THE UNIVERSITY OF MELBOURNE

Department of Biochemistry and Pharmacology

Research Projects 2025

Welcome

The Department of Biochemistry and Pharmacology is a teaching and research Department of the School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences based on the main campus in the Melbourne Biomedical Precinct in Parkville.

The Department of Biochemistry and Pharmacology has teaching responsibilities and very active research programs and expertise that underpin our key themes of molecular understanding of disease, translational research and drug discovery and development. Our department houses 30+ research groups working in the areas of biophysics, cell biology, chemical biology, pharmacology, computational biology, drug design, immunology, metabolism, proteomics and structural biology. Disease foci include infection, cancer, neurodegeneration, respiratory disease, inflammatory/ autoimmune diseases and genetic diseases. We place a strong emphasis on research and research training with over 75 graduate research students currently enrolled.

The Department is situated within the University of Melbourne's Parkville Biomedical Precinct, one of the largest biomedical research precincts in the world that is home to several research institutes that are household names. Laboratories in our department are located both in the Medical Building and in the Bio21 Molecular Science and Biotechnology Institute, a multidisciplinary research centre specialising in biochemistry, drug discovery, neuroscience, environmental science, dentistry and engineering. In addition to housing the research facilities of CSL, Australia's largest pharmaceutical and biotechnology company, the Bio21 Institute also hosts the University's major technology platforms including the Melbourne Advanced Microscopy Facility, the Magnetic Resonance Facility, the Melbourne Mass spectrometry and Proteomics Facility, Metabolomics Australia, the Macromolecular Interactions Facility, a peptide synthesis facility, as well as High Performance Computing and facilities for animal models. The department and the Bio21 Institute provide outstanding career opportunities for staff and superb training facilities and research environment for our students.

It is a great pleasure to introduce you to the research projects that are on offer by the Department of Biochemistry and Pharmacology for 2025.

Most projects offered will be in our departmental laboratories on the 8th and 9th floors of the Medical Building and in the Bio21 Molecular Science and Biotechnology Institute. The remainder will be conducted in affiliated research institutes with external supervisors and co-supervision by Department staff.

The Department of Biochemistry and Pharmacology Honours and Masters courses are directed at students with above average academic ability. Both courses aim to transition students from formal lectures and teaching, to self-directed learning and exploration of your own scientific problem. We will introduce you to skills in communication, data analysis and assessment of scientific papers. Your supervisor and their laboratory staff will guide you through the challenges, strengthen your technical skills and introduce you to the excitement of research - its rewards and its disappointments. You will have the opportunity to use the latest in equipment and work alongside other researchers to expand biomedical knowledge. The Honours and Masters "experience" will require self-motivation and discipline, and you will learn a lot about your own problem-solving ability. Research Higher Degrees such as a PhD are longer courses with a focus on self-directed research. Graduate researchers are typically students with both an above average academic ability and a desire to further develop a specific field of research. Entry into these programs requires completion of an Honours or Masters degree.

It is not a simple task to select a project, laboratory and supervisor. We suggest you talk to several potential supervisors, as well as to their current Honours, Masters or Graduate Researchers, to gain some appreciation of the research problems being addressed and the related techniques. You will find them friendly and welcoming! We hope you will join us in The Department of Biochemistry and Pharmacology for a 2025 Honours, Masters, or PhD project.

How to apply

Honours

What is Honours?

Honours is a fourth-year undergraduate course that consists of a major research project complemented by 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 Honours or Biomedicine Honours.

Meeting the minimum Faculty level entry requirements is not a guarantee of admission and students must be accepted by a supervisor to gain 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 finishes in November. Mid-year entry is also possible, commencing late 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. We suggest you provide the potential supervisor with a recent academic transcript on first contact. 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 a course application online, 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 instructions 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 before the closing date.

More information including application dates and the online application form can be found in the following links:

mdhs-study.unimelb.edu.au/degrees/honours/apply-now

biomedicalsciences.unimelb.edu.au/departments/department-of-biochemistry-and-pharmacology/study/honours-and-masters-by-coursework-biochemistry-and-pharmacology

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, alongside 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.

Note

- 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 Masters of Biomedical Science?

Masters is a two year (full time) course consisting of 125 points of research and 75 points of coursework. The course can be commenced in Semster 1 or Semester 2 each year.

How to apply

- 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.
- 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. We suggest you include an academic transcript and any other relevant information when making first contact with a potential supervisor. Once your project has been endorsed, you will be allocated to this project in SONIA.

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

https://biomedicalsciences.unimelb.edu.au/departments/department-of-biochemistry-and-pharmacology/study/honours-and-masters-by-coursework-biochemistry-and-pharmacology

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

How to apply

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 and awards

Honours

Honours applicants who accept and enrol in an Honours course will automatically be considered for available Honours Scholarships and Awards. 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**

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

Research Higher 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**

DBP laboratories and available projects

Anderson and Zhuang Group

Contact: Professor Gary Anderson
Location: Medical Building
Email: gpa@unimelb.edu.au
Website: go.unimelb.edu.au/2z5i

Key focus areas

- Therapeutics and translation
- Molecular mechanisms of disease
- Lung Health
- Immunopharmacology
- Cellular Imaging and Structural Biology

Our research is focused on understanding the molecular basis of chronic degenerative lung diseases, in particular severe refractory asthma, Chronic Obstructive Lung Disease (COPD), Asthma-COPD Overlap, the COPD-lung cancer interface and fibrotic lung diseases. We are interested in understanding the reasons why lung disease becomes chronic and resists the normal processes that help resolve tissue damage, as well as why the damaged lung is so susceptible to subsequent infections. Our research also focuses on developing and testing experimental medicines in preclinical models. We work with leading clinicians/researchers at the RMH and internationally to translate our basic findings into useful medicines.

Project: CUREasthma: Defining novel asthma endotypes and reversing epithelial cell fate using novel therapeutics

This project addresses a major but much under-appreciated problem that asthma research has stagnated in the presence of effective therapeutics. Compared to other diseases, disease modification is often the therapeutic goal. However, for asthma this has not been the case. This project is aligned with a developing national initiative to re-prioritise asthma research that the end goal should be a 'cure' rather than small incremental steps towards improving current therapeutics. The aim of this project is to identify novel asthma endotypes, and validate novel therapeutics as to whether these can be disease modifying in pre-clinical asthma models.

Project supervisor:

Professor Gary Anderson

Project Co-supervisor:

Dr Ao Wen Zhuang

Project Availability:

- Honours
- PhD

Project: Investigating pre-COPD models to discover what drives irreversible damage and development of co-morbidities

This project addresses a major but much under-appreciated problem- vaccinations do not work well in patients suffering Chronic Obstructive Pulmonary Disease (COPD). COPD afflicts 1 in 20 Australian and is the 5th leading cause of death (AIHW 2019). Globally COPD afflicts more than 300 million people and is the third leading cause of death. The aim of this project is to understand the early states of COPD where the disease could be reversible (recently termed pre-COPD). This project utilises pre-clinical models (genetic and physiological) and apply novel methodologies of spatial transcriptomics and integrated -omics to identify the crucial drivers that may lead to molecular "switches" that transition the lung from a reversible damage to irreversible.

Project supervisor:

Professor Gary Anderson

Project Co-supervisor:

Dr Ao Wen Zhuang

Project Availability:

- Honours
- PhD

Bathgate Group

Contact: Professor Ross Bathgate
Location: The Florey Institute of Neuroscience and Mental Health
Email: bathgate@florey.edu.au
Website: go.unimelb.edu.au/id5i

Key focus areas

- Drug Design
- 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, A/Professor 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:

Professor Ross Bathgate

Project co-supervisors:

A/Professor Daniel Scott, Professor Paul Gooley, A/Professor 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:

Professor Ross Bathgate

Project co supervisor:

Professor Akhter Hossain
Dr Susan Northfield

Project availability:

- 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:

Professor Ross Bathgate

Project co-supervisors:

Dr Martina Kocan
Dr Brad Hoare

Project availability:

- Master of Biomedical science
- Honours

Cox Group

Contact: A/Professor Andrew Cox
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Website: go.unimelb.edu.au/pd5i

Key focus areas

- 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:

A/Professor 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:

A/Professor Andrew Cox

Project availability:

- PhD
- Master of Biomedical science
- Honours

Crack Group

Contact: Professor Peter Crack
Location: Bio21 Molecular Science and Biotechnology Institute
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Website: go.unimelb.edu.au/fz5i

Key focus areas

- Neurodegeneration
- Neurotrauma
- Neuroinflammation
- Cell Signalling
- Biomedical neuroscience
- Infection and Immunity

The Crack group is run by Professor Peter Crack. The Neuropharmacology laboratory looks to understand how fundamental cellular signalling pathways can predispose the brain to exacerbated neurotrauma or neuropathology. In understanding how these pathways contribute to neural dysfunction we may be able to identify novel therapeutics that can be used to combat traumatic brain injury, Alzheimer's disease and Parkinson's disease.

Project: Innate immunity, neuroinflammation and chronic neurodegeneration – a focus on Alzheimer's disease

A major new area of research in our laboratory is the role that the innate immune system plays in the progression of chronic neuronal pathology. It is now appreciated that the central nervous system (CNS) does exhibit features of inflammation, and in response to injury, infection or disease, resident CNS cells generate inflammatory mediators, including proinflammatory cytokines, prostaglandins, free radicals and complement, which in turn induce chemokines and adhesion molecules, recruit immune cells, and activate glial cells. Activation of the innate immune system is an important component of this inflammatory response. We have discovered that neuroinflammation is mediated by the generation of type-I interferons. Type-I interferons are the master regulators of the neuroinflammatory response seen in Alzheimer's disease. The molecular mechanisms that are influenced by the type-I interferon signalling comprises new targets for therapeutic intervention into acute neurological conditions such as stroke and neurotrauma and chronic neurological diseases such as Alzheimer's disease.

Skill acquisition: In vivo disease models, histology, immunohistochemistry, morphometry, quantitative PCR, FACS analysis of cell populations, cell and tissue culture, ELISA, molecular biology and western blotting.

Project supervisor:

Professor Peter Crack

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: Understanding traumatic brain injury

Traumatic brain injury (TBI) represents the major cause of death in young individuals in industrialised countries. Despite the improvement of neurosurgical procedures as well as critical care management, morbidity and mortality are still high and approximately 25% of these patients remain with permanent disabilities becoming a familiar, social and economic burden for society. A better understanding of events occurring in the brain after traumatic brain injury is essential to identify ways to limit the damage and ultimately improve the outcome. This project will focus on the role that neuroinflammation plays in the progression of neural injury after TBI. By altering the pathways that control neuroinflammation by either molecular or therapeutic means we are able to influence the outcome after TBI. The data generated by this project will be used to further understand the molecular pathways that are changed in the brain after TBI.

Skill acquisition: In vivo disease models, histology, immunohistochemistry, morphometry, quantitative PCR, FACS analysis of cell populations, cell and tissue culture, ELISA, molecular biology, and western blotting.

Project supervisor:

Professor Peter Crack

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: The use of bioactive matrices to treat traumatic brain injury

Traumatic brain injury (TBI) represents the major cause of death in young individuals in industrialised countries. Despite the improvement of neurosurgical procedures as well as critical care management, morbidity and mortality are still high and approximately 25% of these patients remain with permanent disabilities becoming a familiar, social and economic burden for society. There are no treatments available for traumatic brain injury. We are investigating the use of biomaterials to re-direct the brain's endogenous neural stem cells to facilitate neural repair after TBI. This project will determine whether reconstructing functional neural circuitry via cell-based therapies represents a viable, alternative therapeutic strategy to improve clinical outcome.

Skill acquisition: In vivo disease models, histology, immunohistochemistry, morphometry, quantitative PCR, FACS analysis of cell populations, cell and tissue culture, ELISA, molecular biology and western blotting.

Project supervisor:

Professor Peter Crack

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: The role of neuroinflammation in Parkinson's disease

Parkinson's disease (PD) is a progressive neurological disease that is characterized by the loss of dopaminergic neurons, primarily in the substantia nigra. The loss of these neurons leads to a motor handicap, associated depression, pain and general decreased quality of life. The mechanism for the loss of the dopaminergic neurons is unknown although it is hypothesised that protein mis-folding, oxidative stress and neuro-inflammation may contribute to the cell death. We hypothesise that the neuroinflammatory response triggers deleterious events (e.g., oxidative stress and cytokine-receptor-mediated apoptosis), potentiating dopaminergic cell death and contributing to disease progression. This project proposes to study the molecular and cellular events associated with neuro-inflammation in an animal model of PD with a focus on the involvement of neuro-inflammation in the progression of PD. There is a growing body evidence that the gut plays a role in PD. This project will investigate this hypothesis using a combination of gut organoids and gut motility assays. A multi-disciplinary approach using an alpha-synuclein in vivo mouse model of PD coupled with in vitro studies to investigate the specific molecular pathways involved will investigate the role that neuro-inflammation plays in the progression of PD.

Skill acquisition: The techniques involved in this project entail a mouse model of PD, immunohistochemistry, primary neural cell culture, ELISA, QPCR analysis, siRNA and western analysis and data analysis.

Project supervisor:

Professor Peter Crack

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: Neuroinflammation and its contribution to an autism-like phenotype

There is growing evidence in the literature that neuroinflammation plays a role in cognitive function. Microglial activation has been shown to be involved in synapse formation and maintenance. Recent studies have suggested that neuro-inflammation plays a growing role in the pathogenesis of autism spectrum disorder (ASD). Previous work from our laboratory highlights that the type-I interferon (IFN) system is a master regulator of neuroinflammation in both acute and chronic neuropathology. This project will utilise a well-established genetic mouse model of autism and investigate if there is any attributable effect to type-I IFN signalling in the progression of the autism like phenotype in this mouse.

Skill acquisition: In vivo disease models, histology, immunohistochemistry, morphometry, quantitative PCR, FACS analysis of cell populations, cell and tissue culture, ELISA, molecular biology and western blotting.

Project supervisor:

Professor Peter Crack

Project co-supervisors:

A/Professor Elisa Hill

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: The bioinformatic analysis of neuroinflammatory pathways seen in Alzheimer's and Parkinson's disease

Neuroinflammation is increasingly being attributed to the causation and exacerbation of both acute and chronic neuropathologies. The emerging field of bioinformatics will be used to identify proteins and signal transduction pathways that contribute to the production of neuroinflammation. This project be largely in silico based and will utilize the skills that are provided by the core bioinformatics facility located in the Melbourne Brain Centre under the guidance of Dr Victoria Perreau. This approach enables hypothesis generation through leverage of genomic, transcriptomic, phenotypic and proteomic datasets to understand complex systems. The student will focus on understanding complex interplay of signal transduction networks that control the neuroinflammatory response.

Skill acquisition: Bioinformatics, systems biology, pathway analysis.

Project supervisor:

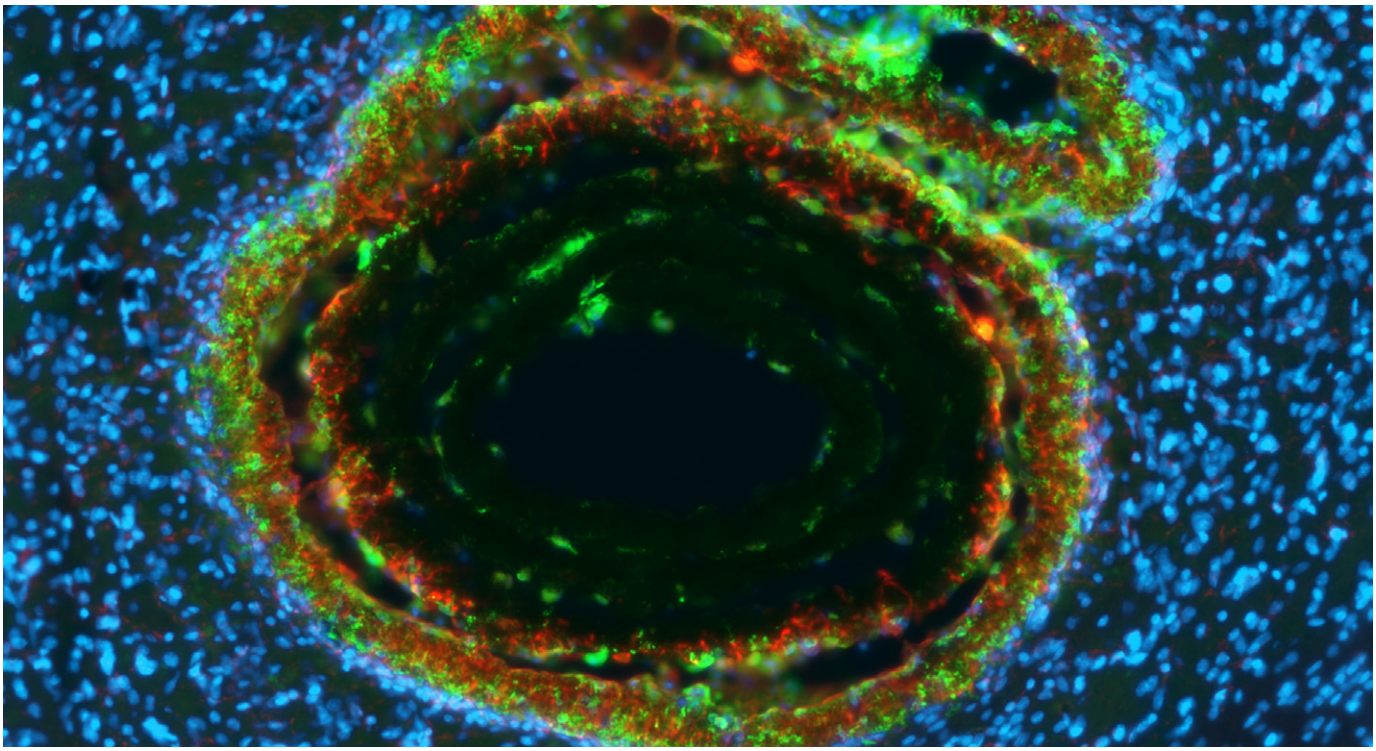
Professor Peter Crack

Project co-supervisors:

Dr Victoria Perreau

Project availability:

- PhD
- Honours
- Master of Biomedical science



Edgington-Mitchell Group

Contact: Dr Laura Edgington-Mitchell
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Key focus areas

- 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: Unravelling the contribution of proteases to health and disease

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

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Key focus areas

- Structural Biology
- Discovery Research
- Biophysics
- Pathogens
- Cell Biology

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:

- 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: Molecular Characterisation of human oral microbiome

The oral microbiota of humans exhibits significant diversity and a complex ecosystem, encompassing bacteria, microeukaryotes, archaea, and viruses. Microbial dysbiosis in the oral microbiota can result in periodontitis and several systemic diseases, including oral cancer, pancreatic cancer, cardiovascular diseases, and neurodegenerative pathologies such as Alzheimer's disease. We are using state-of-the-art electron and confocal microscopy, mass spectrometry, and biochemical methods to understand the architectural and molecular details of our oral microbiome.

Project supervisor:

Dr Debnath Ghoshal

Project Availability:

- Honours
- Master of Biomedical Science
- PhD

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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Key focus areas

- Cell Biology
- Organelles
- Immunology
- Proteomics
- Neurodegeneration
- 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 ɣ-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:

Professor Paul Gleeson

Project co-supervisors:

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:

Professor 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:

Professor Paul Gleeson

Project availability:

- PhD
- Master of Biomedical science
- Honours

Gooley Group

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Key focus areas

- 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:

Professor Paul Gooley

Project availability:

- Master of Biomedical science
- Honours

Project: The complex binding mode of the peptide hormone H2 relaxin to its receptor RXFP1

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:

Professor Paul Gooley

Project co-supervisors:

A/Professor Daniel Scott
Professor Ross Bathgate
A/Professor Mike Griffin

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Probing the conformational dynamics of G protein-coupled receptors with NMR

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:

Professor Paul Gooley

Project co-supervisor:

A/Professor Daniel Scott

Project availability:

- PhD
- Master of Biomedical science
- Honours

Griffin Group

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Key focus areas

- Structural Biology
- Biophysics
- Drug Design
- Cancer
- Neurodegeneration
- 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/Professor 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/Professor 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/Professor Michael Griffin

Project co-supervisor:

Dr Hayley Newton

Project availability:

- PhD
- Master of Biomedical science
- Honours

Grinter Group

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Key focus areas

- Microbiology
- Biochemistry
- Structural Biology
- Computational Biology
- Genetics

The Grinter lab studies how bacteria survive and compete in diverse environments from the human host, to soils, and extreme environments. We study how bacterial pathogens steal heme and iron from host proteins, how soil bacteria utilise gases in the air like CO and H2 as an energy source, and how bacteria produce protein antibiotics to kill each other. We utilise a combination of cutting edge biochemistry, structural bioloy, cellular microbiology and genetics to not just understand these processes, but use them as the basis for new biotechnology and antibiotics to treat resistant bacteria.

Project: Using AI to design inhibitors of bacterial iron-piracy

Project Description. Many bacterial pathogens satisfy their requirement for the essential nutrient iron by stealing it directly from host proteins that utilise it as a cofactor, either in the form of heme or free iron. To achieve this bacteria use specalised cell surface proteins and integral membrane transporters. We are studying this process in two important bacterial pathogens (Escherichia coli and Hemophilus influenzae) which utilise membrane protein transporters to extract heme from host hemoglobin and import it into the cell. In addition to understanding this process, we are using cutting-edge artificial intelligence to design novel proteins that bind to and inhibit these transporters. Projects under this theme we advance the objectives of this project, and will span a range of techniques from computational structural biology, to cellular microbiology and genetics, to biochemsitry and experimental structural biology.

Project supervisor:

Dr Rhys Grinter

Project Availability:

- Honours
- Master of Biomedical Science
- PhD

Project: Targeting multidrug resistant pathogens using protein antibiotic

Gram-negative bacteria are some of the most important human and animal pathogens. These bacteria are famously resistant to antibiotics, in part due to thier impermeable outer membrane. Antibiotic resistance (AMR) is one of the greatest threats to human health, with around 5 million deaths assocaited to AMR in 2019. This number is rapidly growing and of the six leading pathogens for deaths associated with resistance (Escherichia coli, followed by Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa), four are Gram-negative bacteria.

In this project we are developing a novel family of lectin like protein antibiotics (Llp) as a therapy for treating mutidrug resistant P. aeruginosa infection. Llps are potent inhibitors of bacterial growth, with a novel mechanism of action targeting protein assembly in the outer membrane. We are working to understand the molecular details of the mechanism of action of Llps, which will allow us to harness thier potential as antimicrobials.

Projects under this theme we advance the objectives of this project, and will span a range of techniques from computational structural biology, to cellular microbiology and genetics, to biochemsitry and experimental structural biology.

Project supervisor:

Dr Rhys Grinter

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Project: Understanding novel mechanisms of quinone reduction outside the membrane

Respiratory electron transport chains (ETCs) are the bioelectrical circuits that power cellular life. The relatively well-developed general models of ETCs are based on mitochondria in eukaryotic cells. In contrast, the ETCs of bacteria and archaea are orders of magnitude more complex, exhibiting incredible diversity.

Respiratory quinones (and quinone like molecules) are the universal energy transducers for ETCs, accepting electrons from fuel compounds and carrying them to proton-pumping oxidases within the membrane. Despite decades of seminal work into the role of quinones in ETCs, we still only have a rudimentary understanding of the enzymes, mechanisms, and electrochemistry that underpins the function of these essential molecules.

In this project we integrate microbiology, structural biology, bioelectrochemistry and computational modelling to revolutionise our understanding of the what, how, and why of quinone function in the ETCs of bacteria and archaea.

Project supervisor:

Dr Rhys Grinter

Project Availability:

- Honours
- Master of Biomedical Science
- PhD

Harvey Group

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Key focus areas

- Cell Signalling
- Discovery Research
- Organ growth
- Cell Biology
- Cancer

The Harvey laboratory is interested in organ size control, which is a fundamental biological progress that has been relatively poorly studied compared to many other aspects of developmental biology. As well as specifying the size of all the creatures on our planet, size control is required to generate appropriately functioning organs, whilst its deregulation has been implicated in the genesis of cancers. Primarily, we investigate the mechanism by which the Hippo pathway controls tissue growth, with a focus on signalling and transcription. We are also investigating the role of the Hippo pathway in human cancers and how it can be targeted for therapeutic benefit.

Project: Identification of Hippo pathway target genes during organ growth

Project Description. The Hippo pathway is an important regulator of tissue growth. First discovered in the model organism Drosophila as a regulator of eye growth, the Hippo pathway is highly conserved throughout evolution, with core elements present in single-celled metazoan ancestors through to humans. Despite being discovered more than 20 years ago, we still lack a detailed understanding of the complete set of target genes that are regulated by the Hippo pathway in the context of tissue growth.

Project supervisor:

Professor Kieran Harvey

Project Availability:

- Honours

Hatters Group

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Key focus areas

- Proteomics
- Cell Biology
- Computational Biology
- Neurodegeneration
- Organelles
- 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:

Professor 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:

Professor Danny Hatters

Project co-supervisor:

Professor Gavin Reid

Project availability:

- Master of Biomedical science
- Honours

Project: Exploring how protein aggregation causes toxicity in Huntington disease

A signature of Huntington's Disease is the formation of inclusion bodies, which are large micrometre-sized aggregates in neurons by the Huntingtin protein. We know from model systems that these aggregates lead to cytotoxicity. However, we do not understand the mechanisms behind this. Insight into this question is critical to planning new therapeutic strategies for this otherwise incurable and fatal condition. Our lab has uncovered intriguing proteomics data, suggesting that specific endogenous proteins are sequestered inside the inclusion bodies in cell models. This novel finding leads us to hypothesise that their sequestration depletes them from their normal function, potentially explaining the observed toxicity. This unique perspective on the role of these proteins in Huntington's Disease could open up new avenues for therapeutic interventions.

Project: Determining the proteins that bind to specific protein complexes in Huntington Disease

Our lab strongly focuses on developing and applying proteomics methods to understand how specific protein interactions form in neurodegenerative diseases. In this exciting project, you will work with our team to build a new proteomics method dedicated to finding binding partners to a specific complex formed between the Huntingtin Protein and a protein called PCNA, which is involved in DNA mismatch repair. The benchmark approaches to finding protein interactors involve fusing APEX2, an engineered ascorbate peroxidase, to a target protein. APEX2 catalyses biotin-phenols instantly conjugated to proteins within a few nanometres of proximity in the presence of hydrogen peroxide. Here, you will be developing an approach that will restrict the activity of APEX2 to fold only when a specific complex is formed (e.g., Huntingtin and PCNA). The strategy will involve expressing Huntingtin and PCNA fused to two split fragments of APEX2. These fragments should reconstitute into a functional enzyme upon binding between Huntingtin and PCNA. The project will involve testing various design configurations to establish the assay and then implementing it to find novel proteins associated with the Huntingtin:PCNA complex. You will learn molecular cloning, proteomics, cell biology, and imaging methodologies.

Hinde Group

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Key focus areas

- 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

Keenan Group

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Key focus areas

- Immunology
- Epigenetics
- Microscopy
- Infection and Immunity
- Haematopoiesis
- Computational Biology
- Therapeutics and translation

Research in the Keenan laboratory aims to understand how epigenetic mechanisms cause or contribute to immune diseases. We use a variety of cutting-edge molecular techniques particularly Next-Generation Sequencing and CRISPR-based genomic manipulation, coupled with functional analysis of immune responses in vitro and in vivo. The ultimate goal of this research is to develop new therapeutic strategies to restore healthy immunity.

Project: Investigating the role of Kmt2d in haematopoiesis

Project Description. Kmt2d is an epigenetic enzyme frequently mutated in cancers such as leukemias, and is the main causative gene for the developmental disorder Kabuki syndrome (KS). KS patients frequently present with immunological issues such as immune deficiency and autoimmunity, suggesting Kmt2d plays important roles in both the development and function of white blood cells. This project aims to understand how Kmt2d controls the development and function of blood cells using a novel mouse model where Kmt2d is specifically deleted in the haematopoietic compartment using an inducible Cre-loxP system. This project will characterise the phenotype of this novel mouse model using multi-dimensional flow cytometry and fluorescence microscopy in order to assess the role of Kmt2d in predisposition to leukemia / immune deficiency / autoimmunity.

Project supervisor:

Dr Kristin Keenan

Project Co-supervisor:

Dr Michelle Ruhle

Project Availability:

- Honours
- Master of Biomedical Science

Project: Targeting epigenetic mechanisms to improve immunity

Targeting epigenetic mechanisms is emerging as an exciting therapeutic strategy with potential to re-wire the genome in disease. The Keenan lab has particular interest in diseases of the immune system. We have exciting preliminary data that implicates methylation of lysine 4 of histone H3 (H3K4me) as an important molecular controller of the B cell lineage of the immune system, the cell-type responsible for producing functionally diverse antibodies to protect us from infection. This project will investigate the role of H3K4 demethylase enzymes such as LSD1 and JARID1 in B cells using pharmacological and CRISPR/Cas9 approaches. By understanding the molecular regulation of B cells, we hope to develop new therapeutic approaches to improve immune responses to vaccination and infection. Other techniques that will be learned include multi-dimensional flow cytometry, advanced genomics techniques such as RNA-seq/ChIP-seq/ATAC-seq/CUT&Tag/CUT&Run/Hi-C, and mouse models of immune responses. The successful student will ideally know (or be willing to learn) some basic R coding to enable you to interact with your data.

Project supervisor:

Dr Kristin Keenan

Project Co-supervisor:

Dr Michelle Ruhle

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Kristin Brown Group

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Key focus areas

- 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:

A/Professor Kristin Brown

Project availability:

- Master of Biomedical science
- Honours
- PhD

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:

A/Professor Kristin Brown

Project co-supervisor:

A/Professor Andrew Cox

Project availability:

- Master of Biomedical science
- Honours
- PhD

Project: Investigating the role of cellular metabolism in regulating antigen presentation and tumor immune escape

In order to develop and progress, tumours must avoid elimination by the immune system. Understanding the mechanisms that allow tumours to evade the immune system is critical for developing strategies to overcome immune escape and enhance the efficacy of currently existing immunotherapies. Using a variety of in vitro and in vivo techniques, this project will investigate the fundamental mechanisms through which changes in cellular metabolism contribute to immune evasion in cancer and identify strategies to restore tumour elimination by the immune system.

Project supervisor:

A/Professor Kristin Brown

Project availability:

- Master of Biomedical science
- Honours
- PhD

Mackay Group

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Key focus areas

- Neuroinflammation
- Therapeutics and translation
- Cell signalling
- Infection and Immunity
- Lung Health

Our team is focussed largely around the fascinating mast cell and its role in allergic and non-allergic disease. In particular, we want to better understand how these cells are activated, the mediators they release and if we can translate this knowledge to generating new therapeutics.

Project: MRGPRX2-mediated drug hypersensitivity reactions

Exciting new work has identified that mast cells have a receptor called MRGPRX2 that can be directly activated by many clinically used drugs including certain antibiotics. This might explain a significant number of drug hypersensitivity reactions. However, it is unclear as to why only some individuals react so adversely to these drugs. In this project you will examine mast cell activation through MRGPRX2 and identify pathways that enhance the activity of this pathway. This information will hopefully be of utility in better understanding, predicting and treating MRGPRX2-mediated drug hypersensitivity.

Project supervisor:

A/Professor Graham Mackay

Project availability:

- PhD
- Honours
- Master of Biomedical science

Maher Group

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Key focus areas

- Structural Biology
- Protein Chemistry
- Biochemistry
- Bioinorganic chemistry
- Biophysics

Research in the Maher group focuses on investigating the role of trace metals in biological systems, with a particular focus on the structural biology of metalloproteins and integral membrane protein transporters. Our primary techniques are protein chemistry and X-ray crystallography and applications of our research range from the development of novel antibiotics, investigating the foundations of mitochondrial disease and developing new insecticidal agents for applications in agriculture.

Project: Harnessing nutritional immunity for the treatment of infection

Our research sits at the interface of chemistry and biology and investigates the roles of transition metals such as iron, copper, manganese and zinc in biological systems. These trace nutrients are essential for all forms of life – approximately 30% of all proteins bind transition metals and 50% of enzymes requires these cofactors for activity. We have several exciting projects examining the role of transition metals in infection and immunity. We know that bacteria (like all other organisms) require transition metals for life, but that they are also toxic in excess. In fact, these elements form part of the human innate immune response where they are harnessed as antibacterial agents. The investigation of these systems is of critical importance currently, as the world is facing a crisis of antibiotic resistance. At the current trajectory, it is estimated that by 2050, 10 million people per year will die because of antimicrobial resistance. Therefore, there is an urgent need to develop new strategies for the treatment of bacterial infections.

Projects in our lab for 2025 will focus on the organism Klebsiella pneumoniae (which in humans causes pneumonia) and the role of zinc, both as an essential nutrient and an antibacterial agent. These projects will examine proteins that modulate Zn concentrations in the organism, their structures and bioinorganic chemistries, with the ultimate aim of harnessing this knowledge for novel antibacterial design.

Project supervisor:

Professor Megan Maher

Project Availability:

- Honours
- Master of Biomedical Science
- PhD

Project: Charting molecular pathways for complex IV biogenesis

Project Description :The mitochondrial oxidative phosphorylation (OXPHOS) system generates the bulk of cellular ATP, fuelling the energy demands of most eukaryotes. Five multi-subunit protein complexes in the mitochondrial inner membrane, termed complexes I to V, comprise the OXPHOS system. Complex IV is the last complex of the electron transport chain, transferring electrons from cytochrome c to molecular oxygen, and in the process, pumping four protons across the inner membrane. In humans, this complex is composed of 14 subunits and requires copper and heme incorporation for its biogenesis and activity. Assembly of complex IV requires the participation of a host of assembly factor proteins, found in the mitochondrial intermembrane space (IMS), which work together for complex IV assembly. Failures in the assembly pathway can manifest as mitochondrial disease. This project will investigate the mechanisms by which copper is incorporated into complex IV by studying the structures, functions and interactions between assembly factor proteins.

Project supervisor:

Professor Megan Maher

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

McConville Group

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Key focus areas

- Pathogens
- Metabolism
- Drug Design and Resistance
- Metabolomics
- Discovery Research
- Biophysics

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 supervisor:

Professor Malcolm McConville

Project co supervisors

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 CRISPR/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

Professor Malcolm McConville

Project co supervisor

Dr Eleanor Saunders

Project availability:

- PhD
- 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

Professor Malcolm McConville

Project co supervisor

Dr Eleanor Saunders & Dr Fleur Sernee

Project availability:

- PhD
- Master of Biomedical science
- Honours

Menden Group

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Key focus areas

- Computational pharmacogenomics
- Cancer
- Neurodegenerative and inflammatory skin diseases
- Precision medicine
- Artificial Intelligence
- Machine learning
- Biostatistics

The Menden Lab is developing biostatistical, machine learning, and artificial intelligence frameworks applied to biomedical data, unlocking insights into complex diseases, and discovering intervention strategies. By delving into deeply characterized biomedical datasets, we tailor our models using disease-specific insights gleaned from collaborations, literature, and data-driven analyses. In doing so, we empower the next generation of drug target identification, drug repositioning, and precision medicine.

Project: Developing a connectivity map for PDAC

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive and heterogeneous cancer with a 10-year-survival rate of ~1%. PDAC is remarkably resistant to chemotherapies and almost invariably fatal. A better understanding of the biology and therapeutic vulnerabilities is needed to achieve progress. Our collaborators in Germany have screened 100 drugs by RNA-seq on a comprehensive panel of 200 primary murine cell cultures that cover the full spectrum of PDAC heterogeneity and recapitulate the main genetic alterations observed in patients. Based on this unpublished data, the student will build a 'context-specific' connectivity map that incorporates the molecular landscape of PDAC and transcriptional perturbation signatures. In addition, the student will leverage advanced machine learning and systems biology methods to predict potent drug combinations. The most promising compounds and combinations will then be tested in vivo in fully immunocompetent PDAC subtype models where the collaborators will employ single cell RNA-seq to dissect the response of cancer cells and their environment towards drug treatment. The PDAC in vivo models will mimic closer the expected drug response in patients, enabling hypotheses for combinations with immunotherapies, and ultimately strongly increasing translatability to clinics.

Project Supervisor:

A/Professor Michael Menden

Project availability:

- PHD
- Honours
- Master of Biomedical Science

Mintern Group

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Key focus areas

- Immunology
- Vaccines
- Cell Biology
- Protein Receptors
- Cancer
- 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:

Professor 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:

Professor Justine Mintern

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Exploiting nanoparticles as vaccines

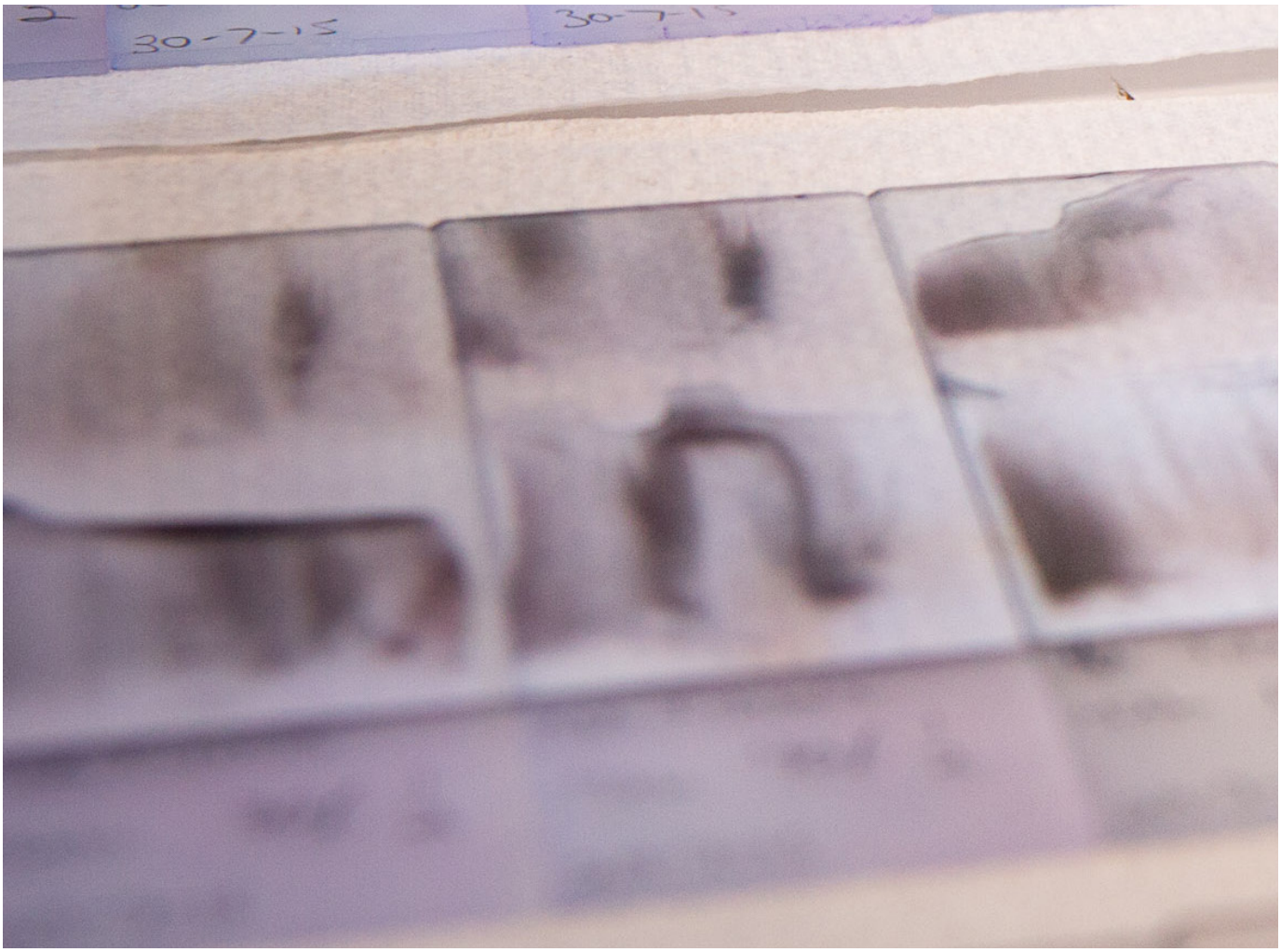
Nanoparticles have exciting potential to serve as modular therapeutic delivery systems that can target any cell type and carry any therapeutic peptide cargo. One emerging application for nanoparticles is their use as next generation vaccines. While there have been significant successes in vaccine research, 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:

Professor Justine Mintern

Project availability:

- PhD
- Master of Biomedical science
- Honours



Parker Group

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Key focus areas

- Pathogens
- Cancer
- Drug Design
- Structural Biology
- Computational Biology
- 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:

Professor Michael Parker

Project co-supervisor:

Dr Claire Weekley

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 small molecule drug discovery projects on APP itself and on immune cell receptors that clear toxic molecules from the brain.

Project supervisor:

Professor Michael Parker

Project co-supervisor:

Dr Emma Van Der Westhuizen

Project availability:

- PhD
- Honours
- Master of Biomedical science

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

The beta-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:

Professor Michael Parker

Project co-supervisor:

Dr Michelle Christie

Project availability:

- PhD
- Honours
- Master of Biomedical science

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.

Principal Supervisor:

Dr Michael Gorman

Project Co-Supervisor:

Dr Larissa Doughty
Dr Claire Weekly

Project availability:

- Honours
- PhD
- Master of Biomedical science

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. We also have projects to develop new antibiotics based on key protein targets in the bacterium that have been discovered by our collaborators.

Project supervisor:

Professor Michael Parker

Project co-supervisor:

Dr Tracy Nero and Dr Michelle Christie

Project availability:

- Honours
- PhD
- Master of Biomedical science

Peter and Wang Group

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Key focus areas

- Cardiovascular pharmacology
- Drug Design
- Translational and Clinical Research
- Molecular Imaging
- Targeted Drug Delivery

The Peter and Wang group focuses on basic and translational research covering a wide variety of themes, including cardiovascular disease, autoimmunity and cancer. We study fundamental disease mechanisms in order to define the key cells and molecules which contribute to the development or outcome of disease. Using this information, we then design, test and implement novel molecular imaging approaches using state of the art technologies (magnetic resonance imaging, ultrasound, computed tomography, positron-emission tomography and 3D fluorescence emission computed tomography). We focus on novel therapeutic approaches, such as biological therapies targeting immune cells; and theranostics, which combine both therapeutics and diagnostics into a single platform.

Project: Activated platelet-targeted drug therapy

Acute thrombosis causes vessel occlusion resulting in ischemic complications, such as myocardial infarction and stroke, and is a major cause of death and disability worldwide. Fast and effective removal/breakdown of thrombosis is crucial to reduce injury and improve recovery. Fibrinolysis is a valuable alternative for the treatment of myocardial infarction when invasive/surgical procedure is not available in a timely fashion. For acute ischemic stroke, fibrinolysis is the only treatment option with a very narrow therapeutic window. However, clinically approved thrombolytics have significant drawbacks, including bleeding complications due to the high systemic concentration required. Thus their use is highly restricted leaving many patients untreated. This project would focus on the development of novel targeted fibrinolytic drug that is directed against activated platelets.

The use of small recombinant antibodies for diagnostic molecular imaging and targeted drug delivery is well established in our lab. When thrombosis occurs, platelets are activated and aggregate together to form a thrombus. Our targeted fibrinolytic drug will locate these activated platelets and accumulate at the site of the clot where they will act to break the clot down. This allows a high potency of drugs for efficient and safe thrombolytic treatment. Due to the targeting properties, we can reduce the concentration of drugs need which would also enable us to eliminate the current bleeding complications associated with the clinically used fibrinolytic drugs. Significance: This project will develop and test a novel fibrinolytic agent with the capability to overcome the current limitations in thrombolytic therapy associated with the risk of bleeding complications. It has the potential to break the fatal link between increased fibrinolytic potency and bleeding complications.

Project supervisor:

Dr Xiaowei Wang

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Project: Diagnosis and therapy of cancer, inflammation and thrombotic diseases

This project would focus on Glycoprotein (GP) IIb/IIIa, which plays an important role in the aggregation of platelets. GPIIb/IIIa is the most abundant platelet receptor and it undergoes a change in confirmation when activated. For this reason, this molecule has been chosen as the target epitope for molecular imaging. The use of small recombinant antibodies for diagnostic molecular imaging and targeted drug delivery are well established in our lab. We propose to conjugate activated GPIIb/IIIa targeting recombinant antibodies to different contrast agents for their respective imaging modality. These recombinant antibodies can be used for both diagnostic imaging and targeted delivery of pharmacological treatment. Our group has access to a variety of clinically available imaging modalities, including magnetic resonance imaging (MRI), ultrasound, computed tomography (CT) and positron-emission tomography (PET), as well as the latest preclinical scanners, such as new 19-Flourine MRI technology and 3D fluorescence emission computed tomography (FLECT).

Aims: This project aims to investigate activated platelet targeted contrast agents for detection of inflammation, cancer and/or thrombosis using molecular imaging, thereby providing a better diagnostic technology. By harnessing the targeting ability of the antibodies, we can then conjugate drugs onto them for side-effect free, targeted drug delivery.

Significance: With steadily increasing health care expenses, a promising translational imaging application can fulfil the need for a cost-effective and non-invasive diagnostic tool. Employing a targeted drug delivery approach will enable treatment of thrombosis.

Project supervisor:

Dr Karlheinz Peter

Project Availability:

- Master of Biomedical Science
- Honours

Project: Diagnosis and therapy of inflammatory diseases using molecular imaging

Cardiovascular diseases, such as heart attacks and strokes, are major causes of death and disability in Australia and worldwide. These events are caused by chronic inflammation, atherosclerosis and acute thrombosis.

The use of small recombinant antibodies for diagnostic molecular imaging and targeted drug delivery are well established in our lab. This project would focus on the Vascular Cell Adhesion Molecule-1 (VCAM-1), which is an endothelial surface molecule that is most strongly and specifically upregulated during inflammation. For this reason, this molecule has been chosen as an additional target epitope for molecular imaging of inflammation. We propose to conjugate VCAM-1 targeting recombinant antibodies to different contrast agents for their respective imaging modality. We would use these recombinant antibodies for diagnostic imaging and targeted delivery of pharmacological treatment. Our group has access to a variety of clinically available imaging modalities, including magnetic resonance imaging (MRI), ultrasound, computed tomography (CT) and positron-emission tomography (PET), as well as latest preclinical scanners, such as new 19-Flourine MRI technology and 3D fluorescence emission computed tomography (FLECT).

Aims: This project aims to investigate whether VCAM-1 targeted contrast agents will enhance inflamed vessels using molecular imaging, thereby providing a better diagnostic technology. By harnessing the targeting ability of the antibodies, we can then conjugate drugs onto these antibodies for side-effect free, targeted drug delivery.

Significance: With steadily increasing health care expenses, a promising translational imaging application can fulfil the need for a cost-effective and non-invasive diagnostic tool. Employing a targeted drug delivery approach will enable treatment of inflammation that may prevent downstream catastrophic events of heart attacks and strokes.

Project supervisor:

Dr Xiaowei Wang

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Project: Understanding the role of the microbiome in chronic cardiovascular inflammation

In recent years it has been demonstrated that the microbiome, composed of trillions of microbes inhabiting our bodies, can significantly influence disease susceptibility and severity. Mechanistically, the microbiome has been shown to elicit this influence by regulating metabolism and the immune system. Atherosclerosis is a disease of chronic inflammation and metabolic dysfunction, however, whether the microbiome plays a role in determining an individual's susceptibility to atherosclerosis or the disease's severity is unknown. This project will explore the role of the microbiome in the development of atherosclerosis with a key focus on how the microbiome influences the immune system. In addition, this research will define and test strategies for the therapeutic manipulation of the microbiome in the context of atherosclerosis and chronic inflammation.

Project supervisor:

Dr Yung Chih Chen

Project Availability:

- Honours
- Master of Biomedical Science

Project: Developing nanoparticles for targeted theranostics delivery of drug and gene therapeutics

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. Atherosclerosis, a chronic inflammatory disease, is the underlying cause of most CVDs. Therefore early detection, prevention or regression of atherosclerosis may prevent devastating events such as heart attacks from occurring. We will create bio-compatible nanoparticles as contrast agents for imaging and drug carriers. These nanoparticles gives us the flexibility to incorporate drugs to increase their payload and/or apply them in gene delivery. By targeting these nanoparticles to the biomarkers of atherosclerosis, we can investigate their functions as novel theranostic (simultaneous diagnosis and therapy) approaches. Therefore this project would also focus on Vascular Cell Adhesion Molecule-1, which is one of the endothelial surface molecules most strongly and specifically up-regulated in inflammation. We propose to conjugate VCAM-1 targeting recombinant antibodies onto nanoparticles for diagnosis imaging and targeted delivery of pharmacological or genetic treatment. Significance: With steadily increasing health care expenses, targeted theranostic nanoparticles can provide early diagnosis and treatment of atherosclerosis, thereby preventing further CVDs.

Project supervisor:

Dr Xiaowei Wang

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Project: Immunity, Chronic Inflammation and Cardiovascular Disease

Atherosclerosis is a disease characterised by the formation of chronically inflamed lipid laden plaques in medium and large arteries, such as those that supply the heart and brain with blood. The rupture of these plaques causes blood clots which can block these arteries, and is the primary cause of myocardial infarction (heart attacks), strokes, and the majority of cardiovascular disease mortality. Despite recognition that inflammation is a key feature of atherosclerosis and the most likely cause of plaque rupture, it is not fully understood what drives the chronicity of pro-atherosclerotic immune responses. With a particular focus on the adaptive immune system (T & B cells); we aim to deeply characterise the immune landscape in atherosclerosis using state-of-the-art technologies, identify the causes of immune dysregulation and chronic atherosclerotic inflammation and define the role these pathways play in the development and outcome of cardiovascular disease. There is the opportunity to pursue several avenues for research projects, including: 1)Deep characterisation of adaptive immune responses in human and murine cardiovascular disease. 2) Defining the role of sexual dimorphism in the immune response in cardiovascular disease. 3) The role of conventional vs unconventional T cells in atherosclerosis and myocardial infarction. 4)Modulating adaptive immunity for the treatment of cardiovascular disease.

Project supervisor:

Dr Karlheinz Peter

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Ralph Group

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Key focus areas

- 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:

Professor 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:

Professor Stuart Ralph

Project co-supervisor:

Dr 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:

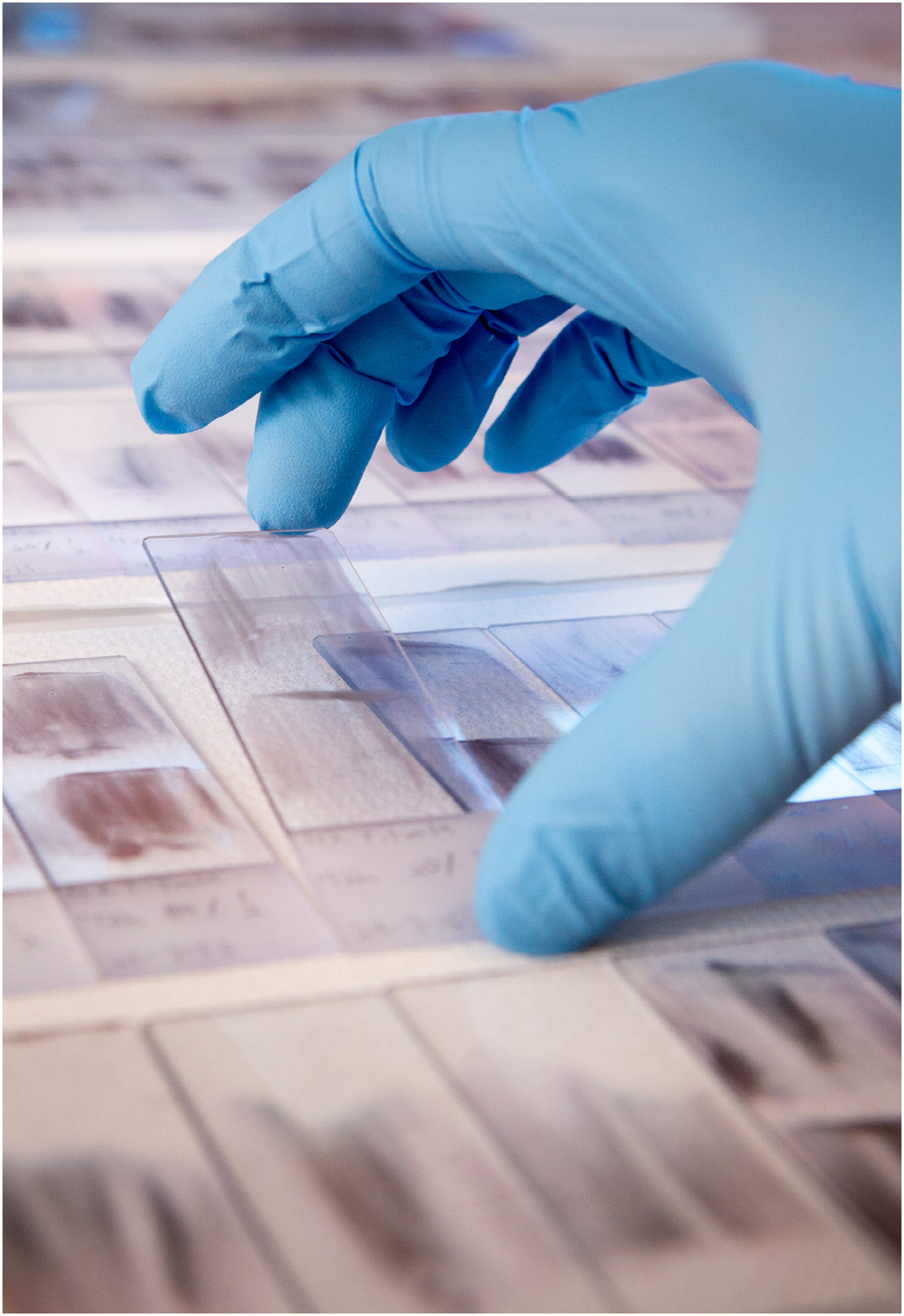
Professor Stuart Ralph

Project co-supervisor:

Professor Karin Verspoor

Project availability:

- PhD
- Master of Biomedical science
- Honours



Robyn Brown Group

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Key focus areas

- Neuropharmacology
- Motivated Behaviour

The Brown group aims to understand the neural mechanisms underlying pathological forms of motivated behaviour such as compulsive forms of eating and addiction, as well as explore the impact of high-fat high-sugar foods on brain and behaviour. We use a multi-disciplinary approach including behavioural models, electrophysiology, chemogenetics, optogenetics, fibre photometry, viral methods and transgenic mouse models.

Project: Why do woman overeat? Investigating neural circuits underlying 'emotional' eating

It is well established that stress and emotional state trigger binge eating. Notably, stress-related binge eating disproportionately affects females more than males, yet the precise biological mechanisms underscoring this sexual dimorphism remain underexplored. This has in part been due to the lack of robust animal models to recapitulate the human condition. To address this gap, we recently established a highly reproducible model of emotional stress-induced bingeing in female mice that is independent of caloric restriction commonly used in other models. Crucially, stress-induced bingeing in our model still occurred in ovariectomised mice, indicating that factors other than ovarian hormones must be involved. Our animal model provides an ideal tool to dissect the brain networks underscoring the stress-induced drive to eat in females. The aim of this project is to investigate the neural circuits underlying stress-induced binge eating using advanced techniques such as fibre photometry and viral tracing techniques

Project supervisor:

Dr Robyn Brown

Project co supervisor

Dr Priya Sumithran

Project availability:

- PhD
- Honours
- Master of Biomedical science

Project: Gut-brain mechanisms underlying the negative and positive health outcomes following bariatric surgery

Bariatric surgery is remarkably successful as it produces profound and sustained weight loss in combination with metabolic benefits. These benefits are thought to occur via actions on the gut-brain axis which lead to alterations in the neuroendocrine regulation of appetite and glycaemia. Furthermore, the hedonic responses to high-fat, high-sugar foods are dampened after bariatric surgery and decreased levels of compulsive forms of eating behaviour such as emotional eating and binge eating are observed. The precise mechanism responsible for these positive effects on eating behaviour is currently unknown. Evidence is also emerging which shows that subset of patients experience adverse mental health effects, including suicide, self-harm, depression and substance use disorders. The causative and contributing factors behind these adverse effects are not well understood. This project explores the utility of using a mouse model of bariatric surgery to determine the mechanisms underlying the impact of this procedure on affective behaviour including depression-like and anxiety-like behaviour, as well as operant responding for palatable food and drugs of abuse. Neurochemical analysis of brain tissue will investigate the changes in central gut hormones and their receptors potentially responsible for these changes in behaviour.

Project supervisor:

Dr Robyn Brown

Project co supervisor

Dr Priya Sumithran

Project availability:

- PhD
- Honours
- Master of Biomedical Science

Project: Diet-induce obesity: is it an addiction?

Difficultyin managing food intake, especially highly palatable food, can result inobesity and substantial associated health liabilities. A cardinal feature ofthe pathological over-eating often underlying obesity is that although theindividual can describe the negative consequences of their behaviour, they canhave great difficulty intervening and changing their behaviour. Thus,difficulty in reducing food consumption and actual behaviour suggests thepresence of impairments in how information from the frontal cortex isintegrating with basal ganglia circuitry to direct behaviour. We have foundthat rats prone to diet-induced obesity display some of the features ofaddiction-like behaviour towards palatable food. This provides importantpreliminary evidence to support our central hypothesis that the pathologicalover-eating commonly observed in diet-induced obesity shares common featureswith the compulsive drug-taking observed in drug addiction. This project aimsto understand potential endophenotypes underlying addictive behaviour towardsjunk food in rats prone to obesity and will use a combination of chemogeneticsand fMRI to assess cortico-striatal changes associated with the emergence ofthe addictive behaviour.

Project Supervisor:

Dr Robyn Brown

Project Co-supervisor:

DianaSketriene (UoM) and Bianca Jupp (Monash)

Project availability:

- PhD
- Master ofBiomedical Science
- Honours

The role of bombesin-3 system in controlling palatable food and fluid intake

This project aims to investigate a population of nerve cells (neurons) that decreases palatable food and fluid intake using cutting-edge genetically encoded techniques. Understanding this neural population is significant because highly palatable foods are ubiquitous in society and often ingested to excess, which disrupts energy homeostasis. Expected outcomes of this project include a thorough characterisation of a neural population which decreases palatable food and fluid intake, and the construction of a neural circuit map by tracing the neural projections. Expected benefits include a detailed understanding of the brain circuits regulating intake of highly palatable foods and fluids, which are often consumed to excess in today’s society.

Project Supervisor:

Dr Robyn Brown

Project Co-supervisor:

Dr Phil Ryan

Project availability:

- PhD
- Master of Biomedical Science
- Honours

Rouiller Group

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Key focus areas

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

The Rouiller group uses cryo-EM to determine the structures of medically important protein complexes. Lab members investigate how protein complexes function as molecular machines and in the context of health and disease. Projects in the Rouiller lab are relevant for treatment of cancer and neurological diseases as well as for treatment and prevention of infectious diseases.

Project: Molecular mechanisms regulating the unfoldase p97

Protein unfolding by enzymes, called unfoldases, is emerging as an important molecular mechanism that drives many functions in cells. The unfoldase activity of these enzymes must be highly regulated to assure unfolding of the correct substrate at the right time and maintenance of a healthy organism. The molecular mechanisms regulating unfoldases activity are currently **unknown.In** this project, you will study the molecular mechanisms regulating the function of one the best characterised unfoldase in human, the AAA ATPase p97. In human, p97 interacts with over 40 cofactors that regulate its activity. Using a combination of biochemical and biophysical assays, including HDX and cross-linking mass-spectrometry and cryo-electron microscopy, you will assess how cofactors interact with p97, modify its conformations, dynamic properties and activity. Several projects are available to study the impact of the most abundant cofactors p47, p37, Udf1-Npl4 and FAF1.

The goal of this project is to increase knowledge on the molecular mechanisms that regulate p97 in human. This research will facilitate the development of treatments for diseases where p97 has been identified as a potential drug target, including cancer and neurological diseases.

This project is ideal for a student with a strong background in biochemistry and who is interested in developing skills in protein science, including structural biology, mass-spectrometry and combined modern biophysical approaches in order to better understand how molecular machines function.

Project supervisor:

A/Professor Isabelle Rouiller

Project availability:

- PhD
- 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. The HIV-1 envelope glycoprotein trimer (Env), the only viral protein on the surface of virion, is thereby the main target to prevent infection. The challenge is that, at the surface of the virus, Env adopts a compact, closed conformation that is not recognized by antibodies inducing ADCC. After binding to its receptor at the surface of T cells, Env undergoes conformational changes and becomes more vulnerable to ADCC. Non-neutralizing antibodies increase the stability of this vulnerable conformation. In this project, you will use single particle cryo-EM and electron-tomography combined with subtomogram averaging to determine the high-resolution 3-dimentional structures of the HIV-1 envelope glycoprotein Env in conformations that are the vulnerable to ADCC. The changes of conformation are induced by binding of Env to its receptor (or receptor mimetic) and stabilised by binding of antibodies (Alsahafi et al., Cell Host & Microbe, 2019). The long-term goal of the research proposed here is to inform the development of new strategies for utilizing the ADCC response to eradicate HIV-1 infection.

This project is ideal for a student with a strong computational background who is interested in combining computational biology and structural biology to conduct impactful research for human health.

Project supervisor:

A/Professor 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. In this project, you will 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/Professor Isabelle Rouiller

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Deconstructing a microbial unfolding machine to target major killers

Cells from all kingdoms of life contain several protease systems that remove unwanted intracellular proteins. Protease systems cooperate with a subset of AAA ATPases (ATPases associated with diverse cellular activities) named unfoldases. These molecular machines unfold and deliver proteins into protease complexes. The best characterised unfoldase is the AAA ATPase p97. In human, p97 is a proven target for the treatment of various diseases including cancer and neurological diseases.

Homologs of p97 have been identified in pathogens causing devastating diseases including tuberculosis and malaria. The dependence of Mycobacterium tuberculosis (the causative agent of Tuberculosis) and Plasmodium falciparum (the causative agent of malaria) on p97 homologs for protein degradation has identified p97 as a potential new target in the treatment of these infectious diseases. The structures of p97 homologues from Mycobacterium tuberculosis, Plasmodium falciparum and other parasites are currently unknown. The specific functions of p97 in these organisms are also unknown.

Two projects are available to determine the structure of p97 homologs from 1) Mycobacterium tuberculosis and 2) Plasmodium falciparum. In these projects, you will use single particle cryo-EM to determine the structure of p97 homologs and combine a variety of biochemical, biophysical and mass-spectrometry approaches to characterise the assembly, dynamic properties and biological functions of p97 homologs. The goal of this project is to increase knowledge on these important molecular machines in mycobacteria and protozoa with the long term objective to develop inhibitors that would be specific to p97 from pathogens versus human p97.

This project is ideal for a student with a strong background in biochemistry and who is interested in developing skills in protein science, including structural biology, mass-spectrometry and combined modern biophysical approaches.

Project supervisor:

A/Professor Isabelle Rouiller

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Control of OPA1 activity by acetylation in neurological diseases

In neurons, mitochondria are highly dynamic organelles that undergo frequent fission and fusion. Fusion and fission of mitochondria is necessary to meet the constantly changing energy demands of neurons. A balance between fusion and fission is essential to maintain healthy neurons. Excessive fission causes mitochondrial fragmentation and is associated with metabolic deficits and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and optic nerve degeneration. Mitochondrial fission and fusion are regulated by large dynamin like GTPases. OPA1 regulates inner membrane fusion and OPA1 mutations in humans cause a variety of neurodegenerative disorders including optic atrophy and Parkinson's disease. Lysine acetylation has emerged as a key post-translational modification in mitochondria and neurodegeneration.

OPA1 is acetylated at lysine 288. In this project, you will assess how OPA1 acetylation affects the GTPase activity of OPA1, its conformation and its ability to interact with the mitochondrial inner membrane lipids. You will use a combination of biochemical and biophysical assays, including HDX and cross-linking mass-spectrometry and cryo-electron microscopy. The long-term goal of the research proposed here is to gain an understanding of the importance of OPA1 acetylation in maintaining healthy neurons and the relevance of OPA1 acetylation in neurological diseases. This project is ideal for a student with a strong background in biochemistry and who is interested in developing skills in protein science, including structural biology, mass-spectrometry and combined modern biophysical approaches in order to better understand neurological diseases.

Project supervisor:

A/Professor Isabelle Rouiller

Project availability:

- Master of Biomedical science
- Honours

Schneider-Futschik Group

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Key focus areas

- Lung Health
- Cardio-Respiratory
- Neuropharmacology
- Infection and Immunity

The Cystic Fibrosis Pharmacology group is are interested in the mechanisms of drug action, drug-drug interactions and drug safety of cystic fibrosis drugs during pregnancy and breastfeeding.

Project: Cystic fibrosis receptors during developmental stages

The cystic fibrosis modulators have transformed clinical outcomes for many CF patients by improving survival and general health. However, the much greater prevalence of CF women reaching childbearing age means increasing numbers of women taking these medications face very difficult decisions when it comes to having a family. This study will aid clinicians in prescribing CFTR modulators to pregnant women on how these drugs will transfer across essential barriers during different developmental stages.

Project supervisor:

Dr Elena Schneider-Futschik

Project co-supervisor:

Norman Saunders

- Master of Biomedical science
- Honours

Project: Cystic fibrosis and inflammation

In this study, we will correlate the functional manifestations of cystic fibrosis with pathological changes in histopathology; and investigate whether administration of ivacaftor, the first CF gene modulator that has significantly improved the life of patients with CF; is beneficial in improving inflammation.

Project supervisor:

Dr Elena Schneider-Futschik

Project availability:

- Honours

Project: Drug safety of respiratory treatments

Drug safety and efficacy of drugs used for respiratory diseases incl lung infections and inflammation. We are interested in understanding drug safety and efficacy of different drugs for respiratory diseases

Project supervisor:

Dr Elena Schneider-Futschik

Project availability:

- PhD
- Master of Biomedical Science
- Honours

Scott/Draper-Joyce Group

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Key focus areas

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

The Scott/Draper-Joyce 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, NMR, fluorescence microscopy, cryo-electron microscopy, computational modelling, nanobody/antibody discovery, and rational drug design.

Fragment-based drug discovery using stabilized α1-adrenoceptors

α1A- and α1B-adrenoceptors (α1A-AR and α1B-AR) are closely related GPCRs that modulate the peripheral and central nervous systems in response to binding epinephrine and norepinephrine. α1A-AR and α1B-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 α1A-AR and α1B-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 α1A-AR or α1B-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 α1A-AR and α1B-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 α1B-AR over α1A-AR, one of which was subsequently shown to exhibit 10-fold selectivity for inhibiting α1B-AR signalling. Another hit was a selective α1A-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 α1A-AR and α1B-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 Alaa Abdul-Ridhha

Project co-supervisors:

A/Professor Daniel Scott

Project availability:

- PhD
- Master of Biomedical science
- Honours

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:

A/Professor Daniel Scott

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Ultrasonically driven neuromodulation using mechano-responsive proteins

The spatiotemporal nuances that underly neuronal signalling are vital for normal nervous system function but are mostly not understood. In recent years optogenetics has revolutionised the study of neuronal networks by allowing precise, optical activation or inhibition of specific neurons in living, free moving animals. To do this however, fibre optics and/or lasers must be surgically implanted into animals, which is challenging and may interfere with behaviour. This project aims to investigate targeted acoustic mechanical stimulation from micro-engineered systems on neurons and neuronal tissue. Importantly, this also seeks to improve understanding of the parameters required to activate native and transfected mechano-responsive proteins, including Piezo1/Piezo2. The development of this understanding will lead to new, potentially less invasive methodologies for neural interaction studies and potentially future treatment modalities. This interdisciplinary project lies at the intersection of multiple fields and will utilize techniques in biomedical engineering, protein engineering, microfluidics, microsystems engineering, 3D printing, cell signalling and neurobiology.

Project supervisor:

Dr David Collins (Biomedical Engineering)

Project co-supervisors:

A/Professor Daniel Scott

Project availability:

- PhD
- Master of Biomedical science
- Honours

Project: Structural biology of G protein-coupled receptors toward improved drug discovery

G protein-coupled receptors (GPCRs) are the largest class of membrane proteins (>800 gene members), with a wide variety of physiological functions. GPCRs have been implicated in a variety of disease states (CNS disorders, cancer, diabetes, etc.) and have proved highly tractable drug discovery targets, with >30% of current FDA-approved drugs acting through these receptors. A deeper understanding of the detailed structural & molecular mechanism underlying drug action at GPCRs is crucial for the rational design of improved medicines. We use a suite of techniques around biochemistry and structural biology, including cutting-edge single- particle cryo-EM, to obtain molecular level insights into how GPCRs can be targeted. Obtaining high-resolution cryo-EM structures of GPCRs can then be used to rational design improved drugs (small molecules or biologics), which we can test in a variety of molecular pharmacology assays to monitor improved efficacy or binding. This project focuses on using novel protein expression and purification techniques to obtain GPCR samples that can be used for structural biology (cryo-EM). Insights obtained from cryo-EM can be used to rationally investigate molecular pharmacology of these GPCRs, providing detailed insights into drug action and how it can be improved for desired properties i.e. more efficacious & safer therapeutics.

Project supervisor:

Dr Chris Draper-Joyce

Project co-supervisors:

A/Professor Daniel Scott

Project availability:

- PhD
- Master of Biomedical science
- Honours

Shakeel Group

Contact: Dr Shabih Shakeel
Email: shabih.shakeel@unimelb.edu.au

Key focus areas

- Structural Biology
- Biophysics
- Biochemistry
- Epigenetics
- Cancer

The focus of our lab is to understand the structural basis of assembly and function of various genome-associated multiprotein complexes. We primarily use electron cryo-microscopy to investigate these complexes, complemented by biochemical and biophysical characterization and in vitro and in vivo functional assays.

Project: Structural and functional analysis of epigenetic multi-protein complexes in genome regulation

DNA activity is tightly controlled, and its integrity is protected to control gene expression and cell fate, without altering the underlying genetic code. Such level of regulation is achieved through the compaction of DNA into a complex three-dimensional structure in which genes are inactive, known as heterochromatin – the genomic 'dark matter' of a cell. This epigenetic control is crucial for human development and health because it defines the identity, and therefore the role, of every cell in the body. Unsurprisingly, malfunction of these processes leads to cancer, developmental defects, ageing and susceptibility to infectious diseases.

This exciting project will focus on understanding the structural basis of how various multi-protein complexes regulate heterochromatin. Students will use insect cell expression system to produce these complexes, followed by in vitro reconstitution of their activities and cryo-electron microscopy and mass spectrometry to elucidate atomic details of them.

Project supervisor:

Dr Shabih Shakeel

Project Availability:

- Honours

Stewart Group

Contact: Professor Alastair Stewart
Location: Medical Building
Email: astew@unimelb.edu.au
Website: go.unimelb.edu.au/kw8r

Key focus areas

Mechanopharmacology

Chronopharmacology

The group is investigating inflammation and fibrosis mechanisms using novel bioassays for target identification and drug discovery and characterisation. A range of system pharmacology-based analytical approaches are applied using transcriptomic and proteomic data from well-qualified clinical and experimental specimens. The lab has extensive links to Biomedical Engineering, Chemistry, Physics and several clinical centres and is the headquarters of the ARC-industry Transformation Training Centre in Personalised Therapeutic Technologies.

Project: "CLOCK-off Time" for inflammation and remodelling in chronic inflammatory diseases: Casein Kinase 1 delta inhibitor

Chronic inflammatory diseases (including asthma and chronic obstructive pulmonary disease) exhibit a marked time of day variation in symptoms, airway inflammation and airway physiology. There is growing evidence supporting that the molecular clock is important in the pathogenesis of chronic inflammatory diseases. If time of day is important, then it follows that treatment of chronic inflammatory diseases should also be tailored to the most efficacious time of the day, known as "chronotherapy". Casein kinase 1 δ (CK1δ) has been implicated as a major regulator of the biochemical oscillator that determines circadian rhythm. Our laboratory has implicated CK1δ in signalling some of the fibrogenic and inflammatory actions of TGF-β, including the ability to switch off the anti-inflammatory effects of glucocorticoids. We hypothesize that CK1δ inhibitors reset the CLOCK to suppress inflammation. In this project, you will characterise the anti-inflammatory potential of CK1δ inhibitor class using primary human cells obtained from peripheral blood and/or from the airways. Methods to be used will include immunoassay, real-time quantitative PCR, cell culture and high content screening using plate-based confocal microscopy.

Reference:

Li, M., C. R. Keenan, G. Lopez-Campos, J. E. Mangum, Q. Chen, D. Prodanovic, Y. C. Xia, S. Y. Langenbach, T. Harris, V. Hofferek, G. E. Reid and A. G. Stewart (2019). "A Non-canonical Pathway with Potential for Safer Modulation of Transforming Growth Factor-beta1 in Steroid-Resistant Airway Diseases." iScience 12: 232-246.

Lachapelle, P., ^ Li, M., Douglass J., Stewart, A.G. Safer approaches to therapeutic modulation of TGF-b1 signaling in respiratory disease. Pharmacology & Therapeutics. 187: 98-113.

Keenan, C. R., Langenbach, S. Y., Jativa, F., Harris, T., Li, M., Chen, Q., Xia, Y., Gao, B., Schuliga, M.J., Jaffar, J., Prodanovic, D., Tu, Y., Berhan, A., Lee, P., Westall, G.P., Stewart, A.G. (2018). Casein Kinase 1δ/ε Inhibitor, PF670462 Attenuates the Fibrogenic Effects of Transforming Growth Factor-β in Pulmonary Fibrosis. Frontiers in Pharmacology. 9:738.

Xia, Y. C., Radwan, A., Keenan, C. R., Langenbach, S. Y., Li, M., Radojicic, D., Londrigan, S. L., Gualano, R. C., & Stewart, A. G. (2017). Glucocorticoid insensitivity in virally infected airway epithelial cells is dependent on transforming growth factor-b activity. PLOS Pathogens, 13, e1006138.

Project supervisor:

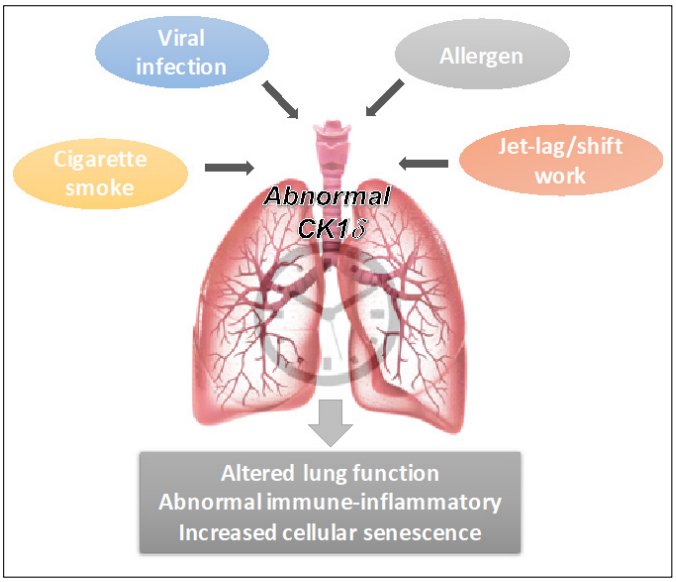
Professor Alastair Stewart

Project co-supervisor:

Dr Meina Li

Project availability:

- PhD
- Honours
- Master of Biomedical science



Stojanovski Group

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Website: go.unimelb.edu.au/8z5i

Key focus areas

- Organelles
- Cell Biology
- Metabolism
- Pathogens
- Mitochondrial Disease

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 trans**Location:** 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:

A/Professor 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:

A/Professor Diana Stojanovski

Project co-supervisor:

Dr Hayley Newton (PDI)

Project availability:

- PhD
- Master of Biomedical science

Stroud Group

Contact: A/Professor David Stroud
Email: david.stroud@unimelb.edu.au

Key focus areas

- Functional genomics
- Proteomics
- Inborn errors of metabolism
- Medical genetics
- Translational and Clinical Research
- Mitochondrial disease
- CRISPR-Cas9
- Organelles

Lab Description Research in the Stroud laboratory aims to raise the diagnostic rate for monogenic rare diseases, including mitochondrial disease, understand rare disease pathology, and ultimately improve human health through the application new mass- spectrometry based technologies to functional genomics.

Project: Rapid functional genomics for rare genetic disorders through the development of clinical proteomics

Project Description Rare diseases are defined as a disease affecting less than 5 in 10,000 people. While rare diseases are individually rare, there are more than 7,000 conditions with most being pediatric disorders and having devastating outcomes. Rare diseases are typically monogenic where mutations in a single gene explains patient pathology. An accurate molecular diagnosis is critical as it can guide treatment and enable access to family planning approaches such as pre-implantation genetic testing. The front line approach for diagnosis of suspected rare disease is whole genomic sequencing, however less than half of patients will not receive a definitive answer. The most common reason for this is lack of biochemical evidence supporting pathogenicity of novel mutations in known and novel genes.

Our lab has developed a quantitative proteomics-based approach to rapidly generate functional data linking novel variants to pathogenicity (see: Lunke et al., 2023 Nature Medicine; Amarasekera et al., 2023 Human Molecular Genetics for examples). Through our Australian Government funded initiative RDMassSpec, we are actively recruiting undiagnosed patients with suspected mitochondrial and non-mitochondrial rare genetic disease (see: https://go.unimelb.edu.au/obi8) and in parallel developing the technique for routine clinical use through automation of sample preparation, benchmarking of utility against groups of patients with a known diagnosis, and demonstrating utility in diagnosis of non-mitochondrial disorders. We have multiple Honours and Master projects available and would be happy to discuss a project within this research theme that aligns with your specific interests and career goals. When undertaking a project in this theme you will become skilled in cell culture, proteomics sample prep and data analysis, application of various functional assays such as Seahorse XF oxygen consumption rate measurements, and potentially the use of CRISPR/Cas9 and molecular biology approaches to generate and analyse disease models. You will also become familiar with the analysis of human genomic data and curation, and will work alongside clinicians, medical scientists, genetic counsellors and clinical genetics experts.

Project supervisor:

A/Professor David Stroud

Co-Supervisor:

Dr Daniella Hock

Project Availability:

- Master of Biomedical Science
- PhD
- Honours

Project: Dissecting the function of the mitochondrial disease associated ATAD3 gene cluster and its pathogenic variants

Mitochondrial disease encompasses a heterogenous group of rare neurometabolic disorders caused by mutations in ~350 known genes, affecting 1:5000 live births. Among the most common causes of mitochondrial disease, often leading to perinatal fatalities, are variants in the ATPase family AAA+ domain-containing protein 3 (ATAD3) locus. Typically conserved as a single gene among metazoans, the human equivalent has duplicated into three highly homologous paralogs; ATAD3A, and the hominid-specific ATAD3B and ATAD3C. Despite being implicated in a range of key mitochondrial processes, their precise molecular roles have yet to be resolved. To dissect the functional roles of ATAD3 proteins and the mechanism of pathogenicity behind many of the different mutations detected in patients, our lab established a novel human ATAD3 disease model in cell culture where the entire 80,000 bp locus has been replaced by an inducible ATAD3A through gene-editing. In this project you will use this tool to generate vital clinical information around the pathogenicity of ATAD3 mutants identified in patients by characterising their individual impacts on cell viability and growth, mitochondrial function. Depending on your specific interests you will also aim to address key outstanding questions around ATAD3 protein function, such as sub-mitochondrial localisation, import into mitochondria and assembly into functional complexes, and the role of the AAA+ ATPase in ATAD3 protein function. We have multiple Honours and Master projects available and would be happy to discuss a project within this research theme that aligns with your specific interests and career goals. When undertaking a project in this theme you will become skilled in cell culture, molecular biology and biochemistry techniques such as cloning, SDS-PAGE and Western blotting, proteomics sample prep and data analysis, immunoprecipitation, viral transduction, and various functional assays such as Seahorse XF oxygen consumption rate measurement.

Project supervisor:

A/Professor David Stroud

Project Co-supervisor:

Dr Ann Frazier

Project Availability:

- PhD
- Master of Biomedical Science
- Honours

Project: Forward CRISPR/Cas9 genetic screen to identify novel mitochondrial protein function

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 the OXPHOS complexes and >50 others known as assembly factors are needed for their biogenesis and regulation. Our lab recently identified a protein factor that accumulates in mitochondria when the OXPHOS system is damaged, either through mutations in genes affecting OXPHOS function, hypoxia, or inhibition of OXPHOS through treatment with small molecule inhibitors. In this project you will harness this knowledge to perform a forward CRISPR/Cas9 genetic screen with the goal of identifying new proteins involved in maintenance of mitochondrial OXPHOS function. Throughout your Honours or Masters research project you will become skilled in cell culture, molecular biology and biochemistry techniques such as cloning, lentivirus transduction, imaging approaches such as confocal fluorescence microscopy, fluorescence activated cell sorting, and bioinformatic approaches related to genetic screening.

Project supervisor:

A Professor David Stroud

Project Availability:

- Master of Biomedical Science
- Honours

Villadangos Group

Contact: Professor Jose Villadangos
Location: Bio21 Molecular Science and Biotechnology Institute / Doherty Institute
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Key focus areas

- Immunology
- Pathogens
- Protein Receptors
- Cell Biology
- Cancer
- Metabolism
- Organelles
- Viral host

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: 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: Investigating the role of dendritic cell O-GlcNAcylation in adipose tissue homeostasis and immune function

This project will delineate how the addition of a small sugar to cellular proteins, known as O-GlcNAcylation, links nutrient-sensing and immunity in fat tissue. This project will determine how the loss of O-GlcNAcylation in dendritic cells (an important immune cell type), impacts fat tissue development and function in mice fed on a normal diet or a high fat diet that mimics a high calorie Western diet. The outcomes include breakthrough new knowledge, publications and commercial opportunities.

Project supervisor:

Dr Adam Balic

Project Co-Supervisor:

Professor Jose Villadangos

Project Availability:

- Master of Biomedical Science
- Phd
- Honours

Project: Harnessing the power of RNA technology for vaccines and therapeutics

mRNA vaccines are a new category of vaccines that are revolutionizing medicine. They emerged during the COVID-19 pandemic, with the formulations by Pfizer and Moderna playing a central role in the fight against the disease. These advanced vaccines constitute a new frontier in vaccine development against infectious pathogens and cancer. Despite evidence of robust T cell and B cell immunity induced by mRNA vaccines, little is known about the cascade of immune events that lead to the priming of adaptive immunity. This project will investigate which cells capture and express the mRNA following vaccination and how mRNA-encoded antigens are presented to T cells and B cells. It will use a variety of techniques, including mRNA vaccine generation, animal work, gene editing and spectral flow cytometry. Outcomes from this project will provide new insights into the mechanism of action of mRNA vaccines and create opportunities for publications and commercial development.

Project supervisor:

Professor Jose Villadangos

Project Co-Supervisor:

Dr Christophe Macri

Project Availability:

- PhD
- Master of Biomedical Science
- Honours

Project: Regulation of Complement by Membrane Receptor Ubiquitination

A fundamental component of our innate immune system is the complement system. The complement system consists of more than 50 plasma proteins and receptors that interact with pathogens, thereby providing an immediate line of defence against pathogenic intruders. The most abundant complement protein is C3. The activation of C3 must be tightly controlled, as binding of C3 to healthy cells can induce severe damage and can lead to autoimmunity. We have discovered that C3 forms a complex with MHC class II molecules (MHC II), expressed by Dendritic Cells. The C3 that is attached to MHC II is marked by the regulatory protein ubiquitin, a process called ubiquitination, which leads to internalization and degradation of MHC II-C3. This is a highly significant finding because formation of MHC II-C3 complexes may be a novel mechanism for capturing and eliminating potentially harmful C3. In this project, we will investigate the molecular mechanisms behind the MHC II-C3 complex formation and the regulation of C3 levels through ubiquitination. We will unravel which pathways of complement activation are involved and characterize the MHC II carbohydrate structure that enables C3 binding through a variety of biochemical techniques, supplemented with immunological techniques including spectral flow cytometry, cell culture, and animal models. These findings may contribute to the development of therapeutic strategies for complement-mediated diseases by manipulating receptor ubiquitination.

Project supervisor:

Professor Jose Villadangos

Project Co-Supervisor:

Dr Anouk Becker

Project Availability:

- Master of Biomedical Science
- Phd
- Honours

Project: Regulation of Complement by Membrane Receptor Ubiquitination

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Project supervisor:

Professor Jose Villadangos

Project Co-Supervisor:

Dr Anouk Becker

Project Availability:

- Master of Biomedical Science
- Phd
- Honours

Project: The immune signature of sepsis

There is an urgent need for treatments of sepsis, which is a dysregulated immune response to infection causing one in five deaths globally. Although this burden is highest in low-income countries, over 10% of Australian Intensive Care Unit (ICU) admissions are due to sepsis, with ~25% of these patients dying in hospital. Currently, there are no therapies to reverse sepsis-induced organ failure. Phase 1 clinical trials are now testing the use of mega dose sodium ascorbate (a formulation of Vitamin C) to treat sepsis.

This project will use blood samples from Phase 1 human clinical trials and blood and tissue samples from large animal studies of sepsis. We will perform detailed immune phenotype analysis and functional cellular assays using flow cytometry as our main research tool to investigate how the immune signature of sepsis changes over time in ICU and with treatment. This will help us understand the immunological signature of sepsis and identify patients most likely to benefit from treatment.

Project supervisor:

Dr Laura Cook

Project Co-Supervisor:

Professor Jose Villadangos

Project Availability:

- Master of Biomedical Science
- Phd
- Honours

Project: Regulating macrophage 'eating' for cancer and pathogen control

The surface receptor SIRPα plays an important role in regulating phagocytosis by macrophages. This is an vital innate defence mechanism against pathogens and also tumors. We previously found that following sepsis in humans and mice, SIRPa surface levels decreased and this lead to reduced phagocytosis and loss of antimicrobial immunity. However, little is known about the molecular regulation of SIRPα and what causes it to go up or down. This project will use whole-genome wide CRISPR screens to investigate the molecular mechanism of SIRPα modulation. It will define new targets for therapeutics to boost macrophage function against infectious diseases and cancer.

Further reading: A Roquilly… and JA Villadangos. 2020. Alveolar macrophages are epigenetically altered after inflammation, leading to long-term lung immunoparalysis. Nat Immunol 21:636-48. PMID 32581370.

Project supervisor:

Dr Hamish McWilliam

Project Co-Supervisor:

Professor Jose Villadangos

Project Availability:

- Master of Biomedical Science
- Phd
- 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
- MSc
- 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

Professor 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:

Professor Jose Villadangos

Project co-supervisor

Dr Laura Cook

Project availability:

- PhD
- Honours
- Master of Biomedical science

Walker Group

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Key focus areas

- Neuropharmacology
- Behavioural neuroscience
- Metabolism

The Addiction Neuroscience Group at the Florey Institute are interested in understanding how the brain controls drug and alcohol consumption; how drugs change the brain; and how we can leverage this information to identify novel treatment options. We use a mix of basic pharmacology, advanced neuroscience techniques (DREADDs, fiber photometry), and molecular assays to answer these questions.

Project: How hunger signalling changes decision making under conflict

Decision-making is one of the most important and fundamental biological processes executed by the mammalian brain. When faced with a choice between actions or goals with conflicting positive and negative outcomes, animals must weigh up between the potential risks and rewards of each option. Physiological pressures such as hunger, stress and reproductive prospects can influence decision-making processes, as animals must consider the need for resources within their environment and the potential threats to their survival. This project aims to understand how the brain integrates information about homeostatic need state (e.g hunger, thirst) and treat detection to make appropriate decisions.

Project supervisor:

Dr Leigh Walker

Project Availability:

- Master of Biomedical Science
- Honours

Wickramasinghe Group

Contact: Dr Vihandha Wickramasinghe
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Email: vi.wickramasinghe@petermac.org
Website: go.unimelb.edu.au/hv5i

Key focus areas

- Cell Biology
- Cancer
- Discovery Research
- Cell signalling

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:

- Honours

Willems-Jones Group

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Email: amber.willems@unimelb.edu.au

Key focus areas

- Scholarship of Teaching and Learning (SoTL)
- Quantitative Literacy
- Biochemistry Education

My research interests fall into the theme of Scholarship of Teaching and learning and Biochemistry Education. My research is currently based on three interconnecting themes (1) fostering inquiry-based learning skills, (2) improving student self-regulatory learning, and (3) enabling students to develop academic judgement; but I also have a keen interest in exploring the quantitative literacy skills of university students given the anecdotal observation that students in the biomedical sciences have a distinct disinterest in mathematics.

Project: Improving quantitative literacy skills for biochemistry students using targeted feedback and e-learning resources

Quantitative literacy is, in essence, being familiar with the manipulation of numerical information, including possessing the skills one requires to analyse data. Limited skills in quantitative literacy can have a profound impact on a student's academic performance and enjoyment in the biomedical sciences, particularly in applied subjects where a greater understanding of data interpretation is demanded. Helping students to identify, target and improve their limitations in this knowledge domain will have a lasting benefit for students not only in terms of their ability to perform in their subject(s), but also in terms of their overall confidence in approaching quantitative problems. This study will take an evidence-based approach to measure quantitative literacy skills - and associated student confidence - of students enrolled in second- and third-year biochemistry and molecular biology practical subjects. The study has the potential to foster improvements in student learning outcomes, particularly with respect to student competency in the quantitative literacy domain.

The overarching research question is: Does student understanding in areas of quantitative literacy improve through the delivery of targeted e-learning resources? The project will involved collecting and analysing data on quantitative literacy skills and confidence (using a QL questionnaire) from students in these BMB classes at the start and end of semester (i.e. pre and post 'intervention'). Upon analysis of week-1 data, feedback will be provided to direct students to the necessary e-learning modules to help them improve their understanding where student competence is reduced. Improvements in skill will be determined based on examination of the week-12 completion of the QL questionnaire (i.e. post 'intervention').

Project supervisor:

Dr Amber Willems Jones

Project Availability:

- Master of Biomedical Science
- Honours

Ziogas Group

Contact: A/Professor James Ziogas
Location: Medical Building
Email: jamesz@unimelb.edu.au

Key focus areas

- Cardiovascular pharmacology
- Molecular mechanisms of disease
- Therapeutics and translation
- Sub-arachnoid haemorrhage

Project: Cerebrospinal fluid biomarkers for aneurysmal subarachnoid haemorrhage

In the days following aneurysmal subarachnoid haemorrhage (aSAH) development of cerebral vasospasm (CVS) can lead to a general decrease in consciousness, delayed ischaemic neural deficits and cerebral infarction. The progression to a vasospastic state and its neurological sequelae represents an acutely debilitating pathology with a poor clinical prognosis and, for survivors, a high burden of disease (Rowland et al., 2012). Calcium channel antagonists such as nimodipine, which can ameliorate some of the vasoconstriction and excitotoxicity, are routinely given following surgical coiling or clipping of the aneurysm. However, further clinical intervention, currently hyperdynamic therapy or angioplasty, upon progression to a symptomatic vasospasm remains a necessity. In most cases, these interventions restore cerebral perfusion but have the potential for significant complications. Identification of appropriate biomarkers for the vasoconstriction and neurological sequelae has the potential to inform improved post-surgical management of aSAH.

Hypothesis: Development of CVS involves identifiable changes in the ratio of vasoactive, inflammatory and excitotoxic mediators following aSAH.

Specific aim: To obtain a temporal profile of functional, proteomic and metabolomic markers in cerebrospinal fluid (CSF) from patients following aSAH.

Nature of the work

The Department of Surgery at the Royal Melbourne Hospital (RMH) has 60-70 cases of aSAH per annum and collects CSF as part of the routine care of patients post- surgery. We have received approval from the RMH Human research ethics committee (MH Project number 2012.50) to undertake proteomic and metabolomic analysis of the CSF from these patients. Preliminary data indicate that ratiometric changes in certain proteins in the 10 – 40 kDa range may predict the likelihood of a patient developing CVS. This project will seek to extend these studies to include an analysis of proteins in higher and lower MW ranges (Rowland MJ, Hadjipavlou G, Klly M, Westbrook J & Pattison KTS. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. British Journal of Anaesthesia 109: 315-29).

Project supervisor:

Associate Professor James Ziogas

Project availability:

- PhD
- Honours
- Master of Biomedical science

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