



THE UNIVERSITY OF
MELBOURNE

PHARMACOLOGY AND THERAPEUTICS

2020



RESEARCH PROJECTS
HONOURS, MASTERS
AND PHD

WELCOME

It is a great pleasure to introduce you to the research projects that are on offer by the Department of Pharmacology and Therapeutics for 2020.

Most projects offered will be in our spacious, high quality research laboratories on the 8th and 9th floors of the Medical Building. The remainder will be conducted in affiliated Research Institutes with external supervisors and co-supervision by Department staff. The Department of Pharmacology and Therapeutics Honours and Masters Course is directed at students with above average academic ability. The year is a transition year 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 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.

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 Students 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 Pharmacology & Therapeutics for the 2020 Honours and Masters Year. We aim to give you the best opportunity to 'have a go' at solving a research problem, teach you important skills for future employment in various biomedical vocations and provide a solid basis for those who want to go further in a research career. Very best wishes for the next step in your journey!

Professor Daniel Hoyer

Honours & MBiomedSci Co-ordinator
Chair and Head
Department of Pharmacology and Therapeutics
Deputy Head, School of Biomedical Sciences
FMDHS, The University of Melbourne

Professor Gary Anderson Dr Graham Mackay

Honours & MBiomedSci Co-ordinator



HOW TO APPLY

HONOURS

What is Honours?

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

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

What are the entry requirements?

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

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

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

How long is Honours?

Honours is a one-year course consisting of 75 points of research and 25 points of coursework, that commences mid-February and finishes in November.

How to apply

STEP 1: Contact Potential Supervisor(s)

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

Applicants must contact potential supervisors either before or soon after submitting an online application for entry to an MDHS Honours course. Department and Institute Honours project booklets and websites, the individual information sessions held by departments and institutes are ways of helping you to make initial contact with potential Honours supervisors. However, if you are seriously considering a project you should arrange to meet your potential supervisor more formally to get a much better idea about the project and their expectations.

STEP 2: Online Application

Lodge an online application

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

STEP 3: Project Preference

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

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

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 the Honours as a PhD pathway. Students undertake a major research project and discipline-specific coursework subjects. In addition, a suite of professional business and communication subjects are offered to complement and enhance the research undertaken and to progress students' career opportunities.

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

What are the entry requirements?

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

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?

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

How to apply

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

Selecting a Project

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

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

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



UNIVERSITY OF THE DISTRICTS OF COLUMBIA

RESEARCH HIGHER DEGREES

What is a PhD?

A PhD (Doctor of Philosophy) is a 3-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 a shorter period of time of 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 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 Masters 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% or (University of Melbourne) equivalent.

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

- a four-year Bachelor 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% or higher; or
- a Masters 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 (University of Melbourne) 75% 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. If possible, try to get some work experience in the lab to get an idea about the environment.

For future information regarding Research Higher Degrees at the University of Melbourne see the following links:

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/

How to apply

1. Review the list of prospective projects and supervisors in this handbook or online at biomedicalsciences.unimelb.edu.au/departments/pharmacology#research
2. Identify projects of interest and contact the project supervisor to explain your research interests and provide your curriculum vitae (CV) and academic transcripts.
3. Once confirmed a project and supervisor apply online at study.unimelb.edu.au/how-to-apply/graduate-research

SCHOLARSHIPS

Honours

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

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

The Dept. of Pharmacology and Therapeutics offers financial support for Honours/Masters students to attend and present their research at a scientific conference commonly, The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT).

Graduate degrees

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

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



PROJECTS



ANDERSON GROUP

Contact: **Andrew Jarnicki**

Location: **Department of Pharmacology and Therapeutics**

Email: andrew.jarnicki@unimelb.edu.au



Therapeutics and translation



Molecular mechanisms of disease



Lung Health



Immunopharmacology

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: Developing Lung Organoids for treatment of Fibrotic Disease and Asthma

Organoids are three dimensional self-organising cellular structures that represent the most advanced and cutting-edge method of testing therapeutic drugs in a cell culture system. While historically two-dimensional cultures of cells were used to assess therapeutic drugs, organoids represent an advancement in that their 3D organisation allows incorporation of different cell types, and also more closely mimics tissues structures found in the body where adjacent cells can talk and influence each other in response to stimuli. Organoids can be therefore superior in predicting drug effectiveness than other current methods when determining drug treatments in patients. They represent an enormous potential in the future treatment of lung disease, as the technology allows cells from afflicted individuals to be grown into organoids and tested for the personalised response against a range of therapeutic drugs to determine which drug may be beneficial in their individual case.

Here we are interested in developing lung organoids to particularly examine fibrotic diseases as well as asthma. You will develop organoids from both lung epithelial and fibroblast cells with or without other structural support cells. You will then test different drugs on the organoids that are formed from cells from diseased lungs i.e. have fibrotic disease or asthma. The drugs have been selected through extensive research to target specific molecules we think are novel and important in lung disease.

You will develop a number of laboratory techniques including in vivo disease induction, tissue culture, PCR, western blotting and FACs as well as other key skills including project design, experimental planning, data analysis and scientific writing.

Project supervisor
[Dr. Andrew Jarnicki](#)

Project co-supervisors
[Professor Gary Anderson](#)
[Dr. Joe Ciccotosto](#)
[Dr. Robert o'Donoghue](#)

- PhD
- Honours
- Master of Biomedical Science

Project: Improving the development of treatments for fibrotic lung disease through superior pre-clinical modelling.

Idiopathic pulmonary fibrosis (IPF) is a fatal disease with half of patients succumbing to the lethal effects of this disease within 3 years. Much of the biology and clinical progression of IPF remains poorly understood, however smoking tobacco is a known risk factor for the development of IPF and there is some common biology to chronic lung diseases such as emphysema and lung cancer. In fact, some IPF patients have concurrent emphysema or lung cancer upon diagnosis. The current pre-clinical models of IPF have a poor record in translating successful treatments from the laboratory to clinic, in part, due to their inability to mimic molecular or cellular mechanisms that occur during tobacco smoking, emphysema, lung cancer and the

development of fibrotic lung diseases such as IPF. We are interested in developing pre-clinical models that better represent these molecular and cellular mechanisms to improve and develop IPF treatments that will be successful in the laboratory and the clinic.

You will be an essential part of a team investigating the development and progression of IPF in a pre-clinical setting that is testing novel treatments for this fatal disease. There will be opportunities to contribute to international industry collaborations and peer-reviewed publications. You will develop a number of laboratory techniques including in vivo disease modelling, tissue culture, QPCR, western blotting and FACs as well as other key skills including project design, experimental planning, data analysis and scientific writing.

Project supervisor
[Dr. Robert O'Donoghue](#)

Project co-supervisors
[Professor Gary Anderson](#)
[Dr. Andrew Jarnicki](#)

- PhD
- Honours
- Master of Biomedical Science



Contact : **Professor Ross Bathgate**

Location: **The Florey Institute of Neuroscience and Mental Health**

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Therapeutics and translation



Drug Design



Cell Signalling



Cellular Imaging and Structural Biology

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/Prof Paul Gooley). Our studies are complemented by peptide drug development projects and small molecule screening projects with collaborators. Additionally, we are working with pharmaceutical industry partners (eg. Takeda and Novartis) to facilitate drug development efforts. Projects are available on multiple GPCR targets with training in various techniques as outlined above.

Project supervisor
Professor Ross Bathgate

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

- Honours
- Master of Biomedical Science

Project: Peptidomimetic drug design targeting G protein-coupled receptors

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

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

phase peptide synthesis, molecular pharmacology, and animal physiology to carry out these projects. Importantly, we are working with pharmaceutical industry partners (eg. Takeda and Novartis) to develop peptidomimetics therapeutically. Projects are available on multiple additional GPCR targets with training in various techniques as outlined above.

Project supervisor
Prof Ross Bathgate

Project co-supervisor
A/Prof Akhter Hossain
Dr Susan Northfield
Dr John Karas

- Honours
- Master of Biomedical Science

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

GPCRs are the targets for ~30% of all currently used therapeutic drugs. It is critical to understand how these receptors are activated, how they alter cellular function, how such responses are switched off, and how other cellular components can modulate their activity. GPCRs interact with a range of other proteins and these interactions govern their function and modulation. Our laboratory has a range of advanced cutting-edge technologies available for the study of GPCRs allowing interacting partners and signalling profiles to be determined. These include novel Bioluminescence Resonance Energy Techniques (BRET)-based biosensors. BRET is a technology that places light-emitting labels on proteins, enabling their interactions to be examined in living cells, and is uniquely suited to the study of integral membrane proteins

such as GPCRs (Figure). BRET-based biosensors allow us to closely monitor intermolecular signalling in diverse cellular compartments in real time. This project will examine a range of GPCR signalling pathway with a particular focus on the effect of diverse drugs. A complete understanding of the mechanisms of GPCR activation and signalling complexity is crucially important for drug development targeting these receptors. We work with multiple GPCR targets and collaborate with pharmaceutical industry partners including Novartis and Takeda. Projects are available on multiple GPCR targets with training in molecular and cell biology and numerous BRET techniques to study GPCR interactions and cellular signalling.

Project supervisor
Prof Ross Bathgate

Project co-supervisor
Dr Martina Kocan

- Honours
- Master of Biomedical Science

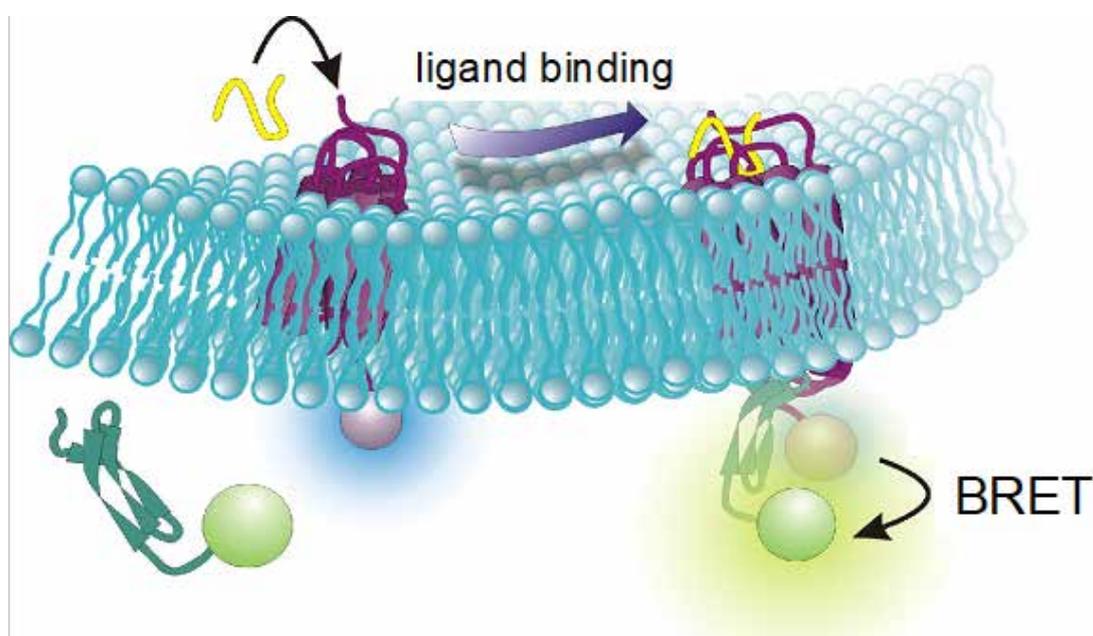


Figure: Detection of interactions between GPCR and intracellular protein using BRET technology

CICCOTOSTO GROUP

Contact: **Joe Ciccotosto**

Location: **Department of Pharmacology and Therapeutics**

Email: jcicco@unimelb.edu.au



Lung Health



Cellular Imaging and Structural Biology



Therapeutics and translation

The Ciccotosto group researches respiratory diseases are highly prevalent in the human population where lung function is often compromised due to several factors such as viral infections, chemical irritants, fibrosis, or allergic responses or a combination of these. The epithelial cell lining of the lung is the first line barrier that plays a critical role in filtering out toxic molecules from entering the circulation. The respiratory diseases is often associated with epithelial cell injury resulting in a compromised epithelial cell barrier making it more leaky and altering the lung function. In addition, treatment strategies for respiratory diseases include inhalation of drug molecules that target specific cell surface markers and often need to pass through the epithelial cell barrier. This project will utilise Fluoro tagged dextran molecules of different molecular weight sizes and establish a robust assay model for monitoring cellular location, distribution and uptake of molecules through the lungs.

Project: Pharmacokinetic and pharmacodynamic analysis of fluorescently tagged molecules with different molecular weights in healthy and respiratory diseased mouse models

Aim of this Project: To examine lung permeability and cellular uptake to different molecular weight molecules in healthy and respiratory diseased mouse models in preparation for screening therapeutic drug compounds.

Techniques: The student will learn animal handling, tissue isolation and dissection. Histological skills including tissue sectioning, staining and microscope imaging. Biochemistry skills including ELISA assay and western blotting.

Project supervisor
Dr Joe Ciccotosto

Project co-supervisors
Dr. Andrew Jarnicki
Dr Robert O'Donoghue
Prof Gary Anderson

- PhD
- Honours
- Master of Biomedical Science

CRACK AND TAYLOR GROUP



Contact : **Professor Peter Crack**
Location: **Department of Pharmacology and Therapeutics**
Email: pcrack@unimelb.edu.au



Neurodegeneration



Neurotrauma



Neuroinflammation



Cell Signalling



Biomedical neuroscience



Infection and Immunity

The Crack and Taylor group is run by Professor Peter Crack and Dr Juliet Taylor. 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 co-supervisor
[Dr Juliet Taylor](#)

- 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 co-supervisor
[Dr Juliet Taylor](#)

- 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 co-supervisor
Dr Juliet Taylor

- 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 (eg, 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
Dr Juliet Taylor

Project co-supervisor
Professor Peter Crack

- 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
Dr Juliet Taylor
A/Prof Elisa Hill

- PhD
- Honours
- Master of Biomedical Science

Project: The bioinformatic analysis of neuroinflammatory pathways seen in alzheimers and parkinsons 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.

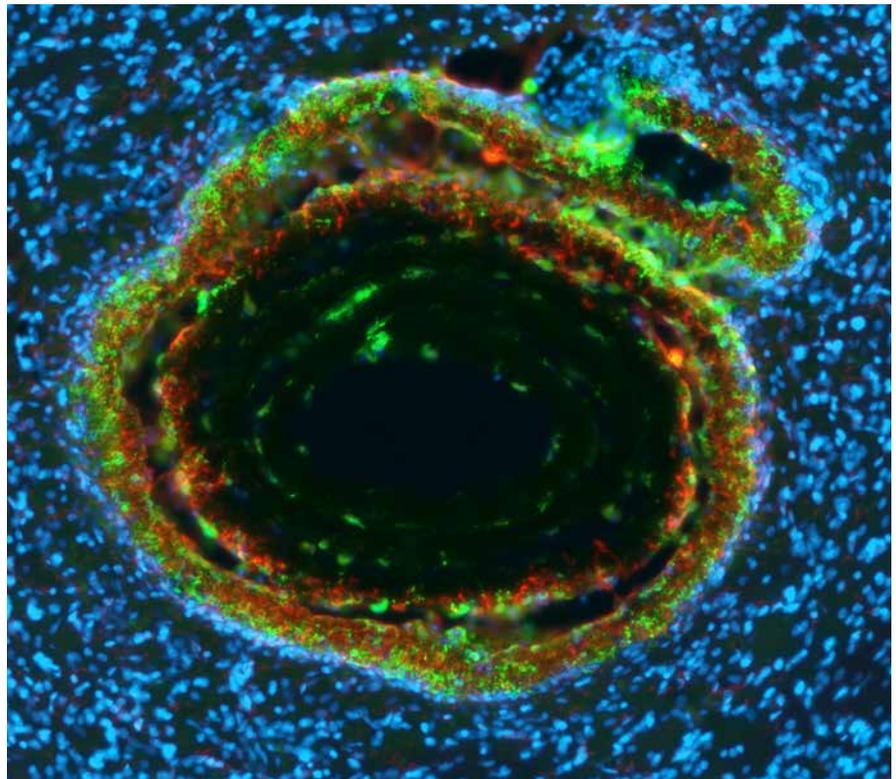
Skill acquisition: Bioinformatics, systems biology, pathway analysis.

Project supervisor
Professor Peter Crack

Project co-supervisors
Dr Juliet Taylor

Dr Victoria Perreau

- PhD
- Honours
- Master of Biomedical Science



CROUCH LABORATORY



Location: **Department of Pharmacology and Therapeutics**

Email: pjcrouch@unimelb.edu.au



Neurodegeneration



Cancer in Biomedicine



Molecular mechanisms of disease



Biomedical neuroscience



Therapeutics and translation

The focus of our research is to elucidate the biochemical basis of human disease. We study degenerative conditions of the central nervous system as well as a diverse range of cancers, and our overarching aim is to generate the information needed to help develop and test new therapeutic options and to improve patient outcomes through enhanced disease detection and characterisation. Recent significant achievements include bench-to-clinic translation of a new drug for motor neurone disease and a first of its kind method for imaging cancer.

To achieve these outcomes, we utilise a broad range of experimental paradigms, ranging from cells grown in culture through to direct examination of human tissue. Our analytical approaches span fundamental techniques (enzyme activity assays, gene expression analysis, histology and western blotting) through to highly sophisticated techniques such as quantitative in situ elemental imaging.

Project: Understanding the biochemical basis of motor neurone disease

Our team has identified an important biochemical change that occurs in tissue afflicted with motor neurone disease, a fatal disorder of the central nervous system for which effective treatments do not yet exist. Moreover, we have demonstrated that therapeutically targeting this change is protective, and our drug is now in the initial stages of clinical testing. However, a better understanding of how this biochemical change relates to the decline of functional motor neurones is still required. We are therefore examining changes to the abundance and functionality of specific proteins which we can relate to what we currently know about the drug's mechanism of action. An increased understanding of these mechanisms will advance our understanding of the causes of motor neurone disease and also the opportunity for additional therapeutic intervention.

Project supervisor
Associate Professor Peter Crouch

Project co-supervisor
Dr James Hilton

Project availability:

- PhD
- Honours
- Master of Biomedical Science

Project: The connection between motor neurone disease and progressive multiple sclerosis

Significant similarities exist between motor neurone disease and progressive forms of multiple sclerosis. In pursuing our motor neurone disease research, we established that some of the similarities with progressive multiple sclerosis may represent opportunity for therapeutic intervention. We have therefore been examining tissue samples from people who had progressive multiple sclerosis and also from models of the disease. We are using the information we have generated from our motor neurone disease research to guide these analyses. More extensive analysis of multiple sclerosis tissue is needed to help us consolidate the connection between the two diseases and therefore to further assess the opportunity to treat the two using a single therapeutic strategy.

Project supervisor
Associate Professor Peter Crouch

Project co-supervisor
Dr James Hilton

Project availability:

- PhD
- Honours
- Master of Biomedical Science

Project: Capturing the elemental signature of human disease

All biological material is defined by its elemental constituents (carbon, sulphur, phosphorous, etc.) and the onset and progression of human disease can therefore be detected and characterised by measuring changes to the abundance and anatomical distribution of these elements. We measure these changes using a quantitative elemental imaging technique known as laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS). We analyse sections of biological material via LA-ICP-MS and the information generated provides an 'elemental image' of the disease. We use LA-ICP-MS to identify the presence of disease (e.g. tumour detection), to determine the biochemical basis of disease (e.g. changes in an elemental co-factor required for specific enzyme activities), and to monitor drug uptake and biodistribution.

Project supervisor
Associate Professor Peter Crouch

Project co-supervisor
Dr Kai Kysenius

Project availability:

- PhD
- Honours
- Master of Biomedical Science

Project: Elucidating the cellular mechanisms of human disease in vitro

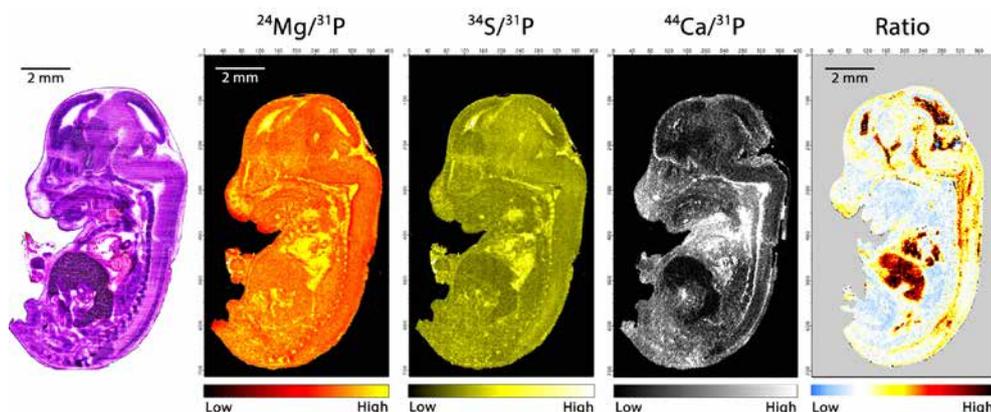
Determining the biochemical changes that occur in human disease-affected tissue is an essential part of our research, but analysing human tissue is rarely amenable to the level of experimental manipulation that is needed to elucidate the cellular mechanistic pathways that cause the disease. In our laboratory we therefore complement our human tissue analyses with cell culture experiments in which specific phenomena can be controlled and examined in detail. We grow cells in the laboratory then we expose them to the conditions needed to induce a response comparable to what we have identified in the human disease. By analysing the treated cells we are able to systematically map the sequence of events that lead to disease. This work is essential for identifying and validating therapeutic targets.

Project supervisor
Associate Professor Peter Crouch

Project co-supervisor
Dr Jeff Liddell

Project availability:

- PhD
- Honours
- Master of Biomedical Science





Contact : **Professor Andrew Gundlach**
 Location: **The Florey Institute of Neuroscience and Mental Health**
 Email: andrew.gundlach@florey.edu.au
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	Neurobiology
	Neuropharmacology
	Neuropsychiatry

	Cell Signalling
	Biomedical neuroscience
	Therapeutics and translation

My laboratory seeks to increase our understanding of the neurobiology of neuropeptide/G-protein-coupled receptor (GPCR) systems in health and disease, with the goal of identifying the physiological role of key neural networks in the brain, and developing novel therapeutics for neuropsychiatric disorders. A primary focus of current projects involving several international collaborations is the relaxin-3/RXFP3 system, and the inhibitory (GABA) projection- and inter-neurons that express the peptide and its receptor. New initiatives are targeting the unexplored relaxin/RXFP1 system in brain and its possible roles in neurovascular coupling and sensory/cognitive processing; and the role of the signalling enzyme, CaMKK2 in regulation of brain and behaviour. Projects on these topics will provide training in techniques such as neurochemical phenotyping of target neurons, cell signalling, neuropharmacology, physiology and behaviour.

Project: Relaxin-3/RXFP3 signalling in control of arousal and complex physiology and behaviour

Neural arousal pathways facilitate heightened awareness, attention and cognition, and are also implicated in reward signals associated with food- and drug-seeking behaviour. Established arousal transmitter systems include serotonin neurons in the raphé nuclei, dopamine neurons in the ventral tegmental area, and orexin (peptide) neurons in the lateral hypothalamus. Anatomical and functional studies also suggest relaxin-3 neurons in nucleus incertus (NI) (image) and the central grey (CG) represent an arousal pathway that modulates behaviours such as feeding, attention (vigilance), motivation and exploration. Therefore, relaxin-3/RXFP3 systems represents a potential target for treating conditions such as insomnia, anorexia, obesity, drug abuse, chronic pain and depression. In a new initiative, we are also exploring the potential interaction of RXFP3 and opioid signalling in the brainstem, in relation to opioid-induced respiratory suppression. Studies so far have examined the impact of pharmacological treatments on respiratory networks, and studies are now required to determine the relative neuroanatomical distribution of the relevant RXFP3 and opioid receptor systems to assess the direct or indirect (network-based) nature of the interactions observed. Projects on this

topic will provide training in techniques such as neurochemical phenotyping of neurons (image), neural tract-tracing, cell signalling detection, neuropharmacology, physiology and behaviour.

Project supervisor
Professor Andrew Gundlach

Project co-supervisors
Dr Mathias Dutschmann
A/Prof Akhter Hossain

- PhD
- Honours
- Master of Biomedical Science

Project: Rare cortical projection-neuron function in arousal, sleep and neuropathology

Experimental and in silico data suggest brain relaxin/RXFP1 signalling regulates neural networks that contribute to arousal, attention, memory, and sensory processing; and key characteristics of cortical 'relaxin' neurons and their RXFP1-positive target cells have been revealed. In mouse cortex, relaxin (not Rxfp1) mRNA is expressed by long-projecting (somatostatin/GABA) neurons, which we hypothesise are capable of morphological, neurochemical and synaptic plasticity in response to specific neural inputs and to acute and chronic brain injury. In contrast, Rxfp1 mRNA is expressed by topographically-distributed inhibitory and excitatory neurons in outer and deep cortical layers which are likely targeted by adjacent or distant relaxin

neurons, but their nature and function are otherwise uncharacterised.

Thus, this project will investigate populations of cortical neurons that synthesize the peptide, relaxin, and their target neurons that express the neural membrane receptor, RXFP1. We propose relaxin/RXFP1 signalling in areas containing sensory, emotional and cognitive circuits regulates processes, including nerve growth and modification of synapses and the surrounding environment, with links to sleep/wake states, and responses to brain injury. We will assess the gene/protein expression profile of relaxin- and RXFP1-positive neurons in mouse brain (image), and the impact of perturbations such as sleep deprivation and brain pathology on this profile. In collaborative studies, we will also explore how relaxin alters the electrical activity of RXFP1-positive cortical neurons in mice. These studies should reveal the therapeutic potential of a specific brain receptor system for alleviating cognitive and emotional symptoms in neurological disorders.

Project supervisor
Prof Andrew Gundlach

Project co-supervisors
A/Prof Akhter Hossain
Dr Laura Jacobson
Dr Mohsen Nategh

- PhD
- Honours
- Master of Biomedical Science

Project: CaMKK2 control of neuronal function and complex behaviour in health and disease

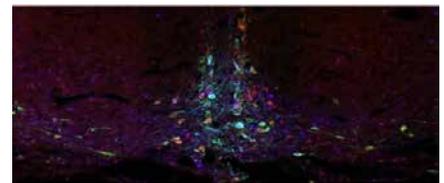
Our research has revealed that Ca²⁺-calmodulin dependent protein kinase-2 (CaMKK2) is a key regulator of neuronal function and associated complex behaviour. Mutations that reduce CaMKK2 expression or activity display a strong association with a spectrum of human psychiatric disorders, including anxiety, bipolar disorder and schizophrenia, indicating that optimal CaMKK2 activity is essential for normal, healthy brain development and function. Notably, the mood-stabilising drug, lithium, a major therapy for multiple psychiatric illnesses, activates CaMKK2. Therefore, understanding central CaMKK2 signalling is of significant translational interest.

However, the neurobiology of CaMKK2, including its upstream regulatory inputs, and its downstream signalling and neural network effects in brain are not fully understood. In this project, we will study the behavioural profile of mice with targeted mutations of a regulatory site in CaMKK2 in a range of validated behavioural assays, as well as the responsiveness of these mice to lithium. We will also determine the neuroanatomical distribution of CaMKK2 within specific types of neurons (image) and neural circuits, and the impact of altered CaMKK2 signalling on specific downstream targets. These studies will provide an improved mechanistic understanding of CaMKK2 function, which is essential to advance our fundamental biological knowledge of this key neuronal enzyme system, and to inform novel treatment strategies for multiple psychiatric conditions.

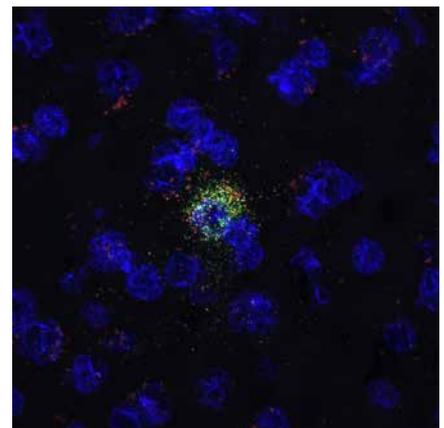
Project supervisor
Professor Andrew Gundlach

Project co-supervisor
Dr John Scott

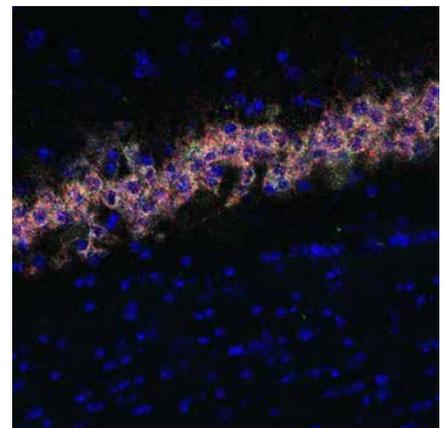
- PhD
- Honours
- Master of Biomedical Science



Nucleus incertus neurons contain relaxin-3 peptide (green) and calcium-binding proteins (red/blue)



Relaxin mRNA (red) and nNOS mRNA (green) in a rare somatostatin neuron (white) in cerebral cortex



CaMKK2 mRNA (white) and BDNF mRNA (green) in excitatory (vGlut2 mRNA, red) neurons in hippocampus

HUGHES & NORTHFIELD GROUP



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Drug Design



Biomedical Neuroscience



Therapeutics and Translation

The Hughes & Northfield group uses chemical biology approaches to develop novel peptide compounds for use against a range of therapeutic targets. Following design of compounds, candidate molecules are synthesised in our laboratory and evaluated using the relevant appropriate in vitro and in vivo assays. Data from these assays is subsequently used to hone the design process, with the goal of producing more active compounds that are specific to the drug target, thus limiting potential off-target effects. We have a range of multidisciplinary research projects on offer for graduate students, with peptide chemistry as a common theme across them all.

Project: Targeting phagocytosis in age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 and is responsible for one-third of irreversible vision loss in Australia. It affects one-in-seven Australians over the age of 50 and is the major cause of legal blindness in people over 80 years old. Without a medical breakthrough, the number of Australians with AMD is expected to increase 70%, to 1.7 million people, by 2030. There are currently no treatments available that prevent the development or progression of AMD.

The P2X7 receptor has been implicated in AMD pathology. Specifically, its most important role is promoting phagocytosis in the eyes, but in AMD this role is underperformed. In this project, the student will use synthetic chemistry approaches to create peptides, based on a known P2X7 modular, which will target the P2X7 receptor. They will analyse the pharmacological actions of these compounds in biological assays; and utilise computational chemistry to identify specific peptide-receptor interactions. The student will learn a range of synthetic peptide chemistry techniques (including solid phase synthesis and reversed-phase HPLC), alongside contemporary pharmacological approaches to study P2X7 activity, and molecular modelling techniques. The project will give the student an outstanding opportunity to “close the loop” on the iterative process of drug design and characterisation.

Project supervisor
Dr Susan Northfield

Project co-supervisor
Prof Erica Fletcher

Project availability

- PhD
- Master of Biomedical Science

Project: Design, synthesis and analysis of peptide mimetics of neurotrophin-3

The neurotrophin protein family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4. All of these neurotrophins bind to Trk-receptors and p75NTR. NT-3 is a protein homodimer that binds primarily to TrkC and p75NTR. Binding of neurotrophins to Trk-receptors occurs via two adjacent loop domains of the protein homodimer. Our lab has previously produced a peptide mimetic of the analogous region of BDNF that binds selectively to TrkB, but at this stage there is no peptide mimetic of NT-3.

NT-3 binding with TrkC has been implicated as a potential treatment for noise-induced hearing loss. We are interested in developing the first dimer peptide mimetics of NT-3 and testing their activity against the TrkC receptor. This project will involve peptide chemistry and pharmacology, allowing the student to synthesise and subsequently test their peptides in HEK cells expressing TrkC.

Project supervisor
Dr Susan Northfield

Project co-supervisor
A/Prof Tony Hughes
Dr John Karas

Project availability

- PhD
- Master of Biomedical Science

Project: Design, synthesis and analysis of peptide mimetics of brain-derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) is part of the neurotrophin protein family. It is a protein homodimer that binds to both the TrkB receptor and p75NTR to exert biological effects. Our lab has previously produced peptide mimetics of two distinct loop regions of BDNF, which are each able to selectively activate one of these receptors. Most recently we have been interested in BDNF's role in myelination, and we've shown that our peptides are able to promote myelin growth in animal models of demyelinating injury, just like BDNF can.

Our peptide mimetics have been shown to be selective for BDNF's receptors and able to promote myelination, but we are interested in producing analogues of our two lead peptides. The student on this project will be involved in the design, synthesis and testing of these new peptides. This project will involve peptide chemistry and pharmacology, allowing the student to synthesise and subsequently test their peptides in TrkB-expressing cells.

Project supervisor
Dr Susan Northfield

Project co-supervisor
A/Prof Tony Hughes
Dr John Karas

Project availability

- PhD
- Master of Biomedical Science

KARAS GROUP



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Email: jkaras@unimelb.edu.au



Chemical synthesis



Drug Design



Therapeutics and Translation



Cancer in Biomedicine

The Karas group seeks to optimize existing drug discovery platforms to identify D-peptide-based lead compounds, which are potentially safer and more effective as therapeutics for metastatic cancer. Our research is underpinned by chemical synthesis of the D-protein target of interest, which can be utilized in a high-throughput screen (mirror-image phage display) and/or to enable simpler structural characterization (racemic protein crystallography). A key focus of the group is to develop improved chemical methods for protein assembly and folding, using techniques such as organic synthesis, peptide synthesis, native chemical ligation, chromatography and mass spectrometry.

Project: Structural characterization of CD151 for the rational design of antimetastatic agents

Cluster of differentiation 151 (CD151) is a member of the tetraspanin family of receptors. It consists of four helical transmembrane domains, one small extracellular loop and a second, larger cysteine-rich loop (EC2). CD151 is expressed in many cell types and interacts with other tetraspanins to organize, modulate and regulate a network of transmembrane proteins. CD151 interacts with laminin-binding integrins through EC2; these complexes modulate cell adhesion, migration and signalling. High CD151 expression is associated with poor prognosis in many cancers and evidence suggests that disruption of the extracellular CD151-integrin complex could be a viable therapeutic strategy for metastatic breast cancer. The structure of CD151 is unknown, therefore, structural characterisation of EC2 should enable the rational design of lead compounds that inhibit the CD151-integrin interaction.

The structure of EC2 will be elucidated via racemic protein crystallography, which involves co-crystallisation of the natural L-protein of interest with its chemically synthesized mirror image (D-EC2). D-EC2 will be assembled via chemical protein synthesis from three fragments via solid-phase peptide synthesis and native chemical ligation. After crystallization with recombinant EC2, its structure can then be determined which will inform the design of inhibitors for molecular modelling studies. The ultimate goal of this project is to develop an anti-metastatic agent that works by interfering with the CD151-integrin complex.

Skill acquisition: solid-phase peptide synthesis, chemical protein synthesis, high performance liquid chromatography (HPLC), mass spectrometry, X-ray crystallography and molecular modelling.

Project supervisor
Dr John Karas

Project co-supervisor
Dr Claire Weekley

- Honours
- Master of Biomedical Science

PETER GROUP



Contact : **Professor Karlheinz Peter**

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Weblink: baker.edu.au/research/research-programs/atherothrombosis

	Cardiovascular pharmacology		Therapeutics and translation
	Drug design		Molecular imaging
	Translational and clinical research		Targeted drug delivery

The Peter 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: 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-Fluorine 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 co-supervisors
Prof Karlheinz Peter

Project availability

- PhD
- Honours
- Master of Biomedical Science

Project: Activated platelet-targeted drug therapy

Acute thrombosis causes vessel occlusion and results in ischemic complications, such as myocardial infarction and stroke. Therefore, it is a major cause of death and disability.

Anti-coagulation and anti-thrombotic drugs are valuable alternatives for the treatment of these acute events where invasive/surgical procedure is not

available in a timely fashion. However, the current clinically approved anti-coagulation and anti-thrombotic drugs have significant drawbacks, including bleeding complications. Thus, their use is highly restricted leaving many patients untreated. The use of small recombinant antibodies for diagnostic molecular imaging and targeted drug delivery is well established in our lab.

This project would focus on the development of novel targeted drugs that are directed against activated platelets.

When thrombosis occurs, there is a thunderstorm of platelet activation and aggregation. Our targeted drugs will locate these activated platelets and accumulate at the site of the clot. This allows a high potency of drugs for efficient and safe thrombolytic treatment. Due to the targeting properties, we can reduce the overall number of drugs needed, therefore there would only be a small concentration of drugs circulating in the blood. This would also enable us to eliminate the current bleeding complications.

Significance: This novel targeted agent promises to overcome the current limitations of bleeding complications associated with the clinical thrombolytic therapy. It has the potential to break the fatal link between increased drug potency and bleeding complications.

Project supervisor
Dr Xiaowei Wang

Project co-supervisors
Prof Karlheinz Peter
Dr Laura Bienvenu

- PhD
- Honours
- Master of Biomedical Science

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 co-supervisors:
[Professor Karlheinz Peter](#)
[Dr Jonathan Noonan](#)

- PhD
- Honours
- Master of Biomedical Science

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

Activated platelets have been shown to play an important role in 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-Fluorine 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
[Prof Karlheinz Peter](#)

Project co-supervisor
[Dr Xiaowei Wang](#)

- PhD
- Honors
- Master of Biomedical Science



Contact : **Professor Norman R Saunders**

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Weblink: www.annualreviews.org/doi/10.1146/annurev-pharmtox-010818-021430



Barrier mechanisms in the developing brain

Barrier mechanisms in the developing brain

The Developmental Neurobiology & Neurotrauma group is interested in the mechanisms that control the internal environment of the developing brain. This involves studying the entry of molecules into the developing brain and mechanisms that exclude drugs and toxins from the brain. This involves a wide range of methods including physiology, pharmacology, morphology and molecular biology (see PMID: 29774535 PMID: PMC6265560 DOI: 10.1113/JP275376)

We are also interested in the response of the immature spinal cord to injury but are not currently working on this.

Project: Entry of drugs into the developing brain

More than 1200 drugs have been prescribed for pregnant and breast-feeding women. In different countries between 65 and 90% of pregnant women take one or more medications. There is almost no information on when in development and to what extent any drugs enter the developing brain in these women. Information on drug entry into the developing brain is an essential prerequisite to designing studies to investigate possible delirious effects of these drugs in fetuses and neonates. We are studying this problem in pregnant and neonatal rats. Interested students are invited to visit the lab to meet people working on this project and to discuss an appropriate project.

Project supervisor
Professor Norman Saunders

Project co-supervisors
Associate Professor Katarzyna Dziegielewska
Dr Mark Habgood

Project availability

- PhD
- Honours

SCHNEIDER-FUTSCHIK GROUP



Contact : **Dr Elena Schneider-Futschik**
Location: **Department of Pharmacology & Therapeutics**
Email: elena.schneider@unimelb.edu.au



**Anti-microbial
pharmacology**



Lung Health



Cardio-Respiratory



Infection and Immunity

Cystic fibrosis (CF) is the most common, genetically acquired, life-shortening chronic illness affecting young Australians today. The disease affects the exocrine mucus glands of the lung, liver, pancreas, and intestines causing progressive multi-system failure such as loss of lung function and pancreatic insufficiency; eventually leading to death, often at a young age. Presently, there is no cure, and patients with CF undergo life-long and extremely costly medical treatments.

Project: Understanding the pharmacology of cystic fibrosis transmembrane conductance regulators

The recent approval of ivacaftor-tezacaftor highlights notable advances in CF therapy, but is dampened by the dearth of understanding on pharmacology. Investigating all aspects of their pharmacology using systems pharmacology will bridge this major knowledge-gap in the field.

Project supervisor
Dr Elena Schneider-Futschik

Project co-supervisor
A/Prof Tony Velkov

- Master of Biomedical Science



Contact : **Prof. Rebecca Ritchie**

Location: **Baker Heart and Diabetes Institute**

Email: Rebecca.Ritchie@baker.edu.au

Weblink: go.unimelb.edu.au/ww8r



Cardiovascular pharmacology



Molecular mechanisms of disease



Therapeutics and translation

The Heart Failure Pharmacology Laboratory seeks to develop better pharmacotherapies to delay, or even prevent, the progression of human heart failure. The team is particularly interested in heart failure resulting from interruptions in coronary blood supply (such as in heart attack) and as a result of diabetes (diabetic complications). Delaying the onset and progression of heart failure will enrich the quality and length of life for over three million Australians at risk of, or already affected by, this debilitating disorder.

Project: Role of Altered Cardiac Glucose Metabolism in the Cardiac Complications of Diabetes

Diabetes affects almost 2 million Australians, increasing heart failure risk and accelerating its onset. Our laboratory has an established track record for identifying mechanisms of diabetes-induced cardiomyopathy, many of which target reactive oxygen species (ROS, also known as free radicals). Building on this experience, we have obtained recent evidence that maladaptive cardiac glucose metabolism, via hexosamine biosynthesis (an alternative fate of glucose), has now emerged as a contributing factor to the cardiac complications of diabetes. GENERAL HYPOTHESIS: that the combined impairments in both systemic glucose handling and cardiac levels of ROS together provide an additional drive towards maladaptive cardiac glucose metabolism, negatively impacting cardiac function and mitochondrial integrity.

AIMS: To demonstrate that cardiac-directed therapeutic targeting of this axis delays or even overcomes diabetes-induced cardiac dysfunction in the intact heart in vivo.

METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac and mitochondrial function, mitochondria isolation. Biochemical techniques: Westerns, ELISA, ROS detection, Seahorse Bioanalyzer, real-time PCR, histology, immunofluorescence.

SIGNIFICANCE: These interventions may ultimately limit heart failure in diabetes-affected patients.

Project supervisor
Prof. Rebecca Ritchie

Project co-supervisor
Dr Darnel Prakoso

- PhD
- Honours
- Master of Biomedical Science

Project: Using the NO Redox Sibling Nitroxyl to Overcome Diabetes-induced Impairments in Cardiac and Vascular NO Signalling

In patients with cardiovascular disease, impaired NO signalling predicts poor outcomes, including mortality. This loss of NO-responsiveness (termed 'NO-resistance') is particularly debilitating in type 2 diabetes, where cardiovascular emergencies occur more frequently, but NO-based pharmacotherapies are unable to effectively counteract platelet aggregation and vasoconstriction. We have now obtained the first evidence that the myocardium, like platelets and vessels, is also susceptible to NO-resistance such that NO can no longer enhance cardiac relaxation. However, the novel NO redox sibling, nitroxyl (HNO), may overcome this. This project explores the extent of NO resistance in type 2 diabetes, and whether HNO can overcome this, in the short-term. Whether HNO over the longer-term limits diabetes-induced myocardial dysfunction and changes in cardiac structure (and whether HNO is superior to NO in this context).

Putative independent mediators of HNO cardioprotection include cGMP-mediated ROS suppression, and thiol-mediated preservation of cardiac calcium handling proteins, whose activity is abnormally affected in cardiac pathologies such as diabetes. Ultimately, HNO-based strategies may offer new treatment options for cardiac disease. Methods include: in vivo models of diabetic cardiac disease, isolated rodent hearts, assessment of cardiac and vascular function, biochemical techniques: Westerns, ROS detection, ELISA, real-time PCR, histology.

Project supervisor
Prof. Rebecca Ritchie

Project co-supervisor
Prof Owen Woodman

- PhD
- Honours
- Master of Biomedical Science



Project: Combining Drug and Gene Therapy Approaches to Limit Diabetes-induced Cardiac Fibrosis

Diabetes affects almost 2 million Australians, increasing heart failure risk and accelerating its onset. Two key structural changes in the diabetic heart are cardiac fibrosis and hypertrophy of cardiac myocytes, which contribute to the impaired cardiac function evident in the diabetic heart. This project explores whether specifically limiting diabetes-induced cardiac fibrosis, using a cardiac-selective gene therapy approach, alone or combined with targeting diabetes-induced cardiac myocyte hypertrophy via histone deacetylase inhibition, protects cardiac function in the context of type 2 diabetes in vivo.

METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac function, Westerns, ELISA, real-time PCR, histology, immunofluorescence.

SIGNIFICANCE: These interventions may ultimately limit progression to heart failure and death in diabetes-affected patients.

Project supervisor
[Prof. Rebecca Ritchie](#)

Project co-supervisor
[Dr Miles de Blasio](#)

- PhD
- Honours
- Master of Biomedical Science

Project: Defining a clinically-relevant experimental model of heart failure with preserved ejection fraction (HFpEF) as a model of human heart failure.

Project overview: Heart failure with preserved ejection fraction (HFpEF) is becoming more common globally, accounting for approximately half of all heart failure hospital admissions. Clinically, HFpEF is a very complex disease due to the contribution of several underlying comorbidities, including obesity, hypertension and diabetes. It is generally accepted that the lack of treatment options in HFpEF is partly due to the lack of a preclinical model that suitably mimic the pathophysiological mechanisms that underlie the disease. The model to be tested utilises high-fat diet and L-NAME to drive metabolic and hypertensive stress, respectively, recapitulating several systemic and cardiovascular features of HFpEF in humans.

AIM: To characterize the phenotype of this animal model of HFpEF and assess its suitability as a model of human HFpEF.

METHODS: in vivo models of HFpEF, assessment of cardiac function (echocardiography and cardiac catheterization), metabolic caging, western blotting, ROS detection, real-time PCR, histology, immunofluorescence.

SIGNIFICANCE: Identification of a suitable model of HFpEF will help understand disease pathogenesis and drive development of effective therapeutics.

Project supervisor
[Prof. Rebecca Ritchie](#)

Project co-supervisor
[Dr Mitchel Tate](#)

- PhD
- Honours
- Master of Biomedical Science

ROULSTON GROUP



Contact : **Dr Carli Roulston**

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Neuropharmacology



Translational and Clinical Research



Biomedical neuroscience



Therapeutics and translation

Stroke affects ~60,000 Australians each year and is the leading cause of disability in Australia. Most strokes result in vary degrees of permanent brain injury due to a failure of neurons to re-grow at the injury site. This limitation in brain repair is often due to critical events such as inflammation that results in toxic signalling and formation of scar tissue, that together form a major obstacle to plasticity and regeneration. Our focus is to identify new targets and develop new treatments that rescue brain and support recovery. Working closely with both industry partners and leading Neurologists our team is committed to research that is focused on translation of positive outcomes in animal models to clinical success.

Project: Exploring central immune response to stroke to reduce impact and preserve function.

In partnership with Implicit Bioscience we are investigating new treatments that modulate the peripheral immune response to stroke to reduce secondary injury and support recovery during the acute phase. In this project we will assess the effects of Implicit Biosciences lead compound on local brain inflammation at the site of infarct, as well inflammation in regions distal to the lesion. This will include characterising treatment effects on cells within the neurovascular unit for correlation with functional recovery. Knowledge from this project will directly inform future clinical trial design using this compound, as well as provide useful information for treating other forms of brain injury.

Project supervisor
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Project co-supervisor
Professor Peter Crack

- Honours
- Master of Biomedical Science

STEWART GROUP

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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 (CK1 δ) has been implicated as a major regulator of the biochemical oscillator that determines circadian rhythm. Our laboratory has implicated CK1 δ 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 CK1 δ inhibitors reset the CLOCK to suppress inflammation. In this project, you will characterise the anti-inflammatory potential of CK1 δ 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.

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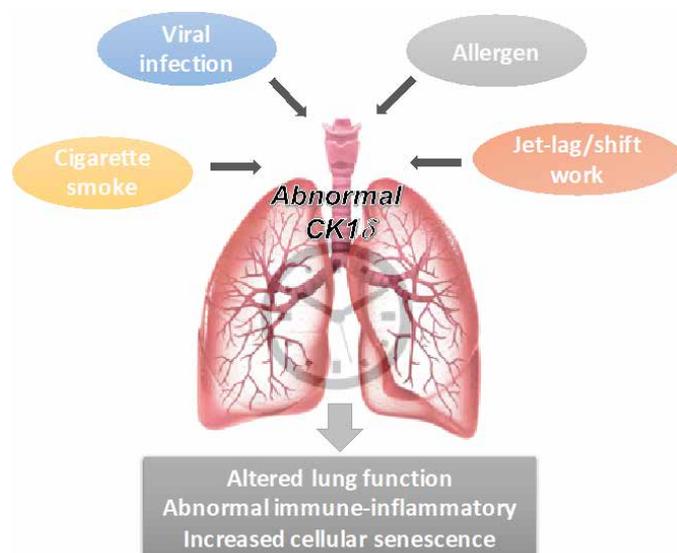
Casein Kinase 1 δ/ϵ Inhibitor, PF670462 Attenuates the Fibrogenic Effects of Transforming Growth Factor- β in Pulmonary Fibrosis. *Frontiers in Pharmacology*. 9:738.

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- β activity. *PLOS Pathogens*, 13, e1006138.

Project supervisor
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Project co-supervisor
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- Honours
- Master of Biomedical Science





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Antibiotics



Antibiotic resistance



Superbugs



Novel antibiotic drug discovery

Our teams internationally leading research aims to develop novel therapeutics to target an urgent global medical challenge, multidrug-resistance (MDR) in Gram-negative ‘superbugs’. Our key programs include the discovery of novel lipopeptide antibiotics and the pharmacology of polymyxins, last-line antibiotics against Gram-negative ‘superbugs’. The group has three major streams designed to provide both short-term and long-term solutions to this major global health problem:

- discovering and developing novel antibiotics and formulations against Gram-negative ‘superbugs’;
- elucidating the mechanisms of activity, resistance and toxicity of lipopeptide antibiotics; and
- investigating the preclinical and clinical pharmacology of antibiotics and their combinations.
- Numerous opportunities exist for both postdoctoral fellows and higher degree by research student to work in these areas and applications are always welcome.

Project: The design of inhibitory drugs for molecular components of the siderophore biosynthetic pathway that are crucial for iron sequestration during mycobacterium tuberculosis (TB) pathogenesis.

TB remains a major health problem in the world, and new anti-tuberculosis drugs are urgently needed to shorten the time for chemotherapy, to combat the spread of drug-resistant TB, and to treat the latent form of TB infection. The rapidly emerging resistance of TB to many front-line antimicrobials highlights the importance of the development of effective antitubercular agents against new targets which cannot easily attain mutational resistance. In this regard, mycobactin siderophores represent novel and ideal targets due to their essential role in the vital processes of iron acquisition and transport during infection by TB. Genetic disruption studies have demonstrated the mycobactin biosynthetic pathway to be essential for host infection.

Because iron plays a key role in the development of the infectious disease state of TB, the mycobactin biosynthetic enzymes represent outstanding and novel candidates as targets for developing antibacterial agents against TB.

This project represents a novel and innovative approach to develop drugs against drug resistant TB based upon:

1. By targeting the ability of TB to attain virulence as opposed to conventional antibiotic drug treatments that target the viability of TB and its ability to replicate.
2. The essential role of the mycobactin biosynthetic machinery in the virulence of TB and the fact we are targeting each enzyme in the pathway, means it is very unlikely to evolve resistance to inhibitory drugs over time.
3. Targeting all of the enzymes in the biosynthetic pathway to further safeguard against resistance.
4. The highly conserved nature and complexity of this pathway means drugs that come into development are likely to be effective against all drug resistant TB strains.

The implementation of drugs that emerge from this work will lead to safer and shorter dosing regimes, by inhibiting the virulence of TB, this allows the hosts natural immune system to rapidly eliminate the infection. More importantly, this will limit the spread and emergence of resistant TB. These drugs will be of considerable benefit in immunocompromised individuals such as AIDS patients that often suffer prolonged TB infections. Moreover, given that these enzymes are unique to bacteria, drug therapies should have little or no toxic effects on the host.

The principle aim(s) of this project include:

1. Clone, and purify recombinant forms of each enzyme in the mycobactin biosynthetic pathway.
2. Obtain high resolution crystallographic structures of each enzyme using synchrotron radiation.
3. In silico screening, together with conventional high-throughput robotic screening of each enzyme target with fragment and several compound libraries.
4. Obtain high resolution crystallographic structures of each enzyme-drug complex using synchrotron radiation.
5. Test each lead compound for the ability to inhibit mycobactin biosynthesis in laboratory cultures of TB and in the test tube with the reconstituted biosynthetic pathway.

Project supervisor

Assoc Prof Tony Velkov

Project availability

- Honours
- Master of Biomedical Science

Project: Design and development of antibiotics against multidrug resistant bacteria

Polymyxins are cyclic heptapeptides with a tripeptide side chain linked to a fatty acid tail (Fig 1). They are polycations at physiological pH owing to the five L- α,γ -diaminobutyric acid (Dab) residues. They have a narrow spectrum of activity which is mainly against Gram-negative bacteria. Currently, they are mainly used as last-line antibiotics for multidrug resistant (MDR) Gram-negative infections. Although the incidence of resistance to polymyxins is currently relatively low, resistance can emerge rapidly in vitro in *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*, and polymyxin resistance in hospitalised patients has been increasingly reported. There is only one amino acid difference between colistin and polymyxin B and, not surprisingly, cross resistance exists. In essence, resistance to polymyxins implies a total lack of antibiotics for treatment of life-threatening infections caused by these MDR Gram-negative 'superbugs'. Numerous hospitals worldwide have experienced outbreaks of infections caused by *P. aeruginosa*, *A. baumannii* or *K. pneumoniae* that are resistant to all commercially available antibiotics, including the last-line therapies colistin (polymyxin E) and polymyxin B. As reviewed above, infection with MDR Gram-negative pathogens is a major public health problem worldwide and as such there is an urgent need for new antibiotics active against MDR infections.

The principle aim(s) of this project include:

1. Determine the mechanism of action of novel polymyxin antibiotics active against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*, in particular polymyxin-resistant strains.
2. Assess the synthetic peptides against polymyxin- susceptible and -resistant strains, for (a) antibacterial activity, (b) potential for development of resistance, and (c) interactions with LPS.
3. Investigate for highly active analogs their (a) stability in human plasma, (b) potential haemolytic effects, (c) pharmacokinetics and potential nephrotoxicity in animals, followed by (d) proof-of-concept studies using animal infection models.

Project supervisor
[Assoc Prof Tony Velkov](#)

Project availability

- Honours
- Master of Biomedical Science

Project: Plasma protein binding of antibiotics

Plasma protein binding has been implicated as a major factor limiting the active free concentration of many clinically important antibiotics. This in turn translates into reduced antibacterial activity, the need for dose escalation and in certain cases where the antibacterial agent is highly bound, limits its intravenous use. However, the actual plasma components, albumin, AGP, lipoproteins, or globulins that bind most clinically important antibiotics remain to be fully elucidated. Therefore, an understanding of the structure-activity relationships (SAR) that drive the binding of antibiotics to important plasma drug transporters such as AGP is of great clinical relevance. This study will utilize protein-ligand binding assays techniques to investigate and characterize drug binding to AGP and HSA on a broad range of pharmaceutical drugs, in the hope to develop an understanding to increase the pharmacodynamic activity of future novel antibiotic drugs.

Project supervisor
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Project availability

- Honours
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WRIGHT GROUP



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Cardiovascular pharmacology



Neuropharmacology



Venom & Antivenom Research

The Cardiovascular Therapeutics Unit has research interests across diverse areas of cardiovascular and autonomic pharmacology. Research areas include cannabinoid pharmacology in the vasculature and roles in the autonomic and sensory nervous systems, endothelin pharmacology in the setting of pulmonary hypertension, snake venom toxinology and vascular reactivity in hypertension.

Project: The cardiovascular and neuromuscular pharmacology of venoms from African spitting cobras

Snakebite envenomation is listed as a Category A Neglected Tropical Disease by the World Health Organisation. Most snakebite cases (95%) occur in developing countries, particularly in African and Asian regions, where access and/or proximity to appropriate medical care is very limited. Moreover, even if available, many antivenoms are ineffective against envenomation by particular snake species and side-effects of their use can be severe. Snakes produce a wide range of toxins that affect different organ systems. Besides the neurological effects and toxic potential on various muscles and the blood-clotting cascade, snake venoms are also known to affect the cardiovascular system. This project will examine the pharmacology of venoms from the family of African spitting cobras, some of which have been little studied - for example *Naja ashei*. The cardiovascular, autonomic and neuromuscular effects of each venom will be studied in rodent isolated tissues in vitro, including cardiac, vascular and hemidiaphragm preparations. The effects of the venom on sympathetic, parasympathetic and sensory neurotransmission will be assessed in these tissues, as applicable. Various commercially available antivenoms will be tested in these bioassays to determine their effectiveness against specific cobra venoms.

In this project, the student will learn classical analytical pharmacological techniques and analyses. There may also be scope for testing a particular venom/antivenom pairing in anaesthetised rats in vivo whereby sophisticated haemodynamic techniques will be learned, together with haematological assays (this will depend on the interest of the student).

This project will be co-supervised by colleagues from the Australian Venom Research Unit in the department. There may be an opportunity for the student (depending on their background and interests) to apply proteomics techniques in this project.

Project supervisor
[A/Prof Christine Wright](#)

Project co-supervisors
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- Honours
- Master of Biomedical Science

Project: Understanding perivascular nerves in the coordinated control of vascular resistance

Abnormal activation of sympathetic nerves contributes to both the development and progression of high blood pressure. Multiple mechanisms have been proposed to drive augmented sympathetic activation of blood vessels in hypertension. One proposed mechanism is the failure of peripheral regulatory mechanisms that apply a 'brake' to sympathetic-mediated activation of the vasculature. Control of vascular resistance reflects coordinated changes in arterial diameter by different types of perivascular

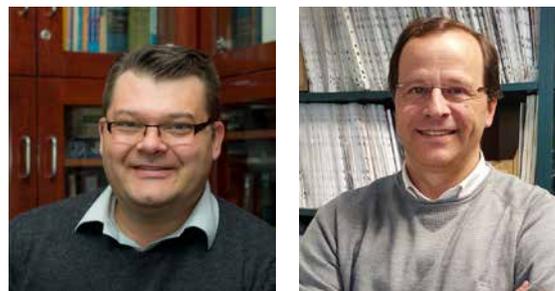
nerves. In addition to postganglionic sympathetic neurons, resistance arteries receive innervation from nitric-oxide containing neurons and sensory afferent neurons that release calcitonin gene-related peptide (CGRP), a potent vasodilator. Immunohistochemical studies in rat mesenteric resistance arteries demonstrate a close anatomical relationship between the different types of perivascular nerve fibres which may facilitate cross-regulation. This project will strengthen our understanding of how the different types of perivascular nerves interact with the sympathetic nervous system to regulate the function of the cardiovascular system. Students who undertake this research project will utilise techniques that assess cardiac and vascular function ex vivo and in vivo. The student will also assess structural changes in cardiovascular tissue using a combination of histology and stereology. To complement functional and structural data, immunostaining will be used to determine the distribution and density of various perivascular nerve fibres.

Project supervisor
[Dr Makhala Khammy](#)

Project co-supervisor
[A/Prof Christine Wright](#)

- Honours
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ZIOGAS AND MANGUM GROUP



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Proteomics



Translational and Clinical Research



Neuropharmacology



Neurotrauma

Associate Professor Ziogas collaborates with Dr Mangum on the brain injury research that forms part of this project, but Dr Mangum's laboratory also works on the discovery, validation, and development of new therapeutics for a range of disorders, including cancer, brain injury, and craniofacial defects. The lab is equipped with cutting-edge proteomics equipment that allows high-throughput screening for biomarker & target discovery in clinical samples. We also use complementary molecular, cellular, pre-clinical, and clinical research approaches to translate our work towards health benefit.

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 nimodopine, 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, Killy M, Westbrook J & Pattison KTS. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. *British Journal of Anaesthesia* 109: 315-29.

Project supervisor
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Project co-supervisor
[Dr Jon Mangum](#)

- PhD
- Honours
- Master of Biomedical Science



SARSTEDT

Drift

2.5mg/L
P

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12-

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For more information:

Website: biomedsciences.unimelb.edu.au/departments/pharmacology