Department of Pharmacology
Honours Projects
2024

Our 2023 Honours Students!

MONASH University

www.monash.edu

Welcome to the Pharmacology Department!

The Honours year represents a new adventure, very different to your undergraduate experience, in which you will have the opportunity to undertake a research project, communicate your science to colleagues and peers and learn to critically evaluate scientific concepts and literature.

Your supervisor(s) will be there to guide and advise you along this research journey.
At the very least, you are expected to bring with you the following skills set, in no particular order:

- enthusiasm
- an enquiring mind
- respect & humility
- determination & persistence
- a sense of humour
- a collegial spirit
- patience

This booklet provides information about the research projects on offer in the Department of Pharmacology and we encourage you to identify the areas of research in which you are most interested, contact potential supervisors and discuss the projects with them.

As course convenors, A/Prof Jane Bourke and I can advise on projects, guide you through the application process and help with any queries you may have.

We look forward to welcoming you to the Department of Pharmacology in 2024 and wish you all the best for a rewarding and exciting year of research.

Good luck!

Professor Robert Widdop
Head, Department of Pharmacology

Department of Pharmacology Honours Convenors

A/Prof Jane Bourke
Jane.bourke@monash.edu
Ph: 9905 5197

Prof Rob Widdop
Robert.widdop@monash.edu
Ph: 9905 4858

Pharmacology Honours: Pre-requisites

	Bachelor of Biomedical Science (Hons)	**Bachelor of Science (Hons)**
Pre-requisites	A Distinction average (>70) in 24 points at 3rd year in relevant disciplines within the School of Biomedical Sciences*	A Distinction average (>70) in 24 points at 3rd year level, including 12 points in 3rd year core BMS units (BMS3021, BMS3042) and 12 points in other 3rd year units*
Application closing date	**17 November 2024**	**17 November 2024**
Links to info and application	https://www.monash.edu/discovery-institute/study/honours/so-how-do-i-apply	https://www.monash.edu/discovery-institute/study/honours/so-how-do-i-apply
Commencement date	**19 February 2024**	**19 February 2024**

* There is no pre-requisite in terms of 3rd year PHA units, but the Pharmacology Honours Convenors will need to be satisfied that you have the necessary background in pharmacology to undertake your chosen research project.

Pharmacology Honours Course

The Pharmacology BSc Biomedicine Honours Course comprises 2 units:

- BMH4100 (36 points) – Research Unit
- BMH4200 (12 points) – Coursework Unit

BMH4100
This major focus of this unit is the research project you will conduct under the guidance of your supervisor. The assessment tasks include:

- Literature Review
- Research Seminars (introductory & final)
- Thesis & its defence

BMH4200
This unit provides you with the necessary skills to critically review and evaluate the scientific literature and effectively communicate concepts related to the discipline of pharmacology and your research area both in writing and orally. The assessment tasks include:

- Journal club presentation & participation
- Assessment of data exam
- Written critique of scientific paper exam
- Lay poster presentation

Bachelor of Biomedical Science (BMS) Honours students undertake

- BMS4100 (identical to BMH4100)
- BMS4200 (similar to BMH4200 but administered through the School of Biomedical Sciences)

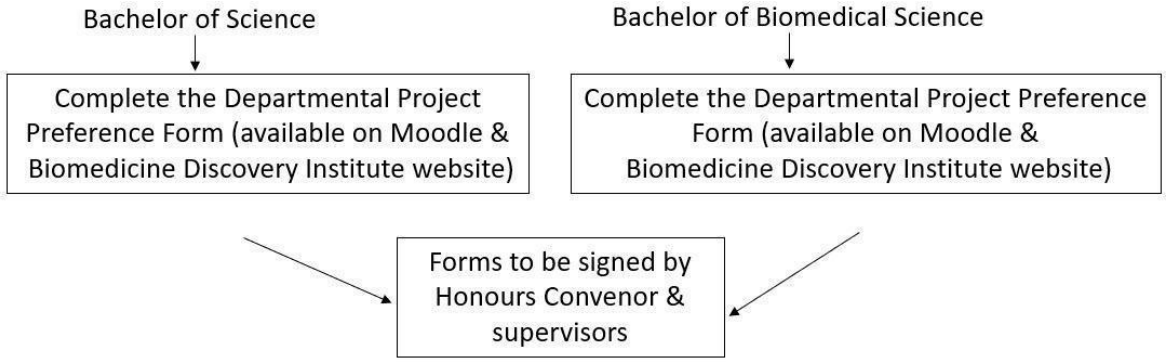
Choosing an Honours Project

The research projects on offer in the Department of Pharmacology and off-campus, with our collaborators, are outlined in the following pages. Once you have identified a few projects that you find interesting, then contact the potential supervisors by email or phone and arrange to meet with them to find out more about the projects on offer. It's a great idea to visit the research labs and meet other members of the research group in order to get a 'feel' for the people you would be working with and type of research you would be undertaking.

Please note that the availability of a supervisor to sign you on for a project will depend on that project still being available and the limit as to how many students a supervisor can take on. At least one of your supervisors must be a member of staff or an adjunct member of staff of the Department of Pharmacology.

How do I apply?

Once you, together with your potential supervisor, have identified a project that would be suitable for your Honours research program, then you will need to complete the following steps:



These forms must be signed by the Honours Convenors of the Pharmacology Department, A/Prof Jane Bourke or Professor Rob Widdop.

Information about how to apply on-line:

- Science or Biomedical Science: Complete on-line project application form via E-admissions by **Friday 17th November**
- Llinks available from https://www.monash.edu/discovery-institute/study/honours/so-how-do-i-apply
- Submit Departmental Project Preference form to Pharmacology Honours Convenor.

All applications will be reviewed and students who meet the eligibility criteria will be informed of their success in obtaining an Honours place by letter, which will be sent out in mid to late December 2023. Students must then notify the Faculty and supervisor of their intention to accept or reject the place. Students will be able to enrol into the Honours course via WES in January 2024.

Honours Projects 2024 – On campus projects

LABS / SUPERVISOR(S)	PROJECT TITLE
Fibrosis Group Chrishan Samuel	• Investigating novel anti-fibrotic therapies
Integrative Cardiovascular Pharmacology Group Adriana Knezic Tracey Gaspari &Robert Widdop Robert Widdop & Yan Wang	• Targeting the AT_2R as a potential treatment for stroke • A novel target in treatment of cardiovascular disease • Potential anti-inflammatory and anti-fibrotic effects of novel AT_2 receptor agonists
Macro Therapeutics Lab Mark Del Borgo	• Bioengineered nanomaterials to deliver drugs
Cardiovascular & Pulmonary Pharmacology Group Brad Broughton & Barbara Kemp-Harper	• Novel therapeutic strategies to treat cardiovascular pathologies including stroke and pulmonary hypertension
Respiratory Pharmacology Group Jane Bourke & Amy Winship Jane Bourke & Belinda Thomas Paris Papagianis & Claudia Nold	• Lung health iIn a changing World – effects of bushfire smoke • Blocking harmful lung damage during acute viral exacerbations of COPD • Breast milk stem cells to prevent gastrointestinal disease in preterm babies
Cancer Drug Discovery and Cellular Aging Group Iman Azimi	• Towards repurposing fda-approved drugs for paediatric medulloblastoma brain cancer • Identification of novel approaches to control cellular ageing
Biomedicine Discovery Institute Jian Li & Tony Velkov	• Pulmonary toxicity of novel polymyxin combination therapies • Systems Pharmacology of novel teixobactin-lipopeptide hybrids

Honours Projects 2024 – Off campus projects

LABS / SUPERVISOR(S)	PROJECT TITLE
Baker Heart & Diabetes Institute Judy de Haan & Arpeeta Sharma Bing Wang & David Kaye David Kaye, Bing Wang & Barbara Kemp-Harper David Kaye & Bing Wang	• Targeting the NLRP3-inflammasome axis in diabetic mice post an acute myocardial infarction • Investigating late-term cardiovascular effects of multiple pregnancies and identifying novel therapeutic targets • How do SGLT-2 inhibitors and GLP-1 agonists work in the setting of heart failure with preserved ejection fraction? • Novel, targeted therapy for heart failure with preserved ejection fraction
Drug Discovery Biology Theme **Monash Institute of Pharmaceutical Sciences** Elva Zhao & Denise Wootten	• Regulation of the glucagon receptor family by RGS proteins

Not all projects listed may be available in 2024, but please contact supervisors if you are interested.

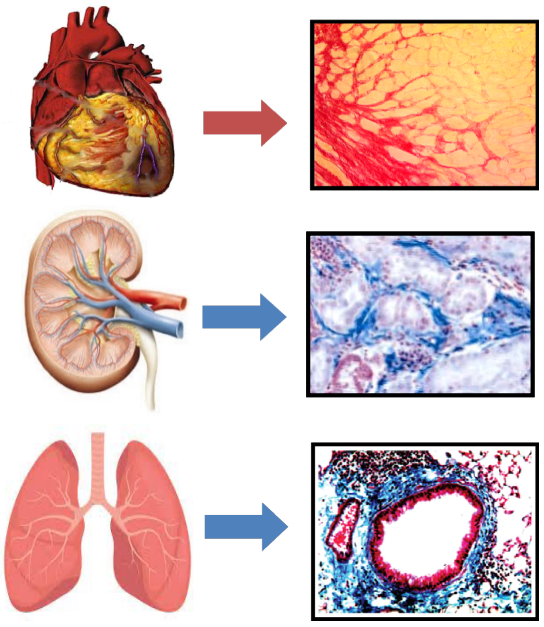
INVESTIGATING NOVEL ANTI-FIBROTIC THERAPIES

Supervisors: Prof Chrishan Samuel
Location: Fibrosis Laboratory
Department of Pharmacology
Monash University, Clayton

Background:
Fibrosis is defined as the hardening and/or scarring of various organs including the heart, kidney and lung; which usually arises from a failed wound healing response to tissue injury and is characterized by an excessive deposition of extracellular matrix components. The eventual replacement of normal tissue with scar tissue leads to organ stiffness and failure. Despite a number of available treatments for patients with various heart and kidney diseases, patients receiving these therapies still progress to end-stage organ failure due to the inability of these treatments to directly target the build-up of fibrosis. Hence, novel and more direct anti-fibrotic therapies are still required.

Project aim:
The Fibrosis Lab aims to identify novel anti-fibrotic (peptide-, stem cell-, cell repair- and combination-based) therapies that will more effectively reduce/reverse fibrosis progression. Additionally, by understanding the mechanisms of action of these potential therapies of future, we aim to delineate new targets that can be utilized to abrogate organ fibrosis and related dysfunction.

Techniques:
Depending on the project involved, animal or cell culture models of heart/kidney/lung disease, as well as blood pressure and functional measurements, protein biochemistry, histological techniques and/or molecular biology may be utilized to evaluate the therapeutic potential of novel anti-fibrotic therapies.



Contact:

Prof Chrishan Samuel
Department of Pharmacology
Monash University
Phone: 9902 0152, Rm E102
chrishan.samuel@ monash.edu

TARGETING THE AT_2R AS A POTENTIAL TREATMENT FOR STROKE

Supervisors: Dr Adriana Knezic & Prof Robert Widdop
Location: Integrative Cardiovascular Pharmacology Lab

Department of Pharmacology
Monash University, Clayton

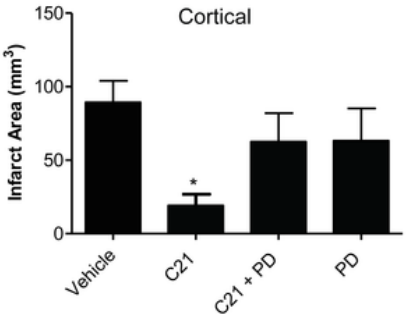
Background:
Stroke is the 2nd leading cause of death word wide, with the only available pharmacological therapy being limited to 10% of patients. Therefore, there is an unmet need to develop new treatments for stroke. Additionally, there is growing interest in assessing the effects of stroke on other organs in the body rather than just focusing on the brain. There is clinical evidence of stroke patients experiencing cardiac problems as a result of their stroke, which has also been observed in animal models of stroke. The Angiotensin Type 2 Receptor (AT_2R) forms part of the protective arm of the renin-angiotensin system (RAS). Its actions oppose those of the AT_1R, including anti-inflammatory, anti-oxidative, anti-fibrotic, and regenerative pathways, all of which would be beneficial in the context of stroke and to also treat any associated cardiac damage. Previous research has demonstrated cardioprotective effects of stimulating the AT_2R in various cardiovascular diseases, as well as a neuroprotective effect of targeting the AT_2R with agonist C21 in the context of stroke. However, our lab has synthesized novel AT_2R agonists which we believe may be more efficacious than C21.

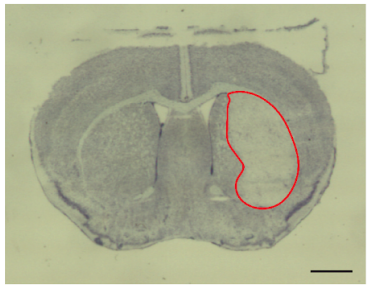
Project aim:
Given the evidence that the AT_2R is neuroprotective and cardioprotective, the current project aims to assess the therapeutic potential of a novel AT_2R agonist to treat the neurological and cardiovascular consequences of stroke. This study will therefore provide valuable information about the AT_2R as a potential therapeutic target for stroke, and will also generate more knowledge of the cardiac changes which occur in rodent stroke models and how they align with what has been observed clinically.

Techniques:
This project will use in vivo techniques to assess the neuroprotective effects of the novel AT_2R agonist in a rodent model of stroke. This will include behavioural techniques to assess stroke symptoms and disability. This project will also include histological techniques, to assess the volume of damage in the brain, and to assess specific cellular responses in the brain and heart post-stroke.

Contacts:

Dr Adriana Knezic
Professor Robert Widdop
Department of Pharmacology
Monash University
Phone: 9905 0095, Rm E119
Adriana.knezic@monash.edu
Robert.widdop@monash.edu





A NOVEL TARGET IN TREATMENT OF CARDIOVASCULAR DISEASE

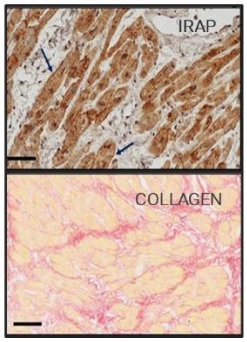
Supervisors: A/Prof Tracey Gaspari & Prof Robert Widdop
Location: IRAP & Integrative Cardiovascular Pharmacology Groups
Department of Pharmacology
Monash University, Clayton

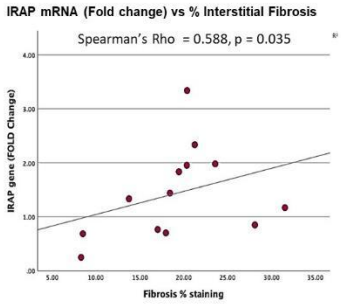
Background:
Cardiovascular diseases (CVDs) remain the world's leading cause of morbidity and mortality, claiming 17 million deaths annually. Risk factors such as ageing, ischemia (such as myocardial infarct) or hypertension, lead to vascular dysfunction, increased fibrosis, chronic heart failure and/or end organ damage. There are few effective treatments currently available highlighting the urgent need to identify new targets and treatment options. We have identified a novel component of the renin angiotensin system, the enzyme, insulin regulated aminopeptidase (IRAP), as one such target and shown that inhibiting this enzyme prevents and reverses fibrosis in a number of disease settings, without altering blood pressure.

Research questions:
1. Evaluate efficacy of novel IRAP inhibitors alone, and in combination with current standards of care to reduce, and importantly reverse organ fibrosis, leading to improved functional outcomes in models of established CVD.
2. Understand the cellular and molecular pathways that contribute to IRAP inhibitor-mediated protective effects.
3. Determine if IRAP expression/activity are biomarkers in chronic disease states

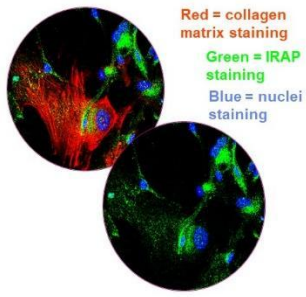
Techniques:
Depending on the project being undertaken a range of methodologies may be used, including: use of preclinical animal models of disease (heart, kidney, lung, blood vessel diseases) or cell culture models of disease, functional measurements in conscious and anaesthetized animals (blood pressure, ultrasound, kidney function), tissue and cell histology, immunohistochemistry and protein assays, biochemical measures and/or enzyme activity assays may be used to determine the therapeutic potential and mechanisms involved in targeting IRAP.

- ***IRAP expression (brown) is increased in fibrotic tissue (red) from patients with heart disease (Aortic Stenosis)***





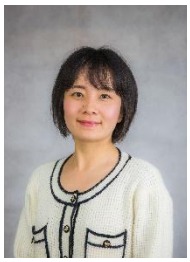
- ***IRAP moves to cell surface under stress, making it druggable in disease***



Contact:
A/Prof Tracey Gaspari, *tracey.gaspari@monash.edu*
Prof Rob Widdop, *robert.widdop@monash.edu*

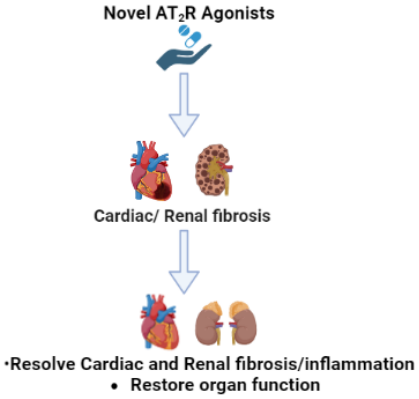
POTENTIAL ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS OF NOVEL AT_2 RECEPTOR AGONISTS

Supervisors: Prof Robert Widdop and Dr Yan Wang
Location: Integrative Cardiovascular Pharmacology Group
Department of Pharmacology
Monash University, Clayton



Background:
The main effector hormone of the renin angiotensin system (RAS) is angiotensin II which can stimulate both angiotensin AT_1 receptors (AT_1R) and AT_2 receptors (AT_2R). There is currently intense interest focusing on the AT_2R cardiovascular function, although there are few selective AT_2R ligands available to delineate such effects. We have synthesised a range of novel angiotensin peptide analogues that exhibit high AT_2R selectivity, based on *in vitro* radioligand binding using overexpressed cells. Many of these selective AT_2R agonists have shown protective effects (e.g. anti-fibrotic and anti-inflammatory) *in vitro* and in animals with the heart and kidney diseases (e.g. high salt diet-induced organ fibrosis), and we are interested in testing such compounds in more severe models of cardiac and renal failure.

Project aim:
The current project will determine the anti-inflammatory and anti-fibrotic effects of novel AT2R ligands in mouse models of cardiac and/or renal failure, and bench mark against the standard AT2R agonist C21 (in Phase II Clinical Trial for IPF).



Techniques:
This project will involve *in vivo* and *in vitro* techniques which may include:

- Animal husbandry
- Heart imaging techniques
- Histological and biochemical tissue analyses
- Cell culture

These studies will provide important mechanistic data to help explain how a number of lead AT_2R compounds protect against organ fibrosis in cardiovascular disease settings.

Contact:
Prof Robert Widdop
robert.widdop@monash.edu
Dr Yan Wang
yan.y.wang@monash.edu
Robert.widdop@monash.edu

BIOENGINEERED NANOMATERIALS TO DELIVER DRUGS

Supervisors: Dr Mark Del Borgo
Location: Macro Therapeutics Group
Department of Pharmacology
Monash University, Clayton

Background:
Many biomolecules like growth factors and gene products are typically high affinity, highly selective compounds primarily responsible for the efficacy of stem cells. However, these molecules have poor absorption, are biologically unstable and are rapidly cleared from the body. Therefore, an alternate delivery strategy for these molecules could give rise to new therapeutic paradigms for a host of diseases.

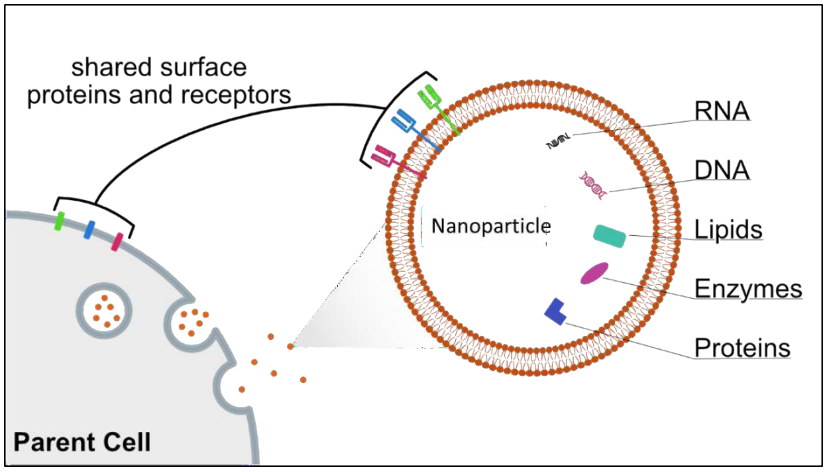
We have a unique platform technology where we can tailor biomaterials to resemble the packaging that cells utilize to deliver these products (exosomes). We can then further modify these particles to enable tailored delivery to specific sites.

The Honours project for 2023 will focus on the development of nanoparticles that are able to infiltrate the blood brain barrier. We will neuronal cell markers as a means to enable penetration into the brain and deliver chemotherapeutics for the treatment of glioblastoma. We hope to visualize entry of our particles in cancer cells and, with any luck, the selective killing of glioblastoma cells.

Project aim:
The aim of this Honours project is to develop nanoparticles that mimic exosomes which allow entry through the BBB and into glioblastoma cells.

Techniques:
You will become familiar with techniques such as dynamic light scattering, atomic force microscopy, cell culture, fluorescence microscopy and FACS.

Contacts:
Dr Mark Del Borgo
Department of Pharmacology
Monash University
Phone: 9902 9537, Rm E116c
mark.delborgo@monash.edu



NOVEL THERAPEUTIC STRATEGIES TO TREAT CARDIOVASCULAR PATHOLOGIES INCLUDING STROKE AND PULMONARY HYPERTENSION

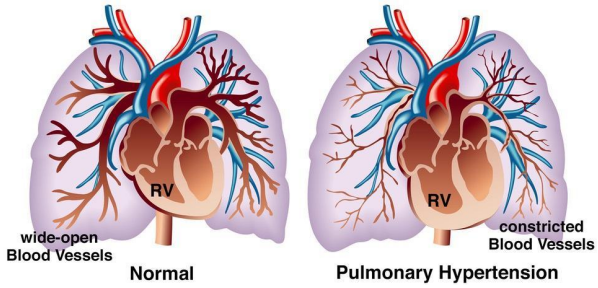
Supervisors: Dr Brad Broughton & Associate Professor Barb Kemp-Harper
Location: Cardiovascular & Pulmonary Pharmacology Group
Department of Pharmacology
Monash University, Clayton


Background:
Cardiovascular diseases, encompassing stroke, systemic and pulmonary hypertension, remain the leading cause of death globally, accounting for 17.9 million deaths each year.
Stroke is Australia's leading cause of disability and a high proportion of patients will unfortunately suffer a recurrent stroke. It involves numerous complex, yet poorly understood mechanisms that lead to brain cell death and has very few treatment options.
Pulmonary hypertension is an incurable disease and a major cause of death and illness throughout the world. Whilst there has been advancement in the treatment of pulmonary hypertension, current treatment is not optimal, with 5 year survival of ~50%. New therapeutic strategies are urgently needed.

Research aim:
Our research aims to identify novel pharmacological, dietary and/or cell-based therapies that can limit the pathophysiology of diseases such as stroke and pulmonary hypertension.

Potential Projects:
- Impact of high fibre diet on long-term outcomes following ischaemic stroke
- Impact of high fibre diet on long-term outcomes in pulmonary hypertension
- Novel antifibrotic therapies in the treatment of pulmonary hypertension

Techniques:
Techniques used in our research programs include pre-clinical mouse models of stroke (photothrombotic stroke) and pulmonary hypertension (chronic hypoxia) and involve the measurement of blood pressure, functional tests, cell culture and ex vivo assays to assess vascular function (myography), detect inflammation (RT-PCR, immunofluorescence) and remodeling (histochemical staining).



Contacts:
Dr Brad Broughton
Department of Pharmacology
Monash University
Phone: 9905 0915, Rm E140
bradley.broughton@monash.edu

A/Prof Barbara Kemp-Harper
Department of Pharmacology
Monash University
Phone: 9905 4674
Barbara.Kemp@monash.edu

LUNG HEALTH IN A CHANGING WORLD – EFFECTS OF BUSHFIRE SMOKE

Supervisors: A/Prof Jane Bourke and
Dr Amy Winship
Location: Respiratory Pharmacology, Monash
Anatomy and Developmental Biology, Monash


Background: Climate change is real, resulting in hotter days, more frequent heatwaves and longer and more intense fire seasons. Between July 2019 and March 2020, Australia experienced an unprecedented number of bushfires known as the Black Summer Bushfires. It has been estimated that the bushfire smoke was responsible for 417 excess deaths and more than 1,300 presentations to the Emergency Department for asthma during the 19 weeks of continuous fires. Recent bushfires around the world reflect the Australian experience, with deleterious effects on lung health of both healthy individuals and those with underlying diseases, including asthma.

Bushfires produce large amounts of smoke, which contains high concentrations of fine particulate matter (PM). $PM_{2.5}$ are particles which are <2.5 micrometers in size, small enough to be inhaled into the lungs and potentially to enter the circulation. PAHs (polycyclic aromatic hydrocarbons) are also present in smoke from burning wood posing an additional risk, particularly when people are exposed to very high levels of bushfire smoke over a short period of time. This project will investigate the effects of bushfires smoke – both particulate matter and PAHs on inflammatory and contractile responses in the lung.

Research question:
What direct effects does bushfire smoke have on airway inflammation and contraction?

Project description: Our research group has unique expertise in the use of precision cut lung slices (PCLS) to study lung disease. PCLS contain all the structural cells present in the lung, including intact airways, providing insights into both inflammatory and contractile responses that are not possible in cell culture studies. In this project, we will be treating PCLS with a range of stimuli derived from bushfire smoke (PM of different sizes, PAHs) to see if there is loss of tissue viability, increased release of pro-inflammatory cytokines and changes in airway response (increased contraction, reduced relaxation) consistent with lung damage. This study will inform the need for improved air monitoring during bushfires, and warnings to avoid exposure for the community, especially those with underlying lung disease.

Techniques: This project will combine preparation of bushfire smoke samples; tissue culture and treatment of PCLS; assessment of viability using MTT and LDH assays; airway contraction and relaxation using phase-contrast microscopy; and inflammatory responses using RT-PCR and ELISAs.

Contacts and Research Information:

A/Prof Jane Bourke, *jane.bourke@monash.edu*
Dr Amy Winship, *amy.winship@monash.edu*
https://www.monash.edu/discovery-institute/bourke-lab/research

BLOCKING HARMFUL LUNG DAMAGE DURING ACUTE VIRAL EXACERBATIONS OF COPD

Supervisors: A/Prof Jane Bourke
Dr Belinda Thomas
Locations: Respiratory Pharmacology, Monash and Centre for Immunity and Infectious Diseases, Hudson Medical Research Institute

Background: Chronic obstructive pulmonary disease (COPD) is the third-most common cause of death worldwide. Patient morbidity and mortality are closely associated with acute exacerbations, commonly triggered by viruses, such as influenza. Treatment of these exacerbations with oral glucocorticoids reduces inflammation but also suppresses the immune response required to combat viral infection.

This Honours project will progress our characterization of the therapeutic potential of the anti-fibrotic drug pirfenidone (PFD) to avert damaging inflammation without suppressing the immune response to infection. We have already demonstrated that treatment with PFD has benefits over steroids in mice overexpressing the profibrotic cytokine TGF-beta and infected with influenza *in vivo*.

Research question:

Is pirfenidone superior to glucocorticoids in treating viral exacerbations of COPD?

Project description: We are now establishing a novel model of COPD, using precision cut lung slices (PCLS). PCLS contain all the structural cells present in the lung, providing additional insights not possible in cell culture studies which usually only look at one cell type. In this project, we will be treating PCLS *ex vivo* with a range of stimuli to mimic different aspects of COPD (TGFb-overexpression for fibrosis; acute exposure to cigarette smoke for inflammation; elastase treatment to disrupt alveoli as seen in emphysema), and infecting PCLS with influenza.

We will be testing the effects of drug treatments on a range of diseases-relevant outcomes (fibrosis; inflammation; structural changes and immune responses) to support clinical translation of PFD for viral exacerbations of COPD.

Techniques: This project will combine preparation, tissue culture and treatment of PCLS with assessment of: infection using plaque assays; structural changes using morphometric analysis; immune and inflammatory responses using RT-PCR and ELISAs.

Contacts and Research Information:

A/Prof Jane Bourke, *jane.bourke@monash.edu*
Dr Belinda Thomas, *belinda.thomas@monash.edu*
https://www.monash.edu/discovery-institute/bourke-lab

BREAST MILK STEM CELLS TO PREVENT GASTROINTESTINAL DISEASE IN PRETERM BABIES

Supervisors: Dr Paris Papagianis,
Prof Claudia Nold (Hudson Institute)
Location: Respiratory Pharmacology Group
Department of Pharmacology
Monash University, Clayton

Background: Premature birth is the leading cause of mortality and morbidity in newborns worldwide. Complications in babies born too early or too small make up the greatest health burden in children under 5. Complications sometimes stretch into early life and adulthood and include lung diseases such as asthma, learning difficulties and brain injury. Necrotising Enterocolitis (NEC) is most common inflammatory intestinal complication in preterm infants (with an up to 30% mortality). Currently there is no direct and effective treatment for NEC.

Although there is great knowledge of the transfer of immunity from mother to child in breastfeeding, we are becoming increasingly aware of other specialised cell types in breast milk. Specifically, breast milk harbors stem cells with potential anti-inflammatory and reparative properties. Harnessing these stem cells from breast milk as a prophylactic or therapeutic treatment to reduce inflammation and injury in premature babies with NEC.

We will collect breast milk from mothers at various lactation stages to identify and characterize different types of stem cells in milk. These breast milk stem cells with anti-inflammatory and reparative properties will then be tested *ex vivo* in intestinal tissue from premature babies. This critical proof of concept study aims demonstrate the therapeutic potential of easily accessed breast milk cells as a novel cell therapy for NEC.

Project aims: 1) Identifying and characterising breast milk stem cells and **2)** establishing robust *ex vivo* assays of intestinal tissues from babies for testing of breast milk stem cell therapies.

Techniques: Flow cytometry will be used to identify and characterise stem cells from milk. The development of intestinal organoids will require tissue culture laboratories, PCR and histology. Please note that some of this work will be conducted at The Hudson Institute of Medical Research.

Contacts:

Dr Paris Papagianis
Respiratory Pharmacology Group, Department of Pharmacology
Monash University
Rm A105, 9 Ancora Imparo Way
paris.papagianis@monash.edu

Prof Claudia Nold
Head, Interventional Immunology in Early Life Diseases
The Ritchie Centre
Hudson Institute of Medical Research
claudia.nold@hudson.org.au

TOWARDS REPURPOSING FDA-APPROVED DRUGS FOR PAEDIATRIC MEDULLOBLASTOMA BRAIN CANCER

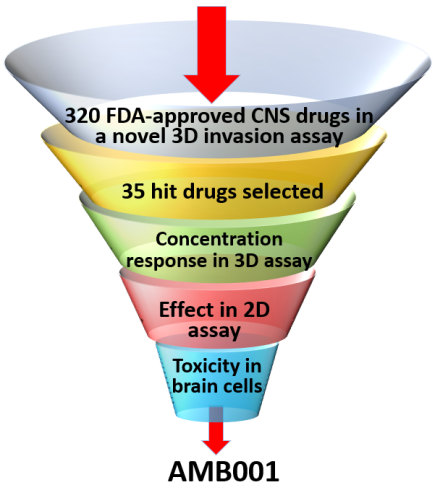
Supervisor: Dr Iman Azimi
Location: Cancer Drug Discovery and Cellular Aging Group
Department of Pharmacology
Monash University, Clayton

Background:

Medulloblastoma (MB) is the most common fatal childhood brain cancer. Current treatment options include surgery, followed by radiotherapy and chemotherapy. Surgery is highly unlikely to remove all tumour without damaging surrounding healthy brain tissue. Radiotherapy and chemotherapy are not completely effective and also harm healthy tissues. As the current treatments for these aggressive subgroups are harsh, surviving children frequently show severely impaired physical, cognitive, social and emotional function for the rest of their lives.

Clearly, new treatments are urgently needed to improve and save the lives of children with MB. One way to identify new treatment options is to identify new therapeutic uses for existing drugs that were originally developed for a different medical condition, a process that is called “drug repurposing”. This approach can significantly shorten the drug development timeline and reduce costs compared to the lengthy and expensive process of creating entirely new drugs.

In our recent studies, we developed a novel high-throughput 3D assay and used this assay to screen a unique library of 320 structurally diverse small molecule drugs currently clinically used for central nervous system diseases. Our screen (**Figure**) resulted in identification of drug AMB001 (coded due to confidentiality), which suppressed MB cell growth with the highest potency, and with minimal toxicity in normal brain cells. Further investigations are required to understand how AMB001 works to suppress MB cells.



Project aim:
In this project, we aim to determine the mechanism of action of AMB001, along with two other drugs that ranked lower but emerged from our screening process, in suppression of MB cancer cells grown in the lab. In addition, we aim to determine if AMB001 can ameliorate invasive behaviors of MB such as metastasis related processes and therapeutic resistance.

Techniques:
This project is expected to utilise in silico data analysis, cell culture techniques, cancer cell functional assays, pharmacological manipulations, high-content cell imaging, and RNA/protein analysis.

Contact:
Dr Iman Azimi
Department of Pharmacology
Monash University
Rm E116A
Iman.azimi@monash.edu

IDENTIFICATION OF NOVEL APPROACHES TO CONTROL CELLULAR AGEING

Supervisor: Dr Iman Azimi
Location: Cancer Drug Discovery and Cellular Aging Group
Department of Pharmacology
Monash University, Clayton

Background:

Cellular aging is a complex biological process involving a gradual decline in cellular function and increased vulnerability to disease. It is associated with a range of age-related disorders, including cancer, cardiovascular disease, and neurodegeneration. Cellular senescence, an integral component of ageing (as well as cancer), emerges as a result of diverse triggers, including telomere attrition, macromolecular damage and signalling from activated oncogenes. Cell senescence is a state in which cells enter a stable growth arrest, losing their ability to divide and proliferate. Targeting and controlling cellular senescence is a promising approach for promoting healthy aging and potentially mitigating age-related pathologies.

Project aim:

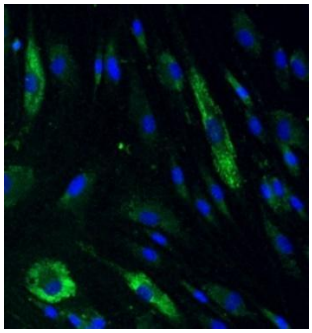
This project aims to test the effect of novel drugs on cellular senescence in an accelerated model of cellular senescence in human fibroblast cells. Different markers of cellular senescence will be assessed in this project such as expression of cell cycle arrest proteins, cell morphology, and senescence-associated secretory phenotype (SASP).

Techniques:

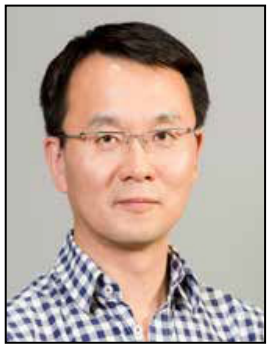
This project is expected to utilise cell culture techniques, cell-based assays, pharmacological manipulations, high-content cell imaging, and RNA/protein analysis.

Contact:

Dr Iman Azimi
Department of Pharmacology
Monash University
Rm E116A
Iman.azimi@monash.edu



PULMONARY TOXICITY OF NOVEL POLYMYXIN COMBINATION THERAPIES



Supervisors: Prof Jian Li and A/Prof Tony Velkov
Location: Laboratory of Antimicrobial Systems Pharmacology
Biomedicine Discovery Institute
Monash University, Clayton

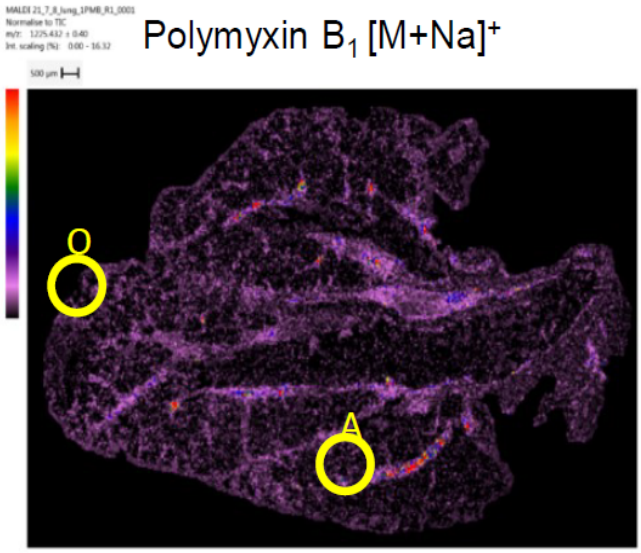
Background:
Current dosing recommendations of parenteral polymyxins are suboptimal for treatment of respiratory tract infections due to poor drug exposure at the infection site. Moreover, nephrotoxicity is the dose-limiting factor and can occur in up to 60% of patients. Pulmonary delivery of polymyxins as monotherapy and in combination with other antibiotics has offered a great promise for bacterial eradication in the respiratory tract. However, we have shown that polymyxins localise in mitochondria of human lung epithelial cells and activate multiple apoptotic pathways.

Project aim:
The aim of this honours project is to investigate the mechanisms of polymyxin-induced toxicity in human lung epithelial cells. The outcomes of this project will provide the much-needed pharmacological information for safer and more efficacious use of polymyxin inhalation therapy against life-threatening lung infections.

Techniques:
This multi-disciplinary project aims to investigate the effect of polymyxins and their synergistic combinations with other classes of antibiotics on lung epithelial cells, using fluorescence activated cell sorting (FACS), multi-omics and cutting-edge mass spectrometry imaging techniques.

Contacts:

Jian Li PhD, FAAM
Professor, NHMRC Principal Research Fellow
Head, Laboratory of Antimicrobial Systems Pharmacology
Monash Biomedicine Discovery Institute, 19 Innovation Walk, Monash University, VIC 3800, Australia
Phone: +61 3 9903 9702
Fax: +61 3 9905 6450
Email: Jian.Li@monash.edu
Web: research.monash.edu/en/persons/jian-



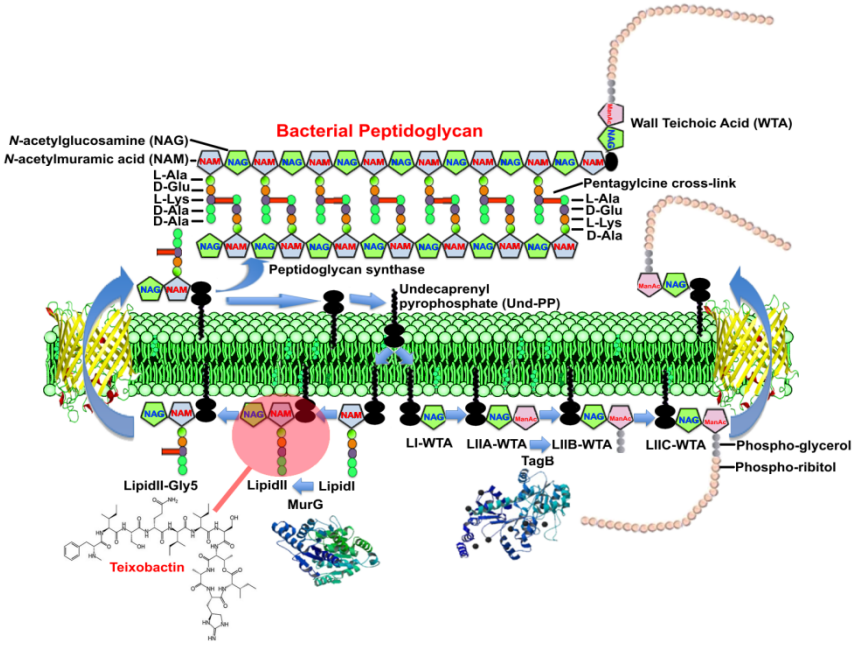
SYSTEMS PHARMACOLOGY OF NOVEL TEIXOBACTIN-LIPOPEPTIDE HYBRIDS

Supervisors: A/Prof Tony Velkov and Prof Jian Li
Location: Laboratory of Antimicrobial Systems Pharmacology
Biomedicine Discovery Institute
Monash University, Clayton

Background:
Our team's internationally leading research aims to develop novel therapeutics to target an urgent global medical challenge, multidrug-resistance (MDR) in Gram-negative 'superbugs'. The group has three major streams designed to provide both short-term and long-term solutions to this major global health problem: discovering and developing novel antibiotics and formulations against Gram-negative 'superbugs'; elucidating the mechanisms of activity, resistance and toxicity of antibiotics such as teixobactin; and investigating the preclinical and clinical pharmacology of antibiotics and their combinations. Numerous opportunities exist for both honors and higher degree by research student to work in these areas and applications are always welcome.

Project aim:
Teixobactins are a recently discovered novel antibiotic class that typically possess a narrow spectrum of activity against Gram-positive bacteria. The most notable property of teixobactin is that it is the first and only extremely 'resistance-resistant' antibiotic against which bacteria cannot readily evolve resistance. We have developed novel teixobactin-lipopeptide hybrids that are superior to native teixobactin as they retain this key anti-resistance property and in addition have a broader-spectrum, with potent activity against PDR Gram-negatives, as well as PDR Gram-positives.

Techniques:
This program will investigate the mechanisms of bacterial killing, lung disposition and potential lung toxicity of teixobactin-lipopeptide hybrids using systems pharmacology and cutting-edge imaging and approaches.



Contacts:

A/Prof. Tony Velkov
Principal Research Fellow
NHMRC CDF Level 2 Industry Fellow Systems Pharmacology, Monash Biomedicine Discovery Institute, 19 Innovation Walk, Monash University, VIC 3800, Australia
Phone: +61 3 9903 9702; Mobile: +61 (0) 447 314 602; Fax: +61 3 9905 6450
Email: Tony.Velkov@monash.edu

TARGETING THE NLRP3-INFLAMMASOME AXIS IN DIABETIC MICE POST AN ACUTE MYOCARDIAL INFARCTION.

Supervisors: Prof Judy de Haan, Dr Arpeeta Sharma
Location: Oxidative Stress Laboratory, Baker Heart and Diabetes Institute 75 Commercial Rd, Melbourne.

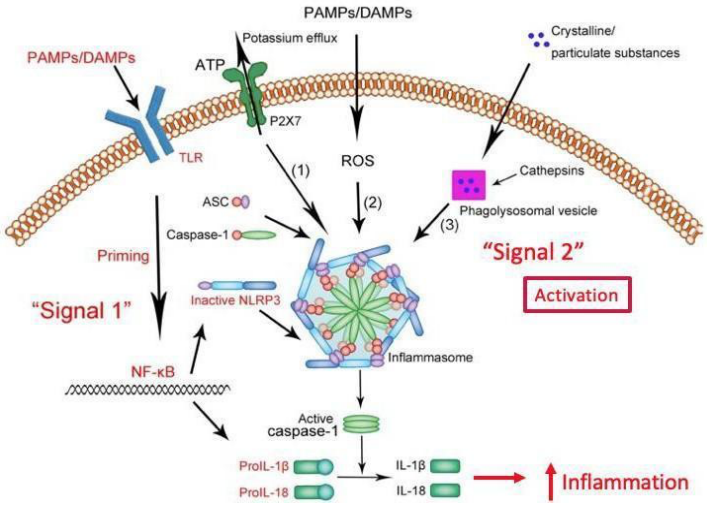
Background:

Patients living with Type2 diabetes are at increased risk of developing cardiovascular disease. In particular, diabetes doubles the risk of dying in the months after a heart attack due to a significantly weakened heart muscle. Currently, treatment options for patients that survive a heart attack are limited, with no treatment specifically targeted at the underlying cause of the worsened cardiac function that occurs after an acute myocardial infarction (AMI).

Inflammation has been shown to play an important role, and interest in developing small molecules to target inflammation has been buoyed with the recent success of the clinical trial called CANTOS. In this trial, use of the antibody canakinumab, specifically designed to lessen Il-1β, a cytokine matured on the NLRP3-inflammasome, showed lower rates of recurrent cardiovascular events independent of lipid lowering, in AMI patients.

Project aim: This project aims to investigate whether targeting the NLRP3 inflammasome pathway in a diabetic mouse model, will lessen inflammation to improve cardiac function after an AMI.

Techniques:
The student will receive training in in vivo mouse models of diabetes and AMI, cell culture, immunohistochemistry, histology, real time PCR and Western Blotting.



Contacts:

Prof Judy de Haan
Oxidative Stress Laboratory
Baker Heart and Diabetes Institute Phone: 85321520
Judy.dehaan@baker.edu.au

INVESTIGATING LATE-TERM CARDIOVASCULAR EFFECTS OF MULTIPLE PREGNANCIES AND IDENTIFYING NOVEL THERAPEUTIC TARGETS

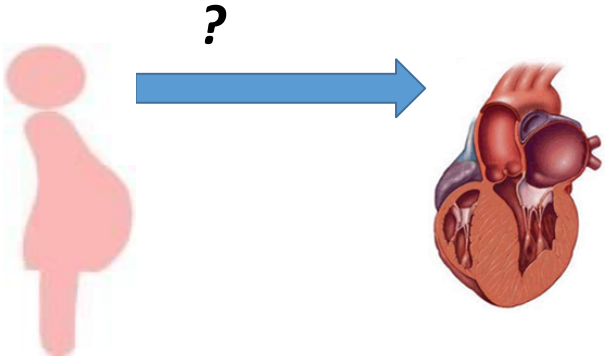
Supervisors: Dr Bing Wang, & Prof David Kaye
Location: Heart Failure Research Group,
Baker Heart and Diabetes Institute, Melbourne

Background:
Clinical studies from our group have shown women who have had more than two pregnancies are at higher risk of developing a sub-type of heart failure known as heart failure with preserved ejection fraction (HFpEF). HFpEF accounts for over 50% of patients with heart failure and current therapies and treatments are ineffective. HFpEF typically occurs in older women who present with other clinical disorders including high blood pressure (hypertension). Importantly, high blood pressure can be caused by detrimental lifestyle choices and behaviour such as lack of exercise and unhealthy eating habits, which are highly prevalent during pregnancy and may continue after child birth. The cellular mechanism(s) by which multiple pregnancies establishes an environment of increased risk for HFpEF is not known. This project will examine the relationship between pregnancy history in mice and cardiac remodelling during aging and hypertension.

Project aim:
The aim of this honours project is to investigate the mechanisms by which multiple pregnancies promotes heart failure. Further, we will investigate whether a drug we have developed (VCP979) can prevent or reverse the development of pregnancy-associated heart damage. This study will have significant implications for the treatment of HFpEF associated with cardiovascular risk factors by identifying a novel therapeutic treatment strategy for this patient population.

Techniques:
It is anticipated that this project will involve developing and monitoring an animal model of pregnancy-related cardiovascular disease, histological and biochemical analysis of fibrosis and inflammation, behavioural and functional assessments (echocardiography, metabolic cages, echoMRI), and assessing immune populations via flow cytometry.

Contacts:
A/Prof Bing Wang
Biomarker Discovery Laboratory
Baker Heart and Diabetes Institute
75 Commercial Road, Melbourne, 3004
Phone: 9903 0648, or 8532 1178
Bing.wang@monash.edu or
bing.wang@baker.edu.au



HOW DO SGLT-2 INHIBITORS and GLP-1 AGONISTS WORK IN THE SETTING OF HEART FAILURE WITH PRESERVED EJECTION FRACTION?

Supervisors: Prof David Kaye, A/Prof Bing Wang and A/Prof Barbara Kemp-Harper

Location: Heart Failure Research Group and Biomarker Discovery Laboratory, Baker Heart and Diabetes Institute; and Cardiovascular & Pulmonary Pharmacology Group Department of Pharmacology Monash University, Clayton

Background:
Heart failure is the commonest cardiovascular cause for hospital admission in people aged >65years. It has become increasingly evident that HF with preserved ejection fraction (HFpEF) is the commonest form of HF, accounting for more than 50% of all cases. The pathophysiology of HFpEF is complex, with major cardiovascular elements related to increased myocardial and arterial stiffness. These features are related to aging and concomitant hypertension. Some evidence suggests that drugs including GLP-1 agonists and SGLT-2 inhibitors may be useful therapies, but their mechanisms of action remain uncertain.

Project aim:
Our laboratory has established models in mice designed to recapitulate features of HFpEF. These studies are performed in aging hypertensive mice and in obese mice. In this study, we will also investigate the physiological, histological, cellular, and molecular properties to explore the mechanisms involved in the effects of SGLT-2 and/or GLP-1 agonists in both the heart and kidney.
.

Techniques:
It is anticipated that this project will involve developing and monitoring an animal model of hypertension- or diet-induced CVD, histological and biochemical analysis of fibrosis and inflammation, behavioral and functional assessments (echocardiography, metabolic cages, echoMRI), and vascular function assessment with myography as well as gene expression (RNA extractions and qPCR).

Contacts:
A/Prof Bing Wang
Biomarker Discovery Laboratory
Baker Heart and Diabetes Institute
75 Commercial Road, Melbourne, 3004
Phone: 9903 0648, or 8532 1178
Bing.wang@monash.edu or bing.wang@baker.edu.au

NOVEL TARGETED THERAPY FOR HEART FAILURE WITH A PRESERVED EJECTION FRACTION

Supervisors: Prof David Kaye and A/Prof Bing Wang
Location: Heart Failure Research Group and Biomarker Discovery Laboratory, Baker Heart and Diabetes Institute

Background:

Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and is associated with high morbidity and mortality currently no effective evidence-based therapies are available, resulting in an emerging epidemic. The cellular and molecular pathophysiology underpinning HFpEF are complex. Accumulating evidence demonstrates that pro-inflammatory and oxidative stress (excessive production of reactive oxygen species (ROS)) pathways are critical contributors to the development and progression of HFpEF. Among many of the pathways activated by inflammation and oxidative stress, apoptosis signalling-regulated kinase 1 (ASK1) is the convergence point and regulates multiple downstream signalling networks that respond to the dual challenges of inflammatory and oxidative stress and are major factors that promote the development of HFpEF pathologies. Hence, ASK1 is likely to be a novel target for HFpEF therapy.

Project aim:

This project is to investigate novel ASK1 inhibitors for the treatment of cardiovascular disease including HFpEF using suitable animal models established in our group. This study will test the ability of the compound/s to both prevent and/or reverse myocardial fibrosis and inflammation associated with the HFpEF phenotype.

Techniques:

It is anticipated that this study will involve the use of animal models in mice, cardiac function measurement with echocardiography and pressure-volume relationship analysis, Western blotting, immunohistochemistry, and gene expression analysis with PCR.

Contacts:

A/Prof Bing Wang and Prof David Kaye

Biomarker Discovery Laboratory and Heart Failure Research Group
Baker Heart and Diabetes Institute
75 Commercial Road, Melbourne, 3004
Phone: 9903 0648, or 8532 1178
Bing.wang@monash.edu or bing.wang@baker.edu.au or David.kaye@baker.edu.au

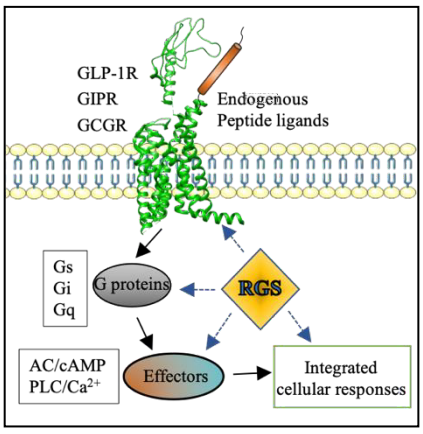
REGULATION OF THE GLUCAGON RECEPTOR FAMILY BY RGS PROTEINS


Supervisors: Prof Denise Wootten, Dr. Elva Zhao
Location: Drug Discovery Biology
Monash Institute of pharmaceutical sciences
Monash University, Parkville

Background:
The glucagon subfamily of receptors are class B1 G protein-coupled receptors (GPCRs) and include the glucagon (GCG) receptor (GCGR), the glucagon-like peptide-1 receptor (GLP-1R) and the glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR). These receptors modulate key physiological functions, for instance, appetite, glucose handling, cardiovascular tone, and immune response. Receptor belonging to the glucagon subfamily are expressed in tissues systems that include the pancreas, adipose and liver. In coordination with intracellular machinery, they initiate distinct physiological responses in both a tissue- and cell- dependent manner. As such, there is a pressing need to understand how these receptors are activated by their cognate peptide ligands, how these interactions are relayed to promote cellular signaling, and how these signals are regulated inside target cells. Moreover, individual endogenous ligands can differentially act on the same receptor to promote different signalling outcomes, a phenomenon termed biased agonism. While substantial advances have been made into understanding the structural and molecular basis for biased agonism, there are key gaps in our knowledge of how intracellular regulators of receptor signalling control the intensity and duration of response that is critical for normal integrated cell and tissue function. In particular, the contribution of Regulators of G protein Signalling (RGS) proteins that selectively modulate the texture of G protein responses is largely unexplored for members of the glucagon receptor family.

Project aim:
The current project aims to interrogate the role of RGS proteins in mediating the function of the GCGR, GLP-1R and GIPR. The primary outcomes of the project will provide mechanistic insights into how signaling mediated by these receptors is regulated by RGS proteins, which will facilitate our understanding of how receptor activation can promote cell and tissue-specific physiological events.

Techniques:
This project will use a broad range of techniques including cell culture, cellular signalling assays (ie, cAMP, ERK1/2 phosphorylation, Ca2+ mobilisation) and resonance energy transfer assays to detect receptor-receptor interactions, receptor interactions with transducers and regulatory proteins and to montior receptor trafficking through different cellular compartments.



Contacts:
Dr. Elva Zhao or A. Prof Denise Wootten
Monash Institute of Pharmaceutical Sciences
Monash University, Parkville Campus
Elva.zhao@monash.edu or denise.wootten@monash.ed