Start your research career at the Walter and Eliza Hall Institute

PROJECTS 2016
Honours and PhD
Our mission
Mastery of disease through discovery

Our vision
To be an innovative medical research institute that engages and enriches society and improves health outcomes through discovery, translation and education.

Research themes
Cancer
Immune disorders
Infectious disease

Our goals
To make discoveries that shape contemporary scientific thinking, increase understanding and improve prevention, diagnosis and treatment of cancers, immune disorders and infectious diseases.

To educate and train world class scientists and to attract, develop and retain the best and brightest workforce.

To provide a vibrant and inspiring organisational culture that encourages, promotes and rewards excellence, collaboration, innovation, creativity and respect.

To engage with our stakeholders to improve outcomes, build support and secure resources for medical research.

To build infrastructure, professional services and funding that sustains our research and maximises the time our scientists can spend making discoveries.
Study with the Walter and Eliza Hall Institute

We offer undergraduate (UROP, Honours) and graduate education (PhDs) as the Department of Medical Biology in the Faculty of Medicine, Dentistry and Health Sciences of The University of Melbourne.

Research projects: 2016 intake
We offer a number of student research project places (Honours and PhD) each year under the institute’s research themes of cancer, immune disorders and infectious diseases.

PhD program
We offer postgraduate training as the Department of Medical Biology of The University of Melbourne. At any one time, around 100 full-time PhD students are enrolled.

Honours program
Honours is a fourth-year program which gives you the opportunity to draw together your previous science, biomedical or health science studies and focus your knowledge, skills and intellect on an exciting piece of original research.

WESA – The Walter and Eliza Hall Student Association
WESA represents the student body on academic issues and, more importantly, makes student life a lot more interesting. Activities include invited speakers, weekly sport, movie nights, pub nights and the famous Annual Student Retreat.

Living in Melbourne
Melbourne is widely regarded as the biotech, cultural, sporting and culinary capital of Australia and offers a vibrant and cosmopolitan lifestyle.
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**INFECTIONIOUS DISEASES**

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Tracking IL-27 in T cell development in pathogen infection  
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**Application checklists**
Cellular and molecular regulators of B cell lymphoma development

Details of project
B cell lymphoma is a frequent cancer of the immune system. Despite improved treatment, a large proportion of patients still succumb to their disease. A detailed understanding of lymphoma pathogenesis is therefore needed to identify new therapeutic approaches. We have recently demonstrated the central importance of immune surveillance by CD8 T cells in the prevention of B cell lymphoma (Afshar-Sterle et al, Nature Medicine 2014 20(3): 283-90). We are now aiming to uncover how CD8 T cells recognise and eradicate malignant cells. We are also identifying molecular pathways that are deregulated in B cell lymphoma and may drive cancer progression. This project involves in vivo and in vitro experiments that employ flow cytometry, transcriptional profiling, western blotting, qPCR, immunohistochemistry and metabolic analysis.

Novel regulators of apoptotic cell death

Details of project
Apoptotic cell death is a fundamental process required for proper development and tissue homeostasis. Unregulated apoptosis causes or promotes diverse pathologies including cancer and degenerative disorders.

Using a novel proteomics approach we have identified several new potential regulators of apoptosis. The project will investigate these proteins and decipher their roles in apoptosis using a variety of cell and molecular biology techniques including proteomics, tissue culture, protein chemistry and microscopy.
Investigating mechanisms of cell death and survival using zebrafish

Details of project
Many genes that control embryonic development are aberrantly expressed or disrupted in cancer.

Our laboratory aims to identify genes that could provide novel targets for cancer therapy. To do this we employ the rapidly developing zebrafish intestinal epithelium as a surrogate tissue for bowel cancer growth. Using an ENU mutagenesis screen, we identified several mutants with defects in intestinal cell growth and proliferation. In three of these (flotte lotte, trinculo and perdita), the cells of the intestinal epithelium undergo programmed cell death. To understand the mechanisms driving this behaviour, the genetic pathways and cellular processes that are disrupted in mutant embryos were identified using RNA-seq.

This project will explore why these pathways are so critical for intestinal epithelial (and potentially cancer) cell survival.

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Preparation and study of combi-drugs of IAP antagonists in cancer

Details of project
Drug combinations are increasingly being used in cancer chemotherapy to maximise the efficacy of the treatment. Recent research in the Silke laboratory has identified a hitherto unknown synergy between IAP antagonists and specific kinase inhibitors. IAP antagonists are drugs that target the cell death machinery and are in late stage clinical trial for treatment of various cancers. In this project we will develop novel bifunctional molecules where known IAP antagonists are chemically linked to kinase inhibitors. Study of the activity of these agents in various cell systems will also be undertaken. We predict such combi-drugs should have greater efficacy against cancer cells compared to a mixture of the two agents. Students with an interest in drug design and synthesis, chemical biology, cancer biology and drug testing are encouraged to apply.

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Preparation of novel BET bromodomain inhibitors for treatment of leukaemia

Details of project
Bromodomain-containing proteins play key roles in transcription control and are known as epigenetic ‘readers’. A specific sub-family, the BET bromodomains, are involved in inflammatory diseases and cancer by controlling the transcription of key disease-related genes. Small molecule inhibitors of BET bromodomains therefore have great potential for the treatment of various diseases and in particular cancer. We have recently identified and patented a family of BET bromodomain inhibitors that show promising activity in preliminary studies. The aim of this project is to prepare further analogues of this series of compounds and to profile the compounds for their activity in cancer models. This project would suit a student with an interest in organic/medicinal chemistry, drug design, cancer biology and/or drug profiling.

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The effects of post-translational modification on cytokine receptor function

Details of project
Cytokine receptors are transmembrane proteins at the cell surface that are responsible for sensing small messenger proteins in the extracellular milieu and transmitting a signal across the plasma membrane to initiate important cellular responses. This general process drives the pathologies of innumerable diseases. The extracellular domain of many cytokine receptors bears an unusual post-translational modification that appears to play a role in receptor folding, trafficking and function. This project provides an opportunity to join a research program investigating this phenomenon, which will deepen our understanding of cytokine receptor function and has the potential to inspire new approaches to treating diseases as diverse as cancer, inflammatory disorders and infectious diseases. Opportunities exist for honours and PhD students interested in protein science, enzymology, proteomics and/or synthetic chemistry.

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Smac-mimetics combined therapy for the treatment of tumors

Details of project
Smac-mimetics were developed to inhibit members of the Inhibitors APOptosis protein (IAP) family, priming cancer cells to undergo apoptosis. Our lab has led research into understanding how Smac-mimetics kill cancer cells (Condon J Med Chem 2014 57:3666; Vince Cell 2007 131:682). We will test whether the clinical Smac-mimetic birinapant can be combined with other clinical drugs to effectively treat cancer. In a preliminary screen of approximately 5000 clinical drugs, we have identified compounds that can synergise with birinapant to kill tumor cells. This project aims to identify the mechanisms of action of these combination therapies with the goal of fast tracking them to the clinic. This project will involve cell biology and molecular biology techniques, followed by studies using primary tumor models and in vivo imaging techniques.

Charcterising the structure and function of the Bcl-2 family protein Bcl-RAMBO

Details of project
Apoptosis and mitophagy (mitochondrial quality control) are fundamental processes required for proper development and tissue homeostasis. Defects in these processes cause or promote diverse pathologies including cancer and degenerative disorders. Bcl-RAMBO is a Bcl-2 protein with proposed roles in both processes (Murakawa Nature Comms 6 epub; Kataoka JBC 276(22):19548-54) that is upregulated in certain cancers. This project aims to characterise the structure and function of this mitochondrial protein. This insight may identify new ways to target apoptosis and mitochondrial quality control therapeutically. The project will utilise in vitro and in vivo models, and a variety of cell and molecular biology techniques including mutagenesis, tissue culture, protein chemistry and crystallography.
**CANCER**

**Investigating the control of apoptotic cell death**

**Details of project**
Apoptotic cell death is a fundamental process required for proper development and tissue homeostasis. Unregulated apoptosis causes or promotes diverse pathologies including cancer and degenerative disorders.

Our research aims to characterise the function of a mitochondrial protein as a new and essential component of the apoptotic machinery. The project will utilise *in vitro* and *in vivo* models, and a variety of cell and molecular biology techniques including mutagenesis, tissue culture and protein chemistry.

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**Emerging role of transmembrane pseudokinases in cancer**

**Details of project**
A subset of receptor tyrosine kinases (RTK) with intracellular pseudokinase domains, called RTK-like, have recently emerged as critical regulators of the Wnt signalling pathway, which controls planar cell polarity and cell-cell adhesion and enables the initiation of cancer metastasis. Despite lacking catalytic activities, pseudokinases are thought to either modulate the catalytic activities of *bona fide* RTKs, or to serve as scaffolding proteins that promote the assembly of signalling complexes. RTK-like may therefore represent a novel class of untapped drug targets, however we do not yet understand precisely how RTK-like orchestrate RTK activity. This project will use a highly integrated approach including targeted genome editing technologies, chemical biology and structural biology to fully elucidate the biological function of specific RTK-like during development and cancer.

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The role of the protein kinase DCLK1 in colorectal and pancreatic cancers

Details of project
Doublecortin-like kinase 1 (DCLK1) has recently emerged as a tumor specific stem cell marker in colorectal and pancreatic cancers. Small interfering RNA (siRNA) has genetically validated DCLK1 as a therapeutic target, but the direct effect of inhibiting DCLK1 using small molecules is yet to be investigated. This project will use an integrated approach including cellular biology, chemical biology, kinase biochemistry and structural biology to develop small molecules that specifically target DCLK1. These compounds will be further examined in cellular assays to advance our understanding of the biological function of DCLK1, including its role in microtubule assembly. Specific ablation of DCLK1 expressing cells or pharmaceutical inhibition of DCLK1 in preclinical models of gastrointestinal cancer will be used to address its role in tumorigenesis. Students with an interest in biochemistry, chemical biology, drug synthesis, structural biology and cancer biology are encouraged to apply.

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Understanding the ATPase domain of the epigenetic regulator, Smchd1

Details of project
Mutations in the epigenetic regulator SMCHD1 are known to underlie the pathogenesis of a form of human muscular dystrophy called FSHD. Precisely how many of these mutations compromise SMCHD1 function remains unclear.

This project will use a range of cell-based and biochemical approaches to delve into the mechanism by which these mutations can perturb SMCHD1 function. This knowledge will be essential to devising new strategies to therapeutically combat FSHD.

Techniques used in this project: cell biology, molecular cloning including mutagenesis, recombinant protein production in bacteria and insect cell hosts, use of recombinant proteins in biochemical and structural studies, primary neural stem cell tissue culture, production of recombinant virus and quantitative gene expression analysis.

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CANCER

Investigating the biology of lung cancer

Details of project
Lung cancer is the leading cause of cancer deaths worldwide. We study squamous cell carcinoma, a subtype of lung cancer for which treatment options have advanced little in recent years. A major goal of our research program is to obtain a better understanding of the genetic changes that underlie squamous cell carcinoma, with the aim of identifying new therapeutic strategies.

Recent large-scale sequencing studies have revealed new genes and pathways that are altered in human lung squamous cell carcinomas. This project will examine the role of one of these signal transduction pathways in lung cancer development.

Our laboratory uses a wide variety of experimental techniques, including pre-clinical models of lung cancer, tissue and tumour pathology, next-generation sequencing, molecular biology, cell culture, microscopy and flow cytometry.

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Structural and biochemical studies on Notch signal transduction

Details of project
The Notch signalling pathway is essential for development and homeostasis of all multicellular animals, and is frequently mutated in cancer. Notch signal transduction begins with binding of ligand to the extracellular domain of the Notch receptor. This initiates a series of proteolytic events that result in the translocation of the intracellular domain of the receptor to the nucleus and transcription of Notch target genes. This project will combine structural and cell biology approaches to understand the molecular details of Notch signal transduction. Depending on the applicant’s interests, a range of techniques will be used, including recombinant protein production, X-ray crystallography, protein:protein interaction techniques, fluorescence microscopy and cell biology.

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Structure based drug discovery targeting pro-apoptotic Bax

Details of project
Apoptosis is a process by which the body protects against rogue cells, such as cells potentially cancerous or infected by viruses. Dysregulation of apoptosis occurs in cancer and can also lead to degenerative diseases (Czabotar, Nature Reviews Mol Cell Biol 2014 15(1):49). We are interested in developing small molecule agents that can target the pro-apoptotic protein Bax. The project will involve solving structures of Bax bound to small drug like molecules using protein crystallography (Czabotar, Cell 2013 152:519). Medicinal chemistry will then be used to develop these compounds into high affinity binders. The project would be suited to students interested in protein crystallography, biophysical and biochemical binding studies and/or medicinal chemistry.

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Deciphering the membrane topology of Bak and Bax apoptotic pores

Details of project
This project addresses how cells die via the mitochondrial pathway of apoptosis. Understanding this process is critical to developing new treatments that either enhance or block apoptosis in diseased cells. Two members of the Bcl-2 protein family, Bak and Bax, are essential for the cell death and act by forming pores in mitochondria. Defining how Bak and Bax change conformation and then self-associate will reveal how they trigger apoptosis (Westphal, Cell Death Differ 2014 21(2):196).

We are using a range of biochemical approaches including exposure of antibody epitopes and cross-linking of cysteine residues placed at specific positions in the Bak protein to map how the activated forms of the proteins perforate the membrane (Alsop, Nat Comm 2015 6:6841).

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Role of Mcl-1 sequestration of Bak in resistance to anti-cancer treatment

Details of project
Inhibition of apoptosis by prosurvival Bcl-2 proteins contributes to oncogenesis and to resistance to cancer treatments. In particular, overexpression of Mcl-1 causes resistance to a range of anti-cancer therapies. Mcl-1 acts by sequestering the BH3-only proteins (Mode 1), but may also sequester activated Bak and Bax (Mode 2), depending on cell context (Westphal, Cell Death Differ 2014 21(2):196).

We aim to understand the protein interactions involved in Mode 2, by performing mitochondrial assays. The project will involve a range of biochemical approaches including cell culture, molecular cloning, flow cytometry, and a range of other protein chemistry techniques (Alsop, Nat Comm 2015 6:6841).

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Probing the control of lineage fate and function in the blood forming system

Details of project
Students will have the opportunity to undergo training in the application of advanced imaging (3D and 4D quantitative imaging), gene expression analysis (population and single-cell levels), and genetic manipulation technologies (CRISPR/Cas9 genome editing) with the goal of understanding how lineage fate and function is instructed during early life. A variety of projects are on offer for promising Honours and PhD candidates. All are within the disciplines of developmental and cellular biology with a broad focus on the blood forming system. Potential projects include:

• deciphering the lineage specific cues that instruct the first blood fate decisions in the early embryo;
• understanding the molecular control of blood stem cell formation; and
• understanding the environmental and molecular mechanisms of pre-natal platelet production.

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Defining the function of the interleukin-11 signalling complex

Details of project
Interleukins are cytokines that interact with receptors on target cells to trigger the activation of numerous pathways that regulate tissue homeostasis. Deregulated cytokine signalling occurs in a number of pathologies, including cancer. IL-11 is a cytokine that, by binding to its specific receptor IL-11R, triggers intracellular signalling that activates the transcription factor STAT3. STAT3 has been implicated in the maintenance of a tumour-promoting, inflammatory microenvironment, and persistent STAT3 activation is a feature of many human cancers of both haematopoietic and epithelial origin. We were the first to solve the structure of the IL-11 ligand, however, our understanding of the details of the IL-11 signalling machinery remains rudimentary. We recently identified mutations in components of the human IL-11 signalling complex and aim to characterise how these impact on the structure and function of this signalling pathway in different diseases. This will establish novel platforms for interventions that are likely to be translated to new treatments.

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New therapeutics for metastatic colorectal and pancreatic cancers

Details of project
Cancers arise when abnormal cells grow out from otherwise normal tissue. The resulting tumours contain many different types of cells, some that help the tumour to grow, and some that fight the tumour. A common feature of all tumours is the bi-directional interactions between tumour cells and the stroma. Tumour cells can stimulate the inflamed stroma, which in turn can enhance the malignant traits of tumour cells. This self-amplifying feedback loop is fuelled by cytokines. For this reason, the concept of combating tumour progression, through inhibition of growth promoting cytokines present in the tumour microenvironment is becoming of great therapeutic interest. This project will examine the source and function of a cytokine called interleukin-11 during tumour metastasis and secondary tumour growth. The project will involve collaborations with clinicians at The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, scientists at the Garvan Institute (Sydney) and industry partners at CSL Ltd.

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Elucidating the role of apoptotic caspases in programmed cell death

Details of project
Caspases are critical mediators of programmed cell death. We recently demonstrated that they are not only involved in killing cells, but in preventing dying cells from signalling to the immune system (White, Cell 2014 159(7):1549). This has raised fundamental questions about how caspases facilitate embryonic development, and how they function in disease settings such as viral infection and cancer. This project will utilise genetics and cell biology to unravel these processes and establish whether drugs that inhibit caspases might have clinical potential.

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Unravelling the genetics and development of erythroleukaemia

Details of project
Erythroleukaemia (EL) is an aggressive subtype of acute myeloid leukaemia (AML). In contrast to other types of AML, very little is currently known of the underlying molecular events responsible for the development and pathogenesis of this disease.

We have recently generated a unique genetic model of EL, enabling us to directly study the mechanisms underpinning malignant transformation of the red blood cell lineage (Carmichael, Proc Natl Acad Sci USA 2012 109(38):15437). This project will utilise a variety of techniques in genetics, molecular biology and cell biology to elucidate the key gene networks and biological processes that drive EL development. The knowledge gained will pave the way for the development of more targeted therapeutic interventions for this disease.

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Exploiting DNA repair defects to treat ovarian cancer

Details of project
Our lab is working to develop strategies to offer a woman with ovarian cancer treatment matched to her type of ovarian cancer. To do this we need to build and study new pre-clinical models that accurately reflect specific features of the many different types of high-grade epithelial ovarian cancer. Loss of DNA repair capability, which is a hallmark of cancer, is an important potential therapeutic target in up to half of ovarian cancers. This project will use novel pre-clinical models to circumvent the mechanisms by which cancers with defective DNA repair evolve to evade treatments targeting defective DNA repair. The student will become proficient in developing and analysing new pre-clinical models, using cell biological, in vivo, molecular and bioinformatics approaches.

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Platelet function in cancer

Details of project
Clinical studies have shown that patients who receive long-term treatment with platelet inhibitors like aspirin have a reduced risk of metastasising tumours (Rothwell Lancet 2011 377(9759):31). In recent studies, platelet counts above normal have been associated with advanced disease and shortened survival, but definitive mechanistic insights are lacking. This project will investigate the molecular regulation of platelet function in cancer progression.

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Role of necroptosis in intestinal inflammation and colon cancer

Details of project
In the search for better treatments for colon cancer, recent attention has focussed on how inflammatory cytokines promote tumour growth. These inflammatory cytokines are released by dying cells, including cancer cells killed by chemotherapy. Necroptosis is a form of programmed cell death implicated in cytokine release. We suspect the necroptosis regulator MLKL (Murphy, Immunity 2013 39(3):443) may contribute to the inflammation that promotes initiation and growth of colon cancer. This project will explore the involvement of MLKL in the development and progression of colon cancer using in vivo models of intestinal inflammation and colon cancer, tissue culture, flow cytometry, ELISA, immunohistochemistry and cell signalling pathway analysis. This will reveal how necroptosis impacts responses to cancer therapy, and whether MLKL or other necroptosis regulators could be new targets for colon cancer therapy.

Biological sequence analysis and genomic variant discovery

Details of project
Next-generation sequencing (NGS) technologies are increasingly used in laboratories and clinics worldwide to facilitate better understanding and diagnosis of diseases. The massive volume of data from these technologies continues to pose significant challenges for bioinformaticians. We are interested in developing novel methods for mapping both long and short NGS reads (and other biological sequences) to a reference genome to find the true origin of biological sequences (Liao et al., Nucleic Acids Research, 2013,41(10):e108). We would also like to develop more accurate methods for detecting genomic variants (e.g. insertions, deletions, translocations etc.) in cancer genomes using NGS data. Prospective PhD students are expected to have a computer science background and/or have strong programming skills. One or two projects are available.
Statistical bioinformatic analyses of RNA-seq and ChIP-seq data

Details of project
A number of projects are available for students to develop new computational and statistical methods for analysing genomic data, especially data from RNA-seq, ChIP-seq and related technologies.

Projects might include the analysis of single cell RNA-seq, or detection of splice variants, or the analysis of higher order expression signatures representing biological pathways or cell fates, or integrative analyses combining information from a number of different technologies. Projects may also include the analysis of data from emerging technologies. Projects will involve collaborations with biomedical researchers in other laboratories working on breast cancer and other diseases.

These projects would suit students with training in mathematics, statistics, computer science, genetics or related fields.

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IMMUNE DISORDERS

Cross-talk between cell death and inflammatory signalling pathways

Details of project
Inhibitor of APoptosis (IAP) proteins repress cell death, including caspase dependent apoptosis and a necrotic death pathway termed necroptosis. As such, IAP antagonists have been developed to induce cancer cell death. We recently revealed how IAP loss and activation of the cell death machinery can also trigger inflammasome-mediated pro-inflammatory cytokine activation. Consistent with this, IAP mutations in people can result in severe systemic inflammatory disease. However, the physiological regulation of IAPs in mammals remains ill defined. This project will use genetic and biochemical approaches to identify the specific stimuli and signalling proteins that control IAP activity, and examine how deletion of these impact cell death and inflammasome driven innate-immunity. This analysis will provide important insights into how the regulation of IAPs impacts human health and disease.

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Divide, die or conquer: homeostatic networks in innate lymphoid cells

Details of project
The innate lymphoid cell (ILC) component of the mammalian immune system rapidly and spontaneously respond to infections through direct recognition of pathogens and activation by inflammatory molecules. Natural killer (NK) cells are the founding member of the ILC family and unlike adaptive lymphocytes whose development critically relies on antigen receptor signals, NK cells are dependent on the cytokine IL-15 for their development.

This project will involve investigating cytokine signals controlling natural killer cell numbers to maintain homeostasis. Using the latest techniques in immunology, cell biology and time lapse imaging this project will dissect the networks that balance signals guiding a natural killer cell to divide, die, or conquer.

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Quantitative analysis of T cell differentiation

Details of project

Our lab is developing a new theory of cell fate regulation based on competition within individual cells for different outcomes such as death, division and differentiation. Experimental work to inform this new theory requires measurement of immune cell fates in large numbers of single cells using flow cytometry or single cell imaging.

We have recently discovered a simple rule explaining how naive CD8 T cells integrate signals determining the number of times they divide before returning to quiescence (Marchingo Science. 2014, 346(6213):1123)

We now want to investigate how these rules affect differentiation into effector or memory cells and whether similar rules govern the expansion of memory cells upon reactivation. We aim to test this in *in vitro* systems and translate these findings to *in vivo* pathogen models.

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Phenotyping and quantitation of immune responses in primary immunodeficiency

Details of project

The balanced interplay of lymphocyte growth, survival and differentiation is essential for a healthy immune system. In patients with immune disorders, this balance is disturbed so that they mediate an immune response that is either too strong (autoimmunity) or insufficient (primary immunodeficiency). We can mimic the processes by which a naïve B cell differentiates into antibody-producing cells by stimulating B cells with appropriate factors, and thus dissect B cell activity in controlled conditions (Hodgkin, JEM 1996 184(1):277; Bryant, JI 2008 181(3):1767; Fliegauf, Bryant AJHG 2015, in press). This project will combine sophisticated 12-panel flow cytometric phenotypic analysis with careful application of quantitative *in vitro* functional analysis of immunodeficient and healthy individuals to unravel the mechanisms that drive protective antibody production and development of immunodeficiency.
Developing new drugs to inhibit the cell death machinery

Details of project
Apoptosis is an important form of programmed cell death. Cancer cells typically evade normal apoptotic signals to become immortal. On the flipside, there are many diseases where unwanted apoptosis occurs, such as heart attack (death of cardiomyocytes), stroke (death of neurons) and organ transplantation (death of transplanted tissue).

We have developed the world’s first inhibitor of Bak, one of the critical mediators of apoptosis, and are striving to develop other potential drugs that block the activity of other components of the apoptotic pathway. The ultimate goal is to develop new drugs that can be used to rescue healthy cells in conditions where pathological apoptosis occurs. The focus of this project is medicinal chemistry.

Design, synthesis and testing of TBK1 inhibitors for treating rheumatoid arthritis

Details of project
This project concerns the design, synthesis and profiling of novel inhibitors of the enzyme TBK1. TBK1 is a kinase activated by specific receptors of the immune system called Toll-like receptors 3 and 4 (TLR3/4). There is growing evidence of a key role of TLR3/4, and thus TBK1, in inflammatory diseases including rheumatoid arthritis.

We are preparing novel compounds that inhibit TBK1 with greater potency and selectivity to compounds currently reported in the literature. The aim of this project is to further optimise these series of compounds and profile them for activity against TBK1 and in models of inflammatory disease.

This project would suit a student with an interest in organic/medicinal chemistry, drug design and testing.
The choreography of cell death by necroptosis

Details of project
The pseudokinase mixed lineage kinase domain-like (MLKL) is the most terminal known obligate effector in the emerging cell death signalling pathway known as necroptosis. Recent data have implicated this pathway in pathological inflammation and ischemic reperfusion injuries and, as a result, MLKL has emerged as a novel therapeutic target.

It is currently unclear how MLKL is activated by its upstream regulators, the protein kinases RIPK1 and RIPK3, and how it induces cell death. This project aims to provide mechanistic insights into these important biological processes using structural, molecular and cellular biology and biochemical approaches.

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Mechanics of T cell receptor activation

Details of project
The T cell antigen receptor (TCR) occupies a central role in vertebrate adaptive immunity, and the mechanism by which it transmits information about the antigenic environment within the body represents a crucial unresolved problem in T cell biology.

The receptor comprises eight separate protein subunits that must work in concert to convert extracellular ligand binding into intracellular biochemical signals.

This project capitalises on recent discoveries in our lab implicating transmembrane structural changes in TCR activation and focuses on mutation of membrane-embedded sequences to evaluate effects on T cell development and function. A student involved in this work will gain expertise in a variety of molecular and cellular immunology techniques and learn about important signalling pathways in T cell-mediated immunity.

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Epigenetic regulation of the immune system

Details of project
Many different immune cells, both innate and adaptive, are essential to ensure protection from infections. Exactly what dictates their development and defines the function of these cells is still unclear.

In this project we will examine how epigenetic modifications to DNA influence immune cell development and function. This project involves applying the latest epigenetic technologies to assess cells deficient in chromatin-modifying factors, to reveal how these factors contribute to innate and adaptive lymphoid cell development and function.

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Investigating the function of RIPK2 using mass spectrometry

Details of project
RIP kinase 2 (RIPK2) is a critical signalling protein for the regulation of immune responses, particularly in the defense to bacterial infections. However we know relatively little of how RIPK2 functions in various cell types or in different diseases.

In this project we will use a newly generated model system to explore the function of RIPK2 in different scenarios, from the role of RIPK2 in inflammatory diseases to its potential role in the progression of solid cancers.

The candidate will learn and use new techniques in cell biology and mass spectrometry and we will work extensively with primary cell types of a newly generated model.

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Associate Professor John Silke (Co-supervisor)
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Elucidating the mechanisms underpinning immune senescence

Details of project
The ability of the adaptive immune system to mount an antibody response against virtually any pathogen relies on a diverse B cell repertoire, and on the continuous generation of newly generated B cells in the bone marrow.

It is well established that the numbers of B cells produced in the bone marrow diminishes with age and this is thought to limit the effectiveness with which the elderly mount protective antibody responses. The mechanisms underpinning this phenomenon are still obscure. We have recently generated a novel model of immune senescence. Using gene expression profiling, cell biology and genome editing techniques, this project will explore the cellular and molecular players involved in the age-related decline in B lymphopoiesis.

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Dr Stephane Chappaz  
(Chair)  
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Identifying new epigenetic approaches to treat autoimmune disease

Details of project
Developing assays to characterise novel immunomodulatory compounds is essential for translating preclinical studies into successful therapeutic interventions for patients with immune disorders and blood cancers. Similarly, identifying off label uses for approved therapeutics will significantly reduce drug development timelines. We have deciphered a set of quantitative rules that all lymphocytes must adhere to when they generate an immune response. These rules describe how immune cells grow, die, and differentiate and provides an innovative system to screen immunomodulatory compounds and assign their effects to immune cell function. In this project we will use this discovery platform to identify and characterise novel epigenetic compounds for treating autoimmune conditions. Additionally, we will pair our modular quantitative approach with epigenetic studies to assign targeted genes with immune cell function.

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IMMUNE DISORDERS

Molecular division regulation in T and B cells

Details of project
The Hodgkin lab is developing a new theory of cell fate regulation based on competition within individual cells for different outcomes. Experimental work to inform this new theory requires measurement of immune cell fates such as death, division and differentiation simultaneously in large numbers of single cells using flow cytometry or single cell imaging.

Our work has discovered that antigen and/or costimulatory signals program T and B cells to undergo a set number of division (Marchingo Science. 2014;346(6213):1123, Turner J Immunol. 2008;181(1):374).

We are now investigating the molecular drivers for this process. We will investigate the consequences on lymphocyte behaviour on a single cell level when these drivers are manipulated (increased or inhibited) to gain a better understanding of the rules that govern lymphocyte expansion.

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Towards a molecular description of plasma cell diversity

Details of project
The differentiation of B cells into plasma cells (PCs) is essential for antibody production, enabling us to fight infection, and is the basis for current vaccination strategies. Different stimuli can elicit PC subsets with distinct lifespans and anatomical localisations. These PC subsets also differ in the isotype and affinity of the antibody they produce. We have recently defined a molecular signature of PCs that enables their demarcation on the basis of location and maturity (Shi, Nature Immunology 2015). This project will investigate how the diversity and function of PC subsets is controlled, by employing genomics techniques, such as conventional and single cell RNA sequencing, as well as vaccination and infection models. This project would suit a student with an interest in both molecular immunology and bioinformatics.

Professor Stephen Nutt (Primary)
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Prevention of type 2 diabetes by adipose tissue-resident Treg cells

Details of project
Visceral adipose tissue (VAT) is a major depot for energy storage, which also regulates glucose homeostasis. Glucose uptake is mediated by insulin signalling, a process that is sensitive to inflammation. Obesity induces inflammation in VAT, which in turn inhibits insulin signalling, leading to type 2 diabetes (T2D). A subset of T cells known as regulatory T (Treg) cells dampens VAT inflammation and prevents T2D development. We recently discovered that the cytokine IL-33 prevents T2D by specifically expanding VAT-Treg cells (Vasanthakumar et al, Nature Immunology 2015 16(5): 544). In this project, we aim to further understand how IL-33 impacts on VAT-Treg development and function. We will perform in vivo and in vitro experiments that employ flow cytometry, transcriptional profiling, western blotting, qPCR, immunohistochemistry and metabolic analysis.

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INFECTION DISEASES

Understanding the development of humoral immunity to malaria

Details of project
Malaria is one of the most serious infectious diseases with 250 million clinical cases annually. This infection is transmitted to humans by Anopheles mosquitoes that are infected with Plasmodium parasites. Unlike other infections like smallpox, which induce life-long protection following a single infection, it is only after years of repeated exposure to the parasite that individuals living in endemic areas develop antibody-mediated immunity to malaria.

Despite the key role that antibodies play in protection against malaria, the cellular processes underlying the slow and imperfect acquisition of immunity remain unknown. Our group investigates development and maintenance of B cell responses to malaria in humans and infection models. We also aim to identify specific antigenic targets of immunity to malaria to inform the design of anti-malaria vaccines.

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Membrane transport studies

Details of project
Ion currents across cell membranes are an essential part of electrical signaling in the mammalian central nervous system, as well as maintaining the function of cardiac, renal and other organs. There are many tens of genes encoding ion channels in humans, reflecting both functional diversity and a complex cellular interplay.

Conduction through selective ion channels is switched on in response to internal and external cues. Our goal is to derive, by careful comparison of structural and functional data, structural and mechanistic features that can be used to differentiate between different channels at an interventional level.

We have a few options for honours projects examining the structure and function of ion channels and other membrane proteins.

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Structure – function analysis of a putative phospholipid scramblase

Details of project
Cellular membranes are bilayers with pronounced compositional phospholipid asymmetry across the two leaflets. Cells invest heavily in maintaining this asymmetry, except under prescribed circumstances such as cell activation, apoptosis or blood coagulation. In such situations asymmetry rapidly collapses due to the action of modifying enzymes called scramblases. It has been hypothesised that Phospholipid Scramblase I (PLSCR1) from the malaria parasite *Plasmodium falciparum* (PfPLSCR1) mediates Ca2+ dependent phospholipid scrambling of the parasite plasma membrane during erythrocyte invasion, a process crucial to the pathogenesis of this deadly parasite. The primary goal of the project is determination of an initial crystal structure of PfPLSCR1. Initial protocols for protein expression and purification, and a scramblase activity assay have been developed.

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Investigating anti-viral immunity

Details of project
Viral infections remain a significant global health issue. It is not clear why some individuals respond to infection with exacerbated and dangerous inflammatory responses. Our research program aims to investigate the intracellular triggers and events that control the balance between good and bad immunity in response to viral infection.

Protein-protein interactions are key to every biological process in all organisms. We are interested in understanding how specific protein complexes are regulated in the context of viral pathogens such as influenza. Our laboratory uses a wide variety of experimental techniques including *in vivo* models of infectious disease, immunoprecipitations/western blotting and proteomics, through to solving the three-dimensional structures of the proteins involved. Several projects are available in this area.

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Antigenic diversity in malaria and implications for vaccine development

Details of project
The antigenic diversity of malaria parasites is well recognised as a major obstacle to the development of a broadly effective malaria vaccine. This project will investigate the extent to which genetic polymorphisms in parasite populations contribute to vaccine failure. This project will use samples from a longitudinal cohort of children exposed to malaria to define the relationship between genetic polymorphism and antigenic diversity. Advanced genomic and sero-epidemiological approaches will be employed to assess risk associated with different malaria parasite genotypes and identify the determinants of immune escape. The project will provide a serotype classification system for use in designing vaccines, and for the preliminary assessment of vaccine efficacy in target populations.

Impact of PROCR gene mutations on severe malaria

Details of project
This project will investigate whether genetics variants of the human endothelial protein C receptor (EPCR) can protect against severe malaria. Members of the Plasmodium PfEMP1 family of proteins have been implicated in severe malaria via adhesion to human EPCR, which normally mediates the cytoprotective effects of protein C. Perturbations of this system via sequestration of soluble EPCR (sEPCR) by PfEMP1 leads to inflammation in the brain and other tissues. A single point mutation in the EPCR gene, PROCR, has been associated with protection against severe malaria, but others have found no link. The impacts of other mutations in PROCR on clinical and severe malaria are unknown. The project will investigate associations between PROCR mutations, sEPCR level and severe malaria in Melanesian children. Students will become proficient in genomic epidemiology including next generation sequencing (NGS), SNP typing, bioinformatics and association analyses.
Tracking the spread of malaria in the Asia Pacific region

Details of project
Highly motivated individuals passionate about global health and infectious disease control are sought to join a team investigating the spread of malaria in countries that aim to eliminate the disease. By studying the genetic structure of malaria parasite populations, students will investigate transmission patterns and the dynamics of parasite populations under the pressure of antimalarial interventions. Genomic analyses will be applied to extensive collections of Plasmodium isolates from endemic countries in the Asia-Pacific region. The results will allow the development of tools for rapid surveillance to track the spread of infections, which will include defining transmission hotspots and the sources of outbreaks and residual malaria. Students will become proficient in molecular biology, genetic epidemiology, next generation sequencing, bioinformatics (Unix, R) and population genetic analyses.

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Home renovations: understanding how Toxoplasma redecorates their host cell

Details of project
Toxoplasma parasites extensively modifies its residing host cell in order to survive in the face of the immune system and to allow acquisition to nutrients for growth. How Toxoplasma sets up life long infection in neural and muscle tissue is completely unknown. We have recently identified a new pathway that Toxoplasma uses to export proteins into the infected host cell. We are interested in further characterising this pathway and identifying new effector molecules that alter the behavior of the host cell to promote intracellular survival of this pathogen. We are especially interested in determining how Toxoplasma is refractory to immune clearance in the brain and how this cunning parasite alters neuronal behavior. This project will utilise the latest molecular genetic techniques (e.g. CRISPR), tissue culture, imaging and potentially quantitative proteomics depending on the student’s interests.

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INFECTIONOUS DISEASES

Let me in! How Toxoplasma invades human cells

Details of project

Toxoplasma, like all apicomplexan parasites, must invade host cells and move through tissue for survival in the human host. Invasion and parasite motility is powered by an actomyosin-based molecular ‘motor’, which is critical for survival in the host.

We are characterising components of the ‘glideosome’ to understand their importance during pathogenesis. We recently identified some novel components, which link of this motor to parasite ligands, which may be potential drug targets for treating toxoplasmosis and malaria.

This project aims to characterise the role of these proteins in Toxoplasma tissue dissemination and host cell invasion. Students will use molecular genetic, imaging and other cellular techniques to understand the role that these molecules play in parasite virulence.

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Protein export to modify human cells during liver-stage malaria

Details of project

This project will involve conditional deletion of the PEXEL protein export machinery in Plasmodium falciparum, which is used to export proteins into red blood cells (Boddey et al Nature 2010; Elsworth et al Nature 2014), and studying the consequences during infection of liver cells.

The project will combine molecular genetics with cell biology to study parasite development and host changes during infection. It will utilise an insectary to transmit the parasite from infected blood into mosquitoes in order to obtain the parasite forms normally injected by mosquitoes into humans, and subsequent infection of cultured liver cells. Students will be working in a dynamic and exciting division that studies malaria, toxoplasmosis, virology and bacteriology.

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Identification of malaria parasite entry receptors

Details of project
Being an obligate intracellular parasite, malaria parasites have to invade red blood cells in order to survive within the human host. One essential step within invasion is the recognition of human red blood cells by malaria parasites, a process involving an intimate interaction between parasite adhesins and red blood cell receptors.

Our lab is interested in identifying novel parasite adhesins involved in red blood cell recognition and how they function in the dynamic process of parasite entry. This project will involve protein expression of these parasite adhesins and defining regions or residues within these proteins that are important for function. We can exploit this crucial information to rationally design a potential vaccine to prevent malaria parasite invasion into human red blood cells.

Immune evasion strategies of malaria parasites

Details of project
The human complement system is the front line defense mechanism against invading pathogens. Self-tissue is protected from indiscriminate complement attack by complement regulators that modulate the complement cascade. The co-existence of humans and microbes throughout evolution has resulted in microorganisms developing ingenious molecular mechanisms to escape complement attack. The acquisition of host complement regulators is by far the most widely used strategy for complement evasion among diverse infectious agents such as viruses, bacteria, fungi and parasites. This project involves identification of complement regulators that are recruited by malaria parasites, and how these prevent killing. The student will investigate the role of parasite surface proteins in recruiting human complement regulators. The results have broad implications in understanding basic parasite biology and immunological responses to malaria infections.
INFECTIONOUS DISEASES

Target identification of potent antimalarial agents

Details of project
Malaria causes approximately 800,000 deaths annually. The future effectiveness of current combination therapies is limited by emerging resistance. New classes of antimalarial drugs must be developed if we are to eliminate malaria. We have used a high throughput screening campaign to discover new drug candidates. This identified a class of novel small molecules that potently kill the malaria parasite. We are now using medicinal chemistry to improve their potency and physicochemical properties. To expedite their development, we aspire to identify how these small molecules act. The project will use complementary genetic and affinity based probe approaches to identify the molecular target of these antimalarial small molecules. The student will learn a multidisciplinary skill set including organic synthesis, molecular modeling, biochemical techniques and parasitology.

Agent-based mathematical modelling of mosquito born infectious diseases

Details of project
These potential projects focus on mathematical simulation modelling of mosquito borne infectious diseases, specifically malaria and dengue (e.g., Karl et al., BMC Inf Dis, 2014 (447)). We have developed several models to address different questions on mosquito borne pathogen biology (e.g., Plasmodium vivax relapses, P.falciparum gametocyte dynamics) and control (e.g., control of imported dengue in Queensland and imported malaria in Thailand). The models range from ‘very simple’ to ‘very complex’. The student will learn the theory of mathematical infectious disease modelling and build mathematical models to address specific questions for disease control. In the process, the student will learn in-depth epidemiology and biology of the modelled vector-borne disease (i.e., malaria or dengue) and will apply basic and advanced statistical techniques to analyse complex epidemiological datasets.
Investigating antimalarial immunity

Details of project
In order to eliminate malaria, control programs require better tools to identify and target residual pockets of high transmission. We are therefore developing novel serological surveillance tools.

Malaria infections elicit strong host immune responses that can persist for months and even years after an infection. Circulating antibodies are thus not only predictive of concurrent but also past infections.

Using high-throughput screens we have recently identified serological markers of recent exposure to *P. vivax* infection in both high and low transmission settings. In this project we will validate these *P. vivax*, as well as further *P. falciparum*, serological markers in cohorts from the Asia-Pacific and Americas, evaluate their use as surveillance tools and study the association between exposure and patterns of naturally acquired immunity.

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Statistical analysis of malaria susceptibility and related phenotypes

Details of project
During this PhD project the candidate will learn to perform statistical analysis of genome-wide association data generated from high-density SNP chips to investigate human host malaria susceptibility loci.

Skills learnt will include specific statistical analysis techniques such as linear modeling, clustering, kernel methods and haplotype analyses. Most statistical analyses will be performed in the statistical programming language R with some analysis on specific software for the task such as PLINK.

The student will become highly proficient in R programming in the UNIX environment and will become expert in known and putative malaria susceptibility loci. Data sets are already available.
INFECTIONOUS DISEASES

Gastrointestinal parasites in Karen refugee children in Thailand

Details of project
The candidate in this PhD project will undertake examination of faecal DNA extracts collected as part of an on-going health intervention in Karen refugee children in Tha Song Yang, Thailand. The candidate will employ molecular diagnostic tools to explore the prevalence of gastrointestinal pathogens, including soil transmitted helminths and diarrhoeal protists, and compare these data with demographic and health metrics including age, symptoms of disease, growth metrics and school performance. The candidate will also explore the impact of these parasitic infections on the development of the gut microbiome in infected children and the effects of oral therapy with Albendazole + Azithromycin on parasite incidence and intensity, and gut microbial community. The candidate will gain skills in the application of molecular diagnostics tools, and the generation and analysis of microbiomic data through community profiling and metagenomic sequencing approaches.

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Post-transcriptional and translational genetic regulation in parasitic protists

Details of project
The candidate in this PhD project will explore the role of antisense, non-coding RNAs and post-translational modifications in genetic regulation in key parasitic protists, with a specific emphasis on parasitic microaerophiles, including Giardia, Trichomonas and Entamoeba.

The candidate will develop skills in next generation sequencing and proteomic technologies and bioinformatic analyses. The candidate will also develop specific knowledge in bioinformatic approaches to compare and correlate antisense, microRNA and other small RNA transcription with messenger RNA transcription and protein expression. Application of these approaches to explore response in these parasites to existing and novel drug compounds will be explored.

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Chemokine-mediated T cell responses to viral infection

Details of project
The initiation and development of productive immune responses involves the coordination of many immune cell types. How these interactions are regulated and their precise location within infected tissues or draining lymph nodes remains unknown. Our work has revealed a role for a chemokine system in providing essential guidance cues for T cells during the initiation of anti-viral immune responses.

This project will investigate the factors that regulate T cell migration, and determine how this leads to protective immunity and immunological memory following viral infection. We will perform cell-based, imaging and molecular profiling experiments to understand the cellular migration underlying optimal T cell immune responses. Our goal is to apply this knowledge to discover alternative approaches for vaccine design and new strategies for clearance of chronic infections.

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T cell memory and anti-viral immunity

Details of project
A major goal is to understand the mechanisms of T cell memory generation that provides protective immunity. We have developed and use a number of in vivo models including acute (influenza) and chronic (herpesvirus, LCMV) infections. These provide us with an unprecedented opportunity to examine the mechanisms that these pathogens employ to infect hosts and elicit immune protection, or to subvert the host responses. Using a variety of approaches including multiparameter flow cytometry, systems biology and global gene expression profiling we aim to define cellular and transcriptional pathways in normal memory T cell differentiation and immune failure.

Experience in many techniques will be gained through this project, including flow cytometry, molecular approaches, transcriptomics and bioinformatics, disease models, immunofluorescent imaging and confocal microscopy.


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INFECTIONIOUS DISEASES

Tracking IL-27 in T cell development in pathogen infection

Details of project

T and B lymphocytes orchestrate immune responses that protect us against infection. To do this, lymphocytes undergo many changes after recognising their cognate antigen such as activation, proliferation and differentiation. These changes are often driven by cytokine production that in turn drives epigenetic changes, allowing immune cells to acquire distinct functional states. IL-27 is a cytokine that plays an important role in regulating B and T lymphocytes, but relatively little is known about how this occurs.

We have generated a novel genetic model that will allow us to track where and when IL-27 is produced, and determine how it regulates protective immunity. Experience in many techniques will be gained through this project, including flow cytometry, molecular approaches, transcriptomics and bioinformatics, disease models, immunofluorescent imaging and confocal microscopy.

Genotypic, haplotypic and transcriptomic diversity in parasitic protists

Details of project

The candidate in this PhD project will develop methods for exploring genotypic, haplotypic and transcriptomic diversity in nonsynchronous and/or heterozygotic populations and high host contaminant mixtures for culturable and non-culturable parasitic protists, including *Giardia*, *Plasmodium*, Cryptosporidium and Leishmania. The project looks at exploring technical approaches for efficient removal of host genetic material without biases (or systematically biasing) parasite material. The student will gain skills in constructing and customising short and long-read sequence libraries for low input and/or high host contaminated samples and develop bioinformatics approaches and sequencing platforms for accurate genotyping, haplotyping and transcriptomic characterisation of highly heterogenous populations of parasites. In addition, the candidate will explore Bayesian and linear modelling approaches to decompose mixed transcriptomic datasets representing multiple parasite stages to identify stage specific signals.
Transcription and epigenetic regulation in malaria transmission stages

Details of project
In this PhD project, the candidate will undertake transcriptomic and epigenetic analyses of the transmissable stages of *Plasmodium vivax*. The candidate will apply and develop strategies to generate these data from low titre infections and single cells. Skills learnt will include bioinformatics investigation of transcriptomic and epigenetic data, technical knowledge in high throughput sequencing techniques, and specific skills in correlating and reconciling systems biological data. The student will gain a high degree of expertise in Unix, R, basic scripting and a variety of world-standard bioinformatics applications. The candidate will also develop substantial expertise into the molecular biology and genetic behaviours of *P. vivax* facilitating transmission and determining developmental fate upon infection of the vertebrate host. Fieldwork in a malaria endemic area is possible.

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Application checklists

Honours
1. Visit wehi.edu.au/studentprojects for a list of prospective Honours projects.
2. Contact potential supervisors and explore suitability for project.
3. If potential match, supervisor requests student to send the following to Sue Hardy, the student administrator at the Walter and Eliza Hall Institute:
   • a cover letter outlining your research interests;
   • curriculum vitae; and
   • academic transcript.
6. Offer dates.
   • 1st round offer Friday 18 December 2015
   • 2nd round offers commence, mid January 2016.

PhD
1. Visit wehi.edu.au/studentprojects for a list of prospective PhD projects.
2. Contact potential supervisors, explore suitability for projects, and agree on a potential research project with your prospective supervisor.
4. Apply for a scholarship from The University of Melbourne
   The closing date for all scholarship applications for The University of Melbourne are:
   • 31 October (to commence in semester one) or
   • 27 May (to commence in semester two).
   
   NOTE: PhD applicants are required to secure their own scholarship.
5. Candidature offer: The Faculty of Medicine, Dentistry, & Health Sciences (MDHS) Student Centre issues formal offer of candidature.
   Scholarship offer: Scholarship results are announced by The University of Melbourne between November and March.