftment, self-renewal and/or differentiation of resident cardiac stem/progenitor cells (CPCs).

This project will elucidate the mechanisms by which the post-MI environment licenses indirect tissue repair, promoting immunomodulatory properties of transplanted MSCs and the direct regenerative activity of cardiac stem/progenitor cells, resulting in improved cardiac repair and regeneration. The Ellison lab has extensive experience and knowledge of CPCs resident in the adult heart and stimulating the heart’s regenerative capacity post-injury.

Over-arching Objectives:
1: Characterising the immunomodulatory and pro-regenerative properties of MSCs and CPCs in vitro and in vivo
2: Elucidating the mechanisms underlying the stimulation of cardiac repair mechanisms by MSC and CPC immunomodulation

One representative publication from each co-supervisor:


15.1 Identification of novel immunomodulatory target checkpoints for Prostate Cancer therapeutics

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**Project Description:**

Prostate cancer is the most common cancer among men. Immunotherapies such as Provenge™ have improved end-stage prostate cancer survival. However, although immune-cells such as CD8 T-cells can infiltrate the prostate, this microenvironment renders these cells suppressive. The cause of this immunosuppression is not clear, although many immune-checkpoint proteins have been recently discovered.

The project aims to use a novel syngeneic human prostate tumour/immune-cell model to identify immunomodulatory molecules in the cancerous prostate. Using syngeneic PBMCs and cells from patient tumours (of varying stagings), mechanisms of immune-tolerance and molecules differentiating indolent/aggressive disease can be determined. Moreover, potent immunotherapeutic agents modifiable to localise to cell-membranes can be assessed using this model (see below). The supervisors provide training in Immunology and Molecular Biology (Genomics/Proteomics), Protein Chemistry, and Clinical Cancer diagnostics.

Objectives/methodologies:

**Years 1-2: Studying immune-effector function of cells from patients with different stagings:** This will involve training including flow-cytometry, ELISA, and isolation/culture of primary-tumour cells.

**Years 2-3: Immunome profiling from patient effector/tumour cells to determine markers of disease progression.** Training will be provided in technologies such as genomic/proteomic microarrays. Antibodies will be raised/obtained to selected inhibitory markers.

**Years 3-4: Assessing novel immunotherapeutic agents in the above model.** Richard Smith has developed a cytotoxic-tailing technology to localise therapeutic proteins/peptides to tissues/organs to reduce systemic-toxicity and increase agent avidity. Training will be provided in protein chemistry to prepare agents modified with cytotoxic “tails” (e.g antibodies from years 2-3) and will assay efficacy of these agents on immune-cell function using assays described in year 1.

References for project


**One representative publication from each co-supervisor:**


The effect of lipid composition on the mechano-transduction of individual live cells

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Project Description:

Are the lipids forming the plasma membrane and nuclear envelope (NE) dynamically modified under mechanical stress? Lipids and proteins are key components of membranes, yet most of the effort to understand mechanotransduction has focused on proteins alone. We will explore whether the lipidome changes in the plasma membranes and NE of cells exposed to mechanical stress. We will subject cultured cells to substrates of different stiffness, and extract their nuclei. Plasma membrane and nuclear lipids will be extracted and analysed by MS to determine their lipidomic profiles. In parallel, we will use Atomic Force Microscopy (AFM) in combination with magnetic tweezers cell stretching experiments to probe the mechanical properties of plasma and nuclear membranes.

We will investigate the effect of mechanical forces on the lipid composition of cells and isolated nuclei. The student will gain expertise in single cell AFM and magnetic tweezers characterisation, combined with cell and molecular biology techniques. She will also gain deep knowledge in mass spectrometry. In Year 1, cell biology experiments will be performed at UE lab and the student will learn how to prepare substrates of different stiffness in SGM lab. Year 2 will be devoted to conduct single cell mechanical experiments using AFM and Magnetic Tweezers (SGM). During Year 3 the student will concentrate on lipidomics (UE). Experiments, analysis and paper writing will continue in Year 3-4.

This is a unique opportunity to explore fundamental biophysical questions of lipids during mechanotransduction at the single cell level, combining cutting-edge nanomechanical biophysical techniques (Garcia-Manyes) and modern cell biology and mass spectrometry (Eggert).

One representative publication from each co-supervisor:


The CXCL8-producing T cell in infants: function in health and HIV

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Project Description:

The human neonatal immune system is not just an immature version of that of the adult but is qualitatively and quantitatively different. Our research focuses on understanding immune cell development and function in the human neonate and how this impacts on disease. We identified that neonates possess robust effector potential in the form of CXCL8 (aka interleukin-8, IL8) and thus dispelled the long held view that the infant immune system was anti-inflammatory. CXCL8 production is imprinted in the thymus during T cell development and the expression of CXCL8 appears to be selected for upon thymic egress suggestive of an important function. CXCL8 producing T cells do not remain as such but these cells represent an intermediate cell en route to classic adaptive immune cell functions such as IFN-γ production. This raises a number of important questions that form the basis of this PhD project:

1. There is an efflux of recent thymic emigrants upon initiation of HIV treatment-this suggests an efflux of CXCL8-producing cells-what is the effect of CXCL8 and these cells upon HIV pathogenesis?
2. Are CXCL8-producing cells protective or pathogenic in infant infections such as sepsis?
3. What are the signals and signalling pathways that allow conversion of CXCL8-producing T cells to IFN-γ-producing cells and other T cell lineages?

Methods will involve multiple cellular and molecular techniques (eg flow cytometry and RNA sequencing) as well as work both in vitro and in vivo mouse models.

One representative publication from each co-supervisor:


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Project Description:

Bone diseases characterised by bone loss, such as osteoporosis and cancers that metastasise to bone, are debilitating diseases that affect millions of people worldwide. There are no cures and current treatments have many side effects. Natural products are chemicals from nature that can be used as the basis for new medicines. Natural products from marine sponges show exceptional promise as potential pharmaceuticals and could offer effective strategies for the treatment of metabolic bone diseases. We are working on a family of natural products from a Great Barrier Reef sponge that shows potent activity on cells that both form and degrade bone. The prospects of using these compounds as tools to manipulate bone cell activity with a view to provide mechanistic data that underpin development of a new medicine is completely novel and represents the aim of the project. The project provides training for the student in multidisciplinary yet complementary skills of biochemical/molecular bone cell biology (Prof Grigoriadis) and pharmacology/pharmaceuticals (Prof Long), to achieve the following project goals:

Year 1: Dose- and time-dependent effects of natural compounds on bone cell differentiation and gene expression in vitro.

Years 2 & 3: Consolidation of in vitro experiments, progressing to translational aspects of the project using in vivo mouse models of bone disease, and investigating new mechanisms of action. Candidate target genes are already established.

Year 4: Finalising experimental work and writing-up.

This studentship offers a mobility component with our project partners at the Australian Institute of Marine Science.

One representative publication from each co-supervisor:


19.1 A Wnt-based Bioengineering Approach To Polarise Osteosarcoma and limit their tumorigenic potential

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Project Description:

The bone cancer Osteosarcoma is the second leading cause of cancer-related deaths in paediatric patients. Despite surgery and chemotherapy, long-term survival rates for patients diagnosed with osteosarcoma have not improved over the last 30 years. Osteosarcoma stem cells (OSCS) derive the growth of tumour. The levels of Lrp5, the receptor of Wnt ligands, are statistically correlated with poor prognosis and Wnt signalling is a therapeutic target for blocking tumorogensis. This project will investigate the cell division of OSCS, and engineer strategies to polarise them in order to direct them to divide asymmetrically, limit their proliferation potential and control cellular fate. We hypothesise that the Wnt signalling pathway could be employed for controlling the cellular polarity and division.

The Habib lab has engineered localised Wnt niches that can induce asymmetric cell division of embryonic and bone stem cells. The combination of our bioengineering approaches with advanced materials that mimic the bone niche (Gentelman lab) provide grounds to explore the mechanistic regulation of the OSSC division and opportunities to limit their tumorigenic potential.

1st - 2nd year: Culturing and characterising OSCS. Employing 3D microscopy to study the division OSCS by establishing a molecular segregation map for cell polarity proteins, Wnt pathway components and cell fate markers. Purification of Wnt proteins will also be done.

3rd - 4th year: Engineering localised Wnt niches in 3D biomaterials and testing their effect on OSCS proliferation and invasion. Flow cytometry to separate between the daughter cells of OSCSs and investigating their tumorigenic potential in in vitro and in vivo transplantation assays.

One representative publication from each co-supervisor:


20.1 The role of the Larp6 RNA binding protein in vertebrate oogenesis, development and fertility

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**Project Description:**

Much human infertility is unexplained. We have found that mutation of the *larp6a* gene leads to defective oogenesis and reduced female fertility. LARP6 is a recently discovered RNA-binding protein involved in regulation of gene expression at the translational level. Its functions are still largely unknown although it has been reported to control collagen production. Furthermore, LARP6’s ability to recognise specific mRNA targets and its molecular mechanisms are still unclear.

Evidence for a role for LARP6 in infertility is growing: drosophila Larp mutants are characterised by female infertility and show defective early embryo development. We mutated the two *Larp6* genes in zebrafish (*larp6a* and *larp6b*) using CRISPR/Cas9 genome editing and discovered an exciting maternal effect mutation in *larp6a*: *larp6a* mutant females have fragile oocytes, small chorion (egg shell) and cytological defects including mis-localisation of other mRNAs leading to reduced fertility.

The PhD project therefore aims to explore:

a) the function of LARP6a, and its mechanism in female infertility  
b) the identification of LARP6a mRNA targets, using CLIPseq technology  
c) the structural biology of LARP6a mRNA binding and its role in mRNA localisation  
d) the function of LARP6b and possible cooperation with LARP6a  
e) the involvement of human LARP6 in infertility

This work will contribute towards identifying whether LARP6 plays a role in fertility and degenerative muscle disorders and how it functions.

For more information on the laboratories, see:  
[http://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/signalling/hughes/hughessimon.aspx](http://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/signalling/hughes/hughessimon.aspx)  
[https://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/structural/conte/contesasi.aspx](https://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/structural/conte/contesasi.aspx)

**Key techniques / transferable skills:**

Molecular biology, protein biochemistry, zebrafish genetics, embryonic development, immunohistochemistry, imaging, biophysical measurements.

**One representative publication from each co-supervisor:**


21.1 The role of the pro-FLG Ca$^{2+}$-binding domain in the formation of the skin barrier and pathogenesis of atopic dermatitis

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Project Description:

Atopic dermatitis (AD) affects 20% of children and 5% of adults in the UK and has a profound effect of patients’ quality of life. A genetic predisposition for skin barrier dysfunction, together with environmental factors, such as exposure to hard water (high CaCO$_3$ levels) and the use of protease containing detergents, results in the typical immunological phenotype of AD.

Normal epidermis displays a marked Ca$^{2+}$ gradient, which controls the expression of filaggrin (FLG) and differentiation of the epidermis. Recent genetic studies have found that loss-of-function mutations in the FLG gene are present in up to 50% of AD patients. Pro-FLG has a Ca$^{2+}$-binding domain of unknown function, which is cleaved off when pro-FLG is proteolytically processed into functional FLG during the biogenesis of the stratum corneum.

We will use CRISPR/Cas9 gene-editing technology to delete the FLG Ca$^{2+}$-binding domain in healthy human embryonic stem cell (hESC) lines. We will then use these isogenic normal and mutated hESC to differentiate various skin cell types and build 3D in vitro models of full thickness skin. The developed model will be used to assess processes related to keratinocyte differentiation and skin barrier integrity to determine the role of the pro-FLG Ca$^{2+}$-binding domain in the formation of a functional skin barrier and the pathogenesis of AD. We will also expose the outer surface our 3D in vitro model to varying CaCO$_3$ levels to assess the effect on skin barrier integrity. The project will inform novel methods of treatment and disease prevention.

One representative publication from each co-supervisor:


22.1 The role of glycosylation in the biological functions of tumour antigen-specific IgE class antibodies

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Project Description:
IgE antibodies are mediators of allergic and anti-parasitic immune responses. These activities have been harnessed for the development of IgE-based antibodies specific for cancer-associated antigens as a novel cancer immunotherapy strategy. Our findings to-date suggest that IgE-based immunotherapeutics effectively restrict tumour growth. Our first-in-class IgE antibody recognising a tumour-associated antigen is undergoing a Phase I clinical trial at Guy’s Hospital headed by co-supervisor Spicer. IgEs are highly glycosylated antibodies, yet the precise effects of IgE glycan moieties on the potency and immune cell-activating mechanisms of IgE against cancer remain unclear. We aim to understand and exploit the role of glycosylation on the biological and anti-tumour functions of IgE class antibodies. The goal is to identify optimised antibodies for immuno-oncology. Firstly, we will generate defined IgE glycoforms by administering inhibitors of glycan biosynthesis (e.g. mannose, fucose, galactose). Year 1 will focus on antibody generation and pharmacological evaluation. Year 2 will entail study of biological functions of IgE glycoforms compared with IgE expressed under native conditions. These include antigen and receptor binding properties (e.g. ELISA, Biacore, flow cytometry), IgE-mediated signalling, phagocytosis/cytotoxicity, apoptosis, proliferation, viability of cancer cells and mast cell degranulation. In Year 3, the most promising antibodies will undergo further selection to confirm potency and early ex vivo safety evaluations in patient blood and serum. These studies will establish IgE structure/function relationships and aid the identification of IgE glycoforms with defined anti-tumour functions. The project has considerable potential to deliver optimized antibodies and expedite translation to benefit patients with solid tumours.

One representative publication from each co-supervisor:

23.1 Dissecting the influence of chromatin modifications on muscle stem programming by a quantitative live cell imaging approach

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Project Description:

Stem cells hold great promise for regenerative biology, but current barriers to their application in a clinical setting include our very limited understanding of how they behave in vivo. Although we know stem cells are very motile and are highly sensitive to environmental cues, how these are interpreted has proven challenging. Further, epigenetic changes, due to diet or exposure to chemicals, likewise can affect stem cell responses.

In this project we propose to use laser microscopy to visualise how muscle stem cells (muSCs) respond to an injury signal and use advanced statistical and computational techniques to reveal the influence of epigenetic signals on these behaviours. Bioinformatics approaches will be implemented to process the data and to identify candidate novel regulators, which may be of value in a therapeutic context to treat patients with muscle wasting disorders such as muscle dystrophies.

Skills Training

This project will provide opportunities to acquire extensive expertise in cell biology and master general approaches of learning from 'big data' that are applicable across many disciplines. Students will learn both experimental and computational skills on how to perform live cell imaging both in vitro and in vivo (zebrafish and mouse models) using confocal, multiphoton and light sheet microscopy. 4D time-lapsed movies will be analysed by using and writing computational tools. Cell culture, molecular biology and use of animal models will also be taught.

Objectives

Year 1-2: analyse cell behaviour to identify candidate regulators of muSC behaviour
Year 3: functionally test candidate regulatory genes
Year 4: perform a pharmacological screen for novel muSC regulators using predictive computational tools

One representative publication from each co-supervisor:


24.1 Investigate a novel, unexplored link between WNT signalling and regulators of cell migration in cancer progression.

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Project Description:

Cancer is a devastating disease: more than one in three people in the UK will develop cancer in their lifetime. WNT signalling is a key pathway controlling morphogenesis in embryos and it has been shown that perturbations of this pathway promote cancer progression. Regulators of the actin cytoskeleton control cell migration and their dysregulation has been implicated in cancer metastasis. In this project, you will investigate a novel, unexplored link between WNT signalling and regulators of the actin cytoskeleton using biochemistry, molecular biology, and advanced live cell imaging in vivo. We have unpublished data showing a novel interaction between a component of the canonical WNT signalling pathway and regulators of the actin cytoskeleton. During your rotation, you will map this interaction by site directed mutagenesis. Thereafter, you will test the functional significance of this interaction in cancer cell proliferation and migration. You will then use CRISPR to genome edit cancer cell lines and employ advanced live cell imaging techniques in cell lines and zebrafish embryos to define the role of this signalling regulation. Taken together, your PhD work will unravel a novel and general mechanism of WNT signalling and how it contributes to embryogenesis and cancer progression.

You will join laboratories studying the regulation of cell migration (Krause laboratory – cancer cell migration and proliferation, regulation of actin cytoskeleton; Linker laboratory – in vivo cell migration, WNT signalling) and will be trained in techniques including protein biochemistry, molecular biology (CRISPR, etc), zebrafish embryology and advanced imaging.

One representative publication from each co-supervisor:


Logan and Nusse, 2004
25.1 Novel functions of long noncoding RNAs in cancer

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Project Description:

Metastasis is the spread of cancer cells around the body and is the cause of ~90% of cancer-related deaths. We have recently identified a new long noncoding RNA (lncRNA), PNCTR, and shown that it can modulate gene expression in metastatic cancer cells by sequestering multiple copies of an important RNA-binding protein, PTBP1. Student joining our team will develop this exciting line of research by focusing on the following questions.

Rotation-Year 1: What types and stages of human cancers are characterized by elevated expression of PNCTR? The student will analyse next-generation RNA-sequencing (RNA-seq) data (Makeyev lab) and measure PNCTR expression in a representative panel of cancer samples including metastatic lesions (Sanz-Moreno lab).

Year 2: How does PNCTR contribute to cancer progression? This will be addressed by altering PNCTR expression using appropriate over-expression and knockdown approaches (Makeyev) and examining the effects of these treatments on cell proliferation and metastasis by appropriate in vitro and in vivo assays (Sanz-Moreno).

Year(s) 3-4: What molecular mechanisms underlie increased expression of PNCTR in cancer cells? This will involve analyses of possible genome rearrangements or/and expression levels of relevant transcription and RNA processing factors in cancer cells (Makeyev/Sanz-Moreno).

In addition to its strong potential for biomedically important discoveries leading to new cancer biomarkers and therapeutic approaches, this research program will allow the student to acquire multidisciplinary skills in bioinformatics (RNA-seq data analysis), RNA biology (RT-(q)PCR, Northern blotting, RNA-FISH) and various cell and cancer biology approaches (high-end microscopy, in-vitro assays for invasion/metastasis, xenografts/allografts in mice).

One representative publication from each co-supervisor:


26.1 HIV-1 mediated reprogramming of T cell gene expression networks

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Project Description:

Virus infection triggers two fundamental types of cellular response: those that inhibit infection (broadly termed immune responses) and those that promote virus production, persistence and/or dissemination (here called reprogramming). The balance between these opposing forms of response dictates the overall outcome of infection and, ultimately, contributes to the pathogenic consequences for the infected host. To date, little is understood regarding the capacity of the pathogenic retrovirus, HIV-1, to reprogramme infected T lymphocytes, or the consequences of such changes for altering cell function. This project will build upon a substantial body of data where we have demonstrated that HIV-1 reorganises the transcriptional landscape of T lymphocytes within the first few hours of infection. We will employ a multi-disciplinary approach including virology, molecular genetics, chromatin-biochemistry, high-throughput nucleic acid sequencing, single-cell analytics and bioinformatics to tackle the following key questions. One, what are the virus determinants that drive these RNA expression changes and through which signalling pathways do they function? Two, what genome-wide alterations in chromatin and epigenetic marks underpin changes in RNA levels, and which steps of RNA biogenesis are regulated? Three, do all cells respond to infection equivalently or is there cell-to-cell variation; and if the latter, what cell-specific signatures underpin the differences? Four, how does reprogramming impact the fate of HIV-1 infection, perhaps by altering virus production, persistence/latency, or sites of provirus integration? Together, insight in these areas will yield new information on the dynamic interplay between HIV-1 and its human host.

One representative publication from each co-supervisor:


Prickett, A.R., Barkas, N., McCole, R.B., Hughes, S., Amante, S.M., Schulz, R., and Oakey, R.J. Genome wide and parental allele specific analysis of CTCF and Cohesin binding sites in mouse brain reveals a tissue-specific binding pattern and an association with differentially methylated regions. Genome Research 2013. 23(10):1624-1635. This paper illustrates the use of genome wide sequencing techniques in understanding gene regulation.
27.1 Role of intrahepatic Tregs in the modulation of liver inflammation and the promotion of tissue regeneration

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Project Description:

Hepatic inflammation of any aetiology is characterized by lymphocyte infiltration. If the inflammation is not controlled it could lead to fibrosis, resulting in cirrhosis or liver failure. The balance of effector and regulatory T cells (Tregs) generally determines the outcome of hepatitis. Tregs are a heterogeneous population with specific properties depending on the homing tissue, including immunoregulation and tissue repair. However, the factors that modulate Treg homeostasis and function in the liver remain unclear. Our previous studies have demonstrated that IL-2 administration preferentially expand Tregs in the liver and increases their suppressive functions. Therefore, we believe that IL-2 therapy can modulate Treg immunoregulation during hepatic inflammation and enhance tissue regeneration.

The objectives of this study are: i) to characterise the phenotype and features of intrahepatic Tregs in humans and mice; ii) to determine the Treg homeostasis and cell-to-cell interactions during chronic liver inflammation; iii) to assess the role of Tregs in the tissue regeneration after hepatic injury; and iv) to evaluate the benefits of combining IL-2 therapy with hepatocyte transplantation to improve regeneration of end-stage liver damage.

In order to achieve our aims, we will employ animal models of acute hepatitis and liver fibrosis (wild-type and Treg-depleted mice), and 3D microfluidic cell cultures (liver-on-chip) to mimic the human hepatic physiology. Single-cell RNAseq and CyTOF analysis will be integrated to characterize new Treg subsets. In addition, we will perform isolation and cell culture techniques from human and mouse (MLR, Treg suppression assays…), cell biology assays (flow cytometry, ELISA…) and molecular analysis (qPCR, DNA sequencing…).

One representative publication from each co-supervisor:


28.1 Identification of host factors that promote assembly of Ebola virus

Co-supervisor 1: Prof Juan Martin-Serrano
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Project Description:

Ebola virus (EBOV) is a filovirus that causes severe haemorrhagic fever. The major EBOV structural component is VP40, the matrix protein that plays a central role in the assembly of infectious viral particles. VP40 expression is sufficient to form viral-like particles that share the filamentous morphology with infectious Ebola virions. Therefore, VP40 is the minimal unit required for assembly that recruits the host factors required for this process, as shown by our observations that VP40 recruits the Endosomal Sorting Required for Transport (ESCRT) machinery to promote viral egress. VP40 promotes assembly by adopting multiple conformations. VP40 dimers change membrane curvature and subsequently assemble into hexamers that form the filaments that shape EBOV virions. The octameric ring conformation of VP40 binds RNA and plays a poorly defined role in EBOV replication.

The aim of this project is the identification of VP40-binding host proteins that are involved in EBOV replication. We have performed a genome-wide screen to identify human proteins that bind either WT or the octamer-locked form of VP40. The student will determine the role of the candidate hits in EBOV replication. The selected open reading frames will be cloned into yeast two-hybrid and co-precipitation plasmids to further validate the interaction with VP40. Co-localization by super-resolution and live-cell microscopy will further confirm the interaction of candidate host proteins with VP40. Expression of the short-listed genes will be disrupted by siRNA and CRISPR-based gene editing to assess their contribution to EBOV assembly and replication, taking advantage of a transcription/replication-competent virus-like particle (trVLP) system.

One representative publication from each co-supervisor:


29.1 Identification of type 1 diabetes-associated non-canonical spliced epitopes and their immunological role in the autoimmune response

Co-supervisor 1: Michele Mishto
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Project Description:

The project aims to identify MHC class I (MHC-I)-restricted epitopes associated with Type 1 diabetes (T1D) and produced by proteasome-catalysed peptide splicing.

We recently showed that the latter activity of proteasome produces around 30% of the self antigenic epitopes in human cells (Liepe et al., Science 2016). Spliced epitopes can trigger a CD8+ T cell response against cancer and infection (Mishto and Liepe, Trends Imm. 2017). An autoimmune cytotoxic T cell (CTL) response is responsible for the killing of β cells, which is the cause of the T1D. The identification and elimination of autoreactive CTLs specific for T1D-associated epitopes is one of the promising therapies to defeat T1DM (Harbige et al., J. Autoimm. 2017).

The ground-breaking discovery of the unexpected frequency of spliced self antigenic peptides opened a window to a large, and so far unforeseen, pool of epitopes and their potential importance in autoimmune CTL responses. The systematic identification of MHC-I-restricted spliced peptides is now feasible (Liepe et al., Science 2016). That methodology, which relies on a combination of cellular biology, mass spectrometry and bioinformatics approaches, will be applied to carry out the project. The PhD student will work in tight collaboration with the two co-supervisors and a selected group of international collaborators. Upon the identification of the T1D-associated spliced antigenic peptides, the PhD student will test patient-specific recognition by CTLs of the epitope candidates using peptide-HLA tetramer reagents and deep immunophenotyping by flow cytometry and will further characterise the cellular processing and presentation pathways involved by applying biochemical and molecular biology methods, which are well established in the groups of the two co-supervisors.

One representative publication from each co-supervisor:


30.1 Explaining the sexual dimorphism in Lupus through genetics

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Project Description:

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects millions of people worldwide. Strikingly 9/10 SLE cases are women, yet little is understood as to why. Hormonal and environmental factors are believed to be partly responsible, and while there is strong evidence for a genetic basis for this dimorphism there is still a gulf in our understanding. There are many avenues ripe for investigation and, with the advent of new technologies and a large amount of data available, a thorough study of the differences in genetics between the sexes is warranted. Current interests include the overlap between SLE associated genetic loci and genes showing sex differences in expression, genetic associations on the X chromosome and the cellular origins of effects.

This PhD will investigate all forms of genetic variation between the sexes that are informative of the sexual dimorphism of SLE. The student will learn and apply cutting edge statistical techniques on the richest data on SLE in the world. A background in statistics is not required but an interest in analyses will be important. The PhD will cover the use of statistical methodology including linear and logistic regression, multivariate analysis, Bayesian analysis, model choice and prediction. The student will learn the statistical language R to a high standard making them very competitive in the current research environment. The student will also learn and run modern genetic analyses software. The study will use the largest collection of SLE genetic data in the world together with gene expression data.

One representative publication from each co-supervisor:


31.1 Role of c-Fos in mucosal infections, immunity and microbiome interactions

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Project Description:

Mucosal infections are a global medical problem that devastate the lives of millions of individuals each year. Using model fungal and bacterial pathogens, we have identified c-Fos as a key transcription factor within epithelial cells that is activated during infection and a critical mediator of mucosal innate immune responses. We hypothesise that c-Fos is a master regulator of host innate responses against mucosal pathogens. With our collaborators, we have generated a mouse that is c-Fos deficient only in oral and vaginal tissues. We will utilise this conditional c-Fos knockout mouse to assess the role of this transcription factor in microbial homeostasis and during mucosal fungal and bacterial infections.

Given the potential role of c-Fos in mucosal immune homeostasis, in **Year One**, the oral, vaginal and gut microbiome (bacteriome and mycobiome) of the conditional c-Fos knockout mice will be determined to identify alterations in microbial composition. The gut microbiome will also be included in this analysis, as alterations in the oral microbiome may be reflected in the gut. In **Years 2 and 3**, the conditional c-Fos knockout mice will be infected with different fungal and bacterial pathogens to determine (i) their susceptibility to infection, and (ii) the role of c-Fos in mediating innate immune responses (e.g. cytokines/chemokines, antimicrobial peptides, neutrophil recruitment). This cutting-edge, multidisciplinary project will combine infection, immunity, imaging and cellular analyses to reveal the role of c-Fos during mucosal infection and immune protection, and may identify c-Fos as a new target for novel antimicrobial therapies against mucosal infections.

**One representative publication from each co-supervisor:**


32.1 Type 1 interferon resistance in the HIV-1 envelope glycoprotein

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Project Description:

A key attribute for the transmission of HIV-1 between individuals is the virus’s intrinsic resistance to the antiviral activities of type-1 interferons (IFN-I). Transmitted viruses have a higher resistance to IFN-I than those isolated from the recipient partner 6 months later. The effects of IFN-I on HIV-1 replication are mediated by interferon-induced genes (ISGs), several of which directly inhibit stages of the virus lifecycle. The Interferon-Induced Transmembrane Proteins (IFITMs) are broadly-acting ISGs that target the cell entry process that is mediated by its envelope glycoprotein (Env). We have found that transmitted HIV-1 strains are IFITM resistant but sensitivity increases over time as Env adapts to escape host antibody responses. Insensitivity to IFITMs contributes substantially to the IFN-I resistance of the transmitted virus. Preliminary data suggests that IFITM/IFN resistance of Env correlates with the structural rearrangements it must undergo when it binds to its receptor CD4. The more stable the Env, the more IFITM resistant. Thus the transmitted Env is structurally constrained by the need to be IFN-resistant. Since this is the structure that an effective vaccine needs to protect against, understanding the molecular basis of these constraints is essential. In this project the student will:

- use molecular and cellular virology, FRET-based assays and super-resolution microscopy to study how the clustering and dynamics of Env/receptor interactions contribute to IFN/IFITM resistance (Yrs 1-2).
- using patient samples from well characterized cohorts, clone and characterize Envs from patients longitudinally and determine how neutralizing antibody escape leads to loss of IFN resistance in Env (Yrs 2-3).

One representative publication from each co-supervisor:


33.1 Inhibition of *Salmonella* and *Shigella* intracellular replication by interferon-stimulated genes.

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**Project Description:**

Type I and III interferons (IFNs) are produced in response to non-self by the innate immune system and are better described as inhibitors of viral infections. We found that IFNs block the growth of *Salmonella* within host cells. IFNs function by inducing a large family of 300 proteins termed Interferon stimulated genes (ISGs), with a wide range of different functions. **This project seeks to determine which ISG(s) are responsible for IFN-mediated inhibition of bacterial growth, using *Salmonella Typhimurium* and *Shigella sonnei* as models.** These pathogenic bacteria cause disease using type III secretion systems (T3SS), molecular needles that enable the transport of virulence proteins into host cells. Both pathogens replicate intracellularly but *Salmonella* replicates within specialised phagosomes while *Shigella* escapes the phagosome and replicates in the cytosol. We expect different sets of ISGs will affect the intracellular replication of these bacteria.

We will first perform an expression screen using an ISG library. Individual ISGs will be expressed and their ability to block intracellular bacterial replication will be assessed. Bacterial replication in infected cells will be assessed via plating of live bacteria or flow cytometry. In parallel we will perform an siRNA screen of known ISGs. ISGs will be knocked down and infection assays will be carried out in the presence of IFNs. Positive hits will be cells that no longer control bacterial infection in the presence of IFN (Year 1 and 2). Identified ISGs will be further studied to determine which step of the bacterial intracellular lifecycle they affect (Year 3). Finally, the roles of ISGs in inhibition of bacterial virulence will then potentially be studied in well-established *in vivo* models (Year 3).

This project will investigate both aspects of host pathogen interactions, as well as bridge the fields of virology and bacteriology as IFNs and ISGs are normally considered as antiviral factors. Techniques involved will be:

- Molecular Biology
- Tissue culture
- Flow cytometry
- Microbiology
- Infection assays with different bacterial pathogens
- Biochemistry (western immunoblotting, immunoprecipitation)
- Microscopy
- *In vivo* infection models
One representative publication from each co-supervisor:


34.1 Understanding regulation of cellular energy metabolism

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**Project Description:**

Cellular energy metabolism occurs through oxidative phosphorylation in mitochondria and glycolysis in the cytoplasm. In humans, differentiated cells tend to rely on oxidative phosphorylation but dividing cells or abnormally proliferating cancers often adopt aerobic glycolysis that favours increased macromolecular synthesis, a phenomenon known as Warburg effect. How is energy production regulated? How do cells choose a particular energy generation route, and how do they switch between alternative strategies? How do these metabolic choices affect the rates of cellular growth? We want to answer these fundamental, yet surprisingly poorly understood questions by combining precise spatiotemporal imaging of cellular energy metabolic pathways with the awesome power of genetic engineering. We will visualize energy metabolites such as glucose, ATP, glutamate and others in real time using Förster Resonance Energy Transfer (FRET)-based sensors and probe how fluctuations in nutrient availability, cellular differentiation, chronological aging and genetic perturbations of metabolic regulation affect their intracellular flux. To speed up our research by straightforward genome editing, we will initially use two yeast species that exhibit divergent energy production pathways. We will eventually translate our research to human cells with a view of understanding how altered energy metabolism contributes to disease.

**Year 1. Development of genetically encoded FRET-based biosensors to report metabolic activity (SO and SAB).**

**Year 2. Understanding spatiotemporal regulation of metabolic sensors at a single-cell level in response to environmental and genetic perturbations (SO and SAB).**

**Years 3-4. Studying the mechanisms underlying regulation of energy metabolism and preparing experimental results for publication (SO and SAB).**

**One representative publication from each co-supervisor:**


35.1 Long range interactions of regulatory elements influencing gene expression in bronchial epithelial cells

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Project Description:

Asthma is a complex disease involving multiple cell types which affects over 5 million people and costs over £1 billion per year. In asthmatic subjects, gene expression in the primary barrier, bronchial epithelial cells, is perturbed through poorly understood mechanisms. A key abnormality, which may be amenable to therapeutic intervention, is altered signalling through long-range regulatory elements, such as enhancers. To fully understand the transcriptional defect, it is crucial to have comprehensive knowledge of regulatory elements that influence transcription. This task is not trivial; regulatory elements can be positioned at great distances (megabase range) from the genes they control.

We have developed a method called Capture Hi-C (CHI-C) to identify regulatory interactions of gene promoters on a genome-wide scale (Mifsud et al. 2015 Nature Genetics). We find that different cell types form distinct regulatory contacts. By applying this technique in leukaemia patient samples, we have identified disease specific interactions, which may be determinants of malignant phenotypes and could potentially reveal critical prognostic information.

In this project, we will apply these methodologies to asthma samples, to better understand the regulatory defects. The student will generate and bioinformatically analyse CHi-C libraries from asthmatic and control samples. These datasets will be integrated with existing NGS datasets (ChIPseq; RNAseq) to provide novel insights into disease pathogenesis, identifying biomarkers and therapeutic targets with translational potential.

In months 1-18, the student will generate and sequence CHi-C libraries. In years 2-3, he/she will validate targets and develop strong computational skills to carry out extensive bioinformatics analyses.

One representative publication from each co-supervisor:

Mifsud B et al. 2015. Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C. Nature Genetics. DOI: 10.1038/ng.3286.

36.1 Determining how a novel complex promotes tumour growth, by protecting an iron-sulphur cluster from cancer-associated oxidative stress.

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Project Description:

Solid tumours generate elevated levels of reactive oxygen species (ROS), that compromise their ability to grow. Iron-sulphur (Fe-S) clusters, essential cofactors for numerous proteins, are particularly ROS-labile. Strategies cancer cells evolve to limit damage to Fe-S clusters remain uncharacterised. We have identified a heterodimeric complex, composed of the proteins Lto1 and Yae1, that protect the Fe-S cluster located at the N terminus of ABCE1, an enzyme crucial for ribosome biogenesis and function. Not surprisingly, one of the members of this complex is overexpressed in many solid tumours. To exploit this complex as a drug target, we aim to understand how the complex protects Fe-S clusters.

Year 1:

ABCE1 will be cloned into an E.coli expression vector. Following purification, the Fe-S clusters will be re-constituted under anaerobic conditions in the presence of the IscU Fe-S cluster re-assembly enzyme using techniques established in Pastore’s lab. UV absorbance spectra will be used to assess holo-protein stability.

Year 2:

Yae1/Lto1 will be expressed in E.coli. Purification of the heterodimer will be followed by assembly of the ABCE1/Yae1/Lto1 complex, and determination of its structure via a combination of NMR and SAXS studies.

Year 3:

A series of mutants will be expressed in vivo which should compromise the function of the heterotrimer. This will be carried out by exploiting the tractable molecular genetics of the baker’s yeast model system, and will be used to assess the physiological relevance of the biophysical data generated during the project.

Training: Protein purification/biophysical techniques (Pastore). Gene cloning/molecular genetic analysis (Panaretou).

One representative publication from each co-supervisor:

Zhai C, Li Y, Mascarenhas C, Lin Q, Li K, Vyrides I, Grant CM, Panaretou B. (2014) The function of ORAOV1/LTO1, a gene that is overexpressed frequently in cancer: essential roles in the function and biogenesis of the ribosome. Oncogene 33: 484

37.1 Exploring novel molecular mechanisms driving skin fibrosis

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Project Description:

Keloids are abnormal fibro-proliferative scars that often occur after burns or other skin injuries and continue to extend beyond the original wound boundaries. They are refractory to treatment, have a tendency to recur even after surgical excision, and can continue to increase in size, leading to significant deleterious impacts on tissue function. Keloids may also occur spontaneously or through inherited traits and whilst a number of genes or loci have been implicated in susceptibility to developing keloids, the underlying molecular mechanisms remain unclear. Using whole exome data from multiple pedigrees with autosomal dominant transmission of keloid susceptibility, we have identified a novel mutation in the gene encoding for the secreted protein TSG6 (also known as TNFAIP6) that segregates with individuals prone to keloid scars. TSG6 is known to have anti-inflammatory properties and it has also been suggested to be involved in fibrosis. The goal of this project is to define the molecular mechanisms by which TSG6 regulates fibrosis with a view to understanding the potential for modulating TSG6 as a potential therapy for keloid scars. The aims of the project are:

- Use CRISPR/Cas9 to generate TSG6 knockout and mutant knockin fibroblasts and characterise the effects of WT and mutant TSG6 expression and secretion on fibroblast proliferation, differentiation and collagen production using 3D dermal-equivalent models. Validate in cells from patients (Years 1/2)
- Define the signalling changes in TSG6-deficient/mutant fibroblasts using total and phosphoproteomic analysis and follow-up with specific inhibitors to define roles in phenotypic changes (Years 2/3)
- Analyse the interplay between TSG6-deficient/mutant fibroblasts and keratinocytes using co-culture organotypic models (Years 3/4)
- Determine the capacity for exogenous TSG6 addition to reduce fibrosis in dermal models (Year 4)

Data arising from this study will shed light on the mechanisms driving dermal fibrosis and inform on potential novel therapeutics for future use in the clinic.

One representative publication from each co-supervisor:

38.1 Modulation of host immunity to prevent bacterial infection

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Project Description:

Antimicrobial resistance is a major global concern. To develop new strategies to tackle antimicrobial resistance, an understanding of the cascade of events leading to colonisation, persistence and ultimately the pathogenesis of an invading microorganism in response to the host environment is essential. The immune system present in host provides the key protection against invading microorganisms and can prevent events leading to infection. The overwhelming evidence indicates that ATP and ADP are important endogenous signalling molecules in immunity and inflammation. We hypothesise that activating purinergic receptors P2Y1 and P2Y14 would strengthen the host immune system against infection by a resistant pathogenic microorganism, and protect the host from the bacterial challenge, because we have reported that these receptors are responsible for inflammatory responses in murine models of lung inflammation. The PhD project would test this hypothesis by developing selective P2Y1 and P2Y14 agonists using a combination of advanced in silico and medicinal chemistry techniques. The developed agonists will be tested initially in vitro and subsequently in vivo in mice to assess their ability to modulate the immune system, involving, haematological, cell activation, chemotaxis, bacteria killing assays, The student will learn specialised in vivo skills, advanced microscopy, flow cytometry, and various haematological laboratory techniques. This will be followed by the bacterial challenge of agonists treated mice to evaluate the relationship between immune system mediated protections from bacterial infection.

Specific deliverables and work plan of the project includes -
Year 1 and 2: In silico design and synthesis of P2Y1 and P2Y14 receptor agonists

Year 3: Use the synthesised compounds as chemical tools to study immune modulation using biochemical and cellular assays.

Year 4: In vivo evaluation of P2Y1 and P2Y14 agonists for their ability to protect hosts from the bacterial challenge.

One representative publication from each co-supervisor:


39.1 The molecular basis of erythrocyte cation transport abnormalities in sickle cell disease

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Project Description:

Sickle cell disease (SCD) is the most common serious inherited disease in the world. It is characterised by haemoglobin polymerisation, which increases red cell rigidity leading to vaso-occlusion. Increased erythrocyte cation loss is central to red cell pathology, causing cellular dehydration. Three pathways are implicated in increased cation loss: K-Cl cotransport, the Gardos channel and Psickle. The exact molecular identity and control of these pathways is poorly understood. This project involves characterising the cation transport properties of established immortalized human erythroid progenitor cell lines, using patch clamping and ion flux measurements, performed in conjunction with Dr John Gibson (Cambridge University). Gene editing techniques, including CRISPR-Cas9, will be used to inactivate and modify genes known to be involved in cation transport in the erythroid cultures, and cation measurements repeated to identify any effects on red cell phenotype. This will potentially identify genes central to the pathology of erythrocyte dehydration in SCD and novel therapeutic targets. The candidate will develop skills in red cell physiology, erythroid culture techniques, cation transport, CRISPR-Cas9 and other gene editing technology, flow cytometry and clinical haematology.

Objectives:

Year 1: learn basic techniques of erythroid culture, cation transport measurements and gene editing.  
Review literature on genetics of erythroid cation transport. Measure cation transport on erythroid cultures.

Year 2: Edit selected cation transport genes and measure physiological changes in red cells.  
Year 3: Complete experiments and write-up thesis.

One representative publication from each co-supervisor:


40.1 Monocytes and monocyte-derived cells as therapeutic targets in kidney disease

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Project Description:

Introduction: Glomerulonephritis is a leading cause of kidney failure resulting in a need for dialysis and transplantation. Monocyte and monocyte-derived cells play an important role in kidney disease. They can affect both the inflammatory component of the disease and the resolution. Resolution may occur with scarring or fibrosis which results in an irreversible decline in function of the kidney. There is good evidence that monocyte-derived cells can contribute to kidney fibrosis.

Aims: The overall aim of this project is to understand how monocytes and monocyte-derived cells cause inflammation and fibrosis in glomerulonephritis and to develop therapies to improve outcomes.

Project plan: Year 1: The student will use pre-clinical models of immune-mediated kidney disease (glomerulonephritis) established in the laboratory of supervisor A. They will examine in detail the phenotype of cells present in the circulation and kidney during the development of disease. Year 2: Pro-fibrotic cells are mobilised from the bone marrow during vascular injury in a model established in the laboratory of supervisor B. These cells will be isolated and transferred in to mice with glomerulonephritis in order to examine their effect on disease. Year 3: We are developing therapeutic strategies that target monocytes and monocyte-derived cells. They will be tested in these models of glomerulonephritis.

Skills and training: The students will learn to conduct experiments in these pre-clinical models. They will be proficient in many techniques including flow cytometry, protein purification, histological methods.

One representative publication from each co-supervisor:


41.1 Nutritional genomics as an emerging tool for the prevention of cardiovascular disease

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Project Description:

Nutritional genomics is an emerging science which combines the study of nutrition and genetics to investigate how genes and nutrients interact, and how people respond to food differently based on their genetic makeup. As diet is one of the most important modifiable risk factors for cardiovascular disease (CVD), nutrigenomics represents a very promising approach for the prevention of CVD, potentially enabling better outcomes through optimisation of individuals’ diets. The aim of this project is to investigate this two-way relationship between food and genes: can the food we eat affect the way our genes are expressed, and can our genes influence how our bodies respond to food? More specifically, this work will focus on the nutrigenomic effects of certain natural compounds from fruits and vegetables called polyphenols, which are believed to be cardioprotective. Specific objectives:

1) To analyse gene expression profiles of individuals participating in nutritional intervention studies with CVD outcomes to elucidate genes and cell signalling pathways affected by polyphenol consumption, and whether intervention decreases CVD risk (Year 1)
2) To analyse genetic polymorphisms associated with CVD to understand whether they mediate differential gene expression in response to polyphenol intake (Year 2)
3) To merge other omics and clinical data obtained from the same studies to investigate how transcriptomics correlate with, for example, metabolomics and metagenomics (Year 3)

The student has opportunity to tailor above project according to their areas of interest, e.g., genomics, bioinformatics and big data management.

One representative publication from each co-supervisor:


42.1 Modeling diabetes using induced Pluripotent Stem Cells (iPSCs): investigating the regulation of Ngn3 in iPSCs to beta cell differentiation.

Co-supervisor 1: Rocio Sancho  
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**Project Description:**

**Diabetes** is caused by the irreversible loss of insulin-producing beta cells in the pancreas. Insulin injections is used in patients to control glucose levels however the risk of complications is high. In the last decade, **stem cell research** has shed new light on novel therapies for diabetes. Efficient protocols have been described to induce differentiation of skin-derived **induced pluripotent stem cell (iPSCs)** into insulin-producing beta like cells. However, the process is still inefficient and the beta cells generated as often not fully functional. One of the key embryonic transcription factors crucial to initiate a beta cell fate program in iPSCs is **Neurogenin3 (Ngn3)**. Ngn3 is a very unstable protein and its molecular regulation during iPSCs to Beta-like cell differentiation has never been explored.

The goal of the proposed PhD project is to understand how the pro-endocrine factor Ngn3 is regulated during iPSCs to beta cell differentiation, to enable us to optimise the regulating pathways to improve the efficiency of beta cell generation and achieve fully functional beta cells.

- During the rotation project the PhD student will set up pilot screens for novel regulators and interactors of Ngn3 in human iPSCs. 0+4 students will also familiarise with all the techniques required for screen validation by characterising a protein already identified as a regulator of Ngn3.

- The goal of year 1/2 is to perform Crispr/Cas9 screening for Ngn3-regulators using flow cytometry, and identify Ngn3 interacting proteins using immunoprecipitation and mass spectrometry using human iPSCs (from HiPSCi).

- In year 2/3 biochemical and functional validation of the top 3 screen hits will be performed.

- In the final year functional (insulin release, calcium measuring, in vivo mouse kidney transplantation, ex vivo engraftment on decellularised pancreas, alginate encapsulation-transplantation) will be performed in collaboration with Dr. Aileen King and Professor Peter Jones to assess the physiological function of the newly generated beta cells.

During this project, the PhD student will acquire exceptional technical skills in the **CSCRM** (Bioinformatics, iPSCs culturing and differentiation, fluorescence microscopy, flow cytometry, molecular Biology, gene editing – Crispr/Cas9 and In vivo models of diabetes). In addition, the student will be immersed in all the activities organized by the **CSCRM** at KCL, and will benefit from the iPSCs expertise in **CSCRM**.
One representative publication from each co-supervisor:


43.1 Role of fat tissue gene expression in Type 2 Diabetes and Obesity

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Project Description:

Type 2 Diabetes and obesity-related traits are global epidemics. In the UK alone, ~4 million people are living with diabetes and 10% of the NHS budget is spent on diabetes. Understanding the molecular mechanisms underlying genetic risk of diabetes will help direct novel treatments and prevention. We have previously shown that gene expression in adipose (fat) tissue mediates a subset of Type 2 Diabetes associated GWAS loci, including a master trans-regulator at the KLF14 locus which regulates 400 genes. This project will seek to identify novel regulatory variants that influence gene expression and use them to interpret disease associations, with a particular focus on Type 2 Diabetes and obesity-related traits. In particular this project will focus on two under-explored classes of regulatory variants, rare variants and trans-eQTLs. The student will utilize a unique multi-tissue RNAseq data set from deeply-phenotyped twins from the TwinsUK cohort, and integrate this newly generated matched whole genome sequence data. The student will be taught how to analyze high-throughput sequencing data to answer important biological questions. More broadly the student will undergo training in genomic analysis, bioinformatics (including programming) and scientific writing.

Objectives:

Year 1: Identify regulatory variants (eQTLs, rare variants and splicing) utilizing RNAseq data from multiple tissues and matched whole genome sequence.

Year 2: Identify trans-eQTLs in adipose tissue in a large multi-centre dataset.

Year 3: Integrate identified regulatory variants with Type 2 Diabetes and obesity-related traits to elucidate underlying regulatory mechanisms mediating disease risk and response.

One representative publication from each co-supervisor:


44.1 Structural and functional determinants of kinesin-1-dependent cellular transport in neurodegeneration and aging

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Project Description:

Misregulation or disruption of these cellular transport processes can contribute to many human diseases ranging from neurodegenerative conditions such as Alzheimer's disease to cancer and even contribute to viral infections by HIV-1 or bacterial infections. Molecular motor proteins are used for the cellular transport of cargoes. Kinesin-1 is a tetrameric motor that moves its cargos unidirectionally along microtubules in an ATP-dependent manner. How specific molecules are recognised as cargos is a very important question and we have recently made a critical step towards the structural elucidation of the mechanism for cargo recognition by kinesin-1 (1). We are now looking for a highly motivated graduate with an interest in structural biology to study other exciting aspects of this critically important transport system. In particular, we will focus on the protein complex between kinesin-1, JIP1, and JIP3 for which we have exciting preliminary data. The student will gain experience in molecular biology as well as in the overexpression and purification techniques for macromolecular complexes. The student will also develop a strong foundation in advanced structural biology techniques (for example X-ray crystallography, cryo-EM, SAXS), complementary biophysical methods (ITC, fluorescence polarization), and cellular/functional assays. The project will develop in Year 1 with the molecular biology/biochemistry component while carrying out already some structural biology/biophysical experiments. In the following years emphasis will be given to the structural biology/functional components of the work. Functional studies will be carried out taking advantage of a novel in vivo assay (2) to study the biology of ageing *Drosophila* neurons.

One representative publication from each co-supervisor:


Investigating human regulatory T cell subsets in autoimmunity and transplantation

Co-Supervisor 1A: Dr Timothy Tree

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Co-Supervisor 1B: To be confirmed

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Collaborating Clinician: Dr Pratik Chowdry
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Project Description

Regulatory T cells (Tregs) form a key part of immune regulation. A reduction in Treg frequency or function has been implicated in the pathogenesis of a variety of autoimmune diseases and transplant rejection. Such observations have fuelled interest in developing therapies that invigorate Tregs for use in these conditions, some of which are being tested at KCL. However, work from our and other laboratories has revealed that Tregs are not a simple single homogenous group of cells but are in fact a heterogeneous mixture of cellular sub-phenotypes with distinct developmental states, capacities and targets of suppression. This project will use cutting edge technologies to investigate the functional properties of different Treg subsets, defining their cellular and molecular characteristics. Work will particularly focus on identifying Treg subsets capable of suppressing key immune effectors known to play a key role in tissue destruction in type 1 diabetes (T1D) and transplant rejection. We will then measure the frequency and stability of relevant Treg subsets in clinical samples from patients with T1D, those undergoing organ transplantation and relevant controls.

This project will include comprehensive training in modern cellular and molecular immunology and lead to the acquisition of a wide range of skills including cell culture, FACS and cell sorting, recombinant DNA technology and the performance of a wide range of analysis of immune cell function.

Yearly objectives:
**Y1** Isolation and basic functional assessment of Treg subsets

**Y2** Detailed cellular and molecular characterization of key Treg subsets

**Y3** Investigate Treg sub-populations in patient cohorts

**One representative publication from each co-supervisor:**


46.1 Dissecting the heterogeneity of tumour-infiltrating phagocytes: implications for tissue remodelling and immunotherapy.

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Project Description:

BACKGROUND:

Tumour-infiltrating phagocytes (TIPs) are important components of the tumour microenvironment. TIPs release a variety of immuno-suppressive factors, thus dampening the adaptive immune response of Th1 and CD8+ cytotoxic lymphocytes to tumours.

Most TIPs derive from infiltrating monocytes and accumulate either inside or at the invasive margin of tumours, and participate in tissue remodelling by multiple mechanisms.

Tumours secrete factors actively instructing monocyte recruitment and differentiation into TIPs. For example, oncogenic variants of Kras driving lung cancer induce GMCSF secretion that promotes recruitment and differentiation. However, how tumour-derived factors shape TIP phenotype and pro-tumorigenic function remains ill-defined.

AIMS:

Overall, this project intends to characterize TIP diversity and function in relation with tumour-derived instructive factors. This investigation will be performed in the context of lung adenocarcinoma. Using a combination of mouse models of inducible oncogenes as well as transplanted human tumour lines in immune-deficient mice, we aim to:

1- define and characterize the heterogeneity of TIPs in relationship with tumour-derived hematopoietic growth factors using unbiased high dimensional flow cytometry and single cell transcriptome analysis.

2- decipher the molecular mechanisms by which diverse TIPs influence tissue remodelling and neoplastic growth.

3- design and evaluate TIP reprogramming immunotherapeutic interventions for efficient re-purposing of TIPs into anti-tumoural effectors (e.g. by blocking tumour-derived factors influencing TIP recruitment or activation).

The student will be trained in the area of cancer immunology, will use in vitro and in vivo models, and will learn the techniques associated with transcriptional profiling and bioinformatics, flow cytometry, and histology and microscopy.

One representative publication from each co-supervisor:

47.1 Therapeutic target discovery in severe inflammatory skin disease

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Project Description:

Human genetics is a valuable tool to prioritise molecular targets for therapeutic drug development. This project aims to utilise large-scale genomics data across many thousands of individuals (already collected) to both characterise the genetic contributants to inflammatory skin diseases and identify molecular targets for therapeutic intervention.

Our group has been at the forefront of research seeking to identify genomic loci contributing to the genetic basis of psoriasis and acne, including recent large-scale genome-wide investigations. We are currently in the process generating genomewide genotyping data on in excess of 6,500 individuals with severe acne and 10,000 individuals with psoriasis. The proposed project will utilize these data to identify further risk loci and fine mapping of these signals. The project will employ cutting edge analytical approaches aimed at integrating these data with large publicly available genomic data and transcriptomic experiments relating to skin biology. The approach will identify putative therapeutic targets whose activity is disrupted by genetic variation that predisposes these common inflammatory disorders, highlighting critical points in the disease-causing pathway can be evaluated for therapeutic manipulation.

The supervisors will provide a world-class training in contemporary genome science, statistics, bioinformatics and provide the opportunity for interaction with research groups in academia and industry. The work will be undertaken in a multidisciplinary environment supported by core facilities and underpinned by a longstanding collaboration between geneticists and dermatologists.

One representative publication from each co-supervisor:


Improving skeletal muscle function in the muscle wasting disease FSHD

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Project Description:
Facioscapulohumeral muscular dystrophy (FSHD) is characterised by muscle weakness, where muscle wastes and connective tissue becomes deregulated, so scar tissue forms. FSHD is caused by ectopic expression of a transcription factor called DUX4. FSHD muscle cells are sensitive to oxidative stress, and treatment of FSHD patients with anti-oxidants vitamin E, vitamin C, zinc, and selenomethionine improves some muscle function measurements (clinicaltrials.gov:NCT01596803) (doi:10.1016/j.freeradbiomed.2014.09.014). Analysis of our FSHD gene expression (RNA-Seq) data has also implicated mediators of oxidative stress and mitochondrial generation, indicating activation of mitochondrial biogenesis as a therapeutic strategy. We have good preliminary data that several nutritional supplements target this pathway, improving muscle formation.

Hypothesis
Improving protection against oxidative stress and enhancing mitochondrial biogenesis will improve muscle function in FSHD.

Objectives
Year 1: Screen nutritional supplements that can affect mitochondrial biosynthesis/protect against oxidative stress on FSHD myoblasts/fibroblasts. Characterise connective tissue perturbation by analysing gene expression data from FSHD muscle biopsies.
Year 2: Test selected nutritional supplements on a range of FSHD patient cells lines.
Year 3: Measure effects of nutritional supplements on muscle and connective tissue expressing DUX4 both in vitro and in animal models.
Year 4: Investigate interaction of nutritional supplements with known/novel signalling pathways to identify mechanism.

Skills training
Molecular Biology (e.g. cloning), Cell Biology (mouse/human cell culture, retroviral-transduction, siRNA-mediated gene-knockdown), Animal Models, Gene Expression/Protein Analysis (RT-qPCR, Western blotting, immunolabeling), Imaging/Time-Lapse using state-of-the-art confocal/multiphoton microscopy and Bioinformatics.

Expertise
Zammit: muscle stem cell function in health and disease.
Logan: muscle associated connective tissue and its disease associations.

One representative publication from each co-supervisor:
Tbx4 and Tbx5 acting in connective tissue are required for limb muscle and tendon patterning. Hasson, P; DeLaurier, A; Bennett, M; Grigorieva, E; Naiche, LA; Papaioannou, VE; Mohun, TJ and Logan, MPO (2010) Developmental Cell 18, 148-156
49.1 Tackling hearing loss: development, regeneration and reconstruction of the ear

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Co-supervisor 2: Mr Dan Jiang
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Project Description:

Birth defects associated with the middle and external ear lead to conductive hearing loss where sound fails to pass to the inner ear. Our knowledge of how these birth defects arise is limited, hampering our ability to correct defects. We aim to study the development of the ear taking advantage of mouse mutants with aberrant ear development and data from patients attending the Ear Clinic at St Thomas’ Hospital. The project is a collaboration between an expert in ear development in mice (Prof Tucker) and a clinician specialising in ear surgery (Prof Jiang). Overall we aim to understand how the ear forms and integrates so that ear defects can be more successfully repaired and the ear reconstructed during surgery.

Aim 1 (year 1): To investigate the normal process of external ear formation during mouse embryonic development.

Aim 2 (year 1 & 2): To understand the mechanisms behind ear defects using mouse models of human syndromes associated with external ear defects. These will include 22q11.2 deletion syndrome (Tbx1 mice), Branchio-oto-renal syndrome (Eya1 mice), LADD syndrome (Fgf10 mice), and holoprosencephaly (Gas1 mice).

Aim 3 (year 2 & 3): To analyse CT scans from patients with ear defects to correlate the findings from the mouse with humans, and to assess the success of reconstructive surgery.

Skills training: The student will be trained in a range of molecular biology techniques, anatomy and regenerative biology, while having access to clinical data. In addition critical thinking, presentation and writing skills will be taught.

One representative publication from each co-supervisor:
