THE UNIVERSITY OF MELBOURNE

PHARMACOLOGY AND THERAPEUTICS

2021

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 2021.

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 2021 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!

Associate Professor Christine Wright

Honours & MBiomedSci Co-ordinator
Department of Pharmacology and Therapeutics
FMDHS, The University of Melbourne

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: http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#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 Master 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: https://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 Master's marks are considered
International Market recognition	Australian Honours degree may not be recognised overseas, as many countries do not have an equivalent degree.	Recognised as a graduate Master's degree

RESEARCH HIGHER DEGREES

What is a PhD?

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

What is a MPhil?

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

What are the entry requirements?

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

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

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

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

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

https://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) can 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.

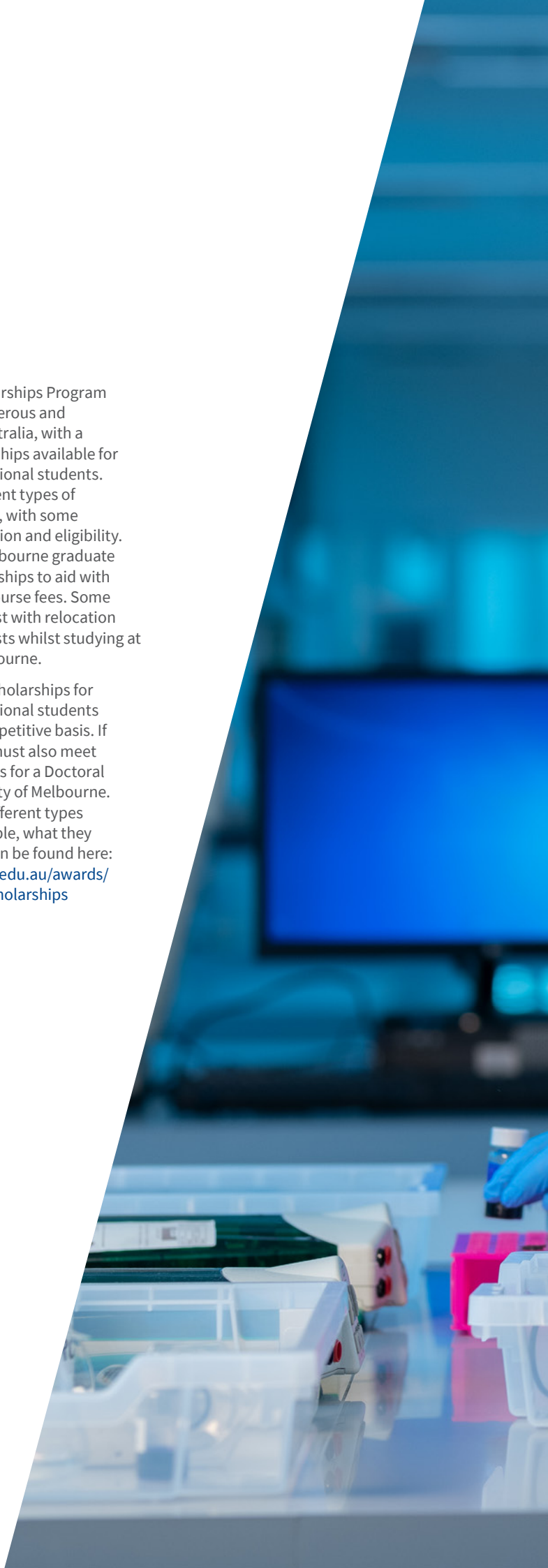
Highly ranked full-time students who have enrolled in an MDHS program through the Bachelor of Biomedicine (Degree with Honours) and the Bachelor of Science (Degree with Honours) and demonstrated a level of financial needs will automatically be considered for an Frances Elizabeth Thomson Trust Scholarship. 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: **Dr. Andrew Jarnicki**
Email: **andrew.jarnicki@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**

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

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: Understanding the role of the microbiome in lung viral infections

This project addresses a major but much under-appreciated problem- vaccinations do not work well in patients suffering Chronic Obstructive Pulmonary Disease (COPD). COPD afflicts 1 in 20 Australian and is the 5th leading cause of death (AIHW 2019). Globally COPD afflicts more than 300 million people and is the third leading cause of death. An overwhelming proportion of disease burden is due to infection. It is now clear that there is a strong reciprocal association between gut health and distal diseases, and that the manipulation of the gut microbiome and its subsequent metabolite production affects immunity and disease outcomes, including altering vaccine potency. Diet, antibiotic exposure, and smoking are the main factors affecting microbiota composition. The aim here is to determine how diet can alter the gut microbiome, and how this affects immune responses to a flu vaccine. Antibody production, critical early gene expression and alterations in flu specific immune cell responses will be examined.

Project supervisor
Dr. Andrew Jarnicki

Project co-supervisors
Professor Gary Anderson
Dr. Joe Ciccotosto
Dr. Robert O'Donoghue

Project Availability
- PhD
- Honours
- Master of Biomedical Science

Project: Using machine learning to improve the characterisation and quantification of fibrotic lung.

Pulmonary fibrosis is severe untreatable feature of some acute and chronic lung diseases, it has recently been recognised as a consequence of severe COVID-19-induced pneumonia. Fibrosis is essentially scar tissue that replaces functional lung tissue and is a feature of Idiopathic pulmonary fibrosis (IPF) where it is progressive in nature and always causes the demise of the patient. Fibrosis is also observed in Acute Respiratory Distress Syndrome (ARDS) where it develops rapidly, does not usually progress but can leave patients with permanent lung damage and lifelong reduced physical capacity. The current pre-clinical models of pulmonary fibrosis 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, viral infections 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 fibrosis treatments that will be successful in the laboratory and the clinic.

The aim of this project is to combine 'wet lab' methods with machine learning to improve the characterisation and quantification of fibrosis in mouse models with real world relevance to IPF and ARDS. You will use a number of laboratory techniques including in vivo disease modelling, tissue culture, QPCR, western blotting and FACs as well as machine learning methodologies using the facilities located within the Biological Optical Microscopy Platform (BOMP).

Project supervisor
Dr. Robert O'Donoghue

Project co-supervisors
Professor Gary Anderson
Dr. Andrew Jarnicki

Project Availability
- PhD
- Honours
- Master of Biomedical Science

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

Project Availability
- PhD
- Honours
- Master of Biomedical Science

CRACK AND TAYLOR GROUP

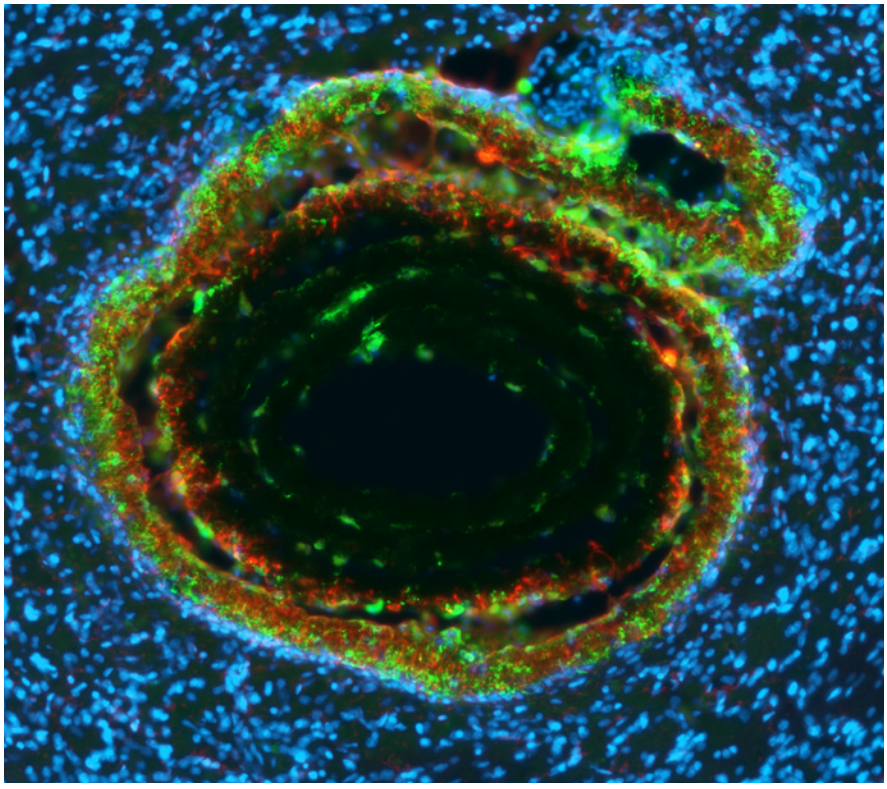
Contact: **Professor Peter Crack**
Email: **pcrack@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**

Neurodegeneration	**Cell Signalling**
Neurotrauma	**Biomedical neuroscience**
Neuroinflammation	**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

Project Availability
- PhD
- Honours
- Master of Biomedical Science

Project: Understanding traumatic brain injury

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

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

Project supervisor
Professor Peter Crack

Project co-supervisor
Dr Juliet Taylor

Project Availability
- PhD
- Honours
- Master of Biomedical Science

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

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

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

Project supervisor
Professor Peter Crack

Project co-supervisor
Dr Juliet Taylor

Project Availability
- PhD
- Honours
- Master of Biomedical Science

Project: The role of neuroinflammation in Parkinson's disease

Parkinson's disease (PD) is a progressive neurological disease that is characterized by the loss of dopaminergic neurons, primarily in the substantia nigra. The loss of these neurons leads to a motor handicap, associated depression, pain and general decreased quality of life. The mechanism for the loss of the dopaminergeric 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

Project Availability
- PhD
- Honours
- Master of Biomedical Science

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

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

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

Project supervisor
Professor Peter Crack

Project co-supervisors
Dr Juliet Taylor
A/Prof Elisa Hill

Project Availability
- PhD
- Honours
- Master of Biomedical Science

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

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

Skill acquisition: Bioinformatics, systems biology, pathway analysis.

Project supervisor
Professor Peter Crack

Project co-supervisors
Dr Juliet Taylor
Dr Victoria Perreau

Project Availability
- PhD
- Honours
- Master of Biomedical Science

CROUCH LABORATORY

Contact: **Assoc. Prof. Peter Crouch**
Email: **pjcrouch@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**

- **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
A/Prof Peter Crouch

Project co-supervisor
Dr James Hilton

Project availability:
- PhD
- Honours
- Master of Biomedical Science

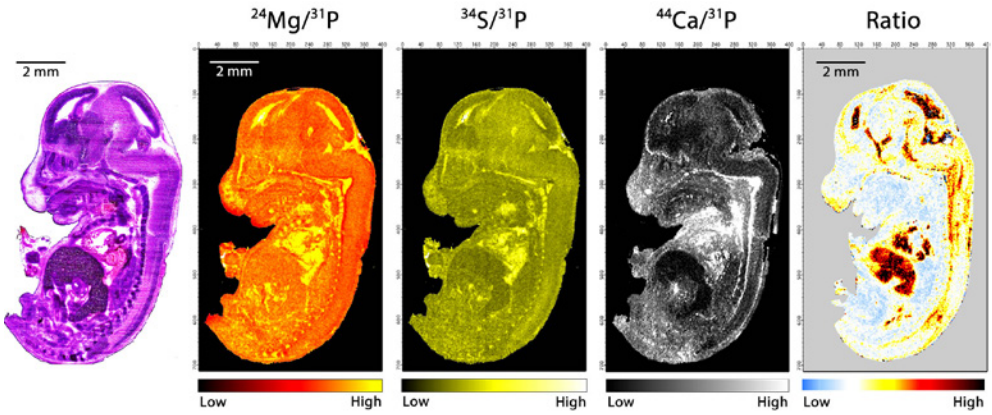
Project: The connection between motor neurone disease and progressive multiple sclerosis

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
A/Prof 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
A/Prof Peter Crouch

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
A/Prof Peter Crouch

Project co-supervisor
Dr Jeff Liddell

Project availability:
- PhD
- Honours
- Master of Biomedical Science

GUNDLACH GROUP

Contact: **Professor Andrew Gundlach**
Email: **andrew.gundlach@florey.edu.au**
Location: **The Florey Institute of Neuroscience and Mental Health**
Weblink: **go.unimelb.edu.au/5b8r**

Neurobiology	**Cell Signalling**
Neuropharmacology	**Biomedical neuroscience**
Neuropsychiatry	**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.

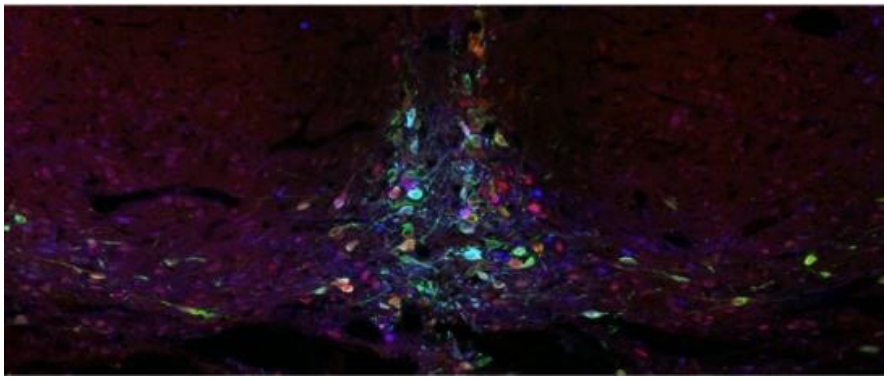
Project: Relaxin-3/RXFP3 signalling in control of arousal and complex physiology and behaviour

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 raphe 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

Project availability:
- PhD
- Honours
- Master of Biomedical Science



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

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
Dr Laura Jacobson
Dr Mohsen Nategh

Project availability:
- PhD
- Honours
- Master of Biomedical Science

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

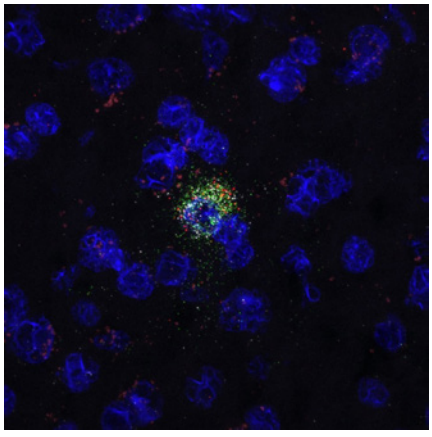
Our research has revealed that Ca2+-calmodulin dependent protein kinase kinase-2 (CaMKK2) is a key regulator of neuronal function and associated complex behaviour. Mutations that reduce CaMKK2 expression or activity display a strong association with a spectrum of human psychiatric disorders, including 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.

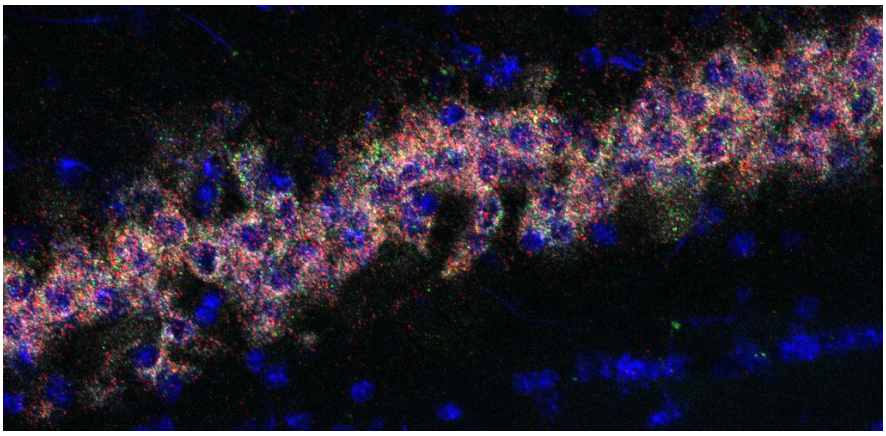
Project supervisor
Professor Andrew Gundlach

Project co-supervisor
Dr John Scott

Project availability:
- PhD
- Honours
- Master of Biomedical Science



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

MACKAY GROUP

Contact: **Dr Graham Mackay**
Email: **gmackay@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**

- **Neuroinflammation**
- **Therapeutics and translation**
- **Cell Signalling**
- **Infection and Immunity**
- **Lung Health**

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

Project: The role of mast cell-derived macrophage migration inhibitory factor (MIF) in Alzheimer's disease

Macrophage migratory inhibitor factor (MIF) is a multi-functional cytokine that has both intracellular and extracellular actions and possesses enzymatic activity alongside the ability to stimulate its receptor. In this project you will examine the stimulus-induced release of MIF from immune cells that are thought to play an important role in Alzheimer's disease (AD) pathology, with a focus on the mast cell. You will also examine the expression of MIF in samples taken from animal models of AD and from patients with the disease. Combined, the project will lead to a better understanding of the role of MIF in driving the inflammatory neurodegeneration observed in AD.

Project supervisor
Dr Graham Mackay

Project co-supervisor
Prof Peter Crack

Project availability:
- PhD
- Honours
- Master of Biomedical Science

Project: MRGPRX2-mediated drug hypersensitivity drug reactions.

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

Project supervisor
Dr Graham Mackay

Project availability:
- PhD
- Honours
- Master of Biomedical Science

PETER AND WANG GROUP

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Weblink: **http://go.unimelb.edu.au/6ngj**

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

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

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

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

Project supervisor
Dr Xiaowei Wang

Project co-supervisor
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

Project availability:
- 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-supervisor
Prof Karlheinz Peter

Project availability:
- 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-Flourine MRI technology and 3D fluorescence emission computed tomography (FLECT).

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

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

Project supervisor
Prof Karlheinz Peter

Project co-supervisor
Dr Xiaowei Wang

Project availability:
- PhD
- Honours
- Master of Biomedical Science

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

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

Project supervisor
Dr Xiaowei Wang

Project co-supervisor
Prof Karlheinz Peter

Project availability:
- PhD
- Honours
- Master of Biomedical Science

Project: Immunity, Chronic Inflammation and Cardiovascular Disease

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

1. Deep characterisation of adaptive immune responses in human and murine cardiovascular disease.
2. Defining the role of sexual dimorphism in the immune response in cardiovascular disease.
3. The role of conventional vs unconventional T cells in atherosclerosis and myocardial infarction.
4. Modulating adaptive immunity for the treatment of cardiovascular disease.

Project supervisor
Prof Karlheinz Peter

Project co-supervisor
Dr Jonathan Noonan

Project availability:
- PhD
- Honours
- Master of Biomedical Science

SCHNEIDER-FUTSCHIK GROUP

Contact: **Dr Elena Schneider-Futschik**
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Location: **Department of Pharmacology & Therapeutics**

Lung Health
Cardio-Respiratory
Neuropharmacology
Infection and Immunity

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

Project Cystic fibrosis receptors during developmental stages

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

Project supervisor
Dr Elena Schneider-Futschik

Project co-supervisor
Norman Saunders

Project availability:
- Honours
- Master of Biomedical Science

Project: Cystic fibrosis and inflammation

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

Project supervisor
Dr Elena Schneider-Futschik

Project availability:
- Honours

STEWART GROUP

Contact: **Professor Alastair Stewart**
Email: **astew@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**
Website: **go.unimelb.edu.au/kw8r**

Mechanopharmacology

Chronopharmacology

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

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

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

Reference:

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

Lachapelle, P., ^ Li, M., Douglass J., Stewart, A.G. Safer approaches to therapeutic modulation of TGF-β1 signaling in respiratory disease. Pharmacology & Therapeutics. 187: 98-113.

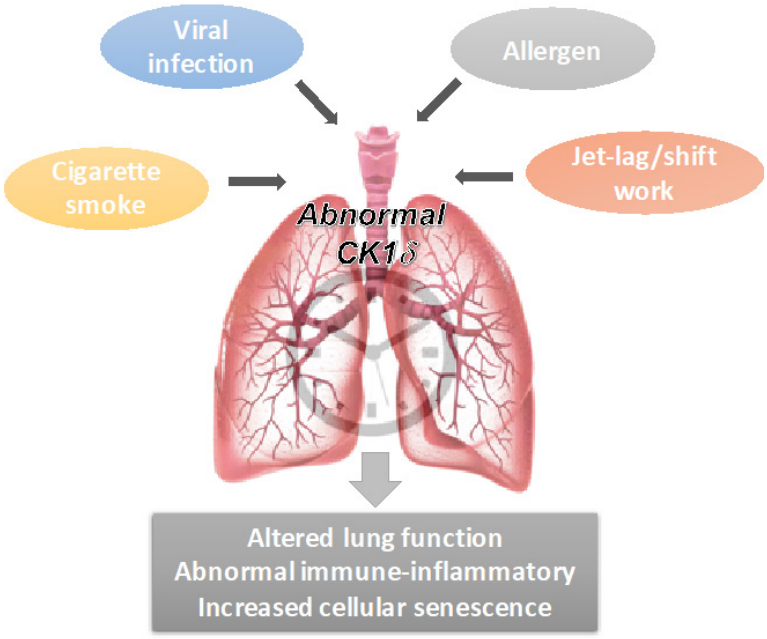
Keenan, C. R., Langenbach, S. Y., Jativa, F., Harris, T., Li, M., Chen, Q., Xia, Y., Gao, B., Schuliga, M.J., Jaffar, J., Prodanovic, D., Tu, Y., Berhan, A., Lee, P., Westall, G.P., Stewart, A.G. (2018). Casein Kinase 1δ/ε Inhibitor, PF670462 Attenuates the Fibrogenic Effects of Transforming Growth Factor-β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

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

Project supervisor
Prof Alastair Stewart

Project co-supervisor
Dr Meina Li

Project availability:
- PhD
- Honours
- Master of Biomedical Science



VELKOV GROUP

Contact: **Associate Professor Tony Velkov**
Email: **tony.velkov@unimelb.edu.au**
Location: **Department of Pharmacology and Therapeutics**

Antibiotics	**Superbugs**
Antibiotic resistance	**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 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 regimens, 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- through-put 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 analogues 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 be utilizing 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
Assoc Prof Tony Velkov

Project co-supervisor
Prof Jian Li

Project availability:
- Master of Biomedical Science

Project: Super resolution 3D-SIM microscopy imaging studies of methicillin-resistant Staphylococcus aureus (MRSA) to examine morphotypes associated with glycopeptide antibiotic tolerance

Super resolution 3D-SIM microscopy imaging studies of methicillin-resistant Staphylococcus aureus (MRSA) to examine morphotypes associated with glycopeptide antibiotic tolerance

This project will employ state-of-the-art 3D-SIM imaging to elucidate the morphological transitions in MRSA in response to new generation glycopeptide antibiotics namely dalbavancin, ortivancin and televancin, and draw comparisons with the progenitor compound vancomycin.

Project supervisor
Assoc Prof Tony Velkov

Project co-supervisor
Prof Jian Li

Project availability:
- Master of Biomedical Science

Project: Transcriptomics studies of the killing mechanism of texiobactin against methicillin-resistant Staphylococcus aureus (MRSA)

Texiobactin is a recently discovered antibacterial compound isolated from uncultivable (i.e. unable to be grown under conventional laboratory culture conditions) soil bacteria; the compound represents a new class of antibiotics displaying a novel mechanism of action against Gram-positive bacteria, this project will examine the transcriptomics response of MRSA to texiobactin.

Project supervisor
Assoc Prof Tony Velkov

Project co-supervisor
Prof Jian Li

Project availability:
- Honours
- Master of Biomedical Science

WRIGHT AND KHAMMY GROUP

Contact: **Assoc. Prof Christine Wright & Dr Makhala Khammy**

Email: **cewright@unimelb.edu.au/ mmkhammy@unimelb.edu.au**

Location: **Department of Pharmacology and Therapeutics**

Cardiovascular pharmacology

Neuropharmacology

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, snake venom toxinology and vascular reactivity in hypertension.

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 availability:
- Honours

Project: Is cardiorespiratory regulation affected by perinatal cannabinoid exposure?

Cannabis is the most widely consumed illicit drug in Australia and globally, even amongst pregnant women. As social attitudes towards cannabis use shift towards perceived harmlessness, the prevalence of cannabis use in pregnant women is expected to increase. Thus, research on the effects of cannabis exposure during pregnancy on the offspring is urgently needed.

One of the major active constituents of cannabis, a cannabinoid called Δ9-tetrahydrocannabinol (THC), can cross the placenta and blood-brain barrier to alter the activity of the endocannabinoid system. The endocannabinoid system, composed of endogenous cannabinoids and their receptors (CB1 and CB2), is present in both the central and peripheral nervous system from early developmental stages and is critical for optimal neurodevelopment. While cognitive, motor and behavioural impairments from perinatal cannabis exposure are well-documented in both preclinical and clinical studies, there is scarce information about the effect of perinatal cannabis exposure on the cardio-respiratory function of offspring. This is concerning, given evidence that endocannabinoids and exogenous cannabinoids can alter respiratory and cardiovascular function in adults.

Using a rodent model, this study will investigate how perinatal THC exposure affects cardiovascular and respiratory function in young and adult offspring. Students who undertake this research project will utilise techniques that assess cardiac and vascular function ex vivo and in vivo. The study will also incorporate the use of whole-body plethysmography to assess respiratory function and immunohistochemistry to determine the distribution of cannabinoid receptors in the brain and peripheral tissues of offspring. This project will provide insight into the long-term cardiorespiratory impact of early-life exposure to cannabis.

Project supervisor
Dr Makhala Khammy

Project co-supervisors
Dr Mariana Melo
Dr Aung Aung Kywe Moe

Project availability:
- Master of Biomedical Science

ZIOGAS GROUP

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Location: **Department of Pharmacology and Therapeutics**

Cardiovascular pharmacology

Molecular mechanisms of disease

Therapeutics and translation

Sub-arachnoid haemorrhage

Project: Cerebrospinal fluid biomarkers for aneurysmal subarachnoid haemorrhage

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

In most cases, these interventions restore cerebral perfusion but have the potential for significant complications. Identification of appropriate biomarkers for the vasoconstriction and neurological sequelae has the potential to inform improved post-surgical management of aSAH.

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

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

Nature of the work

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

Project supervisor
Associate Professor James Ziogas

Project availability:
- PhD
- Honours
- Master of Biomedical Science


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