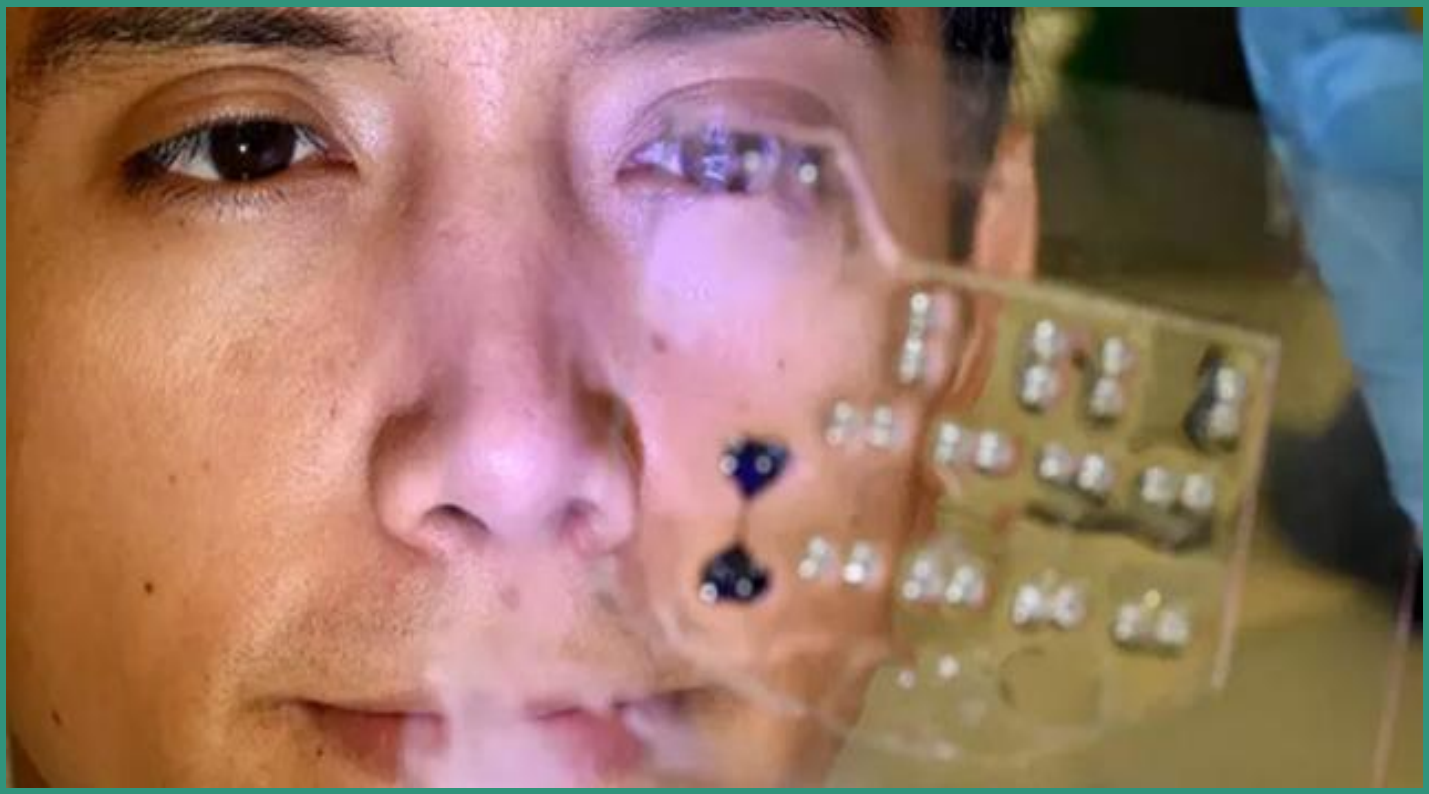
# Project Booklet



PHARMACOLOGY & THERAPEUTICS


THE UNIVERSITY OF MELBOURNE

## Honours & MBiomedSci 2018

# PROSPECTIVE STUDENTS

It is a great pleasure to introduce you to the projects that are on offer by the Department of Pharmacology and Therapeutics for 2018. 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.

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.

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.

We hope you will join us in Pharmacology & Therapeutics for the 2018 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

**Dr Graham Mackay**
**Professor Alastair Stewart**
Honours & MBiomedSci Co-ordinators

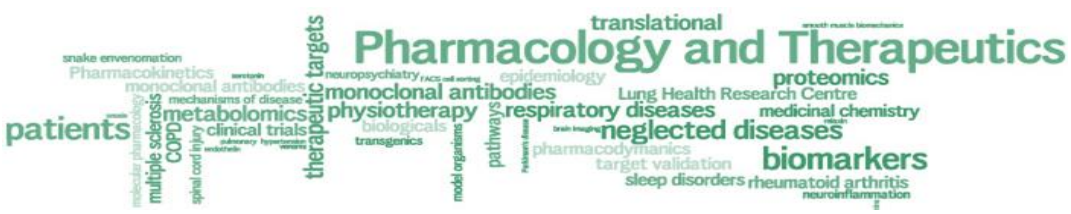
*"If you think research is expensive, try disease"*

- Mary Lasker

# CONTENTS

**PROJECTS ARE AVAILABLE IN THE FOLLOWING RESEARCH GROUPS**





# Neuropeptide Receptor Laboratory

**Supervisor:** **Prof Ross Bathgate**
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**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:**

1. Sethi A, Bruell S, Patil N, Hossain MA, Scott DJ, Petrie EJ, **Bathgate RAD***, Gooley PR* (2016) The complex binding mode of the peptide hormone H2 relaxin to its receptor RXFP1. Nature Communications, 7: 11344
2. Bruell S, Sethi A, Smith N, Scott DJ, Hossain MA, Wu Q-P, Guo Z-Y, Petrie EJ, Gooley PR, **Bathgate RAD** (2017) Distinct activation modes of the Relaxin Family Peptide Receptor 2 in response to insulin-like peptide 3 and relaxin. Scientific Reports 7: 3294
3. Diepenhorst NA, Petrie EJ, Chen CZ, Wong A, Hossain MA, **Bathgate RAD*,** Gooley PR* (2015) Investigation of interactions at the extracellular loops of the relaxin family peptide receptor 1 (RXFP1). Journal of Biological Chemistry, 289: 34938-34952
4. Kong RCK, Petrie EJ, Mohanty B, Ling J, Lee JCY, Gooley PR and **Bathgate RAD** (2013) RXFP1 utilises hydrophobic moieties on a signalling surface of the LDLa module to mediate receptor activation. Journal of Biological Chemistry 288: 28138-28151
5. **Bathgate RAD**, Halls ML, Van der Westhuizen ET, Callander GE, Kocan M and Summers RJ (2012) Relaxin Family Peptides and Their Receptors. Physiological Reviews. 93: 405–480

## STRUCTURE-BASED DRUG DESIGN TARGETING G PROTEIN-COUPLED RECEPTORS

**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 $\alpha_{1A}$- and $\alpha_{1B}$-adrenoceptors ($\alpha_{1A}$-AR and $\alpha_{1B}$-AR). The stability of these receptors in the purified state has allowed us to probe the binding of non-selective and selective ligands with NMR 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 $\alpha_{1A}$-AR and $\alpha_{1B}$-AR to guide SBDD and increase our knowledge of the structure and function of $\alpha_1$-ARs. Designed, selective $\alpha_1$-AR ligands will be critical tools for understanding the precise roles of these receptors in the body and could be candidates for treating heart disease, epilepsy and neurodegenerative diseases.

**Recent Publications:**

1. **Scott DJ,** Kummer L, Egloff P, **Bathgate RAD**, Plückthun A. Biochim Biophys Acta (BBA)- Biomembranes, 2014, 1838: 2817-24
2. Egloff et al, *PNAS*, 2014, 111:E655-662.
3. **Scott DJ**, Plückthun A: *J. Mol. Biol*. 2013, 425:662-667.
4. **Scott DJ**, Kummer L, Tremmel D, Pluckthun A: *Curr. Opin. Chem. Biol*. 2013, 17:427-435.

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

**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.

## VIRAL-MEDIATED MODULATION OF NEUROPEPTIDE GPCR FUNCTION IN BRAIN

**Co-supervisor: Prof Andrew Gundlach**

Mental illness is a large and increasing health and economic burden worldwide and more research is urgently required to identify new and innovative therapies. In this regard, neuropeptide GPCRs may be better therapeutic targets than receptors for the 'primary' transmitters (i.e. amino acids and monoamines), as they offer reduced side-effects, due to their modulatory actions. However assessing the therapeutic potential of neuropeptides is complicated by the difficulties of delivering peptides to the brain and hence alternative approaches are needed. We utilize viral gene transfer by adeno-associated viral (AAV) or lentiviral particles to transduce specific neuronal populations, allowing the chronic modulation of neuropeptide or peptide GPCR function. We target specific neuropeptide systems by either gene silencing or by overexpression of peptide agonists or antagonists in adult animals [1,2], thus avoiding potential compensation that can occur in gene knockout animals. Such viral targeting allows assessment of long-term modulation of neuropeptide systems on complex behaviours which are assessed in state-of-the-art rodent behavioural facilities at the Florey Institute of Neuroscience and Mental Health.

We are also utilizing viruses to express excitatory and inhibitory 'designer receptors exclusively activated by designer drugs' (DREADDs), GPCRs activated only by an artificial ligand which allows a pharmacogenetics approach to selectively and reversibly activate or inhibit specific neuropeptide expressing neurons and assess effects on physiology and behaviour in freely-moving animals [3]. This complementary approach assesses the role of the neuropeptide expressing neural circuits in the modulation of behaviour and can be extended to studies in genetic models of social, cognitive and other deficits seen in psychiatric illnesses. We have employed these strategies to demonstrate that the neuropeptide relaxin-3 has putative roles in regulating behaviours which are perturbed in mental illnesses such as anxiety, depression, sleep dysfunction and dementia [4].

Students will receive training in molecular cloning, viral production, stereotaxic surgery; behavioural assays and analysis; mRNA/peptide/protein analysis; and light/confocal microscopy.

**Recent Publications:**

1. Callander GE, Ganella DE, Ma S, Wimmer V, Gundlach AL, Thomas WG, Bathgate RAD (2012) Silencing relaxin-3 in nucleus incertus of adult rodents: a viral vector-based

approach to investigate neuropeptide function. PLoS One. 7, e42300.
2. Ganella DE, Callander GE, Ma S, Gundlach AL, Bathgate RAD (2013) Modulation of feeding by chronic rAAV expression of a relaxin-3 peptide agonist in rat hypothalamus. Gene Therapy 20, 703-71.
3. Ma S, Allocca G, Ong-Pålsson EKE, Hawkes D, McDougall SJ, Williams SJ, Bathgate RAD, Gundlach AL. (2016) Nucleus incertus promotes cortical desynchronization and behavioral arousal. Brain Structure and Function 222: 515-537.
4. Ma S, Gundlach AL (2015). Ascending control of arousal and motivation: Role of nucleus incertus and its peptide neuromodulators in behavioural responses to stress. J Neuroendocrinol 27, 457-467.

## 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.

# Tumourigenesis & Cancer Therapeutics

**Supervisor:** Dr Nicholas Clemons
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**Location:** Peter MacCallum Cancer Centre, VCCC
**Co-Supervisor:** Prof. Wayne Phillips

## TARGETING REDOX BALANCE IN MUTANT P53 CANCERS

The tumour suppressor p53 is mutated in over half of all cancers and is associated with tumourigenesis, resistance to chemotherapy and poor prognosis. We have recently shown that mutant p53 suppresses glutathione synthesis, disrupting redox balance and providing a weakness that we can exploit using therapies that target anti-oxidant synthesis. This project will determine the mechanism by which mutant p53 suppresses this pathway and develop novel therapeutic strategies in in vitro and in vivo models to target this Achilles heel.

*This project is suitable for Honours or MBiomedSci. There is one position available for 2018.*

# Neuropharmacology Laboratory

**Supervisor:** A/Prof Peter Crack
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**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 in jury 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:** A/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:** A/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:** A/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.

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**Telephone:** 8344 8417
**Location:** Department of Pharmacology and Therapeutics
**Co-Supervisor:** A/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 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. 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:** A/Prof Peter Crack
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**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 ultilise 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.*

# Translational Neuropharmacology / Proteomics and Calcium Biology / The Florey Institute of Neuroscience and Mental Health

## EXPLORING PROTEIN CHANGES ASSOCIATED WITH SLEEP DISRUPTION IN ALZHEIMER'S DISEASE

**Supervisor:** Dr Laura Jacobson
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**Location:** Department of Pharmacology and Therapeutics / Florey Institute of Neuroscience and Mental Health
**Co-Supervisors:** Dr Jonathan Mangum, Prof Daniel Hoyer (Department of Pharmacology & Therapeutics)

Alzheimer's disease (AD) is commonly accompanied by sleep disturbances which occur early in the development of the disease, prior to cognitive impairment. Sleep is important for brain health – disrupted sleep reduces attention, memory and cognitive flexibility, in addition to a number of other detrimental effects. In this regard, disrupted sleep in AD may contribute directly to the progression of the disease. Interestingly, improving sleep in animal models of AD has been shown to reduce the development of some classic pathological hallmarks of the AD brain. The mechanisms driving sleep alterations in AD are not well understood, and neither is how improving sleep may help to ameliorate / slow the development of brain pathology. The aim of this project is to determine alterations in protein pathways implicated in sleep disturbances in AD, and what processes are engaged in their repair when sleep is enhanced.

The project will use proteomics to explore protein changes in the brains of tau transgenic mice – a protein that accumulates into neurofibrillary tangles in AD – and how this relates to sleep in these mice both under control conditions and after treatment with a drug that enhances sleep. The sleep drug used will be the newly-approved orexin receptor antagonist suvorexant, which has a novel and mechanism of action in comparison to classic sleep medications. Orexin is a neuropeptide involved in the regulation of sleep and wake, and it is also disrupted in AD. In addition to analysing brain samples from these mice, the degree to which these changes are reflected in the plasma and cerebrospinal fluid (CSF) will be explored. These studies will highlight changes in proteins involved in neuronal network alterations in AD, and will provide insights into potential biomarkers of these processes in more accessible biofluids. The student will learn the basics of proteomics and bioinformatic analyses, sleep pharmacology and the analysis of sleep-wake electroencephalography (EEG) and electromyography (EMG) collectively known as polysomnography (PSG), using a newly developed analysis software.

*This project will be offered at Honours or Masters Level. There is one position available for 2018.*

## DEFINING THE EFFECTS OF OREXIN RECEPTOR ANTAGONISTS ON SLEEP ARCHITECTURE AND CONSOLIDATION OF MEMORY

**Supervisor:** Prof Daniel Hoyer
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**Location:** Department of Pharmacology and Therapeutics / Florey Institute of Neuroscience and Mental Health
**Co-Supervisor:** Dr Laura Jacobson

Sleep is important for mental health and well-being in many ways, and in particular for the consolidation of memory. Broadly, there are two types of sleep: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM and NREM sleep are thought to promote consolidation of different types of memory, with REM sleep promoting procedural and emotional types of memories, while NREM sleep consolidates declarative memories – such as facts, spatial and temporal contexts.

Recently a new type of sleep drug has been developed: orexin receptor antagonists, which block the signaling of the neuropeptide orexin, which controls wakefulness, arousal and sleep brain networks. Orexin signals via two receptors, the orexin 1 and orexin 2 receptors. Drugs that block either both receptors or the orexin 2 receptor alone promote sleep in animals and humans. They also promote a different kind of sleep architecture with regard to REM

and NREM in comparison to commonly prescribed sleep medications, such as the GABAA receptor positive modulators, e.g. zolpidem (AmbienTM or StillnoxTM) and other Z drugs. The
effects of orexin receptor antagonists on memory consolidation during sleep, however, have not been examined. This project explores the effects of orexin receptor antagonist-induced sleep on the balance of REM and NREM sleep and their consequences for the consolidation of different types of memory in mice. These studies will contribute to the understanding of the effects of different types of sleep medications on sleep-induced memory consolidation, and more generally the effects of sleep architecture on memory consolidation. The student will learn the basics of small animal surgery and cognitive tasks used in rodents, sleep pharmacology and the analysis of sleep-wake electroencephalography (EEG) and electromyography (EMG) collectively known as polysomnography (PSG), using a newly developed analysis software.

*This project will be offered at Honours or Masters Level. There is one position available for 2018.*

# Anti-Allergic Therapeutics & Proteomics Laboratories

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**Telephone:** 8344 3932
**Location:** Department of Pharmacology and Therapeutics
**Co-Supervisor:** Dr Jeremy McComish (Royal Melbourne Hospital)

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

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:**

1. Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. N Engl J Med. 2015;373:1885-6.
2. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy. 2017;72:519-533

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

# Molecular Oncology Laboratory
# Oncogenic Signalling and Growth Control

**Supervisor:** Prof Grant McArthur
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**Telephone:** 8559 5297
**Location:** Molecular Oncology Laboratory, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre
**Co-Supervisor:** Dr Lorey Smith

## METABOLIC REPROGRAMMING IN RESPONSE TO TARGETED THERAPIES IN BRAFV600E MELANOMA.

BRAF is the most commonly mutated oncogene in melanoma, and the development of therapies, such as Vemurafenib, targeting BRAFV600 represents a clear example of successful targeting of an oncogene for the treatment of cancer. However, despite initial profound responses, acquisition of BRAF inhibitor resistance represents a major challenge in the clinical management of BRAFV600 melanoma. Importantly, work from our laboratory revealed that BRAFV600 regulates aerobic glycolysis in melanoma, and treatment with Vemurafenib suppresses this glycolytic response (Parmenter et al, Cancer Discovery, 2014). Aerobic glycolysis represents a key metabolic adaptation observed in many cancers and accommodates elevated energetic and biomass demands. Because glycolysis is often restored upon development of BRAF inhibitor resistance, these observations suggest glycolysis is important for patient responses to BRAF inhibition and highlight the need for further investigation of glycolysis as a potential therapeutic target in BRAFV600 melanoma patients.

In order to further explore BRAF-mediated glycolysis we have now performed a whole genome siRNA screen to identify enhancers of BRAF inhibition within the context of viability and glycolysis in BRAFV600 melanoma cells. This approach uncovered novel complexes and pathways that may couple glycolysis to survival pathways in BRAFV600 melanoma. This honours project will involve functional characterization of novel regulators of BRAFV600-driven glycolysis using both experimental and bioinformatics techniques to assess their potential as novel therapeutic targets.

*This project will be offered at Honours or Masters Level.*

# Drug Design Laboratory

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**Telephone:** 8344 8304
**Location:** Department of Pharmacology and Therapeutics
**Co-Supervisors:** Dr Jessica Fletcher (Department of Anatomy & Neuroscience), A/Prof Richard Hughes (Department of Pharmacology & Therapeutics).

## BDNF MIMETICS: SYNTHESIS AND ANALYSIS OF NOVEL PEPTIDE NEUROTROPHIN MIMETICS AS POTENTIAL MODULATORS OF MYELINATION

Brain-derived neurotrophic factor (BDNF) has complex actions on myelination in the peripheral and central nervous systems, mediated via its two receptors, TrkB and p75NTR. Our laboratory has previously designed and synthesised small, cyclic peptide-based mimetics of BDNF that act selectively through each of these two receptors. These BDNF mimetics offer a unique opportunity to dissect the actions of TrkB and p75NTR in myelination, as well as offering an entrée into novel therapeutic approaches for the treatment of demyelinating diseases, such as multiple sclerosis.

In this project, the student will use synthetic chemistry approaches to create novel analogues of the BDNF mimetics, 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 myelination (including co-culture techniques, immunohistochemistry, confocal and high resolution microscopy). 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.*

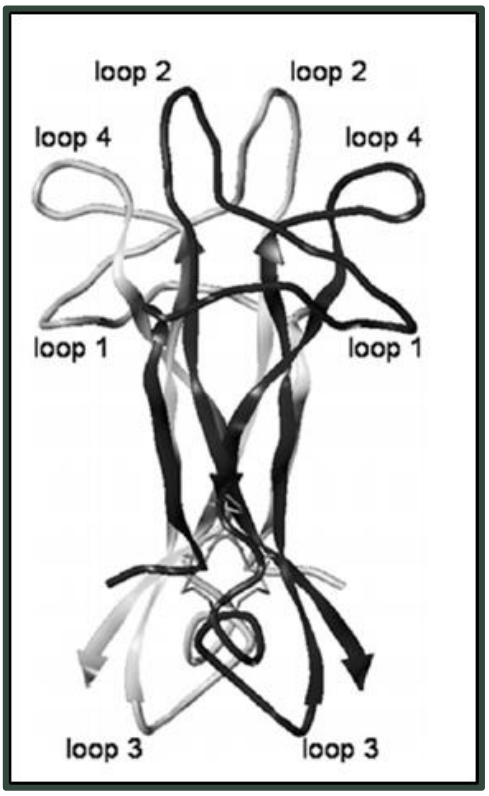


**Figure:** Structure of the neurotrophin homodimer, brain-derived neurotrophic factor (BDNF). One monomer chain is shown in grey and the other in white. Antiparallel β-sheets are shown as broad ribbons. The solvent exposed loops have all been clearly labelled. (Adapted from J.Pep.Sci,(2006), 12, p515-524)

## NT-3 MIMETICS: SYNTHESIS AND ANALYSIS OF NOVEL PEPTIDE NEUROTROPHIN MIMETICS

**Supervisor:** **Dr Susan Northfield**
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**Telephone:** **8344 8304**
**Location:** **Department of Pharmacology and Therapeutics**
**Co-Supervisors:** **Dr Simon Murray (Department of Anatomy & Neuroscience), A/Prof Richard Hughes (Department of Pharmacology & Therapeutics).**

The neurotrophin protein family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4. All of these neurotrophins bind to Trk-receptors and p75NTR. NT-3 is a protein homodimer that binds primarily to TrkC and p75NTR. Binding of neurotrophins to Trk-receptors occurs via the two adjacent loop-2 domains of the protein homodimer. Our lab has previously produced a peptide mimetic of the loop-2 region of BDNF that binds selectively to TrkB, but at this stage there is no mimetic of NT-3 loop-2.

NT-3 binding with TrkC has been implicated as a potential treatment for noise-induced hearing loss. We are interested in developing the first dimer peptide mimetics of NT-3 loop-2 and testing their activity against the TrkC receptor. At this stage we have a simple peptide mimetic synthesised and ready to test against TrkC. This project will involve some peptide chemistry and pharmacology, beginning with testing the activity of our initial compound and then synthesising and testing a more complex NT-3 peptide mimetic.

*The project is suitable for a Masters of Biomedical Sciences.*

# Lung Disease Research Laboratory

**Supervisor:** **Prof Gary Anderson**
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**Telephone:** **8344 8602**
**Location:** **Department of Pharmacology & Therapeutics**
**Co-Supervisors:** **Dr Andrew Jarnicki (Department of Pharmacology & Therapeutics)**

## POTENTIAL EXACERBATION OF IDIOPATHIC PULMONARY DISEASE BY GASTRIC REFLUX

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:**

1. Liu, G. et al. Fibulin-1 regulates the pathogenesis of tissue remodeling in respiratory diseases. JCI Insight 1, 1–18 (2016).
2. MD, P. M. K. et al. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. The Lancet Respiratory 4, 381–389 (2016).
3. Ryerson, C. J., Cottin, V., Brown, K. K. & Collard, H. R. Acute exacerbation of idiopathic pulmonary fibrosis: Shifting the paradigm. European Respiratory Journal 46, 512–520 (2015).
4. O'Donoghue, R. J. J. et al. Genetic partitioning of interleukin-6 signalling in mice dissociates Stat3 from Smad3-mediated lung fibrosis. EMBO Mol Med 4, 939–951 (2012).

*This project is suitable for an Honours or Masters candidate.*

# Immunopharmacology Laboratory

**Supervisor:** **Prof Alastair Stewart**
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**Telephone:** **8344 5675**
**Location:** **Department of Pharmacology & Therapeutics**

## GLUCOCORTICOID RESPONSIVENESS IN THE LUNG: IMPACT OF INFLAMMATION AND INFECTION

**Co-Supervisor(s):** **Dr Connie Xia (Pharmacology and Therapeutics);**
**Dr Sarah Londrigan (Peter Doherty Institute;);**
**Prof Jo Douglass (Clinical Immunology and Allergy, Royal Melbourne Hospital).**

http://biomedicalsciences.unimelb.edu.au/sbs-research-groups/pharmacology-and-therapeutics-research/lung-health-research-centre/immunopharmacology

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 severe asthma by GCS and a more profound GCS 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. We have evidence that TGFβ induces resistance to actions of GCS in the respiratory epithelium. Preliminary evidence suggests that respiratory viruses increase the availability of TGFβ. We will now establish whether blocking TGFβ 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 asthmatic airway. In addition, monocyte/macrophages will be isolated from induced sputum and peripheral blood of asthmatics who respond well to steroids, those who respond poorly and from control subjects. Gene expression is measured by quantitative RT-PCR and RNA-seq Western; 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:**

1. Keenan, CR., Mok, J.S.L., Harris, T., Xia, Y., Salem, S.,and Stewart, A.G. (2014). Bronchial epithelial cells are rendered insensitive to glucocorticoid transactivation by Transforming growth factor-β. Respiratory Research. 15:55.
2. Keenan C.R., S. Salem, Fietz, E. Gualano, R. and A.G. Stewart (2012). Glucocorticoid-resistant asthma and novel anti-inflammatory drugs. Drug Discovery Today 17;1031-1038.
3. Keenan CR, Radojicic D, Li M, Radwan A, Stewart AG. (2015). Heterogeneity in mechanisms influencing glucocorticoid sensitivity: the need for a systems biology approach to treatment of glucocorticoid-resistant inflammation. Pharmacol Ther. 150:81-93.
4. S. Salem, T. Harris, J. Mok Shiueh Lian, M. Yuen Sin Li, C.R. Keenan, M.J. Schuliga, and A.G. Stewart (2012). Transforming growth factor-β impairs glucocorticoid activity in the A549 lung adenocarcinoma cell line. Br J Pharmacol. 166:2036-2048.

*Available as a Masters or Honours project.*

## SOFT ENVIRONMENTS FOR NOVEL DRUG DISCOVERY

**Supervisor:** Prof Alastair Stewart
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**Telephone:** 8344 5675
**Location:** Department of Pharmacology & Therapeutics
**Co-Supervisor(s):** 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 environment of cells used to assay drugs has a major impact on the outcome. Most assays are currently performed on monolayers of cells in stiff plastic dishes. There is growing interest in efforts to make the assay environment 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 inter-disciplinary pursuit of "Mechanopharmacology". 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 that are rigid. This inter-disciplinary 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:**

1. Krishnan, R., Park, J-A., Seow, C.Y., Lee, P.V.S., Stewart, A.G. (2016). Cellular biomechanics in drug screening and evaluation: Mechanopharmacology. Trends in Pharmacological Sciences 37:87-100.
2. Stewart, Alastair G. Translational Pharmacology. Frontiers in Pharmacology – Translational Pharmacology doi: 10.3389/fphar.2017.00008.

*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
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**Co-Supervisor(s):** 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 supra-chiasmatic nucleus, responding to light input, peripheral cells also demonstrate circadian rhythm. Our laboratory has established that CK1δ is also involved in signalling of some remodelling and inflammatory actions of TGF-β including the ability to switch off the anti-inflammatory effects of glucorticoids. 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 (sputum-derived macrophages). Methods will include immunoassay, real-time quantitative PCR, cell culture and high content screening using plate-based confocal microscopy (Operetta).

**Reference:**

1. Yuxiu C. Xia[1], Asmaa Radwan[1], Christine R. Keenan[1], Shenna Y. Langenbach[1], Meina Li[1], Danica Radojicic[1], Sarah L. Londrigan[2], Rosa C. Gualano[1], Alastair G. Stewart. Glucocorticoid insensitivity in virally infected airway epithelial cells is dependent on transforming growth factor-β activity. PLOS Pathogens http://dx.doi.org/10.1371/journal.ppat.1006138.

*Available as a Masters or Honours project.*

# Australian Venom Research Unit (AVRU)

**Supervisor:** Dr Timothy Jackson
**E-mail:** timothy.jackson@unimelb.edu.au
**Location:** AVRU, Department of Pharmacology and Therapeutics
**Co-supervisor:** A/Prof Christine Wright (Department of Pharmacology & Therapeutics)

## A MULTIDISCIPLINARY INVESTIGATION OF THE VENOM AND EVOLUTIONARY SYSTEMATICS OF BLACK WHIP SNAKES

The Australian Venom Research Unit is offering an Honours or MBioMedSci project investigating the venomics (including toxin pharmacology) and evolutionary systematics of "black whip snakes" from Australia and Papua New Guinea.

According to current taxonomy, the lesser black whip snake (*Demansia vestigiata*) occurs in both Australia and New Guinea, whereas the greater black whip snake (*Demansia papuensis*) occurs only in Australia. The systematics of this group, and indeed of the entire genus *Demansia*, have long been controversial. Recently, molecular phylogenies including representatives of the majority of Australasian elapid snake genera have largely resolved the relationship of *Demasia* to the rest of the clade. These studies have supported the hypothesis that *Demansia* are, despite being an almost exclusively Australian genus, closely aligned with the Melanesian elapids that occur in New Guinea, as well as with Australian taxa that exhibit characteristics more commonly associated with their Melanesian cousins. *Demansia* is thus an interesting genus, because it may represent an intermediate evolutionary point between the plesiomorphic (similar to the ancestral state) Melanesian elapids, and the classic Australian species such as taipans (*Oxyuranus*) and brown snakes (*Pseudonaja*).

From a toxinological perspective, the venom of *Demansia* also seems to occupy a middle zone between that of plesiomorphic skink specialists and that of Australian species that include mammals in their diet. Despite this interesting fact, and despite the fact that black whip snakes have been responsible for numerous unpleasant bites (primarily to snake handlers), their venom has been little investigated. Crucially, the ability of antibodies contained within currently manufactured antivenoms to bind and neutralise toxins present in *Demansia* venoms is completely unknown.

This is a multidisciplinary project that will aim to comprehensively characterise the venom proteomes of black whip snakes from both Australia (both species) and New Guinea (*D. vestigiata*). The ability of available antivenoms to bind the toxins present in these venoms will be investigated, as will the ability of those antivenoms to neutralise key pharmacological effects of those toxins. In tandem, a molecular approach will be used to investigate the evolutionary relationships between the two species, and between *D. vestigiata* in Australia and New Guinea.

Depending on the successful candidate, this project will potentially involve training in various protein chemistry (proteomics), molecular biology and pharmacological techniques. Proteomic and molecular techniques may include liquid chromatography, affinity chromatography, electrophoresis (gel and capillary), mass spectrometry and PCR. Various *in vitro* analytical pharmacological preparations may be utilised, including small blood vessels, cardiac tissues and phrenic nerve-hemidiaphragm assays. To facilitate data analysis and preparation, the candidate will be trained in advanced data manipulation, graphing, statistical and bioinformatics programs, as appropriate.

# Biomarker Discovery

**Supervisor:** A/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 vasconstriction 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.

1. Dorsch N (2011). A Clinical review of cerebral vasospasm and delayed ischaemia following aneurysm rupture. Acta Neurochir Suppl 110: 5-6.

# Heart Failure Pharmacology (Baker IDI Heart & Diabetes Institute)

**Supervisor:** **Prof Rebecca Ritchie,**
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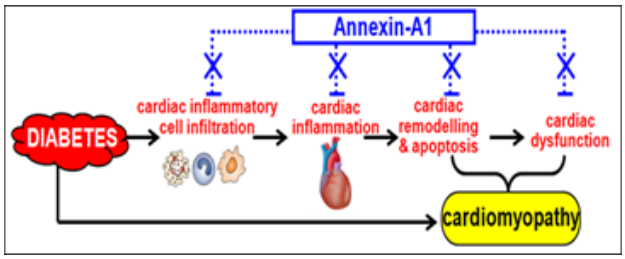
**Telephone:** **8532 1392**
**Location:** **Baker IDI Heart & Diabetes Institute**
**75 Commercial Rd, Melbourne**

## 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.




We have demonstrated that the endogenous anti-inflammatory protein annexin-A1 can protect the heart from severe, acute inflammatory insults, but its ability to protect the heart against chronic, low-grade inflammatory results (such as diabetes represents), is not known. Given that annexin-A1 also facilitates the resolution of inflammation, it represents an exciting target for the cardiac complications of diabetes.

GENERAL HYPOTHESIS: Enhancing anti-inflammatory annexin-A1 in the heart limits type 2 diabetes-induced cardiomyopathy by reducing cardiac inflammation and protecting cardiac contractile function and cardiac muscle relaxation.

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:**

1. Huynh K, Bernardo BC, McMullen JR*, Ritchie RH*. Diabetic cardiomyopathy: Mechanisms and new treatment strategies targeting antioxidant signaling pathways. (2014). Pharmacol Ther 142: 375-415

2. Qin CX, Yang YH*, May LM*, Gao XM, Stewart A, Tu Y Woodman OL, Ritchie RH. (2015). Cardioprotective potential of annexin-A1 mimetics in myocardial infarction. Pharmacol Ther 148:47-65.

*This project can be tailored to Honours or Masters.*

## TARGETING ALTERED CARDIAC GLUCOSE METABOLISM IN THE CARDIAC COMPLICATIONS OF DIABETES

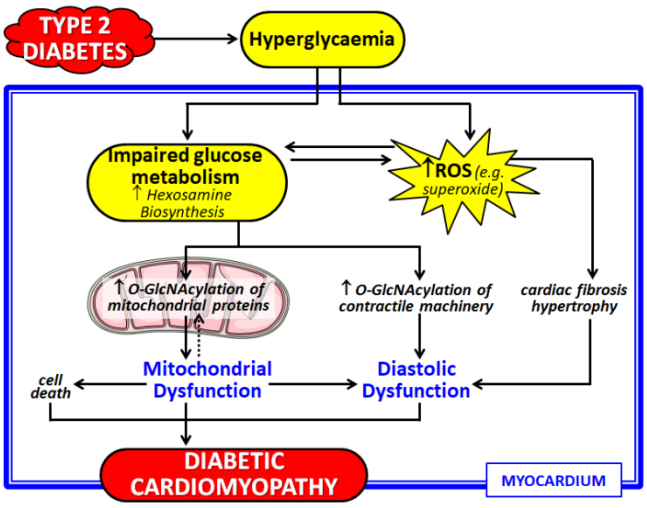
**Co-Supervisor: Dr Miles De Blasio**

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:**

1. Huynh K, Bernardo BC, McMullen JR*, Ritchie RH*. Diabetic cardiomyopathy: Mechanisms and new treatment strategies targeting antioxidant signaling pathways. (2014). Pharmacol Ther 142: 375-415
2. Qin CX*, Sleaby R*, Davidoff AJ, Bell JR, De Blasio MJ, Delbridge LM, Chatham JC, Ritchie RH. (2017). Insights into the role of maladaptive hexosamine biosynthesis and O-GlcNAcylation in development of diabetic cardiac complications. Pharmacol Res 116: 45–56.
3. Prakoso D*, De Blasio MJ*, Qin CX, Rosli S, Kiriazis H, Qian HW, Du XJ, Weeks KL, Gregorevic P, McMullen JR#, Ritchie RH#. (2017). Phosphoinositide 3-kinase (p110α) gene delivery limits diabetes-induced cardiac NADPH oxidase and cardiomyopathy in a mouse model with established diastolic dysfunction. Clinical Science 131: 1345-1360.

*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 and Diabetes Institute), Dr Barbara Kemp-Harper (Monash University).**

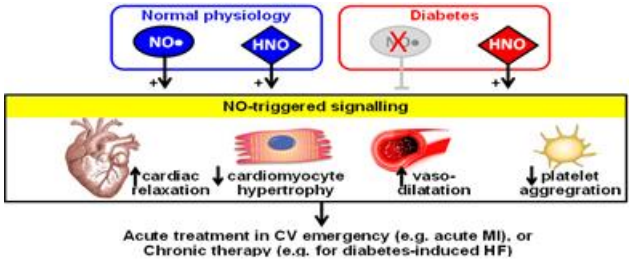
In patients with cardiovascular disease, impaired NO• signalling is an independent predictor of poor outcomes, including mortality. This loss of NO•-responsiveness (termed 'NO•-resistance') is particularly debilitating in type 2 diabetes (T2D), where cardiovascular emergencies occur more frequently, 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:**

1. Cao N, Wong YG, Rosli S, Kiriazis H, Huynh K, Qin C, Du XJ, Kemp-Harper BK, Ritchie RH. (2015). Chronic administration of the nitroxyl donor 1-nitrosocyclohexyl acetate limits left ventricular diastolic dysfunction in a mouse model of diabetes in vivo. Circ Heart Fail 8:572-581.
2. Chin KC, Michel L, Qin CX, Cao N, Woodman OL*, Ritchie RH*. (2016). The HNO donor Angeli's salt offers potential haemodynamic advantages over NO• or dobutamine in ischaemia-reperfusion injury in the rat heart ex vivo. Pharmacol Res 104: 165-175
3. Kemp-Harper BK, Horowitz JD, Ritchie RH. (2016). Therapeutic potential of nitroxyl (HNO) donors in the management of acute decompensated heart failure (ADHF). Drugs 76(14): 1321-1412.

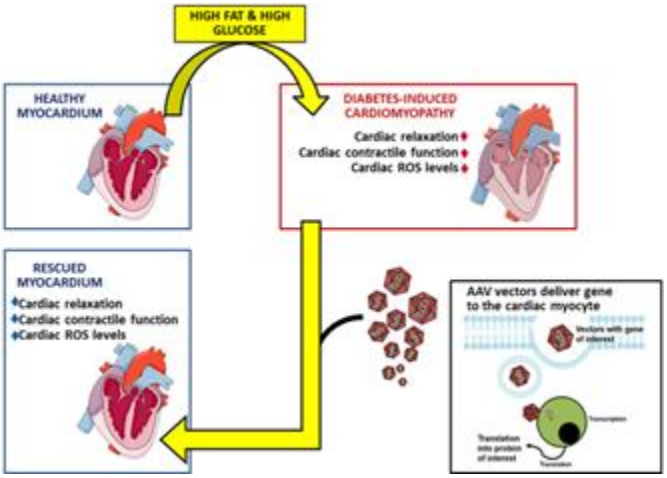
*This project can be tailored to Honours or Masters*.

## 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-occuring 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:**


1. Tate M, Grieve DJ, Ritchie RH. Are targeted therapies for diabetic cardiomyopathy on the horizon? (2017) Clinical Science 131: 897–915
2. Prakoso D*, De Blasio MJ*, Qin CX, Rosli S, Kiriazis H, Qian HW, Du XJ, Weeks KL, Gregorevic P, McMullen JR#, Ritchie RH#. (2017). Phosphoinositide 3-kinase (p110α) gene delivery limits diabetes-induced cardiac NADPH oxidase and cardiomyopathy in a mouse model with established diastolic dysfunction. Clinical Science 131: 1345-1360.


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


**Supervisor:** **Prof Owen Woodman**
**Email:** **owen.woodman@baker.edu.au**
**Telephone:** **8532 1392**
**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**


1. Leo CH, Hart JL, Woodman OL. (2011) 3',4'-dihydroxyflavonol restores endothelium-dependent relaxation in small mesenteric artery from rats with type 1 and type 2 diabetes. European Journal of Pharmacology, 659, 193-198.
2. Leo CH, Hart JL, Woodman OL. (2011) 3',4'-Dihydroxyflavonol reduces superoxide and improves nitric oxide function in diabetic rat mesenteric arteries. PLoS ONE, 6, e20813.
3. Lim NR, Thomas CJ, Silva LS, Yeap YY, Bell JR, Delbridge LMD, Bogoyevitch MA, Woodman OL, Williams SJ, May CN, Ng DCH. (2013) Cardioprotective 3',4'-dihydroxyflavonol attenuation of JNK and p38MAPK signalling involves CaMKII inhibition. Biochemical Journal, 456, 149-161.


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


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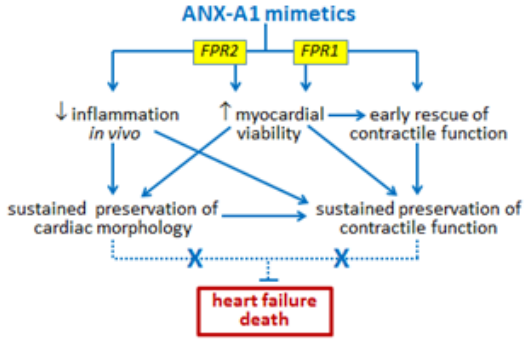
**Facsimile:** **8532 1100**
**Location:** **Baker IDI Heart & Diabetes Institute 75 Commercial Rd, Melbourne**
**Co-Supervisor: Prof Rebecca Ritchie**


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. T

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:**

1. Qin C, Buxton KD, Pepe S, Cao AH, Venardos KM, Love JE, Kaye DM, Yang YH, Morand EF, Ritchie RH. (2013). Reperfusion-induced myocardial dysfunction is prevented by endogenous annexin-A1 and its N-terminal derived peptide Ac-ANX-A12-26. Br J Pharmacol 168: 238–252
2. Qin CX, Yang YH*, May LM*, Gao XM, Stewart A, Tu Y Woodman OL, Ritchie RH. (2015). Cardioprotective potential of annexin-A1 mimetics in myocardial infarction. Pharmacol Ther 148:47-65.
3. Qin CX*, May LT*, Li R, Cao N, Rosli S, Deo M, Alexander AE, Horlock D, Bourke JE, Yang YH, Stewart AG, Kaye DM, Du XJ, Sexton PM, Christopoulos A, Gao XM#, Ritchie RH#. (2017). Small-molecule-biased formyl peptide receptor agonist compound17b protects against myocardial ischaemia-reperfusion injury in mice. Nature Communications 8, 14232, pages 1-13, doi: 10.1038/ncomms14232.

*This project can be tailored to Honours or Masters.*

*All projects offered by Heart Failure Pharmacology in 2018 can be tailored to Honours or Masters. We envision offering a total of 2 places in 2018.*

# Anti-Infectives Laboratory

**Supervisor:** A/Prof Tony Velkov
**Email:** tony.velkov@monash.edu
**Location:** Department of Pharmacology & Therapeutics

## 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.

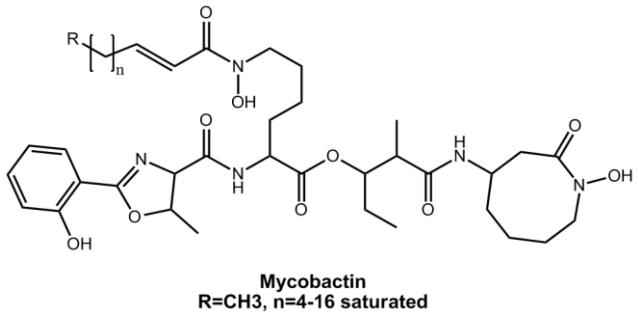



**Figure 1**. Chemical structure of the essential virulence factor Mycobactin from *M. tuberculosis*

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

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

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

***The principle aim(s) of this project include:***

1. Clone, and purify recombinant forms of each enzyme in the mycobactin biosynthetic pathway.
2. Obtain high resolution crystallographic structures of each enzyme using synchrotron radiation.
3. *In silico* screening, together with conventional high-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.

*Available as Honours or Masters Project.*

## DESIGN AND DEVELOPMENT OF ANTIBIOTICS AGAINST MULTIDRUG RESISTANT BACTERIA

**Supervisor:** A/Prof Tony Velkov
**Email:** tony.velkov@monash.edu
**Location:** Department of Pharmacology & Therapeutics

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.

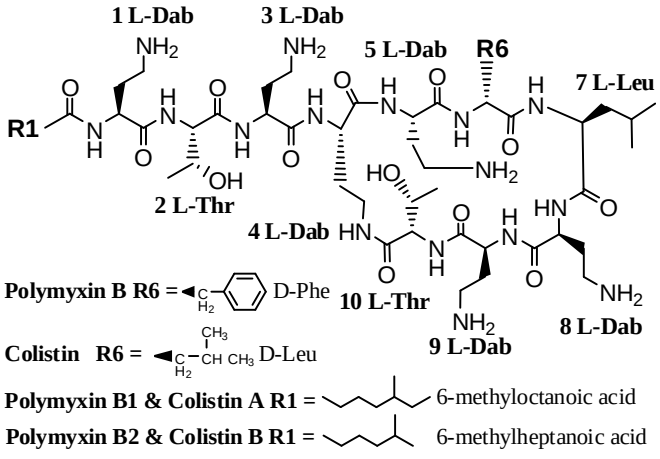



**Fig. 1:** Structures of polymyxins. Thr: threonine; Leu: leucine; Phe: phenylalanine; Dab: α,γ-diaminobutyric acid.

***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

**Supervisor:** A/Prof Tony Velkov
**Email:** tony.velkov@monash.edu
**Location:** Department of Pharmacology & Therapeutics

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 2018 can be tailored to Honours or Masters. We envision offering a total of 4 places in 2018.*

# 2018 COURSE OUTLINE

| | |
|---|---|
| **BSc & BBioMedSci HONOURS** | |
| **PHRM40002 ADVANCED TOPICS IN PHARMACOLOGY (SEMESTER 1) 12.5 PTS** | |
| Manuscript Evaluation Examination | 30% * |
| Theory Project | 70% * |
| **BIOM40001 INTRODUCTION TO BIOMEDICAL RESEARCH (SEMESTER 1) 12.5 PTS** | |
| 2 Assignments | 50% each |
| **PHRM40001 + 40006 RESEARCH PROJECT 75 PTS** | |
| Oral Research Presentation I & II | 15% * |
| Literature Review | 10% * |
| Research Thesis | 75% * |
| Note: After each assessment, you will be given a grade on the LMS.<br>H1 80% +<br>H2A 75-79%<br>H2B 70-74%<br>H3 65-60%<br>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.<br><br>MBiomedSci Handbook is available on the following website:<br>https://handbook.unimelb.edu.au/courses/mc-bmedsc | |


* Subject to change in 2018

The Department of Pharmacology and Therapeutics will be having their **3rd Year Student Dinner on 17th August 2017** where you can meet with your lecturers and potential supervisors.

There will also be an Honours Information Session on Thursday 5th October 2017 from 4 – 6pm in the Department Practical Class (Room E805, Level 8, Medical Building)

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

# HOW TO APPLY - MDHS HONOURS

**Timely applications for 2018 start-year entry into MDHS Honours occur from Friday 25 August to Friday 11 November 2016.**
**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 Friday 25 August - Friday 11 November 2017**

**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** 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** 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 (HATS).***

Once you have submitted an online course application, you will receive an email with login details to access the Honours project pref\erence 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 ten project preferences. You must only preference projects after making contact with the relevant supervisor(s).

The Honours project preference system - SONIA will open from mid-September and close on Friday 24 November 2017. You are allowed to change your preferences by the closing date.

**STEP 4: Offers**

Round 1 offer for entry into 2018 will be sent to you by Friday 22 December 2017. 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.

**Department of Pharmacology and Therapeutics**
Level 8, Medical Building 181
Corner of Grattan Street and
Royal Parade, Parkville

**UNIVERSITY OF MELBOURNE**
VIC 3010


*"Research is to see what others have seen but to think what no one has thought. – Szent-Gyorgi"*


*For more information about the department visit us at:*
http://biomedicalsciences.unimelb.edu.au/departments/pharmacology