THE UNIVERSITY OF MELBOURNE

bio21 institute

BIOCHEMISTRY & MOLECULAR BIOLOGY

2021

RESEARCH PROJECTS
HONOURS, MASTERS
AND PHD

WELCOME

The Department of Biochemistry and Molecular Biology is a teaching and research Department of the School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences based on the main campus at Parkville.

The Department of Biochemistry and Molecular Biology has teaching responsibilities to medical, biomedicine and science students and has very active research programs with strong graduate research training.

The Biochemistry and Molecular Biology department houses 20+ research groups working in the areas of biophysics, cell biology, chemical biology, computational biology, drug design and resistance, genomics, immunology, metabolism, proteomics and structural biology. Disease focus includes infection, cancer, neurodegeneration and genetic diseases. We place a strong emphasis on research and research training with over 70 graduate research students currently enrolled.

The Department is situated within the University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, a multidisciplinary research centre specialising in medical, agricultural and environmental biotechnology which supports major technology platforms around mass spectrometry (proteomics/metabolomics/ analytical), advanced electron and fluorescence microscopy, NMR and protein structural characterization.

The Department has expertise in a broad range of technologies: cryo-electron tomography, flow cytometry, genetic manipulation of primary cells and whole organisms, viral delivery systems, animal models, DNA and RNA sequencing, CRISPR/Cas9 gene modification, high-resolution fluorescence imaging, light microscopy imaging, mass spectrometry, proteomics, metabolomics, nuclear magnetic resonance spectroscopy, bioinformatics, cryo-electron microscopy, small-angle X-ray scattering and X-ray crystallography.

The Department has a dynamic research profile and has established an extensive set of collaborations with other University Departments both within and outside the Bio21 Molecular Science and Biotechnology Institute.

The School of Biomedical Sciences is part of the Faculty of Medicine Dentistry and Health Sciences. It comprises the Departments of Anatomy and Neuroscience, Biochemistry and Molecular Biology, Microbiology and Immunology, Pharmacology and Therapeutics, and Physiology.

Situated on the University's Parkville Campus in a rich medical and research precinct the School has much to offer students, research and teaching staff alike.

HOW TO APPLY

HONOURS

What is Honours?

Honours is a fourth-year undergraduate course that consists of a combination of a research project and coursework subjects. The course is designed to develop the student's capacity to solve problems, to analyse data, to read and think critically, and to communicate clearly.

Honours can give you a taste of what working as a scientist would be like as a career, allows you to demonstrate academic excellence in an area of special interest to you, and provides an entry point for further research higher degree study (i.e. PhD). These skills are highly sought after by employers in biological, medical and industrial areas.

What are the entry requirements?

To be considered for entry, applicants must have completed a suitable undergraduate degree (Bachelor of Biomedicine, Bachelor of Science or equivalent) with a major in a relevant discipline with a WAM (weighted average mark) of at least H3 (65%) or equivalent.

Students who have completed or are due to complete a Bachelor of Biomedicine at the University of Melbourne should apply to complete Biomedicine Honours. Students who have completed or are due to complete a Bachelor of Science at the University of Melbourne or an equivalent course at another institution should apply to complete Science or Biomedicine Honours.

Meeting the minimum Faculty level is not a guarantee of admission and students must be accepted by a supervisor before entry into the course.

How long is Honours?

Honours is a one-year course consisting of 75 points of research and 25 points of coursework, that commences mid-February and finish in November. Mid-year entry is also possible, commencing in July and finishing in June the following year.

How to apply

STEP 1: Contact Potential Supervisor(s)

Decide which departments, institutes, supervisors and projects you wish to apply for and make contact with the relevant supervisor.

Applicants must contact potential supervisors either before or soon after submitting an online application for entry to an MDHS Honours course. Department and Institute Honours project booklets and websites, the individual information sessions held by departments and institutes are ways of helping you to make contact with potential Honours supervisors.

STEP 2: Online Application

Lodge an online application

1. Apply online and select either the 'Returning Applicants', 'Current Students and Previous Students' or 'First Time Applicants'. Do not select the 'First Time Applicants' option if you have previously completed study or applied to any program at The University of Melbourne.
2. Select 'MDHS Specialisations' as requirement response in the online application form.
3. Provide original or certified transcript(s) for any study not undertaken at The University of Melbourne. You are not required to provide transcripts for study undertaken at this university.

STEP 3: Project Preference

Once you have submitted an online course application, you will receive an email within 3 working days with your personal login details to access the Honours Project Preference System - SONIA. Please follow the instruction in the email to set up your password and select your preferences for projects offered within MDHS departments. You may select up to 4 project preferences in Round 1 or 3 project preferences in Round 2, 3 and mid year. You must only preference projects after making contact with the relevant supervisor(s). You are allowed to log into SONIA to change your preferences any time by the closing date.

More information including application dates and online application:
mdhs-study.unimelb.edu.au/degrees/honours/apply-now

biomedicalsciences.unimelb.edu.au/departments/biochemistry/study/honours-and-masters

MASTER OF BIOMEDICAL SCIENCE

What is the Master of Biomedical Science?

The Master of Biomedical Science at the University of Melbourne is a coursework master's degree incorporating a substantial research project. This course is an alternative to Honours as a PhD pathway. Students undertake a major research project and discipline-specific coursework subjects. In addition, a suite of professional business and communication subjects are offered to complement and enhance the research undertaken and to progress students' career opportunities.

The course encourages students to think innovatively and provides an awareness of the health and economic benefits of biomedical research. Graduates of this course gain an understanding of the research process, specialist knowledge and professional skills that are attractive to employers.

What are the entry requirements?

To be considered for entry, applicants must have completed a suitable undergraduate degree with a major in a relevant discipline with a WAM (weighted average mark) of at least H3 (65%) or equivalent. Meeting this requirement does not guarantee selection.

Notes

- Quotas may be applied to the degree as a whole, or to individual disciplines, and preference may be given to applicants with evidence of appropriate preparation or potential to undertake research.
- Entry is subject to the capacity of a participating department to provide adequate supervision in a research project appropriate to the interests and preparation of the individual student, and is subject to the agreement of an academic staff member to supervise the project.
- Students entering this course are expected to organise an academic supervisor in the relevant academic unit, and select a research project, as part of the application process. You will be provided with a list of current projects once your application has been assessed and deemed eligible. The theme and scope of the research project is negotiated between the student and supervisor prior to commencement of the course.

How long is the Master of Biomedical Science?

The Master's is a two-year (full time) course consisting of 125 points of research and 75 points of coursework. The course can be commenced at the start of the year or at mid-year.

How to apply

1. Apply online and select either Current Students and Previous Students or First Time Applicants. Do not select the First Time Applicants option if you have previously completed study or applied to any program at The University of Melbourne.
2. Provide original or certified transcript(s) for any study not undertaken at The University of Melbourne.

Selecting a Project

Once you have submitted an online course application, you will receive an email with your personal login details to access the Master of Biomedical Science Project Preference System - SONIA. Please follow the instruction in the email to set up your password and review projects offered within MDHS departments. You must make direct contact with the supervisor and obtain permission to work on their project before submitting your project preference. Once your project has been endorsed, you will be allocated to this project in SONIA.

More information including application dates and online application:
study.unimelb.edu.au/find/courses/graduate/master-of-biomedical-science/how-to-apply/

biomedicalsciences.unimelb.edu.au/departments/biochemistry/study/honours-and-masters

Difference between Honours and the Master of Biomedical Science

	Honours	Masters
Duration	1 year (full time)	2 years (full time), part time available
Level	Undergraduate	Graduate
CSP (commonwealth supported places) available?	Yes	Limited
PhD Scholarship scoring	Considers marks from 3rd year of Bachelor's degree and Honours marks	Only Masters marks are considered
International Market recognition	Australian Honours degrees may not be recognised overseas, as many countries do not have an equivalent degree.	Recognised as a graduate master's degree

RESEARCH HIGHER DEGREES

What is a PhD?

A PhD (Doctor of Philosophy) is a three-year supervised research degree with the possibility of up to 12 months extension. A candidate may be required to supplement their research with enrolment in additional subjects if considered necessary. The research is written up as a thesis (80,000 – 100,000 words) and examined by external experts in the field.

What is a MPhil?

A MPhil (Master of Philosophy) is similar to a PhD but carried out over 18 months to 2 years. The research work is written up as a thesis (30,000 – 40,000 words) which demonstrates your knowledge and contribution to the field of research.

What are the entry requirements?

To be considered for entry into a PhD, applicants must have completed

- a four-year bachelor's degree (BSc Hons, BBiomed Hons) in a relevant discipline which includes a substantial research component equivalent to at least 25% of one year full time study and achieved a minimum WAM of 80% (University of Melbourne) or equivalent; or
- a master's degree in a relevant discipline which includes a substantial research component equivalent to at least 25% of one year of full time study and achieved a minimum weighted average of 80% (University of Melbourne) or equivalent.

To be considered for entry into a MPhil, applicants must have completed

- a four-year bachelor's degree (BSc Hons, BBiomed Hons) in a relevant discipline which includes a substantial research component equivalent to at least 25% of one year full time study and achieved a minimum WAM of 75% (University of Melbourne) or higher; or
- a master's degree in a relevant discipline which includes a substantial research component equivalent to at least 25% of one year of full-time study and achieved a minimum weighted average of 75% (University of Melbourne) or higher.

Choosing a supervisor and research area

A critical element of success is choosing a research area that interests you. Departmental websites have information on the range of research areas on offer, as well as areas of interest of academic staff members who can supervise your project.

It is very important for you to talk to supervisors as well as current or previous students. It is one thing to be interested in the project but you need to get along with your supervisor too.

For future information regarding Research Higher Degrees:

study.unimelb.edu.au/find/courses/graduate/doctor-of-philosophy-medicine-dentistry-and-health-sciences/

study.unimelb.edu.au/find/courses/graduate/master-of-philosophy-mdhs-biomedical-science/

biomedicalsciences.unimelb.edu.au/departments/biochemistry/research/graduate-research-opportunities

How to apply

1. Review the list of prospective projects and supervisors in this handbook or online.
2. Identify projects of interest and contact the project supervisor to explain your research interests and provide your curriculum vitae (CV) and academic transcripts.

Once confirmed a project and supervisor apply online at https://study.unimelb.edu.au/how-to-apply/graduate-research

SCHOLARSHIPS

Honours

Honours applicants who accept and enrol in an Honours course will automatically be considered for available Honours Scholarships. These are awarded on academic merit.

Highly ranked full-time students who have enrolled in an MDHS program through the Bachelor of Biomedicine (Degree with Honours) and the Bachelor of Science (Degree with Honours) and demonstrated a level of financial needs will automatically be considered for an Frances Elizabeth Thomson Trust Scholarship. The Scholarship will award eligible students with a one-off payment of $5,000. mdhs.unimelb.edu.au/study/scholarships/n/frances-elizabeth-thomson

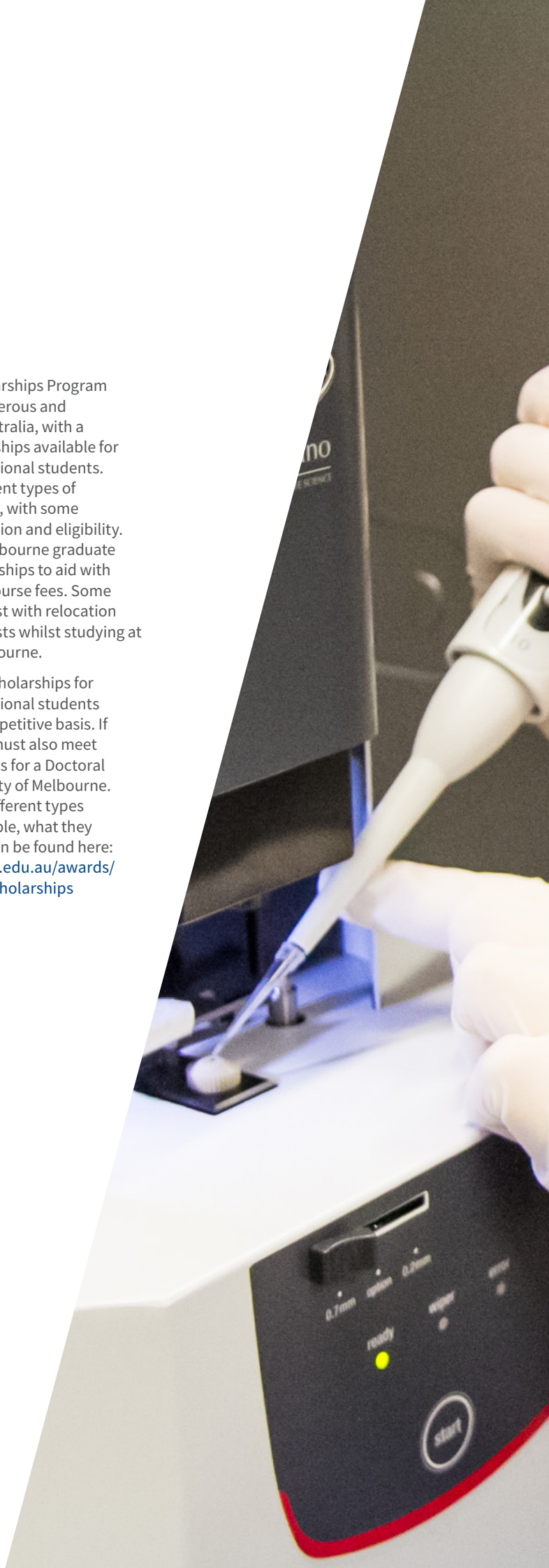
A scholarship of $5,000 is available to any full-time student enrolled in Department of Biochemistry and Molecular Biology Honours with a third year WAM > 85 (not including University of Melbourne Breadth subjects or equivalent) undertaking Honours in a laboratory located at Bio21 Institute.

The highest ranked Department of Biochemistry and Molecular Biology Honours student for each year will be awarded the Grimwade Honours prize of $2,000.

Graduate degrees

The Melbourne Scholarships Program is one of the most generous and comprehensive in Australia, with a wide range of scholarships available for domestic and international students. There are many different types of scholarships available, with some varying in value, duration and eligibility. Most University of Melbourne graduate students have scholarships to aid with living expenses and course fees. Some scholarships also assist with relocation fees and insurance costs whilst studying at the University of Melbourne.

Graduate Research Scholarships for domestic and international students are awarded on a competitive basis. If successful, students must also meet the entry requirements for a Doctoral degree at the University of Melbourne. More details on the different types of scholarships available, what they cover and eligibility can be found here: scholarships.unimelb.edu.au/awards/graduate-research-scholarships



PROJECTS

ASCHER GROUP

Contact: **A/Prof David Ascher**
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- **Computational Biology**
- **Genomics**
- **Structural Biology**
- **Drug Design and Resistance**
- **Personalised Medicine**

The Ascher group develops new computational tools to investigate and understand the relationship between protein sequence, structure and function and phenotype. The lab uses these to drive improvements in and personalisation of patient treatment, and to guide drug discovery.

Project: Treating the person not the disease

We have developed a range of computational tools to deconvolute the molecular mechanisms of a mutation giving rise to different phenotypes. In collaboration with clinical partners we have shown that even though patients may present the same disease, they may arise from many different mutations that alter a patient's outcome or how they may respond to a particular treatment. By analysing these mutations and predicting their effects on protein structure and function we are trying to revolutionise treatment strategies, an important step towards personalised medicine. We are currently working on a range of diseases including genetic diseases (Alkaptonuria, Urea cycle disorders, VHL), cancer (renal carcinomas), and drug/vaccine resistance (TB, cancer, malaria, HIV, influenza). These projects combine both computational (bioinformatics) and experimental (protein expression, biophysics, structural biology) approaches to unravel the molecular mechanisms driving these mutations and derive novel predictive methods. This information is then used to help identify and guide the development of novel therapies to treat these conditions. One of the ultimate goals of these projects will be the development of webservers enabling the rapid analysis of mutations to help guide clinical decisions

Project supervisor
A/Prof David Ascher

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Finding clarity within a blizzard- guiding the solution of cryo-EM structures

The recent explosion in the power of cryo-electron microscopy has revolutionised the structural biology field, especially the characterisation of large protein complexes. This is helping us tackle very important biological problems in a way that they could never before. There are, however, inherent limitations that not only pose difficulties to the structure solving stage, i.e., properly positioning a protein chain within an electron density map, but also potentially introducing errors that might be propagated to the refined structure. This is especially relevant for medium resolution structures (4-8 Å). The problem is analogous to looking through blurry (or drunk) glasses and, without good points of reference, not being able to orientate yourself. To improve this procedure, we can leverage the power of our existing structural and evolutionary knowledge accumulated over decades and deposited in structural databases in order to help guide the proposal of a more effective methods for this molecule placement. This project will use structural bioinformatics and machine learning to develop novel computational tools to aid cryo-EM and low-resolution crystal structure solving, analysing protein residue environments, protein interaction interfaces, and protein functional sites. These methods will be brought together into an integrated platform for the evaluation and validation of medium resolution protein structures.

Project supervisor
A/Prof David Ascher

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: small molecules for BIG targets- Targeting protein-protein interactions with fragments

Most proteins work within a network of interactions with other proteins, and the ability to selectively target specific interactions, modulating protein function and providing the opportunity to develop more selective and effective drugs. But while drugs are usually around 100 Å, proteins interact tightly using way larger protein-protein interfaces, ranging from 1000-6000 Å. This raises the challenge of how we can use a small molecule to affect an interface many times larger, which until recently was considered to be flat and undruggable. We and others have had success using fragment-based drug discovery to identify novel protein-protein interaction modulators. This allows us to take advantage of hot-spots within the protein interfaces that mediate a large proportion of the binding energy, growing the molecule to improve binding affinity and drug like properties. The crystal structures of many protein interface modulators with their targets have been solved, which opens up the possibility for us to ask: what are the major components of binding affinity? and can we use this information to predict fragments likely to bind to a given interface? Using structural bioinformatics and machine learning, these questions will be answered, leading to the development of novel programs. The students will then also have the opportunity to test these experiments in the lab, using biophysical and structural approaches to test fragment binding.

Project supervisor
A/Prof David Ascher

Project availability

- PhD
- Master of Biomedical science
- Honours

BATHGATE GROUP

Contact : **Professor Ross Bathgate**
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Drug Design and Resistance

Structural Biology

Cell signalling

The Bathgate lab focusses on understanding the interactions of peptide ligands with their G protein-coupled receptor (GPCR) targets for the development of peptide-based drugs and utilizing structure-based drug design to develop novel therapeutics. He works closely with a number of pharmaceutical companies interested in the clinical development of drugs targeting receptors for peptides of the relaxin family. Projects are available on multiple therapeutically relevant GPCR targets with training in various techniques including peptide mimetic design, cell signalling assays, molecular pharmacology, structural biology and structure-based drug design.

Project: Targeting peptide G protein-coupled receptors (GPCRs) for novel drug development

The largest single class of drug targets is the G Protein-Coupled Receptor (GPCR) family, which were targets for ~30% of prescription drugs sold in the USA in 2010. However current drugs only target a small proportion of the GPCR family and peptide GPCRs, although showing great potential as targets for treating many diseases, are poorly targeted with drugs. Modern GPCR drug development is encumbered by a lack of information about the molecular structure underlying GPCR function and the reliance on cell-based assays that are prone to false positives in drug screening. While the past 10 years have seen advances in our knowledge of GPCR structures peptide GPCRs, especially those with large structured ectodomains (ECDs), remain poorly understood. This is mainly because the flexibility of linkers joining the ECDs to the transmembrane domains (TMDs) impedes crystallization. Hence the study of complex peptide receptors requires different approaches. Our laboratory targets peptide GPCRs for drug development utilizing state-of-the-art molecular pharmacology, biochemical and Nuclear magnetic resonance (NMR) techniques. These techniques enable us to map the native peptide binding sites of these receptors and determine the mechanisms of receptor activation as well their cell signalling characteristics.

A complete understanding of the mechanism of ligand binding and activation is required to design drugs targeting these receptors. Furthermore, we are utilizing novel protein engineering techniques that enable these normally highly unstable proteins to be produced and purified for structural studies using advanced protein NMR techniques, crystallography and Cryo-EM (also see projects from Dr Daniel Scott, Prof Paul Gooley). Our studies are complemented by peptide drug development projects and small molecule screening projects with collaborators. Additionally, we are working with pharmaceutical industry partners (eg. Takeda and Novartis) to facilitate drug development efforts. Projects are available on multiple GPCR targets with training in various techniques as outlined above.

Project supervisor
Prof Ross Bathgate

Project co-supervisors
Dr Daniel Scott, Prof Paul Gooley, A/Prof Mike Griffin

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Peptidomimetic drug design targeting G protein-coupled receptors

Currently available drugs in the market fall broadly into two categories. There are ‘small molecule’ drugs (molecular weight of <500 Da) with oral bioavailability and much larger ‘biologics’ (molecular weight of typically >5000 Da) with no oral bioavailability. Due to their small size, small molecule drugs often suffer from reduced target specificity and toxicity. Large biologics, on the other hand, are highly target-specific and thus less toxic than small molecules. Therefore, the compounds that fit between these two molecular weights (500 Da-5000 Da) and possess the advantages of both the small molecule (e.g. bioavailability and stability) and larger biologics (e.g. highly target specific) are of great interest. Peptidomimetics are such compounds that fall into this category.

Relaxin family peptides have complex-two chain and three disulfide bonded structure and our laboratory has recently developed peptidomimetics of human relaxin 2 (B7-33), relaxin 3 (stapled peptide), and insulin-like peptide 5 (analogue 13). Projects are available to further develop these peptidomimetic ligands as molecular probes and drug leads that target their GPCR targets, relaxin family peptide (RXFP) receptors RXFP1, RXFP3 and RXFP4. These receptors are potential drug targets for cardiovascular disease, neurological disorders and gut

dysfunction, respectively. Our laboratory utilizes multidisciplinary cutting-edge technologies including modern solid phase peptide synthesis, molecular pharmacology, and animal physiology to carry out these projects. Importantly, we are working with pharmaceutical industry partners (eg. Takeda and Novartis) to develop peptidomimetics therapeutically. Projects are available on multiple additional GPCR targets with training in various techniques as outlined above.

Project supervisor
Prof Ross Bathgate

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Drug discovery: investigation of signalling by GPCRs using novel cellular biosensors

GPCRs are the targets for ~30% of all currently used therapeutic drugs. It is critical to understand how these receptors are activated, how they alter cellular function, how such responses are switched off, and how other cellular components can modulate their activity. GPCRs interact with a range of other proteins and these interactions govern their function and modulation. Our laboratory has a range of advanced cutting-edge technologies available for the study of GPCRs allowing interacting partners and signalling profiles to be determined. These include novel Bioluminescence Resonance Energy Techniques (BRET)-based biosensors. BRET is a technology that places light-emitting labels on proteins, enabling their interactions to be examined in living cells, and is uniquely suited to the study of integral membrane proteins such as GPCRs (Figure). BRET-based biosensors allow us to closely monitor intermolecular signalling in diverse cellular compartments in real time. This project will examine a range of GPCR signalling pathway with a particular focus on the effect of diverse drugs. A complete understanding of the mechanisms of GPCR activation and signalling complexity is crucially important for drug development targeting these receptors. We work with multiple GPCR targets and collaborate with pharmaceutical industry partners including Novartis and Takeda. Projects are available on multiple GPCR targets with training in molecular and cell biology and numerous BRET techniques to study GPCR interactions and cellular signalling.

Project supervisor
Prof Ross Bathgate

Project co-supervisors
Dr Martina Kocan

Project availability

- PhD
- Master of Biomedical science
- Honours

BROWN GROUP

Contact : **Doctor Kristin Brown**
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Cancer
Metabolism
Cell Biology
Cell signalling
Drug Design and Resistance

Deregulated cellular metabolism is a well-established hallmark of cancer. The Brown group uses a range of molecular biology, cell biology and biochemistry techniques to investigate the ways in which deregulated cellular metabolism contributes to cancer initiation, cancer progression and therapy resistance. The knowledge gained from these studies is applied to the pre-clinical development of novel anticancer therapies.

Project: Fueling chemotherapy resistance in triple-negative breast cancer

Triple-negative breast cancer (TNBC) is a molecularly heterogeneous group of diseases defined by the lack of estrogen receptor (ER), progesterone receptor (PR) and absence of human epidermal growth factor receptor-2 (HER2) amplification. Consequently, TNBCs are impervious to therapies commonly used in other breast cancer subtypes and treatment options are largely limited to conventional chemotherapy agents. Approximately 30% of TNBC patients respond to chemotherapy. Unfortunately, the long-term prognosis for the majority of patients with residual disease after chemotherapy is poor. Identification of novel and actionable strategies to sensitize cancer cells to chemotherapy would represent a major advance for the management of TNBC.

Cancer cells exhibit dramatic alterations in cell metabolism, which support cell growth, proliferation and survival. Indeed, metabolic reprogramming is a recognized hallmark of cancer induced by numerous genetic or epigenetic alterations. Our recent studies suggest that reprogramming of cellular metabolism is also a component of the highly coordinated response to chemotherapy exposure. The aims of this project will be to 1) identify adaptive metabolic reprograming events triggered upon chemotherapy exposure, and 2) identify novel therapeutic approaches to exploit adaptive metabolic reprogramming events and sensitize TNBC cells to chemotherapy. This research will lead to the identification of critical mechanisms driving chemotherapy resistance in TNBC and establish combination therapy strategies with potential to have a major impact on patient survival. Students will gain experience in mammalian cell culture, molecular biology techniques, metabolomics and stable-isotope labelling techniques.

Project supervisor
Dr Kristin Brown

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Cutting off the Fuel Supply to Starve Cancer: Identifying metabolic vulnerabilities in cancer

A universal characteristic of all cancer cells is the reprogramming of cell metabolism to provide the energy and building blocks necessary to support proliferation and survival. Reprogramming of cell metabolism occurs as a consequence of oncogenic mutations and renders cancer cells dependent on a unique set of nutrients. It is now widely recognized that the altered metabolic activity of cancer cells provides a window of opportunity to develop tumour-specific anticancer therapies. Using transcriptomic and metabolomic approaches, the aims of this project will be to: (1) compare and contrast metabolic reprogramming induced by well-described oncogenes; (2) compare and contrast the nutrient requirements of cancer cells dependent on well-described oncogenes and (3) identify and validate key metabolic vulnerabilities that can be targeted for the preclinical development of novel anticancer strategies. Students will gain experience in mammalian cell culture, molecular biology techniques, metabolomics and stable-isotope labelling techniques.

Project supervisor
Dr Kristin Brown

Project co-supervisor
Dr Andrew Cox

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Unravelling the oncogenic activities of serum- and glucocorticoid-regulated kinase 1 (SGK1)

The phosphoinositide 3-kinase (PI3K) pathway has emerged as a master regulator of numerous cellular phenotypes associated with cancer including cell survival, proliferation, growth, altered metabolism and malignant transformation. Deregulation of the PI3K pathway is implicated in virtually all human cancers and the pathway has been aggressively targeted for cancer therapy. Although most work has focused on the Akt kinase family as major downstream effectors of PI3K, the closely related serum- and glucocorticoid-regulated kinase (SGK) family of serine/threonine kinases has by comparison received little attention. The SGK1 isoform was initially discovered as a gene transcriptionally responsive to serum and glucocorticoids in mammary tumour cells. More recently, SGK1 has been shown to play a critical role in driving the expansion of tumour cells and promoting resistance to conventional chemotherapy and targeted therapy agents. However, the molecular mechanisms that enable SGK1 to elicit such oncogenic activities are unknown. This is largely because information regarding the substrates and interaction partners of SGK1 is extremely limited. In this project, students will identify SGK1 substrates and interacting proteins using the proximity-dependent biotin identification (BioID) method. Students will gain experience in mammalian cell culture and proteomics (mass spectrometry) techniques. Targets identified in the BioID screen will be validated using a variety of biochemical and molecular biology techniques.

Project supervisor
Dr Kristin Brown

Project availability

- PhD
- Master of Biomedical science
- Honours

COX GROUP

Contact : **Doctor Andrew Cox**
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Email: **andrew.cox@petermac.org**
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Cell Biology
Cancer
Metabolism
Metabolic Disease

In the Cox laboratory, we use zebrafish (Danio rerio) as a model system to study pathways that regulate liver growth during development, regeneration and cancer. Our lab is especially interested in understanding the mechanisms by which metabolism is reprogrammed in cancer. We employ a wide range of techniques including multiphoton microscopy, metabolomics and transcriptomics in zebrafish models of liver regeneration and cancer. Our ultimate goal is to identify critical metabolic vulnerabilities that can be exploited for the development of therapies to combat cancer.

Project: Fishing for metabolic clues: Role of the Hippo/Yap pathway in reprogramming metabolism in liver cancer.

The Hippo/Yap pathway is an evolutionarily conserved cascade that plays a fundamental role in governing organ size control, stem cell homeostasis and cancer. The Hippo/Yap pathway is regulated by a range of environmental cues including nutrient status. Although many of the inputs into the Hippo pathway have been identified, less is known about the Yap target genes responsible for tissue growth. Using a combination of metabolomic and transcriptomic approaches in zebrafish, we have discovered that Yap reprograms glutamine metabolism in vivo to stimulate nucleotide biosynthesis and fuel premalignant liver growth. Building on this initial investigation, we currently have research projects that aim to 1) Examine how Yap coordinates nutrient sensing to metabolic output in the liver. 2) Elucidate the mechanisms by which Yap reprograms metabolism to fuel liver growth in the context of regeneration and cancer. The students will use a combination of innovative biochemical, genetic and imaging approaches in zebrafish to identify the metabolic dependencies of tissue growth during regeneration and cancer.

Project supervisor
Dr Andrew Cox

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Metabolic rewiring in liver cancer: Role of oxidative stress and the Nrf2 pathway.

Many of the major risks factors for developing liver cancer such as alcohol, obesity, smoking and toxin exposure share in common a role for oxidative stress. Nrf2 is a transcription factor activated by oxidative stress that orchestrates an adaptive response remodeling metabolism and promoting cytoprotection. Recent studies have identified that the Nrf2 pathway is frequently mutated in liver cancer (~12% tumors), causing activation of the pathway in the absence of oxidative stress. We have used transcriptomic and metabolic profiling in Nrf2-/- zebrafish to examine the role Nrf2 plays in remodeling metabolism during liver development and regeneration. Building on these preliminary studies, we currently have research projects that aim to 1) Generate a gain of function Nrf2 mutant (Nrf2D29H), frequently recovered in cancer, and characterize the effect the mutation has on metabolic reprogramming. 2) Examine how deregulation of Nrf2 remodels metabolism to stimulate liver tumorigenesis. The students will use a combination of innovative biochemical, genetic and imaging approaches in zebrafish to identify the metabolic dependencies of tissue growth in liver regeneration and cancer.

Project supervisor
Dr Andrew Cox

Project availability

- PhD
- Master of Biomedical science
- Honours

EDGINGTON-MITCHELL GROUP

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Immunology

Cell Biology

Cancer

Chemical Biology

The Protease Pathophysiology Lab uses a chemical biology approach to understand the mechanisms by which enzymes called proteases contribute to normal cellular function and how these mechanisms can go wrong to cause disease. Our overarching goals are to establish proteases as diagnostic or prognostic biomarkers for inflammation and cancer and as novel drug targets for the treatment of these diseases.

Project: Development of Novel Chemical Tools to Measure Protease Activation

Proteases are enzymes that cleave peptide bonds of proteins. To prevent cleavage at the wrong place or time, and thus protect the body from aberrant proteolysis, most proteases are synthesised as inactive proteins called zymogens. They become activated in response to a conformational change, which can be mediated by alterations in pH or cleavage by other proteases. Once activated, proteases are also subject to spatial and temporal regulation by endogenous inhibitors such as cystatins. As a result of these complex modes of post-translational modification, traditional biochemical methods that survey total protein levels rarely reflect the pool of active, functional enzymes. The ability to specifically measure and modulate the activity of a protease in its native environment is therefore required to define its precise proteolytic functions during health and disease.

To achieve this, efforts from our team and others have focussed on developing activity-based probes (ABPs) for diverse cysteine and serine proteases. These tools capitalise on the catalytic mechanism of proteolysis, combining a protease recognition sequence with a reactive functional group called a warhead. When the catalytic residue of an active protease attacks this warhead, a covalent, irreversible bond forms.

To detect the formation of this bond, and thus measure protease activity, ABPs are tagged with fluorophores that emit light only after protease cleavage. This fluorescence can be visualised using a number of optical imaging applications, including whole animal and tissue imaging, flow cytometry, confocal microscopy, and SDS-PAGE (in-gel fluorescence). The identity of the probe's targets can then be confirmed by immunoprecipitation with protease-specific antibodies or proteomic methods.

This project will involve collaboration with chemists to develop novel activity-based probes for cysteine and serine proteases.

Project supervisor
Dr Laura Edgington-Mitchell

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Understanding the Contribution of Proteases to Oral Cancer Pathology

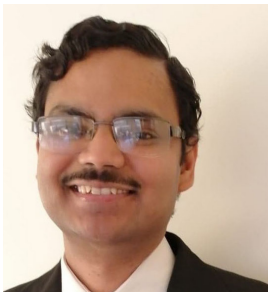
Oral squamous cell carcinoma is the most common head and neck cancer. It is an extremely painful disease for which treatments are limited. Oral cancer often spreads to cervical lymph nodes, and once metastasis occurs, patient survival rates drop below 40%. Current methods to predict the spread of oral cancer are ineffective; thus, most patients undergo radical elective neck dissection to remove all cervical lymph nodes prior to the appearance of metastatic lesions. Our laboratory is investigating the contribution of proteases to oral cancer pain and metastasis. Proteases are a large family of enzymes that function as tiny molecular scissors to cut proteins. This process facilitates protein degradation and turnover, but also contributes to many cellular signalling events that underlie the growth and metastasis of oral cancer. This project aims to understand the functions of key proteases that are activated in human oral cancers using in vitro assays and in vivo mouse models. We will evaluate the utility of protease activity as a biomarker for predicting metastasis and as a potential drug target for the treatment of this deadly disease.

Project supervisor
Dr Laura Edgington-Mitchell

Project availability

- PhD
- Master of Biomedical science
- Honours

GHOSAL GROUP



Contact : **Dr Debnath Ghosal**
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Structural Biology	**Pathogens**
Discovery Research	**Cell Biology**
Biophysics	**Drug Design and Resistance**

We are interested in host-pathogen interaction particularly, how bacterial and viral pathogens utilize complex molecular machines to mediate infection. We use a range of structural (e.g. cryoEM, X-ray crystallography etc) and cell biology techniques to elucidate the structure and function of these molecular machines in situ, in their native context, inside 'living' cells.

Project: Structure and function of bacterial cytoskeletal filaments by cryo-EM

Until early 1990s, cytoskeletal proteins were believed to be the hallmarks of eukaryotic cells. However, in the last three decades, the discovery of bacterial homologs of eukaryotic actin, tubulin and intermediate filament proteins have dramatically changed our perception. One of the key emerging difference between the bacterial and the eukaryotic cytoskeletal systems is that each of the bacterial filaments seem to perform one dedicated function while eukaryotic ones, by virtue of their interaction with a repertoire of adapters and regulatory proteins, perform numerous tasks. We are trying to understand how prokaryotic cytoskeleton was customised for multi-functionality during the evolution of complex eukaryotic cells.

Project supervisor
Dr Debnath Ghosal

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Structural biology in situ: Structure and function of bacterial secretion systems by cryo-EM

Bacteria harbour at least nine different types of secretion systems to transfer macromolecules across cellular envelope. These are sophisticated multi-protein nanomachines that secrete myriads of substrates including proteins, nucleoprotein complexes and variety of small molecules and are central to pathogenesis of multiple human diseases. For example, many pathogenic bacteria utilize the Type III Secretion System (T3SS) to cause diseases such as dysentery (Shigella), typhoid (Salmonella), plague (Yersinia) etc. Other human pathogens employ the Type IV Secretion System (T4SS) to mediate gastric cancer (Helicobacter), brucellosis (Brucella), typhus and spotted fevers (Rickettsia), as well as Legionnaires' disease (Legionella). The T4SS is also associated with the spread of antibiotic resistance, which currently presents a major threat to public health. Therefore, these molecular machines are attractive targets for drug developments to enrich our present repertoire of antibiotics. Structural studies with these molecular machines are extremely challenging due to their large number of components, flexibility and tight integration into the bacterial cell envelope. Electron cryotomography (cryo-ET) has unrivalled power to visualize the native structure of macromolecules in situ. In recent years, improvement in software, detectors and implementation of improved subvolume averaging methods have allowed us to investigate macromolecules in situ at subnanometer resolution. We are harnessing this unique power of cryo-ET and combining it with correlative light and electron microscopy (CLEM), and Focused Ion Beam (FIB) milling to elucidate the structure and function of different bacterial injection modules at molecular resolution.

Project supervisor
Dr Debnath Ghosal

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The Role of Bacterial Secretion Systems in Virulence and in Antibiotic Resistance

Bacteria harbour at least nine different types of secretion systems to transfer macromolecules across cellular envelope. These are sophisticated multi-protein nanomachines that secrete myriads of substrates including proteins, nucleoprotein complexes and variety of small molecules and are central to pathogenesis of multiple human diseases. For example, many pathogenic bacteria utilize the Type III Secretion System (T3SS) to cause diseases such as dysentery (Shigella), typhoid (Salmonella), plague (Yersinia) etc. Other human pathogens employ the Type IV Secretion System (T4SS) to mediate gastric cancer (Helicobacter), brucellosis (Brucella), typhus and spotted fevers (Rickettsia), as well as Legionnaires' disease (Legionella). The T4SS is also associated with the spread of antibiotic resistance, which currently presents a major threat to public health. Therefore, these molecular machines are attractive targets for drug developments to enrich our present repertoire of antibiotics. Structural studies with these molecular machines are extremely challenging due to their large number of components, flexibility and tight integration into the bacterial cell envelope. Electron cryotomography (cryo-ET) has unrivalled power to visualize the native structure of macromolecules in situ. In recent years, improvement in software, detectors and implementation of improved subvolume averaging methods have allowed us to investigate macromolecules in situ at subnanometer resolution. We are harnessing this unique power of cryo-ET and combining it with correlative light and electron microscopy (CLEM), and Focused Ion Beam (FIB) milling to elucidate the structure and function of different bacterial injection modules at molecular resolution.

Project supervisor
Dr Debnath Ghosal

Project availability

- PhD
- Master of Biomedical science
- Honours

GLEESON GROUP

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Cell Biology	**Proteomics**
Organelles	**Neurodegeneration**
Immunology	**Biophysics**

Membrane trafficking underpins many cell processes, including secretion, receptor signalling, endocytosis, antigen presentation, and neural networking. Many diseases arise from defects in membrane trafficking, including Alzheimer's disease. Our aim is to understand the molecular basis of membrane and protein sorting in the secretory and endocytic pathways in a variety of physiological processes using cultured cells and differentiated primary cells, and to exploit this knowledge for the design of new therapeutics.

Project: Intracellular trafficking in neurons and Alzheimer's disease

Alzheimer's disease is characterized by the accumulation of amyloid plaques in the brain consisting of an aggregated form of β-amyloid peptide (Aβ) derived from sequential amyloidogenic processing of the Amyloid Precursor Protein (APP) by membrane-bound proteases BACE1 and γ-secretase. The initial processing of APP by BACE1 is regulated by intracellular sorting events of the enzyme, which is a prime target for therapeutic intervention. We are interested in defining the intracellular trafficking pathways of APP and BACE1 and the sorting signals of these membrane proteins that define their itineraries. We have mapped the itineraries of these cargos in cultured human cell lines and our findings show that the distinct trafficking pathways of APP and BACE1 provides the capacity to finely regulate their co-localization and thereby regulating APP processing and Aβ production. There is considerable evidence that dysregulation of membrane trafficking events is associated with an increased risk of Alzheimer's disease. We are now defining the itineraries of APP and BACE1 in primary neurons, the cell type relevant for this disease. The project will map the post-Golgi anterograde transport pathways of APP and BACE1 in neurons, determine the selective trafficking routes to axons and dendrites, and assess the impact of neuronal signaling on these trafficking pathways.

We have established a powerful new approach to synchronize and analyse the trafficking of newly synthesized membrane cargoes BACE1 and APP in real time. The project will incorporate this new approach with immunofluorescence, FACS and live cell imaging, together with the use of photoactivatable fluorescent probes to track the itineraries of these membrane cargoes. In addition, the role of specific transport machinery in APP and BACE1 transport will be assessed by silencing transport machinery using lentivirus to deliver RNAi. A wide range of other biochemical and cell biological approaches will also be employed

Project supervisor
Prof Paul Gleeson

Project co-supervisor
Dr Lou Fourriere

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The Golgi Apparatus: a new hub for the regulation of mTOR signaling and autophagy in health and disease

Vertebrates have evolved mechanisms for joining the individual Golgi stacks into a ribbon, typically found in a juxtanuclear location in interphase cells. The organization of the Golgi apparatus is highly dynamic and the Golgi ribbon can dissociate and re-organize under a variety of conditions, for example, during mitosis and to reposition the Golgi to accommodate a number of processes, including directed secretion and pathogen invasion. Surprisingly, and despite our knowledge of Golgi dynamics, the fundamental biological relevance of the "ribbon" structure of the Golgi in vertebrates has remained a mystery. The classic functions of the Golgi, namely membrane transport and glycosylation, do not require a ribbon structure and the relevance of the Golgi ribbon structure has been elusive. We have developed a cell-based system to explore the biological functions of the Golgi ribbon and have recently discovered that the Golgi represents a major intracellular hub for control of the mTOR signaling pathway and in regulating autophagy. mTOR signaling regulates many fundamental cell processes including growth and metabolism. Neurodegenerative diseases and cancer are often associated with changes in Golgi morphology and we have shown that the Golgi-localized mTOR signaling pathway are likely to contribute to these diseases.

This project will investigate the role of the Golgi on the higher order functions of metabolism and autophagy in range of condition, including stress. A wide range of technologies will be used in this project including viral transduction, high resolution light microscopy, electron microscopy, flow cytometry, quantitative immunoblotting, proteomics and metabolic analysis.

Project supervisor
Prof Paul Gleeson

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Extending the serum half-life of novel therapeutic proteins

The neonatal Fc receptor (FcRn) plays a critical role in regulating the half-live of a range of serum proteins, including IgG and albumin, in the adult individual. The Fc receptor protects these serum proteins from degradation by binding to IgG and albumin in endosomes after internalization by cells and releasing the proteins back into the plasma. There is considerable interest in exploiting this protective pathway to prolong the life time of engineered therapeutic proteins by attaching the FcRn ligand binding motif to recombinant therapeutic proteins. In collaboration with CSL at Bio21, this project will define the membrane recycling pathway of the FcRn, and the itinerary of albumin-based ligands, information which is critical for the optimizing the life span of therapeutic proteins. The project will analyse the role of FcRn in specific cell types including macrophages, dendritic cells and endothelial cells which are considered to be the major sites for recycling in the body. Both cultured and primary cells, derived from FcRn engineered mice, will be employed. A wide variety of biochemical and cell biological methods will be used including transfection cell systems, trafficking assays, coupled with RNAi silencing of transport machinery, to dissect the pathway of ligand internalization and recycling, the kinetics of recycling using quantitative biochemical assays, as well as mass spec analysis of the recycled ligands to determine if the itinerary of recycling has resulted in post-translational modifications which may impact on function.

Project supervisor
Prof Paul Gleeson

Project availability

- PhD
- Master of Biomedical science
- Honours

GOOLEY GROUP

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Structural biology
Biophysics
Protein receptors
Drug Design
Pathogens

The Gooley group uses structural biology and physical biochemistry methods to study how proteins work normally and in disease. Our current interests are proteins involved in viral-host cell interactions and the mechanisms of ligand-recognition and activation of G protein-coupled receptors.

Project: Defining the host-viral molecular interactions of rabies proteins.

Symptomatic infection by rabies virus causes an incurable and invariably lethal disease. The virus manipulates the immune response of the host cell to avoid detection during replication. To achieve this viral proteins interact with and manipulate the function of proteins of the host cell. Key to this process is the rabies virus P-protein whose full functions are not understood. P-protein interacts with other viral proteins, including the rabies L- and N-proteins, for viral replication, but it also is known to bind the immune-signalling transcription factors STAT1 and STAT2, preventing them from entering the nucleus to activate antiviral in response to interferons. The regions and amino acid residues of P-protein that are involved in these processes are unclear, and the full extent of host protein/P-protein interactions remain to be resolved. This project broadly aims to understand the molecular interactions of P-protein with its multiple targets and includes techniques such as mutagenesis to perturb specific interactions, and characterization of these mutants by cell-based assays. Mutants that lose (or gain) function will be structurally characterized and the impact on their molecular interactions determined using an array of techniques. These studies will lead towards the design of novel anti-virals and vaccines.

Project supervisor
Prof Paul Gooley

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The complex binding mode of the peptide hormone H2 relaxin to its receptor.

The insulin-like hormone relaxin has received recent clinical interest as a treatment for acute heart failure. The biological processes involving relaxin generally are through the activation of the G-protein coupled receptor, RXFP1. However, the molecular details of how relaxin interacts and activates RXFP1 are unclear. In part this is due to the complex multidomain structure of RXFP1: an N-terminal LDLa module essential for activation, a large leucine rich repeat (LRR) domain that is known to contain a relaxin binding site, and a C-terminal transmembrane domain that contains critical regions for activation. Structurally, we have only characterized the LDLa module. However, we have recently discovered that the 32-residue linker between the LDLa module and the LRR domain contains a second relaxin binding site, and therefore we hypothesize that relaxin binds to both this linker and the LRR domain to induce a conformational change, possibly of the linker, that reorients the LDLa module so it can effectively bind and activate the transmembrane domain. This hypothesis requires proving and opens opportunities in understanding receptor activation and the design of novel agonists and antagonists. There are multiple projects available involving mutagenesis of RXFP1 and relaxin, peptide synthesis and cell-based assays to monitor binding and activation of these mutants/analogues; expression and purification of the domains of RXFP1, structural determination of these domains and characterization of their molecular interactions.

Project supervisor
Prof Paul Gooley

Project co-supervisors
Dr Daniel Scott, Prof Ross Bathgate, A/Prof Mike Griffin

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Probing the conformational dynamics of peptide binding G protein-coupled receptors.

G protein-coupled receptors (GPCRs) are a large family of signalling proteins (>800 gene members) located on the surface of all cells in the body, particularly in the brain. GPCR signalling controls virtually every physiological process in the body, making these receptors the targets of many current drugs treating conditions like pain, hypertension, schizophrenia and asthma. GPCRs exist as an ensemble of conformational states (inactive, intermediate and active) in equilibrium, with agonist binding shifting this equilibrium towards active states to stimulate cell signalling. A deeper understanding of the structural basis underlying GPCR signalling is needed to guide the design of improved therapeutics. The low expression levels and instability of GPCRs makes them difficult proteins to biochemically characterize. We have engineered high expressing, stabilized GPCRs that we can isotopically label for structural analysis with NMR. Using NMR we can observe that the receptors are dynamic and as expected that the conformational equilibrium is influenced by the binding of particular ligands (e.g. agonists vs antagonists). This project is focused on introducing NMR probes into these GPCRs so that we can characterize the structure and dynamics of specific domains within the proteins. Ultimately this will give us generic insight into how ligands engage GPCRs and how GPCRs transmit ligand binding signals into the cell.

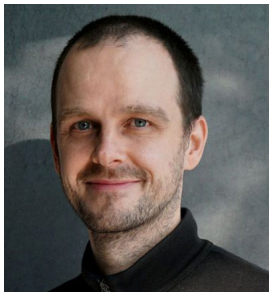
Project supervisor
Prof Paul Gooley

Project co-supervisor
Dr Daniel Scott

Project availability

- PhD
- Master of Biomedical science
- Honours

GRIFFIN GROUP



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Structural Biology	**Cancer**
Biophysics	**Neurodegeneration**
Drug Design	**Pathogens**

We use a wide range of structural biology and biophysical techniques, including X-ray crystallography, cryo-electron microscopy, and analytical ultracentrifugation, to understand the structure, and assembly of proteins into complexes that range from simple homo-dimers to large hetero-oligomers. We are particularly interested in the function and structural mechanisms of multimeric signalling complexes, protein effectors, oligomeric enzymes, and amyloid fibrils.

Project: Apolipoprotein A-I and amyloid fibril formation in disease: how does it change shape and misfold?

Apolipoprotein A-I (apoA-I) binds phospholipid and cholesterol and mediates reverse cholesterol transport; the process by which cholesterol is removed from the body via high density lipoproteins (HDL). High plasma levels of apoA-I provide a number of beneficial effects in the cardiovascular system. However, apoA-I also forms amyloid deposits in atherosclerosis and in hereditary amyloidosis, which leads to failure of vital organs. Amyloid deposition is associated with many debilitating neurological and systemic diseases including Alzheimer's disease, Parkinson's disease, and diabetes type II. Pathological apoA-I amyloid fibrils are generally composed of the N-terminal portion of the protein; however, very little is known about the mechanism of apoA-I amyloid formation in disease.

We have demonstrated that oxidation of the methionine residues of apoA-I leads to amyloid fibril formation by the intact protein, providing a possible mechanism for amyloid deposition in atherosclerosis where oxidative damage to proteins is common. In vivo, the majority of apoA-I is bound to lipid in the form of HDL, which inhibits its propensity to misfold and form amyloid. This project will investigate the structural mechanism by which folded, lipid-bound apoA-I converts to a misfolded form and aggregates into amyloid fibrils. This will be achieved using a variety of biophysical and structural analyses of lipid-bound and lipid free apoA-I, including the use of conformationally-specific antibodies that recognise specific apoA-I structures.

Project supervisor
A/Prof Michael Griffin

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The structure and function of the Interleukin-11 signalling complex, a new cancer target.

Interleukin (IL)-11 is a member of the IL-6 family of cytokines that performs a wide range of biological functions. Recombinant human IL-11 is administered as a standard clinical treatment for chemotherapy-induced thrombocytopenia. Recently, we identified a new role for IL-11 signalling as a potent driver of gastrointestinal cancers, and demonstrated that it is a novel therapeutic target for these diseases. Cell signalling by IL-11 is initiated by binding of soluble IL-11 to its membrane bound, specific receptor, IL-11Rα. This binary complex subsequently engages with the signal transducing receptor, GP130, inducing GP130 dimerisation and resulting in activation of the transcription factor Signal Transducer and Activator of Transcription (STAT)-3.

Despite its importance, our understanding of the structure of the IL-11 signalling complex and the interactions between its components remains rudimentary. Our recent work has produced the first crystal structure and biophysical characterization of IL-11, and we are currently investigating the structural details of the complex between IL-11 and IL-11Rα. This project will use biophysical techniques, including NMR and X-ray crystallography, to understand the interactions between IL-11, IL-11Rα and GP130 that lead to the formation of the active signaling complex.

The ultimate goal is to use this information to design inhibitors of IL-11 signalling that may be useful as cancer therapeutics.

Project supervisor
A/Prof Michael Griffin

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The structure and function of Coxiella burnetii effector protein Cig57: how does it subvert endocytosis within the human host cell?

Coxiella burnetii is an intracellular bacterium that causes the human disease Q fever. *C. burnetii* infects alveolar macrophages, and replicates within a spacious, lysosome-derived vacuole that matures to feature an acidic internal environment characteristic of a lysosome. During infection, over 150 effector proteins are translocated into the host cytoplasm to facilitate intracellular survival of the bacteria. One of these effector proteins, Cig57, is essential for replication of *C. burnetii*.

We have discovered that Cig57 has a role in exploiting clathrin-mediated endocytosis of the eukaryotic host by interacting with the host cell nucleators of clathrin coated vesicles, FCHO1 and FCHO2. However, the functional mechanisms of this effector protein have not yet been determined. Our structural studies of Cig57 indicate that the protein consists of 3 domains. While we have solved the crystal structure of the central domain, the structural and functional properties and interactions of the other domains are unknown. This project will use biophysical and structural approaches to understand the structure of the individual domain components of Cig57 and their interactions with FCHO proteins, with a view to exploiting this information for development of therapeutic agents against Q fever.

Project supervisor
A/Prof Michael Griffin

Project co-supervisor
Dr Hayley Newton

Project availability

- PhD
- Master of Biomedical science
- Honours

HATTERS GROUP

Contact: **Professor Danny Hatters**
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Proteomics	**Neurodegeneration**
Cell Biology	**Organelles**
Computational Biology	**Biophysics**

The Hatters group investigates the molecular origins of neurodegenerative diseases with an emphasis on Huntington and Motor Neuron diseases. The lab is particularly focused on the quality control mechanisms of protein folding, and aberrant mechanisms involving protein misfolding and aggregation. Key interests include developing novel biosensors and tools to explore the biology in cellular and animal models of disease.

Project: Understanding how membrane-less organelles form with optogenetic tools.

Recent research has identified a completely novel phase-separation strategy cells use to organize proteins and nucleic acids together into protein liquid droplet compartments that are distinct to the those traditionally bound by membranes (such as the ER). The fundamental details of these protein liquid droplets are formed is not well understood but defects in how they form appear to be central to neurodegenerative disease mechanisms. In this project, a new optogenetic toolkit will be used to control how protein liquid droplets form in mammalian cells using light. The project test whether several candidate proteins form liquid droplets and design mutations to test how the droplet formation is regulated. The project will involve designing and cloning new constructs, testing their expression in mammalian cells and designing mutations into them.

Project supervisor
Prof Danny Hatters

Project availability
- PhD
- Master of Biomedical science
- Honours

Project: Designing new optogenetic tools for biomedical research

Optogenetics describes the manipulation of gene or protein function using light. This powerful technology has exploded in the last few years because it provides exquisite control of a range of biological functions in biomedical research. In this project, we seek to develop a new way to control the activity of streptavidin using light. Streptavidin binds with extremely high affinity to biotin and hence has been used as one of the best systems in biology to detect and/or capture specific protein:protein interactions. Controlling its activity with light will provide a new way to target protein:protein interactions in a spatially controllable manner. This project will build on prototype designs in the lab and test the efficacy of them for being regulated by light. This will involve cloning genes, modeling protein structures, designing targeted mutations and testing activity in mammalian and bacterial cell culture systems.

Project supervisor
Dr Craig Morton

Project co-supervisor
Prof Danny Hatters

Project availability
- PhD
- Master of Biomedical science
- Honours

Project: Protein quality control mechanisms in neurodegenerative diseases

The protein homeostasis system is vital for cell function, as it ensures that proteins are properly translated, folded, trafficked to their correct cellular locations, and eventually degraded in a tightly controlled and timely manner. As a major task for this system is to prevent damaged and misfolded proteins from accumulating, it has been hypothesized that, when this system becomes unbalanced, proteins can become prone to misfolding leading to their mislocalisation and accumulation as aggregates. Dysfunctional protein aggregation and protein homeostasis imbalance are central pathological features of common neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's, and motor neuron diseases. Our lab has several projects aimed at probing how the proteome becomes destabilized upon protein quality control imbalance and what the mechanisms are that become defective in neurodegenerative disease contexts. Approaches include cell biology approaches (such as microscopy, gene editing, flow cytometry), proteomics and other cutting-edge biochemistry methods.

Project supervisor
Prof Danny Hatters

Project co-supervisor
Prof Gavin Reid

Project availability
- PhD
- Master of Biomedical science
- Honours

HINDE GROUP

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Biophysics

Cell Biology

Cancer

The Hinde group The research focus of the Hinde lab is on the architectural organisation of the cell nucleus and how chromatin dynamics facilitate navigation of the genome. Inside the nucleus of a living cell, DNA is folded into a multi-layered 3D structure called chromatin. At any moment in time, thousands of proteins are diffusing throughout this structural framework - scanning the genome for a target DNA sequence. The question is “does the chromatin network serve as ‘road map’ for molecular traffic during DNA target search?” To investigate this, we are developing microscopy methods - based on fluorescence lifetime and correlation spectroscopy - to track how proteins move throughout the DNA networks of a living cell. Using this technology we have discovered sub-micron rearrangements in chromatin density that direct the diffusive route of DNA repair factors to damage sites and mediate transcription factor accumulation at specific nuclear locations. This body of work demonstrates an active role for 3D chromatin organisation in nuclear factor navigation. This is important because a hallmark of cancer is genome dysregulation.

Project: Imaging transcription factor DNA target search in a living cell

Transcription factors have evolved DNA target search strategies that allow them to efficiently navigate the nuclear space and arrive at their specific DNA sequence. This target search strategy is underpinned by molecular diffusion, which in turn is controlled by the architectural organisation of the cell nucleus and oligomeric state of the transcription factor. Until recently no imaging approach could track the molecular mobility of protein oligomers within the nuclei of live cells. To address this research gap we recently established a new microscopy method to image the transport and binding dynamics of different oligomeric species in live cells (Hinde et al. 2016. Nature Comm. 11047). The overall aim of this project is to use to use this technology to uncover how the spatial compartmentalisation of the cell nucleus regulates transcription factor complex formation and DNA target search in a living cell.

Project supervisor
Dr Elizabeth Hinde

Project co-supervisor
Dr Jieqiong Lou

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Chromatin dynamics and how they regulate the DNA damage response

Tumour suppression relies on the preservation of genome integrity and this is maintained by a cellular surveillance system called the DNA damage response (DDR). Amazingly the DDR can almost instantaneously detect a genomic lesion. However, how it spatiotemporally coordinates DNA repair factor recruitment to that damage site is not currently understood. We recently demonstrated that double-strand breaks (DSB) induce a transient local ‘opening’ of chromatin at the damage site that is bordered by an increased level of chromatin compaction (Hinde et al. 2014 Biophys. J 107(1)). These dynamic rearrangements in local DNA density appear to facilitate DNA repair factor accumulation at only the damage site. By use of a fluorescence microscopy method that can track how proteins move throughout the 3D DNA network of a living cell, the aim of this project is to map the impact of nuclear wide changes in chromatin compaction on DNA damage signalling and repair.

Project supervisor
Dr Elizabeth Hinde

Project co-supervisor
Dr Jieqiong Lou

Project availability

- PhD
- Master of Biomedical science
- Honours

MCCONVILLE GROUP

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Pathogens	**Metabolomics**
Metabolism	**Discovery Research**
Drug Design and Resistance	

The McConville group is interested in understanding how intracellular microbial pathogens, responsible for diseases such as malaria, human leishmaniasis and toxoplasmosis, are able to survive within their human/animal hosts and cause disease. We utilize advanced mass spectrometry approaches, as well as a range of biochemical and genetic techniques to identify microbial metabolic pathways that are switched on during infection and are essential for pathgenesis. We are also interested in identifying metabolic pathways in the host cell that are required for pathogenesis. These studies are directed at understanding fundamental aspects of microbial pathogenesis, as well as developing new anti-microbial or host-directed therapies for these important diseases.

Project: Identification of novel metabolic pathways in Leishmania parasites

Leishmania spp are sandfly-transmitted protozoan parasites that cause a spectrum of serious and potentially lethal diseases in more than 12 million people world-wide. Existing therapies are limited and there is an urgent need to identify new drug targets in these parasites. We have shown that these parasites synthesize a novel carbohydrate reserve material, termed mannogen, that is required for parasite growth in macrophages, the major target cell in the human host. We have recently identified a novel family of enzymes involved in mannogen synthesis and catabolism that are essential for virulence. This project will utilize a range of genetic and biochemical approaches to define the function of new protein that appears to have a key role in initiating (priming) mannogen synthesis. The project will investigate whether this protein is directly involved in mannogen priming (catalytic function), or whether it regulates the activity of the mannogen 'synthases' through protein-protein interactions (chaperone function). It will use in vivo proximity-tagging approaches (to measure protein-protein interactions), expression of recombinant protein, mutagenesis and enzyme assays and analysis of parasite central carbon metabolism using mass spectrometry.

Project supervisors
Prof Malcolm McConville

Project co-supervisor
Dr Julie Ralton
Dr Fleur Sernee

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Genome wide analysis of host responses to Leishmania infection

Antibiotic resistance is an ever-present and increasing threat to humanity. One strategy to prevent or minimize antibiotic/drug resistance in infectious diseases is to develop drugs that target processes in the host cell that are essential for microbial growth, rather than the microbe directly. Such an approach may be useful against multiple pathogens and can complement immune strategies (such as vaccination). This project will investigate whether host-directed therapies can be developed to treat human leishmaniasis, a pathogen that infects 120 million people world-wide. We have identified >100 genes in the macrophage host that are required for Leishmania growth in genome-wide siRNA screen. In this project we will define how individual host genes impact on Leishmania infection using siRNA and/or CRIPR/Cas9 silencing/knock-down strategies. Detailed analysis of macrophage and parasite metabolism will also be investigated in genetically modified macrophages,

providing fundamental information on host-parasite interactions. This project will utilize an array of cell biological (fluorescence microscopy) and metabolomics (mass spectrometry, Seahorse Metabolic Analyzer) approaches.

Project supervisors
Prof Malcolm McConville

Project co-supervisor
Dr Eleanor Saunders

Project availability

- PhD
- MSc
- Honours

Project: Using high through-put genetic and metabolomic approaches to identify new drug targets in parasitic protozoa

Leishmania spp are sandfly-transmitted protozoan parasites that cause a spectrum of serious and potentially lethal diseases in more than 12 million people world-wide. Existing therapies are limited and there is an urgent need to identify new drug targets in these parasites. This project will exploit newly developed CRISPR/Cas9 genetic tools to generate a large panel of parasite mutants with defects in metabolic pathways that are hypothesized to be essential for parasite survival in host cells and infection. The mutants will be characterized using advanced mass spectrometry-based metabolite profiling and 13C-stable isotope labeling to confirm the metabolic defect and identify any unanticipated by-pass pathways. Pooled parasite mutants (genetically bar-coded) will be assessed for loss of infectivity in host cell assays and further characterized biochemically. This project will allow us to develop more comprehensive models of parasite metabolism, and triage metabolic pathways that are potential drug targets in these medically important pathogens

Project supervisors
Prof Malcolm McConville

Project co-supervisor
Dr Eleanor Saunders
Dr Fleur Sernee

Project availability

- PhD
- Master of Biomedical science
- Honours

MINTERN GROUP

Contact : **A/Prof Justine Mintern**
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Email: **jmintern@unimelb.edu.au**
Weblink: **Click here**

Immunology	**Proteomics**
Cell Biology	**Cancer**
Organelles	**Pathogens**

The Mintern group uses models of vaccination, infection and cancer to study mechanisms of immunity. The lab investigates how immunotherapies can be designed to exploit the cell biology of immune cells. Key interests include using nanoparticles as vaccines and investigating the molecular machinery involved in immune cell function.

Project: Manipulating immunity to fight infection and tumours.

Vaccination currently represents the most effective strategy for eliminating infectious disease. While many vaccines are in use worldwide, for several pathogens our current vaccines fail with ensuing uncontrolled disease. This is the case for HIV, malaria and tuberculosis resulting in disease and devastation worldwide. Vaccines also have the potential to prevent and/or treat cancer, however this is currently not a clinical reality. Therefore, vaccine design must be advanced, and to do so, we require a more comprehensive understanding of the cell biology involved. A key question in vaccine biology is how are the proteins involved in this response trafficked to and from specialised immune cell compartments. This project will use CRISPR/Cas9 methodology, together with new mouse models of disease, to investigate the consequence of targeting specific components of the molecular machinery that participate in immune cell protein trafficking.

Project supervisor
A/Prof Justine Mintern

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Decoding the trafficking of immune receptors.

Ubiquitin is a protein tag that once attached to a substrate has important implications for its fate. Attachment of ubiquitin can change the intracellular trafficking route of the protein with important consequences for the cell. The ubiquitin chain attached is often termed a ubiquitin code and will differ for individual proteins. This project will investigate the role of ubiquitin in the tagging and trafficking of immunoreceptors. Specifically, it will investigate the MARCH family. MARCH are membrane associated E3 ligases that are responsible for attaching ubiquitin chains to substrate proteins embedded

in membranes. How MARCH participate in controlling the intracellular trafficking of critical immune molecules in different immune and non immune cell types will be examined. In addition, this project will examine new MARCH substrates, how MARCH are regulated and determine the ubiquitin code generated by distinct MARCH family members. This project will use CRISPR/Cas9 methodology, flow cytometry and mass spectrometry to examine the role of ubiquitin in shuttling key immune molecules to specific destinations in the cell

Project supervisor
A/Prof Justine Mintern

Project availability

- PhD
- MSc
- Honours

Project: Exploiting nanoparticles as vaccines.

Nanoparticles have exciting potential to serve as modular therapeutic delivery systems that can target any cell type and carry any therapeutic peptide cargo. One emerging application for nanoparticles is their use as next generation vaccines. While there have been significant successes in vaccine research, there are still many remaining challenges including developing vaccines against chronic infections such as HIV, malaria, tuberculosis, together with exploiting the potential of vaccination to eliminate cancer. To develop vaccines against chronic disease, nanoparticles are needed that can target the cells responsible for initiating immunity, dendritic cells, and release immunogenic peptides (antigen). Here, we will examine the potential of nanoparticles as carriers that enable effective vaccination. We will investigate how different nanoparticle formulations can be used to elicit immunity to infection and tumours. We will investigate caveospheres, biological nanoparticles consisting of vessicles derived from cell membranes, in addition to synthetic nanoparticles that can be designed with properties that enable manipulation of the endocytic pathway. Nanoparticles will be tested in immune assays including as vaccines against lymphoma and influenza virus infection.

Project supervisor
A/Prof Justine Mintern

Project availability

- PhD
- Master of Biomedical science
- Honours

PARKER GROUP

Contact : **Professsor Michael Parker**
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Email: **mwp@unimelb.edu.au**
Weblink: **Click here**

Pathogens	**Structural Biology**
Cancer	**Computational Biology**
Drug Design and Resistance	**Neurodegeneration**

The focus of our research is to visualise the three-dimensional structures of medically important proteins using structural biology techniques including X-ray crystallography and cryo electron microscopy. A particular focus is proteins that play a role in infection (bacterial, parasitic or viral), cancer (particularly leukaemia, breast and prostate) and neurological diseases (e.g. Alzheimer's, Parkinsons, autism). The structures provide a detailed understanding of how each protein works and how it contributes to disease. Most importantly, the structures can be used to discover drugs using computational and biophysical approaches.

Project: Overcoming cancer drug resistance

Conventional cancer chemotherapy kills rapidly growing cells indiscriminately, causing significant side-effects and can lead to disease re-occurrence and resistance to the drugs. One of our interests is the Glutathione S-Transferase (GST) family of proteins that function by recognising foreign small molecule toxins in the body, causing them to be eliminated from the cell. Unfortunately, commonly used anti-cancer drugs are also recognised as toxic by GSTs, which are often overexpressed in cancer tissues and are associated with transformation to malignancy and the adaptive resistance to anti-cancer drugs. There is thus an urgent need for the design of new anti-cancer drugs that circumvent the development of GST-mediated resistance to treatment. Recently, there has been an increasing interest in the development of metal-based drugs as effective and potent protein targeted chemotherapies. We are investigating, though structural and biochemical means, how a range of ruthenium, arsenic and osmium-based drugs and drug-like compounds interact with GSTs. Students will investigate how these compounds work, as well as any drug-like molecules we develop, using X-ray crystallography and a range of biophysical techniques.

Project supervisor
Prof Michael Parker

Project co-supervisor
Dr Craig Morton

Project availability

- Honours

Project: Improving current approaches to Alzheimer's disease

Alzheimer's disease (AD) is the fourth biggest killer in developed countries. Amyloid precursor protein (APP) plays a central role in the development of AD, through generation of the toxic Abeta peptide by proteolytic breakdown of APP. Here we will use X-ray crystallography at the Australian Synchrotron to determine the 3D atomic structures of Abeta bound to therapeutic antibodies currently in clinical trials in order to understand how these molecules recognise Abeta. We use this information to engineer more potent antibodies as treatments for AD. We also have structure-based drug discovery projects on APP itself and other proteins involved in the production and clearance of the Abeta peptide from the brain.

Project supervisor
Prof Michael Parker

Project availability

- PhD
- Honours

Project: Understanding how bacterial pore-forming toxins punch holes in membranes

The βeta-barrel pore-forming toxins constitute the largest group of functionally related protein toxins. They are expressed in many species in the prokaryotic and eukaryotic kingdoms and are related to the membrane attack complex/perforin (MACPF) family of mammalian immune defence proteins. Despite their widespread occurrence and role in bacterial pathogenesis and immune defence, the detailed mechanism by which they form pores remains an enigma. The overall aim here is to visualise the 3D structures of family members as a basis for functional studies to reveal the molecular details of how these toxins insert into membranes to form beta-barrel pores and how the process is regulated. The structures will shed light on one of the most fundamental biological events (namely, protein insertion into cell membranes) and also provide the basis for the design of novel tools with various biotechnology applications and the design of novel antibiotics.

Project supervisor
Prof Michael Parker

Project co-supervisor
Dr Craig Morton

Project availability

- Honours

Project: Drugging the undruggable to combat cancer

Modulating protein–protein interactions represents a huge potential for cancer therapeutic intervention with over 300,000 protein interaction pairs already identified in the human genome. Historically, targeting these interactions with small molecules was not thought possible because the corresponding interfaces would be “undruggable”. However, the last decade has seen encouraging breakthroughs via refinement of existing techniques and development of new ones, together with the identification and exploitation of unexpected aspects of protein–protein interaction surfaces. In this project we wish to discover new drugs that disrupt protein-protein interactions in cancer using a mixture of techniques including computational biology, protein expression and purification, X-ray crystallography and measurement of protein interactions.

Project supervisor
Prof Michael Parker

Project availability

- Honours
- PhD

Project: New antibiotics to treat deadly infections

Bacterial biofilms are matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces. Bacterial biofilm formation is an extremely common phenomenon with a major economic impact in different industrial, medical and environmental fields. Klebsiella pneumoniae is a Gram-negative, opportunistic pathogen that is frequently associated with infections such as urinary tract infections, pneumonia and septicemia. An important clinical pathogenic mechanism of K. pneumoniae is is its ability to form robust biofilms on inanimate surfaces (eg. plastics used in surgical implants). This project aims to inhibit biofilm formation by targeting adhesion molecules using biophysical, computational and structure-based drug design techniques.

Project supervisor
Prof Michael Parker

Project availability

- Honours
- PhD

Project: Understanding a rare disease to develop treatment for common bone diseases

Remodelling of bone is critical for normal physiological function and becomes dysfunctional in diseases such as Osteoporosis (bone thinning and fragility) and Osteosarcoma (bone cancer), where a paucity of bone material causes debilitating illness that is currently irreversible. Alternatively, mutation of a specific membrane protein, ClC-7, causes a rare inherited disease (Osteopetrosis) in which too much bone material is deposited leading to abnormally increased bone mass. Our preliminary studies have suggested a molecular basis for aberrant function of ClC-7 mutants in Osteopetrosis. The aim of this project is to fully characterise the mechanism of ClC-7 mutations that cause Osteopetrosis in order to develop drugs that mimic the phenotype of these mutations. Uniquely, these drugs would be able to reverse the damage done by a number of debilitating bone diseases. The project will involve a diverse range of experimental approaches, from X-ray crystallography and in silico computational studies to binding studies and functional measurements using advanced electrophysiological techniques and optical assays.

Project supervisor
Prof Michael Parker

Project availability

- Honours

RALPH GROUP

Contact: **Associate Professor Stuart Ralph**
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Weblink: **Click here**

- **Computational Biology**
- **Drug Design and Resistance**
- **Cell Biology**
- **Pathogens**
- **Genomics**

The Ralph group is interested in parasitic diseases, with a primary focus on the causative agent of severe malaria, *Plasmodium falciparum*. The burden of disease-causing parasites is particularly high in developing countries, and inadequate resources are directed towards the development of much needed treatments. Complete genome sequences are available for many of these parasites, so a wealth of data is available from which to search for potential targets for chemotherapeutic interventions. The group's interests lie in identifying and characterising promising drug targets from *Plasmodium falciparum* and other parasites, as well as studying the modes of action and mechanisms of resistance for existing drugs.

Project: tRNA synthetases enzymes as anti-malaria drug targets

We are characterising aminoacyl-tRNA synthetase (aaRS) enzymes as drug targets in Plasmodium. These enzymes catalyse the attachment of amino acids to their relevant tRNA molecules and are essential for protein synthesis. They have recently been recognized as promising drug targets across a broad range of microbes, and we have recently identified Plasmodium aaRSs that are potential targets for new drugs to treat malaria. Plasmodium aaRS enzymes differ from those of humans, so we hope to develop drugs specific for Plasmodium. We are using in silico screening methods to identify likely inhibitors of Plasmodium tRNA synthetases and developing assays to measure specific inhibition of Plasmodium aaRS enzymes. We will also test inhibitors for their ability to kill Plasmodium grown in culture.

Project supervisor
A/Prof Stuart Ralph

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Alternative splicing in malaria and other parasites

Next generation sequencing has revealed that an unexpectedly high proportion of mammalian genes undergo alternatively splicing to produce multiple transcript isoforms. We have recently shown that alternative splicing is also widespread in the human parasites Plasmodium (causative agent of malaria) and Toxoplasma, (causative agent of toxoplasmosis). We have also demonstrated that this mechanism is necessary for parasites differentiating from human to mosquito life-stages. We will now apply novel long-read sequencing techniques to establish the impact of alternative splicing on whole transcripts in a variety of human and veterinary parasites. We will also investigate the implications of alternative splicing on generation of proteome diversity and its consequences for parasite differentiation.

Project supervisor
A/Prof Stuart Ralph

Project co-supervisor
A/Prof Aaron Jex

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Bioinformatic analysis of protein subcellular localisation in human parasites

We are making and validating new bioinformatic tools that predict and classify sub-cellular localisation of proteins. We are interested in automatically extracting information from the literature that specifies the sub-cellular localisation of proteins in the malaria parasite Plasmodium falciparum, and in related related human parasites. Information about sub-cellular localisation in infectious agents is crucial to prioritising targets for drugs and vaccines. We have built a database that details subcellular localisation of hundreds of Plasmodium proteins (http://apiloc.biochem.unimelb.edu.au/apiloc/apiloc), and will use this as a training set for Biomedical Natural Language Processing. The project will involve construction of a tool to recognise and extract records of cellular localisation for proteins as a means to identify proteins on the surface of malaria parasites, as well as tools to predict localisation for novel, uncharacterised proteins.

Project supervisor
A/Prof Stuart Ralph

Project co-supervisor
Prof Karin Verspoor

Project availability

- PhD
- Master of Biomedical science
- Honours

REID GROUP

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Proteomics	**Analytical Biochemistry**
Lipidomics	**Metabolism**
Cancer	**Metabolic Disease**

The main research focus of the Reid laboratory is the development of innovative analytical biochemistry, mass spectrometry, and associated strategies for quantitative lipidome and proteome analysis, and their application toward identifying the functional role of lipids and proteins in the onset and progression of disease, including cancer and neurodegeneration.

Project: Elucidating Functional 'Hallmarks' of Aberrant Lipid Metabolism in Disease

The dysregulation of lipid metabolism is known to be associated with malignancy and metastatic progression in several diseases, including cancer. Recent pilot studies to survey the global 'lipidomic hallmarks' of colorectal cancer (CRC) in our laboratory suggest that variations in the 'lipidome' profiles observed between individual CRC cell lines, or between patient tumour samples versus normal tissue, constitute a complementary taxonomy relative to currently used genomic, transcriptomic and proteomic classifications. In this project, you will apply multi-'omic analysis strategies using advanced lipidome and proteome technologies to identify altered lipid metabolism pathways and key lipid metabolism enzymes that are responsible for these changes at the tissue, cell, or sub-cellular levels, and to characterize changes in their lipid-protein 'interactomes', and then use genetic knock out/in (CRISPR/Cas9) and chemical inhibition, along with functional assays of cellular proliferation, migration and invasion, to probe the functional roles of these alterations in the regulation of cellular homeostasis.

Project supervisor
Prof Gavin Reid

Project co supervisor
A/Prof Oliver Sieber

Project availability

- PhD
- Master of Biomedical science
- Honours

ROUILLER GROUP

Contact: **Associate Professor Isabelle Rouiller**

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Weblink: **Click here**

Structural Biology	**Drug Design and Resistance**
Cancer	**Pathogens**
Neurodegeneration	**Vaccines**

The Rouiller group uses cryo-EM to determine the structures of medically important protein complexes. Lab members investigate how these proteins assemble into molecular machines and study how they function in the context of health and disease. We are particularly interested in proteins relevant for cancer treatment, antibiotic resistance, vaccine development and neurodegenerative diseases.

Project: Targeting the AAA ATPase p97 for cancer treatment

Cancer cells are very dependent on the ubiquitin-mediated degradation pathway (UPD) due to genomic abnormalities and the resulting increased amount of aberrant proteins. Inhibition of the UPD results in the accumulation of abnormal proteins and eventually death of cancer cells. Because the AAA ATPase p97 functions upstream of the proteasome in the UPD, it is a promising target for the treatment of various cancers.

Drugs targeting p97 are in the very early stages of development. Despite promising results in various animal models, drug specificity remains a major challenge for treating cancer in human. The best drug candidates are allosteric inhibitors, that is, non-ATP competitive inhibitors that prevent conformational changes associated with p97's function. Efficient development of such inhibitors require an in-depth understanding of the molecular mechanisms driving p97 function.

Our lab uses a combination of structural biology (cryo-EM), computational biology (Molecular Dynamics and Bioinformatics) and biophysical approaches (fluorescence spectroscopy) in order to understand how p97 functions at the molecular level. The overarching aim of this project is to define strategies at the molecular level to develop specific drugs for p97 that efficiency and specifically target p97 for cancer treatment.

Project supervisor
A/Prof Isabelle Rouiller

Project co supervisor

Dr Ashish Sethi

Project availability

- Master of Biomedical science
- Honours

Project: Destroying the human immunodeficiency virus before infection

Despite numerous advances in treatment and prevention, 37 million people are currently infected with HIV worldwide. The difficulty in treating HIV is that the virus hides inside a subset of the host immune cells, the T-cells. The solution to this problem would be to destroy the virus before it is able to enter the T-cells using the antibody-dependent cellular cytotoxicity (ADCC) mechanism. This mechanism requires recognition of the virus by neutralizing antibodies. The HIV-1 envelope glycoprotein trimer (Env), the only viral protein on the surface of virion, is thereby the main target for neutralizing antibodies. The challenge is that, at the surface of the virus, Env adopts a compact, closed conformation that is largely antibody resistant. After binding to its receptor at the surface of T cells, Env undergoes conformational changes and becomes more vulnerable to ADCC. Non-neutralizing antibodies also increase the stability of this vulnerable conformation.

Our lab is characterising using cryo-EM the conformations adopted by Env in response to chemical mimicking the T cells receptor and to binding of non-neutralizing antibodies. The overarching aim of this project is to define and characterize at the molecular level the exact cocktail of antibodies and chemicals to use in order to induce a conformational change in Env so that is recognised and destroyed by the immune system. This knowledge would allow both treatment of HIV infection and the development of vaccines.

Project supervisors
A/Prof Isabelle Rouiller

Project co supervisor
Dr Mohsen Kazemi

Project availability

- Master of Biomedical science
- Honours

Project: Mechanisms of activation of the pain channel TACAN

Mechanosensitive ion channels (MSC) are the sensors for a number of systems including the senses of touch, hearing and balance. They function as mechanotransducers by generating both electrical and ion flux signal as a response to mechanical stimuli. TACAN was recently been identified as the first ion channel responsible for sensing mechanical pain in neurones. TACAN is particularly interesting because it does not share sequence homology to any known class of ion channel.

This project aims to determine the structure using single particle cryo-EM of TACAN in its closed and open conformations. These structures are essential to understand the organisation of the channel. They will allow building of a model of the molecular mechanisms that control activation of this mechanosensitive ion channel. These structures will serve as a basis for functional studies to reveal the molecular mechanism of TACAN activation. The success of this project will make significant contributions to the fundamental understanding of pain sensing and signal sensing by cells in our body. This knowledge will allow the development of novel drugs to treat chronic pain.

Project supervisor
A/Prof Isabelle Rouiller

Project availability

- Master of Biomedical science
- Honours

Project: Elucidating the translocation mechanism of Anthrax toxins

Bacillus anthracis, the causative agent of Anthrax, secretes three soluble proteins collectively known as “Anthrax Toxin”: the pore-forming “Protective Antigen” (PA); and two enzymes the Lethal Factor (LF) and the Edema Factor (EF). PA is cleaved by host proteases at the cell surface before oligomerizing and forming a prepore complex to which LF and EF bind. After endocytosis of this tripartite complex, the prepore transforms into a narrow transmembrane pore that delivers unfolded LF and EF into the host cytosol. Translocation of the LF and EF toxins through PA pore is remarkably efficient.

The broad aim of our research is to understand the molecular mechanisms driving efficient translocation. There are multiple projects available to 1) solve at high-resolution using single particle cryo-EM the fully loaded PA–LF prepore complex, 2) characterize PA pore conformational changes during translocation. Projects involve mutagenesis, protein expression/purification, biochemical characterisation, single particle cryo-EM and cryo electron tomography.

Project supervisor
A/Prof Isabelle Rouiller

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Characterisation of the changes of the endocytic and secretory pathway of dendritic cells upon activation

Dendritic cells are antigen-presenting cells of the mammalian immune system. Their main function is to process antigen material for presentation to T cells. While it is well known that dendritic cells are activated in the process and that activation is associated with the growth of projections (or dendrites), how they process antigen and the associated morphological changes to the endocytic and secretory pathways are far less understood. The endocytic and secretory pathways are essential for antigen presentation. Most importantly, in which cellular compartments/vesicles the antigen is processed is critical to determine the type of immune response (cellular versus humoral). The aim of this project is to characterize the conformational changes of the endocytic and secretory pathways taking place during dendritic cells activation, using a combination of advance imaging approaches, such as fluorescence microscopy, correlative light and electron microscopy, as well as high resolution Serial Blockface Scanning Electron Microscopy.

Project supervisors
A/Prof Isabelle Rouiller

Project co supervisor
A/Prof Justine Mintern

Project availability

- PhD
- Master of Biomedical science
- Honours

SCOTT GROUP

Contact: **Doctor Daniel Scott**
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Weblink: **Click here** **Click here**

Cell Biology	**Computational Biology**
Drug Design and Resistance	**Neurodegeneration**
Structural Biology	**Biophysics**

The Scott group interrogates the molecular mechanisms underlying cellular signalling and exploits these details to develop new tools for drug discovery. A key focus is on G protein-coupled receptors (GPCRs), the largest, yet potentially most underexploited class of drug targets. Our projects combine a wide range of methods such as: protein engineering, directed evolution, cell-based binding and signalling assays, lentivirus, X-ray crystallography, NMR, fluorescence microscopy, electron microscopy, computational modelling, and rational drug design.

Project: Understanding the structural basis of peptide-activated G protein-coupled receptor signalling to enable drug discovery.

Cell-cell communication via endogenous peptides and their receptors is vital for controlling all aspects of human physiology. In humans, most peptides mediate their actions by binding to cell-surface G protein-coupled receptors (GPCRs), which in response trigger intracellular signalling cascades. Because of the vital roles that peptides play, most of these GPCRs are considered pharmacological drug targets to treat a wide range of diseases. Despite this, only 18% of Class A peptide GPCRs are currently targeted by small molecule drugs, compared to 97% of the aminergic receptor family. This reflects a lack of knowledge about how peptides interact with and activate their cognate GPCRs, which hinders drug development and design.

This project focuses on using novel directed evolution methods to engineer peptide GPCRs that preferentially exist in physiologically relevant conformations for which we do not have crystal or cryo-EM structures. The structures of these engineered GPCRs, bound to various peptides, will be investigated using X-ray crystallography, cryo-EM and NMR. Knowledge gained from these projects will contribute to the design of new drugs to treat a range of diseases and conditions such as: dementia, schizophrenia, chronic pain, heart failure, Parkinson's disease, anxiety and depression. Students will be trained in: protein engineering, protein expression and purification, GPCR pharmacological assays, ligand binding assays, protein thermostability measurements, X-ray crystallography, cryo-EM, NMR and peptide modelling and design.

Project supervisor
Dr Daniel Scott

Project co-supervisors
Dr David Thal
Prof Paul Gooley
A/Prof Mike Griffin

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Determining the molecular basis of disease-causing mutations in synaptic proteins.

Sensory information from the environment is processed at the level of synapses, the most fundamental information-processing units in the nervous system. Vertebrate synapses contain large yet intricately organised signalling complexes comprising neurotransmitter receptors, scaffold proteins, transporters and cell adhesion proteins. Human genetic studies continue to increasingly highlight that disruption of pre- and postsynaptic proteins result in neurodevelopmental disorders. Here we are offering projects investigating the molecular basis of newly discovered disease-causing mutations in human presynaptic (with Sarah Gordon) and postsynaptic (with Jess Nithianantharajah) proteins. We have found that several of these mutations alter the structure and function of the synaptic proteins, knowledge which not only informs us on protein function in normal cells, but may allow specific therapeutic targeting. Depending on the project students will be trained in: protein expression and

purification, protein-protein interaction assays (FRET, BRET etc), protein thermostability measurements, X-ray crystallography, NMR and other biophysical methods, confocal microscopy, lentiviral transductions and have the potential to undertake *in vivo* and *ex vivo* experiments

Project supervisor
Dr Daniel Scott

Project co-supervisors
Dr Jess Nithianantharajah
Dr Sarah Gordon

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Fragment-based drug discovery using stabilized α1-adrenoceptors

α_{1A}- and α_{1B}-adrenoceptors (α_{1A}-AR and α_{1B}-AR) are closely related GPCRs that modulate the peripheral and central nervous systems in response to binding epinephrine and norepinephrine. α_{1A}-AR and α_{1B}-AR are putative drug targets for treating heart failure, epilepsy and Alzheimer's disease. However, these receptors represent prototypical GPCR subtypes, where determining the physiological roles and clinical targeting of α_{1A}-AR and α_{1B}-AR individually has been hindered due to their highly similar agonist binding sites and a subsequent lack of subtype selective tool ligands. Thus there is a need to identify novel, sub-type selective tool ligands to probe the validity of targeting α_{1A}-AR or α_{1B}-AR for these diseases. Fragment screening is a validated approach for identifying and optimizing compounds that are selective for certain protein family members over others, but has not been directly applied to closely related GPCR subtypes. The primary reason for this is that the instability of purified GPCR preparations makes screening with the biophysical methods required for fragment screening challenging. We generated thermostabilized α_{1A}-AR and α_{1B}-AR variants suitable for biophysical studies, allowing the screening of a small, yet diverse fragment library with NMR spectroscopy and surface plasmon resonance. This screen identified two structurally related hits that preferentially bound α_{1B}-AR over α_{1A}-AR, one of which was subsequently shown to exhibit 10-fold selectivity for inhibiting α_{1B}-AR signalling. Another hit was a selective α_{1A}-AR agonist. To develop these hits into tool compounds and potentially drug leads, this project will focus on understanding their structure-activity relationships of the hit molecules at each receptor. This will be probed using traditional molecular pharmacology and using biophysical approaches such as NMR. The resultant information will be used to develop novel compounds to elucidate the individual physiological roles of α_{1A}-AR and α_{1B}-AR and their potential as targets for disease treatments. Students will be trained in: protein expression and purification, GPCR pharmacological assays, ligand binding assays, computational ligand docking and ligand design.

Project supervisor
Dr Daniel Scott

Project co-supervisors
Prof Paul Gooley

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Engineering G protein-coupled receptors for structural biology and drug discovery with directed evolution.

G protein-coupled receptors (GPCRs) are a large family of signalling proteins (>800 gene members) located on the surface of all cells in the body, particularly in the brain. GPCR signalling controls virtually every physiological process in the body, making these receptors the targets of many current drugs treating conditions like pain, hypertension, schizophrenia and asthma. GPCRs exist as an ensemble of conformational states (inactive, intermediate and active) in equilibrium, with agonist binding shifting this equilibrium shift towards active states to stimulate cell signalling. A deeper understanding of the structural basis underlying GPCR signalling is needed to guide the design of improved therapeutics. To do this the major challenges for GPCR structural biology need to be overcome. These include: low expression and purification yields; low protein stability; and the inability to stabilize relevant receptor conformations for analysis. We engineer GPCRs that overcome these issues using in vitro directed evolution methods. Engineered receptors can then be used for crystallography, NMR and other biochemical techniques to further our structural understanding of these proteins and to facilitate structure-based drug design.

This project focuses on developing novel directed evolution methods using lentiviral gene libraries to enable the engineering of GPCRs that preferentially exist in particular, physiologically relevant conformations for which we do not as yet have crystal structures. Such conformationally stabilized receptors will also give us insights into the protein dynamics that control GPCR signalling and provide tools to design new drugs that target and stabilize specific GPCR conformations.

Project supervisor
Dr Daniel Scott

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: How to design a better GPCR drug: understanding the structural basis of ligand selectivity at α1-adrenoceptors.

Most G protein-coupled receptors (GPCRs) are activated though extracellular interactions of natural ligands, such as hormones or neurotransmitters, to the GPCR's ligand binding site. Binding induces a conformational change of the GPCR resulting in the transmission of intracellular signals. The GPCR gene super-family is made up of numerous sub-families that are all activated by the same ligands, but often control different physiological processes. This presents a challenge for drug discovery because synthetic compounds that are identified to bind to the natural receptor binding site will often bind to similar sites on other receptor family members (off targets), causing side effects and unwanted physiological responses. To achieve GPCR selectivity we need new ways to identify and design more selective GPCR targeting drugs. To meet this challenge we need to understand how natural ligands, and drug candidates, bind to receptors at the atomic level. Contemporary structure-based drug design (SBDD) uses atomic resolution methods (X-ray, NMR and Molecular Dynamics) coupled with high-throughput screening (NMR, Surface Plasmon Resonance, Isothermal Titration Calorimetry, and Microscale

Thermophoresis) of small fragment molecules to discover novel leads. A huge challenge for GPCRs is that they are very unstable and "fall apart" during the experiments needed to guide SBDD. We have engineered stabilized variants of two closely related GPCR subtypes, the α_{1A}- and α_{1B}-adrenoceptors (α_{1A}-AR and α_{1B}-AR). The stability of these receptors in the purified state has allowed us to probe the binding of non-selective and selective ligands with NMR to further our understanding of the structural basis of ligand selectivity. Projects are available focuses on mapping the binding of selective and non-selective ligands to α_{1A}-AR and α_{1B}-AR with these methods to guide SBDD and increase our knowledge of the structure and function of α_1-ARs. Designed, selective α_1-AR ligands will be critical tools for understanding the precise roles of these receptors in the body and could be candidates for treating heart disease, epilepsy and neurodegenerative diseases.

Project supervisor
Dr Daniel Scott

Project co-supervisors
Dr Michael Griffin
A/Prof Paul Gooley

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Development of an electromechanical flow-cytometry based cell stimulation system

Cellular activity is based on reactions that occur over incredibly short time scales, with many signalling cascades occurring in less than a millisecond. Despite this, the current suite of cell analysis instrumentation is unable to probe this activity in any high-throughput way. For example, current gold-standard flow cytometry systems require cells of interest to be first loaded into a chamber, whereafter they are individually analysed. However, this process is only ideal for detecting cellular properties that remain constant over time; there is no flow-cytometry based mechanism to detect a cell's short time-scale reactions in a cell's biochemical environment. In this project the student will work to develop a microfluidic system to rapidly inject and mix stimulants with cell samples immediately prior to optical detection in a flow cytometry instrument, thus permitting a new window into short-duration cellular processes. This work has important implications for drug discovery and fundamental biological research. This interdisciplinary project lies at the intersection of biomedical engineering and cell biology and is suited towards a student with an interest in developing aspects of this project related to engineering, electronics or design

Project supervisor
Dr Daniel Scott

Project co-supervisors
Dr David Collins (Biomedical Engineering)

Project availability

- Honours

STOJANOVSKI GROUP

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Organelles	**Pathogens**
Cell Biology	**Mitochondrial Disease**
Metabolism	

The Stojanovski group is working to understand the inner workings of one of the cells most intriguing and important organelles, the Mitochondrion. Mitochondria are the cell's power plant, where sugars from the food we eat are converted into energy that our bodies need to survive. Our lab is interested in how mitochondria are created and how they function in health, but also situations of dysfunction that lead to disease.

Project: The machines and pathways that facilitate mitochondrial protein import in human cells

Inside each mitochondrion is a workforce of approximately 1500 proteins, which collaborate to perform the many critical functions of the organelle. These proteins are trafficked from their site of synthesis in the cytosol to their correct location within mitochondria, a process referred to as 'protein import'. If mitochondrial protein import fails, energy production and general mitochondrial health and function is affected. Therefore, not surprisingly dysfunctional protein import is linked to mitochondrial disease and other human pathologies. In spite of this, our understanding of mitochondrial protein import and import machineries in human cells remains poor.

Our lab is interested in elucidating the molecular architecture of human import machines and elucidate how they govern protein import in mammalian cells. For instance, we recently identified novel metazoan specific subunits, Tim29 and AGK (*Kang et al., 2016; Kang et al., 2017*), which are components of the inner membrane translocation machine, TIM22 complex. Current efforts in the lab are focused on: (i) characterizing known mitochondrial import machines across human cell types; (ii) identifying novel facilitators of these pathways; and (iii) investigating how protein import dysfunction leads to mitochondrial disease.

Projects in this space utilise a variety of cell and molecular biology techniques, including mammalian cell culture, CRISPR/Cas9 gene editing techniques, molecular biology, confocal microscopy, Blue-native PAGE electrophoresis, protein chemistry and proteomics.

Project supervisor
Dr Diana Stojanovski

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Mitochondria as targets during bacterial pathogenesis

Invasion of a human cell by pathogenic bacteria often requires that the bacteria manipulate the eukaryotic cell biology to create a replicative niche and evade killing. To achieve this, intracellular bacterial pathogens transport virulence proteins, termed ***effectors***, into the host cytosol and beyond to other cellular compartments. Effector proteins from different bacteria and viruses are known to target mitochondria and try and manipulate organelle function. We are currently investigating the intracellular bacterial pathogens *Coxiella burnetii* and *Legionella pneumophila*, the causative agents of Q-fever and Legionnaire's disease, respectively.

In collaboration with Dr Hayley Newton we are: (i) working towards establishing the entire repertoire of effector proteins from these two bacterial species that are targeted to mitochondria; (ii) establishing how infection manipulates the mitochondrial proteome and function. Participation in this project will involve characterizing of novel effector proteins, how they are delivered to the mitochondrion and how they interact with mitochondrial proteins to allow these intracellular bacterial pathogens to replicate within a eukaryotic cell.

Projects in this space utilise a range of cell and molecular biology techniques, including mammalian cell culture, bacterial culturing, molecular biology, confocal microscopy, Blue-native PAGE electrophoresis, protein chemistry and proteomics.

Project supervisor
Dr Diana Stojanovski

Project co-supervisor
Dr Hayley Newton (PDI)

Project availability

- PhD
- Master of Biomedical science
-

STROUD GROUP

Contact: **Doctor David Stroud**
Location: **Bio21 Molecular Science and Biotechnology Institute**
Email: **david.stroud@unimelb.edu.au**
Weblink Link: **Click here**

Proteomics

Metabolic Disease

Mitochondrial Disease

Organelles

The Stroud lab uses advanced systems biology techniques to understand the assembly and function of multi-subunit complexes and how their dysfunction underpins a number of important human diseases. We employ a range of mass-spectrometry techniques, including shotgun proteomics, affinity enrichment and BioID proximity studies, metabolic labelling and multi-omics approaches and combine them with patient derived cell lines, CRISPR/Cas9 gene editing, and classical biochemistry. Our research is aimed at both understanding the primary biology underpinning human disease, as well as developing systems biology tools to improve patient diagnostic outcomes.

Project: Using proteomics to diagnose mitochondrial disease

Genetic disorders affecting mitochondrial energy production constitute the most common form of inherited metabolic disease, affecting ~1/5000 births. The diagnosis rate for mitochondrial disease is only ~60%. While whole genome sequencing is routinely applied to patients with suspected mitochondrial disease, sorting through the sheer number of different genomic variants detected in each individual means that for many patients a molecular diagnosis takes months or years. Our lab is developing the use of quantitative proteomics to rapidly prioritise variants of unknown function while simultaneously providing functional validation of their impact on mitochondrial metabolism. With our collaborators we have now used proteomics to assist in the diagnosis of more than 10 patients with suspected mitochondrial disease (see Lake et al., 2017 Am. J. Hum. Genet. and Frazier et al., 2020 Med as examples). We are now focused on further developing the technique for routine use in diagnosis. This project will utilise quantitative proteomics on patient cell lines, system biology analyses. The project will involve development and optimisation of proteomics sample preparation techniques, as well as the use of CRISPR/Cas9 to validate candidate disease genes. You will also become skilled in molecular cloning, protein biochemistry and human cell culture techniques.

Project supervisor
Dr David Stroud

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Assembly of the Commander complex.

Sorting of proteins and lipids into and out of the endomembrane system is crucial for maintaining cellular homeostasis. Defects in the machineries that control this process lead to a number of debilitating diseases, including neurodegeneration, hypercholesterolemia and Wilson's disease. Recently, a new and evolutionarily conserved receptor recycling complex known as Commander was discovered. We and others propose that Commander is an endosomal sorting machinery required for the transport and homeostasis of vital plasma membrane receptors. The principles that govern the assembly of the 16 Commander subunits into the multisubunit complex however, as well as the overall mechanism by which this complex regulates endosomal trafficking in health and disease remains completely unknown. In this project you will use CRISPR/Cas9 to knock out Commander subunits and accessory factors in human

cell lines. You will perform shotgun quantitative proteomics and Blue-Native PAGE to understand the effect of subunit loss on complex assembly. Affinity enrichment and BioID proximity labeling coupled to mass-spectrometry will be used to probe protein-protein interactions. In addition, you will become proficient in molecular cloning, confocal microscopy, protein biochemistry and human cell culture techniques.

Project supervisor
Dr David Stroud

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Biogenesis of mitochondrial complexes

Is has been estimated that, even at rest, our bodies turn over ~70kg of ATP each day. More than 90% of this is generated through mitochondrial oxidative phosphorylation (OXPHOS), which occurs on the five membrane protein complexes comprising the respiratory chain. Mitochondria are comprised of ~1500 different proteins. Over 80 of these are subunits of respiratory chain complexes and >50 others known as assembly factors are needed for their biogenesis and regulation. Many more proteins support energy production indirectly. Surprisingly, we still don't know the functions of ~200 human mitochondrial proteins! This project is focused on characterising selected mitochondrial proteins of unknown function (see Hock et al., 2020 Mol. Cell. Proteom. as an example). Most of these are implicated in mitochondrial disease, the most common form of inherited metabolic disease, affecting ~1/5000 births.Here, you will use CRISPR/Cas9 gene-editing to knock out uncharacterised proteins to validate their involvement in mitochondrial energy generation. You will also utilise newly developed affinity enrichment and BioID proximity labelling tools coupled with mass-spectrometry to identify their protein-protein interactions. Shotgun proteomics as well as metabolomics will be used to understand the impact of protein loss on the proteome and metabolome. In this project you will become familiar with mammalian cell culture, molecular cloning, mass-spectrometry and systems biology, Blue-Native PAGE, bioenergetic measurements, and general protein biochemistry techniques.

Project supervisor
Dr David Stroud

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Multi-omic analysis of exercise induced changes to mitochondria

Mitochondria, better known as the 'powerhouse of the cell', are responsible for oxidative phosphorylation, providing the necessary energy the body needs to function. In addition to generating the bulk of cellular ATP, mitochondria direct a vast array of biological functions essential for cellular homeostasis. A long-standing question in biology concerns the biogenesis and regulation of mitochondria in response to stress and the metabolic needs of the cellular environment. Exercise represents a major challenge to both these pathways while also being arguably one of the most 'natural' perturbations available. While it is already known that high-intensity exercise alters the transcriptomic regulation of genes within the mitochondria differently compared with low-intensity exercise, there is far less literature on the proteomic, metabolomic and lipidomic changes.

In collaboration with our partners at the Institute of Sport, Exercise and Active Living (ISEAL) we have performed longitudinal multi-omics analyses of skeletal muscle from individuals subjected to increased volumes of exercise. In this 'dry-lab' informatics-only project, you will develop new methodologies to analyse this multi-omics dataset and identify the pathways and systems induced or repressed following exercise. You will also be involved in development of an interactive website allowing users to explore the data. As a pre-requisite for this project you will have some experience in programming languages (R, Python or similar) and/or web development frameworks (e.g Django, Flask). As an outcome of this project you will become proficient in the use of bioinformatic packages (e.g Limma, edgeR, mixOmics) as well as interpretation and visualisation of systems biology data.

Project Supervisor:
Dr David Stroud

Project co supervisor:
Dr Nikeisha Caruana

Project availability:

- Honours

TILLEY GROUP

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Pathogens

Cell Biology

Drug Design and Resistance

Structural Biology

Biophysics

The Tilley lab is working as part of a global effort to understand and control malaria. We undertake research in the areas of cell biology and drug development related to the malaria parasite, *Plasmodium falciparum*. We investigate the action of and resistance to artemisinin and are working to design better antimalarial drugs.

Project: Development of Novel Antimalarial Drugs

Would you like to help develop new antimalarial drugs? Each year, Plasmodium falciparum causes more than 200 million cases of malaria, and about 438,000 deaths. Because current antimalarial control is highly dependent on artemisinin combination therapies (ACTs), it is extremely concerning that decreased sensitivity has emerged to all currently used ACTs. In response to this impending crisis, the peak body, Medicines for Malaria Venture (MMV), has declared that novel targets for antimalarial therapies need to be identified and new drugs developed.

As an organism that undergoes rapid growth and cell division, the malaria parasite is very reliant on two major cellular homeostasis pathways: protein translation and proteasomal degradation. For example, peptide boronate proteasome inhibitors under investigation in the Tilley lab show promise as inhibitors of P. falciparum. In this Project, we will study homeostasis pathways in Plasmodium to elucidate their roles, determine how their activities intersect and study the action of test inhibitors. This work will provide the basis for the development of new drugs. The project will use molecular biology, structural biology, protein chemistry and biochemical methods.

Project supervisor
Prof Leann Tilley

Project co-supervisor
Dr Stanley Xie

Project availability

- PhD
- Master of Biomedical science
- Honours

VAN DRIEL GROUP

Contact : **Professor Ian van Driel**
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Email: **i.vandriel@unimelb.edu.au**
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Immunology

Pathogens

The van Driel group investigates innate immune responses in infected tissues are essential for controlling invading pathogens in the early phases of infection preventing the rapid replication and widespread dissemination of pathogens. The van Driel laboratory is seeking to define the main cells and factors that control innate immune responses in *tissues* and particularly the lung and the gut.

Project: Immune responses to pathogenic bacteria

Bacterial infectious diseases account for ~10 x 10^6 deaths annually. Our research is directed toward maximizing the chances of developing more effective vaccines and antimicrobial drugs through a better understanding of how the immune system combats bacterial infections.

Immune responses ***in infected tissues*** are essential for controlling invading pathogens in the early phases of infection. Despite having a vital role, the main cells and factors that control innate immune responses *in tissues* are poorly defined. To gain an integrated understanding of the *in vivo* ***innate immune network*** in lung tissue, we are investigating the immune response to the intracellular lung bacterial pathogen *Legionella pneumophila*. This important opportunistic pathogen causes Legionnaires' disease, a vastly under diagnosed disease that is associated with high rates of morbidity and mortality.

We have revealed a cooperative circuit in the response to *Legionella* infection. Inflammatory dendritic cells induced production of the important cytokine IFNγ by lymphoid. IFNγ, in turn, was necessary for bacterial killing by the inflammatory dendritic cells. Surprisingly, macrophages that engulf bacteria did not respond to IFNγ.

We will continue this project by addressing a number of important questions each of which could be the basis of a research student's project.

Why are macrophages unable to kill bacteria even in the presence of stimulatory cytokines like IFNγ?

We have discovered that another cytokine IL23 plays an important role in combatting *Legionella*. Which cells make IL23 and how does it act to kill bacteria?

Macrophages are the cell type inside which *Legionella* bacteria replicate. Why can't *Legionella* replicate in other similar cells like dendritic cells?

IFNγ can convert inflammatory dendritic cells into bacterial killers. What are the key molecular changes that are induced by IFNγ?

Techniques commonly used in this laboratory:

Flow cytometry, cell culture, use of mice and infection of mice, immunoblotting, immunolocalisation in cells, quantitative PCR, bioinformatic analysis of expression data.

Project supervisor
Prof Ian van Driel

Project co-supervisors
Dr Garret Ng
Prof Elizabeth Hartland

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Role of interferon inducible GTPases in immune defence

Legionella pneumophila is a major cause of Legionnaire's Disease, an acute form of pneumonia. As part of its pathogenesis, *L. pneumophila* infects alveolar macrophages and replicates in an intracellular vacuole that avoids fusion with lysosomes. Whereas macrophages propagate bacterial replication, other immune cell types are required for bacterial killing. In particular, we have discovered that monocyte derived cells (MDC) play an important role in controlling *L. pneumophila* infection in the lung. moDC are recruited to the lung in large numbers early during *L. pneumophila* infection and we believe that MDC internalize and kill the bacteria in an interferon gamma (IFNg) dependent manner. Our RNAseq analysis of lung moDC from wild type and IFNg-deficient mice showed that IFNg induced the expression of multiple interferon inducible GTPases (GBPs/IRGs). While most GBPs and IRGs are not yet characterized, some localize to intracellular pathogen vacuoles and may induce killing through novel mechanisms. We hypothesize that moDC utilize GBPs and IRGs to kill intracellular *L. pneumophila*.

The aims of this project is to:

A. Investigate the intracellular localization of selected GBPs and IRGs during *L. pneumophila* infection

B. Identify GBPs and IRGs that restrict *L. pneumophila* intracellular replication

C. Test selected GBP- and IRG-deficient mice for susceptibility to *L. pneumophila* infection

Techniques commonly used in this laboratory:

Bacterial culture, *in vitro* bacterial infection of cultured cells, enumeration of bacterial replication, RNAi knockdown, confocal laser scanning fluorescence microscopy, construction of stable inducible cell lines, molecular biology including primer design, mutagenesis and PCR, western blotting, immunoprecipitation, mouse infection.

Project supervisor
Prof Ian van Driel

Project co-supervisor
Prof Elizabeth Hartland

Project availability

- PhD
- Master of Biomedical science
- Honours

VILLADANGOS GROUP

Contact: **Professor Jose Villadangos**
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Email: **j.villadangos@unimelb.edu.au**
Weblink: **Click here**

Immunology		**Cancer**	
Pathogens		**Metabolism**	
Cell Biology		**Organelles**	

The Villadangos group studies the first event that triggers adaptive immune responses: the presentation of pathogen or tumour antigens to T cells by Dendritic Cells, B cells and Macrophages. We are characterizing the development, regulation and impairment of antigen presenting cells by pathogens, inflammatory mediators and tumours. We are also dissecting the biochemical machinery involved in antigen capture, processing and presentation. We use this knowledge to understand how T cell-dependent immunity is initiated and maintained, and apply it to design better vaccines and immunotherapies against infectious agents and cancer

Project: Regulation of immune receptor expression and turn-over by ubiquitin ligases

Cell viability and function requires maintenance of the correct protein composition and distribution within the cell at all times. This *proteostasis* is regulated by mechanisms that control protein synthesis, localisation and degradation. Cells can also respond to external signals to alter proteostasis, allowing them to adapt to changes in their environment. In cells of the immune system, expression of many important receptors is regulated by addition of the protein *Ubiquitin* by the MARCH family of ligases. MARCH ubiquitination thus plays major roles in immunity against pathogens and cancer. The MARCHs also play important roles in control of infection by viruses. However we know very little about MARCH specificicity and regulation.

This project will employ biochemical techniques, microscopy, proteomics, and CRISPR-Cas9 technology to characterise the function of the MARCH family; identify novel MARCH substrates; and characterise the machinery involved in ubiquitination by MARCHs. Our goal is to develop novel therapeutic approaches to fight infection and cancer based on manipulation of membrane protein ubiquitination.

Further reading: L Young et al (2008) Nat. Immunol. 9: 1244-1252; J Moffat et al (2013) Curr. Opin. Immunol; 25: 109-114; H Liu et al (2016), J. Exp. Med. 213:1695-1703.

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: A novel link between metabolism and host defence: O-GlcNAc glycosylation

O-GlcNAc glycosylation involves addition of a single sugar, β-N-acetylglucosamine, to serine or threonine residues of proteins. It is a unique type of glycosylation found on nuclear and cytoplasmic proteins. The addition and removal of OGlcNAc is catalysed by OGlcNAc transferase (OGT) and OGlcNAse (OGA) respectively. It is a reversible modification akin to phosphorylation. Indeed, OGlcNAc glycosylation occurs in dynamic interplay with phosphorylation, either on the same or adjacent residues. The cross-talk between these two modifications in turn regulates various cellular processes.

In this project we will characterise the function of OGlcNAc glycosylation in a type of immune cells (*Denditic cells, DC*) that play a critical role in immunity against infection and cancer.

We will identify changes in patterns of glycosylation in different metabolic states and upon encounter of pathogens. The function of glycosylated proteins will be further studied to understand the relevance of their OGlcNAc status in various immune cell activities. Finally, we will characterize how OGT and OGA recognize their substrates and the mechanisms that regulate their function. These studies may allow us to design therapeutic drugs that target O-GlcNAc glycosylation to manipulate immune responses against pathogens or cancer.

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The amyloidogenic protease inhibitor Cystatin C in health and disease

Cystatin C (Cst C) is a secreted protease inhibitor. Its clinical importance as a regulator of extracellular proteolysis in the vascular system is demonstrated by the association between low serum Cst C levels and formation of atherosclerotic plaques, due in part to uncontrolled proteolytic degradation of arterial elastin. A different property of Cst C that makes this protein clinically relevant is that it can form amyloid fibrils, which are found in the cerebral vasculature of patients with neurodegenerative diseases. Such fibrils are believed to originate by a phenomenon known as “domain swapping”, whereby two Cst C monomers associate by “exchanging” subdomains to generate homodimers. These dimers can then be extended by additional rounds of domain swapping and thus form amyloid fibrils. The cells responsible for Cst C production in vascular disease are unknown. Identification of these cells, and characterisation of the mechanisms that control the synthesis and dimerisation of Cst C will lead to the development of therapeutic strategies for the treatment of diseases associated with Cst C.

Further reading: Y Xu et al (2014) J Biol Chem 289:9730-9740.

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Understanding the mechanisms that impair anti-tumour Adoptive Cell Therapy

Tumour cells express neo-antigens that can be recognized by cytotoxic T lymphocytes (CTL). These tumour-specific CTL can be isolated, expanded and inoculated to kill cancer. Unfortunately, in many individuals the tumour ‘fights back’ and inactivates the infused CTL, compromising the therapy. Using a mouse model of lymphoma, we are performing studies to improve outcomes. Our goal is to apply our findings to the clinic and improve the efficacy of adoptive cell therapy. The aims of this project will be to identify genes that control the outcome of adoptive cell therapy, and characterise the interactions between T cells and the tumourr.

Further reading: S Prato et al (2013), J. Immunol. 191: 3534-3544; G Segal et al (2016), J. Immunol. 196: 3935-3942; JA Villadangos et al (2016), Immunol Rev 272:169-182

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Immuno-paralysis following severe infections

Systemic Inflammatory Response Syndrome (SIRS) is a common condition associated with severe infections such as COVID-19. It is characterised by inflammation accompanied with immunosuppression, and the latter can last for several weeks. The immunosuppressed patients are at risk of suffering secondary or opportunistic infections, a major contributor to morbidity and death in intensive care units. Impairment of macrophages and dendritic cells (DC), the primary initiators of T cell immunity, plays a prominent role in this immunosuppression post-SIRS. In this project we will use models of infection to characterise the mechanisms that cause immune cell paralysis and to develop therapies to prevent immunosuppression.

Further reading: NS Wilson et al (2006), Nat. Immunol. 7: 165-172; LJ Young et al (2007), Proc. Natl. Acad. Sci. USA 104: 17753-17758; A. Roquilly et al (2017), Immunity 47:135-147; J Vega-Ramos et al, Curr. Opin. Pharmacol. 17: 64-70.

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: MR1 – a molecular alarm system for bacterial infection

MR1 functions as a molecular alarm system to alert the immune system that a bacterial infection is taking place. It does this by capturing metabolite by-products from bacteria and presenting them at the cell surface to activate a highly abundant T cell subset, called mucosal-associated invariant T (MAIT) cells. MR1 is a highly conserved piece of the mammalian immune repertoire to detect bacterial pathogens, yet basic aspects of its cell biology are not well understood. This project will investigate the molecular machinery underpinning the biology of MR1 molecules, using CRISPR/Cas9 gene editing and cutting-edge cell biology and biochemistry techniques.

Further reading: HEG McWilliam et al (2016), Nat. Immunol. 17: 531-537; HEG McWilliam et al (2017), Trends Immunol 38: 679-689.

Project supervisor:
Prof Jose Villadangos

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: Trogocytosis: a novel communication system between cells of the immune system

Intercellular communication is an inherent property of all metazoans. In most cases, cells communicate via interactions between plasma membrane receptors, or via soluble ligands secreted by one cell and recognised by a receptor on another cell. We will study a third form of communication described decades ago and that is thought to play major roles but remains poorly understood, namely trogocytosis. This activity entails transfer of plasma membrane from one cell to another. We have discovered that a fundamental cellular component of the innate immune system, Marginal Zone B cells (MZBC), constitutively trogocytose plasma membrane from a fundamental cellular component of the adaptive immune system, Dendritic Cells (DC). This trogocytic event is strictly dependent on the formation of a newly-discovered complex comprised of two molecular components: Complement C3 and MHC class II molecules (MHC II). This is in itself a highly significant finding because formation of MHC II-C3 complexes may be a novel mechanism for capturing and eliminating potentially harmful C3 constitutively activated by the so-called "Tick-Over" pathway. In this project we will use a variety of biochemical approaches and high-end microscopy to describe the function of these hitherto unknown interactions between fundamental cellular and molecular components of the immune system.

We will also characterise the molecular mechanisms underpinning trogocytosis, an activity that is believed to play major roles not just in immunity but also in other biological systems.

Project supervisor:
Prof Jose Villadangos

Project co supervisor
A/Prof Justine Mintern
Dr Patrick Schriek

Project availability

- Master of Biomedical science
- Honours

Project: Improving the formation of protective immunity against human viruses

CD4+ helper T cells underpin the generation of life-long protective immunity against infectious disease. They are pivotal for activating CD8+ killer T cells and driving B cell production of neutralising antibodies, which are both required to recover from and prevent infection. However, the CD4+ T cells that are activated following infection are not generally assessed in studies of vaccine efficacy and/or protective immunity. In addition to established functions of effector CD4+ T cells in driving immune memory is an emerging role for regulatory T cells (Tregs), which until now have been under-appreciated in this context. Tregs, in addition to their critical role in maintaining self-tolerance, are important in limiting immunopathology following infection. Further, evidence from mouse studies suggests Tregs are crucial for the generation of memory T cells and also control the homing of immune cells into infected tissues. However, it remains unknown if these are also key functions for human Tregs. This project will investigate the mechanisms of how human Tregs shape immune memory responses using cutting-edge technology including organoid co-culture, gene editing, functional cellular assays and spectral cytometry. Data from this project will form a foundation for designing more efficacious treatment and prevention strategies for infectious diseases.

Project Supervisor
Prof Jose Villadangos

Project cosupervisor
Dr Laura Cook

Project availability

- PhD
- Master of Biomedical science
- Honours

Project: The immune signature of COVID-19 patients

There is an urgent need for both novel treatments and vaccines for SARS-CoV-2, which requires an understanding of protective anti-viral immunity. For such intracellular viral pathogens, there is an emerging appreciation of the importance of long-lived cellular immunity for both viral clearance and generation of protective memory responses. Critical early events shaping anti-viral T cells include cytokine signals from innate cells, such as macrophages, and the presentation of antigen from professional antigen presenting cells, such as dendritic cells. Other pulmonary infections caused by viruses or bacteria cause profound life-threatening immune paralysis, with macrophages and dendritic cells unable to perform these functions. As the ability of dendritic cells to present antigen and provide appropriate signals to T cells is a key step in initial activation and subsequent reactivation of virus-specific cells, aspects of immune paralysis will likely have profound effects on cellular immunity and antibody production. This project will enrol local patient cohorts to investigate whether prolonged immune dysfunction occurs after COVID-19 infection and whether this is associated with impaired generation of immune memory to SARS-CoV-2.

Project Supervisor
Prof Jose Villadangos

Project cosupervisor
Dr Laura Cook

Project availability

- PhD
- Honours
- Master of Biomedical Science

WICKRAMASINGHE GROUP

Contact: **Dr Vihandha Wickramasinghe**
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Cell Biology

Cancer

Discovery Research

Cell signalling

RNA biology and Cancer

The Wickramasinghe laboratory uses cutting-edge cell biology, molecular biology and genetic approaches to understand a critical step in gene expression, messenger RNA export. Nuclear export of mRNA to the cytoplasm is required for gene expression and is deregulated in cancer. Our ultimate goal is to use these fundamental biological insights to develop novel first-in-class inhibitors to treat cancer.

Project: Mechanisms of regulating gene expression via selective mRNA transport

A critical step in the gene expression pathway that is altered in cancer is nuclear export of mRNA. We have demonstrated that mRNA export is not constitutive, but highly selective and can regulate distinct biological processes through poorly understood mechanisms. This project aims to dissect the molecular mechanisms of regulating gene expression via selective mRNA transport. This will establish selective mRNA export as a novel area of research in cancer biology.

Project supervisor
Dr Vihandha Wickramasinghe

Project availability

- PhD
- Master of Biomedical science

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