2018 Third Year Pharmacology Student Dinner
Date & Time: Thursday 16th August 2018 at 6PM
Venue: Main Dining Room @ University House, Professors’ Walk,
The University of Melbourne
https://biomedicalsciences.unimelb.edu.au/departments/pharmacology

Honours Information Session
Date & Time: Thursday, 5th October 2018 at 4pm – 6pm
Venue: Department of Pharmacology & Therapeutics,
Practical Class (Room E805, Level 8, Medical Building)

Intake Key Dates
The following 2019 Intake key dates are taken from the MDHS Honours webpage:
http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

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<td>Round 1 Application Closing Date</td>
<td>Friday 26 October 2018</td>
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<td>Round 1 Project Preferences Submission Deadline</td>
<td>Sunday 28 October 2018</td>
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Cover Image credit: Dr Drew Berry (Walter & Eliza Hall Institute of Medical Research)
(2018 Third Year Pharmacology Student Speaker)
It is a great pleasure to introduce you to the research projects that are on offer by the Department of Pharmacology and Therapeutics for 2019. 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 2019 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-ordinators

“If you think research is expensive, try disease”
- Mary Lasker
STUDENT TESTIMONIALS

Frank Mobilio, BSc (Hons) 2018
I am currently doing my honours year in the Neuropharmacology laboratory. Although it has been a challenging year, I have thoroughly enjoyed every aspect of this experience. I have learnt valuable skills that can be applied to many laboratories around the world and the staff and students are all very helpful and friendly. My honours year has confirmed my passion and enthusiasm to continue in the area of medical research.

Denham Hopper, MC-BMEDSC 2018
Drug Discovery has been my ideal field of research since early high school, so when I saw the Northfield/Hughes lab I knew it was the right fit for me. What I didn’t realise is that the P&T department would exceed my expectations; I’m constantly surrounded by support, I’m always being pushed to do my best, and through department seminars there are regular opportunities to meet/network with people in industry and research.

Nhi Vuong, MC-BMEDSC 2016
As a Master student in the Department of Pharmacology, I have had an opportunity to immerse myself in research while making great friends and meeting the some of the best researchers in their respective fields.

Professor Ross Vlahos, BSc (Hons) 1991, Phd 1996
I am a Principal Research Fellow and Head of the Respiratory Research Group in the School of Health and Biomedical Sciences, RMIT University. My research aims to identify novel strategies for the prevention and treatment of Chronic Obstructive Pulmonary Disease (COPD). My passion for pharmacology was inspired by the wonderful and friendly academic staff who delivered world-class lectures and fun practical classes during my undergraduate studies. I have a very personal interest in drugs used to treat lung diseases because of my grandmother who died prematurely of lung cancer. I owe much of my success to the brilliant pharmacology lecturers and mentors I had during my undergraduate and postgraduate studies and in particular the late Professor Michael Rand, my Honours and PhD supervisor Professor David Story and more recently Professors Alastair Stewart and Gary Anderson.
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PROJECTS ARE AVAILABLE IN THE FOLLOWING RESEARCH GROUPS

## NEUROBIOLOGY
- Neuropeptide Receptor Laboratory – Prof Ross Bathgate  
- Neuropharmacology Laboratory – Assoc Prof Peter Crack  
- Crouch Laboratory – Assoc Prof Peter Crouch  
- Translational Neuropharmacology / The Florey Institute of Neuroscience and Mental Health – Dr Laura Jacobson & Prof Daniel Hoyer

## MECHANOPHARMACOLOGY
- Mechanopharmacology Laboratory – Prof Alastair Stewart

## LUNG HEALTH
- Anti-Allergic Therapeutics – Dr Graham Mackay & Dr Jon Mangum  
- Lung Disease Research Laboratory – Prof Gary Anderson

## HEART & CIRCULATION, ANTI-INFECTIVES, DRUG DESIGN & PROTEOMICS
- Anti-infectives Laboratory – Assoc Prof Tony Velkov  
- Biomarker Discovery – Assoc Prof James Ziogas & Dr Jon Mangum  
- Cardiovascular Therapeutics Unit – Dr Makhala Khammy  
- Drug Design Laboratory – Dr Susan Northfield & Assoc Prof Tony Hughes  
- Heart Failure Pharmacology – Prof Rebecca Ritchie

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Neuropeptide Receptor Laboratory

Supervisor: Prof Ross Bathgate
Email: bathgate@florey.edu.au
Telephone: 9035 6735
Location: Florey Institute of Neuroscience and Mental Health

Up to 4 positions may be offered as Honours or MBioMedSci

TARGETING PEPTIDE G-PROTEIN COUPLED RECEPTORS (GPCRS) FOR NOVEL DRUG DEVELOPMENT

Co-supervisors: Dr Daniel Scott, A/Prof Paul Gooley (Bio21)

The largest single class of drug targets is the G Protein-Coupled Receptor (GPCR) family, which were targets for 13 of the top 50 prescription drugs sold in the USA in 2010 (26%). 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 techniques to study the receptor structures (see project below) and are also studying ligand interactions with receptor domains using soluble receptor domains and NMR (A/Prof Gooley, Bio21). These studies are complemented by peptide drug development projects and small molecule screening projects with collaborators. Additionally, we are working with pharmaceutical industry partners (e.g. Takeda and Novartis) to facilitate drug development efforts.

Projects are available on multiple GPCR targets with training in various techniques as outlined above.

Recent Publications:

STRUCTURE-BASED DRUG DESIGN TARGETING G PROTEIN-COUPLED RECEPTORS

Supervisor/Co-supervisor: Dr Daniel Scott

Most G protein-coupled receptors (GPCRs) are activated though extracellular interactions of natural ligands, such as hormones or neurotransmitters, to the GPCR’s ligand binding site. Binding induces a conformational change of the GPCR resulting in the transmission of intracellular signals. The GPCR gene super-family is made up of numerous sub-families that are all activated by the same ligands, but often control different physiological processes. This presents a challenge for drug discovery because synthetic compounds that are identified to bind to the natural receptor binding site will often bind to similar sites on other receptor family members (off targets), causing side effects and unwanted physiological responses. To achieve GPCR selectivity we need new ways to identify and design more selective GPCR targeting drugs. To meet this challenge we need to understand how natural ligands, and drug candidates, bind to receptors at the atomic level. Contemporary structure-based drug design (SBDD) uses atomic resolution methods (X-ray, NMR and Molecular Dynamics) coupled with high-throughput screening (NMR,
Surface Plasmon Resonance, Isothermal Titration Calorimetry, and Microscale Thermophoresis) of small fragment molecules to discover novel leads. A huge challenge for GPCRs is that they are very unstable and “fall apart” during the experiments needed to guide SBDD. We have engineered stabilized variants of two closely related GPCR subtypes, the α1A- and α1B-adrenoceptors (α1A-AR and α1B-AR). The stability of these receptors in the purified state has allowed us to probe the binding of non-selective and selective ligands with NMR and to conduct fragment screening to identify novel selective ligands.

Projects are available that focus on mapping the binding of selective and non-selective ligands to α1A-AR and α1B-AR to guide SBDD and increase our knowledge of the structure and function of α-ARs. Designed, selective α-AR ligands will be critical tools for understanding the precise roles of these receptors in the body and could be candidates for treating heart disease, epilepsy and neurodegenerative diseases.

Recent Publications:

DRUG DISCOVERY: INVESTIGATION OF SIGNALLING BY GPCRS USING NOVEL CELLULAR BIOSENSORS

Supervisor/Co-supervisor: Dr Martina Kocan

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. 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.

Recent Publications:

PEPTIDOMIMETIC DRUG DESIGN TARGETING G PROTEIN-COUPLED RECEPTORS

Supervisor/Co-supervisor: A/Prof Akhter Hossain

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 the GPCRs, mainly relaxin family peptide (RXFP) receptors RXFP1, RXFP3 and RXFP4. Our laboratory utilizes multidisciplinary cutting-edge technologies including modern solid phase peptide synthesis, molecular pharmacology, and animal physiology to carry out these projects.

Recent Publications:

Projects Overview
Honours, Masters and PhD projects are available on all these topics. Candidates will undergo training in various techniques including molecular cloning, site-directed mutagenesis, cell biology, cell signaling, drug screening techniques, protein expression and purification, protein engineering with directed evolution, robotic assays, saturation transfer difference NMR, fluorescence activated cell sorting (FACS), confocal microscopy, viral expression and animal behavioural phenotyping.
**Neuropharmacology Laboratory**

**Supervisor:** Assoc Prof Peter Crack  
**Email:** pcrack@unimelb.edu.au  
**Telephone:** 8344 8417  
**Location:** Department of Pharmacology and Therapeutics  
**Co-Supervisor:** Dr Juliet Taylor

**INNATE IMMUNITY 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. The innate immune system uses a newly discovered family of receptors to transducer its’ signal called the Toll-like receptors (TLRs). The roll that the TLR’s play in the progression and response to neural injury is an exciting and emerging field of research. The molecular mechanisms that are influenced by the TLRs comprise new targets for therapeutic intervention into acute neurological conditions such as stroke and neurotrauma and chronic neurological diseases such as Alzheimers 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.

This project will be offered at Masters / Honours level.

**OXIDATIVE STRESS AND NEURAL INJURY**

**Supervisor:** Assoc Prof Peter Crack  
**Co-supervisor:** Dr Juliet Taylor

The major focus of our laboratory are the mechanisms that underpin the progression of neural injury. The causes of neural injury are multifactorial so our laboratory’s research is focused on the role that oxidative stress and reactive oxygen species (ROS) play in the predisposition and/or progression of neural injury. Rather than serving solely as harmful by-products of aerobic metabolism, it has become apparent that ROS have a much broader role in the regulation and co-ordination of cellular homeostasis. ROS are used to fine-tune cellular signaling and play an important role in the transduction of message along specific signal transduction pathways. In the event of oxidative stress, which is associated with varied human diseases including neurological disorders, the persistent inactivation of signal transduction pathways by ROS may lead to reduced or ablated, sustained or elevated cellular signaling and predispose or otherwise contribute to disease pathology. In understanding how signal transduction systems are regulated by oxidative stress and ROS we can gain a better understanding how new generation therapeutics can target these pathways in the hope to reduce and or prevent neuronal pathology.

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.

This project will be offered at Masters / Honours level.

**UNDERSTANDING TRAUMATIC BRAIN INJURY**

**Supervisor:** Assoc Prof Peter Crack  
**Co-supervisor:** Dr Juliet Taylor

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.

This project will be offered at Masters / Honours level.
THE BIOINFORMATIC ANALYSIS OF NEUROINFLAMMATORY PATHWAYS SEEN IN NEUROPATHOLOGY

Supervisor: Assoc Prof Peter Crack
Co-supervisors: Dr Juliet Taylor, Dr Victoria Pereau

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 Pereau. 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.

This project will be offered at Honours level only.

THE ROLE OF NEUROINFLAMMATION IN PARKINSON’S DISEASE

Supervisor: Dr Juliet Taylor
Email: jtaylor@unimelb.edu.au
Telephone: 8344 8417
Location: Department of Pharmacology and Therapeutics
Co-Supervisor: Assoc Prof Peter Crack

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. A multi-disciplinary approach using an 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.

This project will be offered at Masters / Honours level.

NEUROINFLAMMATION AND ITS CONTRIBUTION TO AN AUTISM-LIKE PHENOTYPE

Supervisor: Assoc Prof Peter Crack
Email: pcrack@unimelb.edu.au
Telephone: 8344 8417
Location: Department of Pharmacology and Therapeutics
Co-Supervisor: Dr Elisa Hill

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-1 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.

This project will be offered at Masters / Honours level.
The focus of our research is to elucidate the biochemical basis of human disease. Current research in our laboratory addresses degenerative conditions affecting the central nervous system (particularly motor neurone disease and multiple sclerosis) as well as a diverse range of cancers (colorectal cancer, breast cancer, and chondrosarcoma). Our overarching aim is to generate the information needed to better understand the biochemical causes of human disease. We use the information we generate to help develop and test new therapeutic options and to improve patient outcomes via 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.

In 2019 we will recruit up to three new students to our research team. Preference will be given to students interested in Honours, but students interested in Masters or PhD are also encouraged to apply. All applicants will be interviewed and will be expected to articulate why they want to become involved in biomedical research. Some examples of our anticipated research themes for 2019 are listed below.

**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 qualitative 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.

**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. 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.
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 for motor neurone disease 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.

ELUCIDATING THE CELLULAR MECHANISMS OF HUMAN DISEASE

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.

Preference will be given to students interested in Honours, but students interested in Masters or PhD are also encouraged to apply.
DEFINING THE EFFECTS OF STRESS VERSUS HYPERAROUSAL ON TAUOPATHY IN ALZHEIMER’S DISEASE

Chronic psychological stress is associated with an enhanced risk of developing Alzheimer’s disease (AD) and stress has been implicated in hyperphosphorylation of the protein tau in animal models of tauopathy. Excessive wakefulness / arousal, on the other hand has been shown to cause degeneration of brain regions associated with the maintenance of wakefulness (e.g. locus coeruleus, Raphe Nuclei, orexin neurons): these regions are also known to be vulnerable to degeneration in Alzheimer’s disease. However, whether hyperarousal acts similarly or distinctively to stress with regard to the effects on tau pathology has not been investigated. Therefore, the present project assesses the effects of chronic mild stress (CMS) versus chronic intermittent hyperarousal (CIH) on tau pathology in mice harbouring a human tau transgene which carries a mutation that enhances tau hyperphosphorylation. The CMS protocol consists of exposure to a series of mild stressors over several weeks, whereas CIH is generated by exposing mice to a novel, stimulating environment during their normal inactive (light) phase. Mice undergo surgery to install electroencephalography/electromyography (EEG/EMG) head-mounts. After recovery from surgery, sleep-wake activity will be assessed by analysis of recorded EEG/EMG signals ("polysomnography"; PSG), and cognition tested in a spatial learning and memory task. After completion of the in-life part of the study, brains will be taken for the analysis by immunohistochemistry and plasma samples for the analysis of melatonin. Students will learn about current theories underlying AD and FTD, tauopathy, sleep/wake physiology and circadian rhythms. Techniques learned include using transgenic mouse lines, EEG/EMG surgery, PSG, cognitive testing in mice, immunohistochemistry and radio-immunoassay.

This project will be offered at Honours or Masters Level. There is one position available for 2019.

MANIPULATING CIRCADIAN RHYTHM TO MODULATE TAU PATHOLOGY

Alzheimer’s disease (AD) and fronto-temporal dementia (FTD) are associated with altered circadian rhythm and sleep/wake cycles. The reasons for this are unclear, but disruptions in sleep-wakefulness probably contribute to the development of pathology in a feed forward manner. Our lab’s previous data demonstrate altered sleep-wakefulness patterns in human-tau transgenic mice. In the current project, we therefore probe the effects of changing light/dark cycles on the development of tau pathology in tau transgenic mice. The light/dark cycle of the mice will be altered for a number of weeks. The mice then undergo surgery to install electroencephalography / electromyography (EEG/EMG) head-mounts. After recovery from surgery, sleep-wake activity will be assessed by analysis of recorded EEG/EMG signals ("polysomnography"; PSG), and cognition tested in a spatial learning and memory task. After completion of the in-life part of the study, brains will be taken for the analysis by immunohistochemistry and plasma samples for the analysis of melatonin. Students will learn about current theories underlying AD and FTD, tauopathy, sleep/wake physiology and circadian rhythms. Techniques learned include using transgenic mouse lines, EEG/EMG surgery, PSG, cognitive testing in mice, immunohistochemistry and radio-immunoassay.

This project will be offered at Honours or Masters Level. There is one position available for 2019.
DEFINING THE EFFECTS OF THE SLEEP-WAKE CYCLE ON ASTROCYTE PHENOTYPES

Recent research has shown an important role for sleep in the clearance of Alzheimer’s disease associated substrates, such as tau and amyloid beta. Astrocytes in the brain are thought to be important in this process, however, the influence of different component of the sleep-wake cycle on astrocyte status has not been investigated. This project therefore evaluates astrocytic phenotypes in mice during different vigilance states dominated by either wake, NREM or REM sleep. The goal of this project is to define how astrocytes are influenced by the different sleep/wake vigilance states in normal animals and mice harbouring a transgene encoding human tau. Mice will be surgically implanted with electroencephalogram/electromyogram (EEG/EMG) head-mounts. After recovery, mice will be dosed during the dark (active) phase with different hypnotic drugs that induce sleep, but which give a different balance of REM versus NREM sleep. Control mice will be dosed with the inactive vehicle, representing the “awake” group. During the associated NREM, REM or wake-dense periods, mouse brains are harvested. Brains will be assessed by: transcriptomics with immunopanned-extracted astrocytes; immunohistochemistry for the assessment of tau and the localisation of astrocytic water channels, and; in situ-hybridisation to determine the localization of astrocyte genes altered by sleep states with candidate genes selected from the transcriptome analysis. The student will learn about current theories underlying AD, tauopathy, sleep/wake physiology and astrocyte biology. Techniques include transgenic mouse lines, EEG/EMG surgery, analysis of sleep-wake vigilance states, immunopanning, immunohistochemistry and transcriptomic profiling.

This project will be offered at Masters Level. There is one position available for 2019.
Mechanopharmacology Laboratory

Supervisor: Prof Alastair Stewart
Email: astew@unimelb.edu.au
Telephone: 8344 5675
Location: Department of Pharmacology & Therapeutics

GLUCOCORTICOID RESPONSIVENESS IN THE LUNG: IMPACT OF INFLAMMATION AND INFECTION

Co-Supervisor(s): Dr Connie Xia and Dr Meina Li (Pharmacology and Therapeutics); Prof Jo Douglass (Clinical Immunology and Allergy, Royal Melbourne Hospital).

The high level of sensitivity of allergic inflammation to regulation by glucocorticoids (GCs) underlies the therapeutic success of this class of drugs in most cases of asthma, hayfever and urticaria. However, there is a partial resistance to control of severe asthma by GCs and a more profound GC resistance in COPD. Episodes of worsening of asthma and COPD have been explained by patients having an infection of the lower respiratory tract with one or more of several viruses, including respiratory syncytial virus, better known as RSV, Rhinovirus (the common cold) or Flu virus. TGF-β induces resistance to actions of GCs in the respiratory epithelium. Respiratory viruses increase the activity of TGF-β. We will now establish whether blocking TGF-β can restore steroid sensitivity in viral exacerbations of chronic respiratory disease.

In this project there are a range of methodologies that you may use including culture of epithelial cell lines and primary epithelium (in air liquid interface culture) obtained from healthy normal and diseased (asthmatic or COPD) airway. In addition, human monocyte/macrophages will be isolated from asthmatics who respond well to steroids, those who respond poorly and from control subjects. Gene expression will be measured by quantitative RT-PCR and RNA-seq; protein expression is measured by western blotting or enzyme-linked immunosorbent assay; Live cell imaging is used to track the translocation of YFP-tagged wild-type and mutated GRs. Gene expression reporter constructs and interventions using transient cell transfection with silencing RNA or small molecular weight chemical tools will assist in implicating specific pathways in virus responses.

The results you obtain will guide new approaches to reversing steroid resistance in chronic inflammatory diseases.

References:

Available as a Masters or Honours project.
DEVELOPMENT AND APPLICATION OF SOFT CULTURING MICROWENVIRONMENT FOR NOVEL DRUG DISCOVERY

Supervisor: Prof Alastair Stewart  
Email: astew@unimelb.edu.au  
Telephone: 8344 5675  
Location: Department of Pharmacology & Therapeutics  
Co-Supervisor(s):  
Dr Bryan Gao (Pharmacology & Therapeutics)  
Prof Peter Lee (Biomedical Engineering)  
Dr David Simpson (School of Physics)  
Prof Lloyd Hollenberg (School of Physics)  
A/Prof Glen Westall (Alfred Hospital)

The mechanical properties of microenvironment for cell culturing used in drug assays have major impacts on the testing outcome. Most assays are currently performed on monolayers of cells in rigid plastic dishes. There is growing interest in efforts to make the assay condition more tissue-like in order to better predict the pharmacology of the drugs in tissues. We have referred to these new assay systems in an opinion article describing the interdisciplinary pursuit of “Mechano-pharmacology”. In this project, you will develop assays for drug action in 3-dimensional environments of defined physiological stiffness and compare the results to conventional 2D monolayer plastic culture environments. This interdisciplinary project will involve collaborations with Prof Peter Lee in the Department of Biomedical Engineering and Dr David Simpson and Prof Lloyd Hollenberg in the School of Physics. Methods will include immunoassay, real-time quantitative PCR, cell culture and high content screening using plate-based confocal microscopy (Operetta).

References:

Available as a Masters or Honours project.

“CLOCK-OFF TIME” FOR INFLAMMATION AND REMODELLING IN CHRONIC INFLAMMATORY DISEASES: CASEIN KINASE INHIBITORS

Supervisor: Prof Alastair Stewart  
Email: astew@unimelb.edu.au  
Telephone: 8344 5675  
Location: Department of Pharmacology & Therapeutics  
Co-Supervisor(s): Dr Meina Li and Dr Connie Xia (Pharmacology and Therapeutics); Prof Jo Douglass (Clinical Immunology and Allergy, Royal Melbourne Hospital).

Casein kinase 1 δ (CK1δ) has been implicated as a major regulator of the biochemical oscillator that determines circadian rhythm. Whilst most researchers think of the system as operating from the suprachiasmatic nucleus, responding to light input, peripheral cells also demonstrate 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. In this project, you will characterise the anti-inflammatory potential of this drug class using human cells obtained from peripheral blood and/or from the airways. Methods will include immunoassay, real-time quantitative PCR, cell culture and high content screening using plate-based confocal microscopy (Operetta).

Reference:


Available as a Masters or Honours project.
**Anti–Allergic Therapeutics Laboratories**

**MS FOR SM: USING MASS SPECTROMETRY TO BETTER UNDERSTAND AND PREDICT TREATMENT BENEFIT IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS**

**Supervisors:** Dr Graham Mackay and Dr Jonathan Mangum  
**Email:** gmackay@unimelb.edu.au; jonathan.mangum@unimelb.edu.au  
**Telephone:** 8344 3932  
**Location:** Department of Pharmacology and Therapeutics  
**Co-Supervisor:** Dr Jeremy McComish (Royal Melbourne Hospital)

Systemic mastocytosis (SM) is a rare but debilitating condition where there is abnormal growth of mast cells. Not only are mast cells increased in number, but they also become more responsive to stimuli, with increased release of potent mediators such as histamine. Patients can thus experience serious ‘allergy-like’ symptoms in the skin, gut and lung and also in some cases life-threatening anaphylaxis. There are currently no cures for SM, and the present treatments for symptom control are far from optimal.

A therapy that has shown promise in small studies of SM is the anti-IgE therapy omalizumab (Xolair™). The Dept. of Clinical Immunology & Allergy at RMH is currently running a large clinical trial (CI: McComish) of omalizumab’s efficacy in SM. During the trial, we have collected serum, urine and exhaled breath condensate (EBC) from SM patients (both omalizumab and placebo treated) as well as obtaining control specimens from normal healthy volunteers. We aim to use advanced mass spectrometry (made possible by a new state-of-the-art facility within The Dept. of Pharmacology and Therapeutics) to proteomically compare these samples to identify: 1) the proteins that are differentially expressed in SM; 2) proteins that are altered in response to omalizumab.

The study will provide new information about changes in protein expression that occurs in SM. Additionally and excitingly, the study will identify if this profile, or changes to this profile, are associated with omalizumab efficacy. If so, monitoring of these proteins could be used as a biomarker to inform the use of omalizumab in treating SM and perhaps also in its other indications.

**References:**

**The project can be offered as Honours or MC-BMEDSC**

**EMERGENCY MEDICINE: UNDERSTANDING, PREDICTING AND AVOIDING DRUG-INDUCED ANAPHYLAXIS**

**Supervisors:** Dr Graham Mackay  
**Email:** gmackay@unimelb.edu.au  
**Telephone:** 8344 3932  
**Location:** Department of Pharmacology and Therapeutics  
**Co-Supervisor:** Dr Lauren May (Monash Institute of Pharmaceutical Sciences, Monash University)

In pre-clinical development, drugs can fall by the wayside for numerous reasons one being the triggering of sudden adverse effects such as anaphylaxis. Anaphylaxis is often considered as an extreme form of allergy where the culprits are allergen-specific immunoglobulin E (IgE) and mast cells. Whilst drugs can act as allergens, there is increasing evidence that some drugs, such as neuromuscular blocking agents and some antibiotics, can directly activate mast cells in an IgE-independent manner.

Recent work has identified the G protein-coupled receptor MRGPRX2 as being responsible for these ‘pseudo-allergic’ reactions. This discovery means that in theory at least, MRGPRX2 activating compounds could be identified and terminated early on in their development. However, there are species differences in MRGPRX2 that might mean that problematic compounds are missed (false negative) or that compounds safe in humans are withdrawn (false positive).

In this study, you will generate, characterize and compare a range of cell lines that express MRGPRX2 from different Anti-Allergic Therapeutics Laboratories
animals used in pre-clinical drug development. This will facilitate establishment of a drug testing platform that will provide more relevant information as to the likelihood of new compounds possessing pseudo-allergic activity.

_During this project, you will develop technical skills in cell culture, molecular biology and receptor characterization._

References:


This project can be offered as Honours or MC-BMEDSC
POTENTIAL EXACERBATION OF IDIOPATHIC PULMONARY DISEASE BY GASTRIC REFLUX

Supervisor: Prof Gary Anderson
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Location: Department of Pharmacology & Therapeutics

Co-Supervisor: Dr Andrew Jarnicki
Department of Pharmacology & Therapeutics

Idiopathic Pulmonary Disease (IPF) is a lung disease that is progressive, has no cure and is often fatal. Excessive production of fibrosis within the lung results in tissue scarring and this leads to a decreased ability to breathe. Often, patients also experience acute exacerbations, which are the sudden and significant deteriorations of lung function, resulting in rapid worsening of the disease. In other lung diseases, viral infection is the most usual cause of exacerbations but this is not the case in IPF, where the cause in not known. Here we propose that gastric reflux leading to aspiration of stomach contents during sleep may be a key cause. The acidic stomach content (refluxate) can be passed back up the oesophagus, which is indicative of diseases such as gastroesophageal reflux disease (GERD, similar to the heartburn). When the resultant refluxate leaks back up and enters the trachea and the lung, it has the potential to induce inflammation, scarring and infections.

The aim of the project is to test whether refluxate can induce IPF exacerbations by establishing the potential causal links and molecular pathways in an experimental model. Techniques the student will use includes resolution Micro CT imaging and molecular quantification and identification using ELISA, immunohistochemistry, western blot and PCR.

References:

This project is suitable for an Honours or Masters candidate.

LUNG PERMEABILITY ASSAY DEVELOPMENT USING FLUORESCENTLY TAGGED MOLECULES WITH DIFFERENT MOLECULAR WEIGHTS IN HEALTHY AND RESPIRATORY DISEASED MOUSE MODELS

Supervisor: Dr Joe Ciccotosto
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Location: Department of Pharmacology and Therapeutics,
Co-Supervisors: Dr Andrew Jarnicki and Prof Gary Anderson

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 are 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.

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.

This project is suitable for an honours/masters candidate
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 (Figure 1) 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.

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-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.

Figure 1. Chemical structure of the essential virulence factor Mycobactin from M. tuberculosis

Available as Honours or Masters 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.

**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 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.

**Available as Honours or Masters Project**

All projects offered by Anti-Infectives Velkov Laboratory in 2019 can be tailored to Honours or Masters. We envision offering a total of 4 places in 2019.
Biomarker Discovery

Supervisor: Assoc Prof James Ziogas
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Location: Department of Pharmacology and Therapeutics

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 (Dorsch, 2011). 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.

Cardiovascular Therapeutics Unit

Supervisor: Dr Makhala Khammy
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Location: Department of Pharmacology & Therapeutics
Co-supervisor: Assoc Prof Christine Wright
Department of Pharmacology & Therapeutics

MANIPULATING THE ENDOCANNABINOID SYSTEM TO ALTER CARDIOVASCULAR FUNCTION IN HYPERTENSION

Hypertension describes a condition of high blood pressure. Aply dubbed the ‘Silent Killer’, it has no obvious outward symptoms but is a major risk factor for cardiovascular pathologies such as stroke, heart failure and coronary heart disease. There is a clear need for therapies that lower blood pressure and diminish hypertension-related morbidity and mortality.

One mechanism driving high blood pressure is the overactivation of our sympathetic nervous system. Critically, overactivation of our sympathetic nervous system confers damage to cardiovascular tissue independently of its effect on blood pressure. This represents the following rationale: Interventions that normalise sympathetic nerve activity have the potential to lower blood pressure and mitigate cardiovascular damage beyond reductions in blood pressure. It is unclear why sympathetic activation of blood vessels is elevated in hypertension.

One proposed mechanism is the failure of regulatory mechanisms that apply a ‘brake’ to sympathetic activity. Sensory and nitrergic nerves, as well as our endogenous cannabinoid system, are thought to dampen sympathetic nerve-mediated activation in cardiovascular tissue. Yet, there are no anti-hypertensive therapies that target the endocannabinoid system, mostly because we do not have sufficient understanding of how the system interacts and cross-regulates with the sympathetic nervous system in cardiovascular tissue.

This project will use techniques to assess cardiac and vascular function ex vivo in an experimental model of hypertension to investigate the effect of endogenous cannabinoids on nerve-mediated responses in the cardiovascular system. The student will also assess structural changes in cardiovascular tissue using a combination of histology, morphometry and stereology.

This project will be offered at Honours level.
P2X7 RECEPTOR- DERIVED PEPTIDES

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. The annual market for AMD is expected to exceed $25 billion dollars within the next several years. There are currently no treatments available that prevent the development or progression of AMD.

We are developing a group of novel peptides derived from the sequence of the P2X7 receptor, which has been implicated as a potential target for AMD therapeutics.

In this project, the student will use synthetic chemistry approaches to create novel peptides derived from the P2X7 receptor, and analyse the pharmacological actions of these compounds in appropriate assays, with a view to discovering new molecules with improved properties. The student will learn a range of synthetic peptide chemistry techniques (including cyclic peptide design, solid phase synthesis and reversed-phase HPLC), alongside contemporary pharmacological approaches to study P2X7 activity. The project will give the student an outstanding opportunity to “close the loop” on the iterative process of drug design and characterisation.

*The project is suitable for a Masters candidate.*
TARGETING INFLAMMATION IN THE CARDIAC COMPLICATIONS OF DIABETES

Co-Supervisors: Dr Helena Qin and Dr Miles De Blasio

Diabetes is Australia’s fastest growing chronic disease. The disease affects almost 2 million Australians; diabetes increases heart failure risk 2.5-fold and accelerates its onset. The Heart Failure Pharmacology laboratory has an established track record for identifying mechanisms of diabetes-induced heart failure (diabetic cardiomyopathy). Building on this, we have obtained recent evidence that cardiac inflammation is a key contributor to myocardial damage in the diabetic heart. Interventions that target this cardiac inflammation may ultimately limit progression to heart failure and death in diabetes-affected patients.

AIM: To investigate annexin-A1 cardioprotection for the cardiac complications of type 2 diabetes

METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac function and biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence. This project makes use of both genetic approaches for annexin-A1 deficiency and annexin-A1 gene delivery, as well as pharmacological administration of Annexin-A1 peptide mimetics

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

Key publications:

This project can be tailored to Honours or Masters.

TARGETING ALTERED CARDIAC GLUCOSE METABOLISM IN THE CARDIAC COMPLICATIONS OF DIABETES

Co-Supervisor: Dr Miles De Blasio

The increasing global prevalence of type 2 diabetes (T2D) and our aging population has given rise to an epidemic of heart failure. Up to one-third of patients in clinical heart failure trials are diabetic, and diabetes is an independent predictor of poor outcome. Despite the higher rate of heart failure in these patients, no specific treatment for heart failure exists for T2D patients. We have identified novel mechanisms for limiting T2D-associated cardiomyopathy that could pave the way for the development of much-needed, novel therapies that are specific for diabetic heart failure.

The Heart Failure Pharmacology laboratory has an established track record for identifying mechanisms of diabetes-induced heart failure (diabetic cardiomyopathy): this project specifically explores the role of a specific fate...
of glucose metabolism, targeting this with gene delivery approaches.

Increased glucose flux through the hexosamine biosynthesis pathway (HBP) has now emerged as a key mediator of the adverse effects of diabetes on the heart. As a result of this HBP overdrive, increased cardiac levels of the glucose metabolite called beta-N-acetylglucosamine (O-GlcNAc) increases susceptibility of a range of proteins to post-translational O-GlcNAc modification, altering their intrinsic function. The exaggerated flux through the HBP/O-GlcNAc pathway in the diabetic heart is likely provided by the combination of impaired glycaemic control, and increased cardiac levels of reactive oxygen species (ROS). We propose that this maladaptive route of glucose metabolism impairs left ventricular (LV) function, and will focus in particular on O-GlcNAcylation of key components (e.g. mitochondria and/or contractile proteins) within the cardiomyocyte.

AIMS:
1. To demonstrate that cardiac-directed therapeutic targeting of this ROS-hexosamine biosynthesis axis delays or even overcomes diabetes-induced cardiac dysfunction in the intact heart in vivo.
2. To investigate susceptibility of specific components within the cardiomyocyte to O-GlcNAcylation, and how this impacts on diabetes-induced heart failure.

METHODS INCLUDE: in vivo models of diabetic cardiac disease, gene delivery, assessment of cardiac function, human cell cultures and biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence.

Key publications:

This project can be tailored to Honours or Masters.

NITROXYL-BASED THERAPIES TO OVERCOME DIABETES-INDUCED IMPAIRMENTS IN CARDIAC NO SIGNALLING

Co-Supervisors: Dr Helena Qin (Baker IDI Heart & Diabetes Institute), Dr Barbara Kemp-Harper (Monash University)

In patients with cardiovascular disease, impaired NO• signalling is an independent predictor of poor outcomes, including mortality. This loss of NO•-responsiveness (termed ‘NO•-resistance’) is particularly debilitating in type 2 diabetes (T2D), where cardiovascular emergencies occur more frequently, but NO•-based pharmacotherapies are less effective. Identifying strategies to circumvent cardiovascular complications in the diabetic heart and vasculature, both in an acute emergency situation and over the longer-term, will improve prognosis in these patients. We have identified an exciting potential strategy for circumventing this impaired NO• signalling, utilizing the novel NO•-like molecule, nitroxyl (HNO). Further, the growing rise T2D in Australia, together with an aging population, this has given rise to a global epidemic of cardiovascular disease, including heart failure (HF). There is however no specific treatment for diabetes-induced heart diseases such as HF in this setting. Targeting HNO in the cardiovascular complications of type 2 diabetes is a major research focus of the Heart Failure Pharmacology laboratory at the Baker Heart and Diabetes Institute.

Project aims:
1. To determine the extent of NO resistance in type 2 diabetes, and whether HNO can overcome this in the short-term.
2. To investigate over the longer-term whether HNO limits diabetes-induced myocardial dysfunction and changes in cardiac structure, key characteristics of diabetes-induced heart failure (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.

Key publications:

This project can be tailored to Honours or Masters.

COMBINING DRUG AND GENE THERAPY APPROACHES TO LIMIT DIABETES-INDUCED CARDIAC FIBROSIS

Co-Supervisor: Dr Mitchel Tate

Diabetes is Australia’s fastest growing chronic disease. 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, both of which contribute to the impaired cardiac function evident in the diabetic heart. Whether specifically targeting diabetes-induced cardiac fibrosis alone, or diabetes-induced cardiomyocyte hypertrophy alone, is sufficient to restore cardiac function in the context of diabetes, will be investigated.

This project explores whether specifically limiting diabetes-induced cardiac fibrosis, using a cardiac-selective gene therapy approach to enhance a naturally-occurring antifibrotic mechanism, restores cardiac function in the context of type 2 diabetes over the longer-term in vivo. A second arm of the project explores a novel approach aimed at specifically targeting a subtype of histone deacetylase, to limit diabetes-induced cardiac myocyte hypertrophy. Although histone deacetylase (HDAC) inhibitors have been trialled for heart failure, it is not known understood whether such approaches can restore cardiac function in the context of type 2 diabetes over the longer-term in vivo. Lastly, we will examine both therapies in combination. These interventions, alone or in combination, may be particularly effective at reversing pre-existing impairments in cardiac function in the diabetic mouse heart. Ultimately, such approaches may limit progression to heart failure and death in diabetes-affected patients.
AIMS:
1. To determine whether enhancing cardiac gene expression of a regulator of cardiac fibrosis is sufficient to protect cardiac function in the context of type 2 diabetes in vivo
2. To determine whether HDAC4 inhibition to regulate cardiomyocyte hypertrophy is sufficient to protect cardiac function in the context of type 2 diabetes in vivo
3. To investigate the combined effectiveness of both approaches on diabetes-induced heart failure.

METHODS INCLUDE: in vivo models of diabetic cardiac disease, gene delivery, drug treatment, assessment of cardiac function, human cell cultures and biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence.

This project can be tailored to Honours or Masters.

Key publications:

PREVENTION OF CARDIAC REMODELLING AND ENDOTHELIAL DYSFUNCTION IN A MOUSE MODEL OF TYPE 2 DIABETES

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Facsimile: 8532 1100
Location: Baker IDI Heart & Diabetes Institute 75 Commercial Rd, Melbourne
Co-Supervisor: Prof Rebecca Ritchie

Diabetes is Australia’s fastest growing chronic disease, affecting almost 2 million Australians. Coronary heart disease and peripheral vascular diseases are among the most common causes of mortality in diabetic individuals. Diabetic cardiomyopathy is typically characterised by left ventricular (LV) dysfunction, with diastolic dysfunction manifesting early in the disease. Structural abnormalities such as LV hypertrophy and increased cardiac fibrosis occur together with the onset of diastolic dysfunction in the diabetic heart. The presence of these characteristics acts as a predictive indicator of mortality in diabetic patients, necessitating the development of new pharmacological targets to treat LV dysfunction and remodelling in the diabetic heart.

In parallel diabetes causes endothelial dysfunction associated with disorders of both the large and small arteries. We have previously demonstrated that 3’,4’-dihydroxyflavonol (DIOHF) can preserve endothelial function in rodent models of type 1 and type 2 diabetes and a water soluble analogue improves cardiac function and reduces fibrosis in hypertensive/type 1 diabetic rats. The aim of this project is to investigate the ability of DIOHF to preserve cardiac and endothelial function in a mouse model of type 2 diabetes and to investigate the mechanism of action with a particular focus on the possible involvement of CaMKII in both the heart and vasculature.

References

TARGETING INFLAMMATION IN THE ACUTE AND CHRONIC CARDIAC RESPONSE TO MYOCARDIAL INFARCTION

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Facsimile: 8532 1100
Location: Baker IDI Heart & Diabetes Institute 75 Commercial Rd, Melbourne
Co-Supervisor: Prof Rebecca Ritchie

Myocardial infarction (MI, sustained impairment in coronary blood flow) and the resultant heart failure is a major cause of death. Cardiac contractile function often remains impaired over the longer-term, yet there is a
paucity of effective treatments for managing MI beyond restoring vascularization in the first few hours. Finding new drugs that can target MI and the potential to lead to heart failure over the longer-term, is a major research focus of the Heart Failure Pharmacology laboratory at the Baker Heart and Diabetes Institute.

We have shown that the endogenous anti-inflammatory mediator annexin-A1 (ANX-A1) has powerful protective actions against cardiac injury and loss of cardiac contractile function. The GPCR family of formyl peptide receptors (FPRs), and activation of cell survival kinases, are both integral to ANX-A1 cardioprotection. Our most recent work reveals that the ANX-A1/FPR system can reduce early cardiac necrosis, as well as reducing the early inflammatory response to MI. We are presently developing new ANX-A1 drug mimetics, as well as gene therapy approaches for enhancing cardiac ANX-A1, for use in these studies. This project explores the potential for novel ANX-A1 mimetics (including both drug and gene therapy approaches) to reduce cardiac ischaemia-reperfusion injury, over the short- and longer-term, and to investigate the receptor-mediated mechanisms involved.

Project aims:
1. To determine whether cardiac gene delivery of annexin-A1 limits cardiac ischaemia-reperfusion injury over the short- and longer-term
2. To determine whether annexin-A1 as a therapeutic target remains effective in ageing.
3. To investigate the receptor signalling fingerprints in cardiac cell types, to gain new insights into the mechanisms involved in cardioprotection.

METHODS INCLUDE: in vitro and/or in vivo models of cardiac ischaemia, gene delivery, drug treatment, assessment of cardiac function, human cell cultures and biochemical techniques: FPR signalling fingerprints, Westerns, ELISA, real-time PCR, histology, immunofluorescence.

Key publications:

This project can be tailored to Honours or Masters.

All projects offered by Heart Failure Pharmacology in 2019 can be tailored to Honours or Masters. We envision offering a total of 2 places in 2019.
## 2019 COURSE OUTLINE

### BSc & BBioMedSci HONOURS

#### PHRM40002 ADVANCED TOPICS IN PHARMACOLOGY (SEMESTER 1) 12.5 PTS

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#### BIOM40001 INTRODUCTION TO BIOMEDICAL RESEARCH (SEMESTER 1) 12.5 PTS

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#### PHRM40001 + 40006 RESEARCH PROJECT 75 PTS

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<td>10% *</td>
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Note: After each assessment, you will be given a grade on the LMS.

- **H1**: 80% +
- **H2A**: 75-79%
- **H2B**: 70-74%
- **H3**: 65-60%
- **F**: Below 65

### MASTER OF BIOMEDICAL SCIENCE (MBioMedSci)

This is a 2 year degree comprising a 125pts research project and 75 pts of coursework subjects. For details of the prerequisites and coursework subjects, see the handbook entry.


* Subject to change in 2019
The Department of Pharmacology and Therapeutics will be having their 3rd Year Student Dinner on Thursday 16th August 2018 where you can meet with your lecturers and potential supervisors.

The following information is taken from the MDHS Honours webpage: http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

**HOW TO APPLY - MDHS HONOURS**

**Course Codes:**

- **BH-BMED - Bachelor of Biomedicine (Honours):** for students who have successfully completed or are about to complete the Bachelor of Biomedicine at the University of Melbourne.
- **BH-SCI - Bachelor of Science (Honours):** for all other applicants who have successfully completed or are about to complete a Bachelor of Science or equivalent.

For course eligibility details, please browse to the 'Entry Requirements' webpage.

**STEP 1: 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 MDHS Honours Expo and individual information sessions held by departments and institutes are ways of helping you to make contact with potential Honours supervisors.

**STEP 2: Lodge an online application between Monday 27 August – Friday 26 October 2018**

**NOTE:** Applicants must select 'MDHS Specialisations' as their area of interest on their application to ensure their application is directed to the correct area.

Applications for Honours are lodged to MDHS via one of the following processes:

**Currently enrolled University of Melbourne students and alumni**

1. [Apply online](http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now) and select the Returning Applicants, Current Students and Previous Students option.
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.

**External Applicants**

1. [Apply online](http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now) and select the First Time Applicants option. Do not select this option if you have previously completed study or applied to a 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.

Supporting documentation may be submitted to:

**Honours Admissions Team**
**Learning and Teaching Unit**
**Level 1, Brownless Biomedical Library**
**The University of Melbourne**
**VIC 3010 Australia**

*Please include your University of Melbourne Applicant ID or Student ID on all items and correspondence.*
**STEP 3:** Lodge your project preference application in the Honours Application and Tracking System (SONIA).

Once you have submitted an online course application, you will receive an email with login details to access the Honours Project Preference System - SONIA within 3 working days. Please follow the instruction in the email to set up your own password and select your preferences for projects offered within MDHS departments.

You may select up to four project preferences. 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.

**STEP 4: Offers**

Round 1 offer for entry into 2019 will be sent to you by Friday 21 December 2018. Students must accept their offer by the Offer Lapse Date noted in their offer letter.

NOTE: If you have a change of mind about your Round 1 offer, please DO NOT proceed ahead with accepting the offer. You MUST notify our Honours Admissions Team via mdhs-honours@unimelb.edu.au as early as possible. You might be considered for Round 2 under specific circumstances, but that is not guaranteed.

Students who meet the minimum entry requirements but are not made a Round 1 offer may be considered for Round 2 in mid-January.

It is the responsibility of all applicants to ensure they make appropriate arrangements for their mail and email during December and January. The Faculty of Medicine, Dentistry and Health Sciences is not responsible for correspondence that has not been received due to applicants being unavailable during the offer period.

IMPORTANT NOTE: Not all students who meet the minimum entry requirements and make contact with Supervisors may be offered a place in an MDHS Honours course. Entry is conditional upon selection by the relevant Department Selection Committee and is academically competitive.

**HOW TO APPLY FOR MASTER OF BIOMEDICAL SCIENCE (MBIOMEDSCI)**

**STEP 1:**

Find the project or research area you are interested in applying for. This can be done by looking through this booklet or you can also go to our Research Lab pages. Contact the laboratory head to discuss potential projects.

**STEP 2:**

Once you have a potential supervisor and project, applications are made on the following website: http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/apply-now#apply-now

The MBiomedSci is a different degree to Honours and applications are handled independently.
“Research is to see what others have seen but to think what no one has thought. – Szent-Gyorgi”