Department of Pharmacology
Honours Projects
2019

2018 Honours Students

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, Dr Barb Kemp-Harper 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 the Department of Pharmacology in 2019 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

Prof Rob Widdop
Email: Robert.Widdop@monash.edu
Phone: 9905 4858

Dr Barb Kemp-Harper
Email: Barbara.Kemp@monash.edu
Phone: 9905 4674

Pharmacology Honours: Pre-requisites

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<tr>
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<th>BSc Biomedicine</th>
<th>BMS</th>
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<tr>
<td><strong>Pre-requisites</strong></td>
<td>A Distinction average (&gt;70) in 24 points at 3rd year in relevant disciplines within the School of Biomedical Sciences*</td>
<td>A Distinction average (&gt;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*</td>
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<tr>
<td><strong>Application closing date</strong></td>
<td>16th November 2018</td>
<td>16th November 2018</td>
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<td><strong>Application form</strong></td>
<td><a href="https://www.monash.edu/science/current-students/science-honours">https://www.monash.edu/science/current-students/science-honours</a></td>
<td><a href="www.med.monash.edu/biomed/honours/">www.med.monash.edu/biomed/honours/</a></td>
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<tr>
<td><strong>Commencement date</strong></td>
<td>18th February, 2019</td>
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* 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:

- Bachelor of Science: Complete the Departmental Project Preference Form (available on Moodle & Department of Pharmacology website)
- Bachelor of Biomedical Science: Complete the BMS Honours Project Preference Form (available from the Biomedical Sciences Honours website)

Forms to be signed by Pharmacology Honours Convenor & supervisors

These forms must be signed by the Honours Convenors of the Pharmacology Department, Dr Barb Kemp-Harper or Professor Rob Widdop.

Apply on-line via E-admissions by **Friday 16th November**:


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 2018. 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 2019.
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<tr>
<th>LABS / SUPERVISOR(S)</th>
<th>PROJECT TITLE</th>
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| **Education-Based Projects**  
Liz Davis, Klaudia Budzyn, Jennifer Irvine | Evaluation of student approaches to learning |
| **Fibrosis Group**  
Chrislan Samuel, Tracey Gaspari, Anita Pinar | Investigating novel anti-fibrotic therapies |
| **Integrative Cardiovascular Pharmacology Group**  
Tracey Gaspari, Rob Widdop  
Rob Widdop, Mibel Aguilar, Mark Del Borgo | Exploring novel signalling mechanisms associated with insulin-regulated aminopeptidase (IRAP)  
Drug discovery program for AT2 receptor ligands of the RAS |
| **Cardiovascular & Pulmonary Pharmacology Group**  
Barb Kemp-Harper, Rob Widdop, Brad Broughton  
Barb Kemp-Harper, Jane Bourke, Brad Broughton | Targeting the CCL18-CCR8 axis to treat hypertension-associated end organ damage  
Using amnion stem-derived exosomes to improve stroke outcome  
Targeting the CCL18-CCR8 axis to treat pulmonary hypertension |
| **Respiratory Pharmacology Group**  
Jane Bourke, Chrislan Samuel, Simon Royce  
Jane Bourke, Phil Bardin, Belinda Thomas  
Jane Bourke, Rebecca Ritchie, Helena Qin | The ins and outs of calcium – novel approaches to oppose airway contraction in COPD and asthma  
Transforming growth factor β – the link between fibrosis and increased airway contraction?  
Exploring a novel treatment for pulmonary hypertension |
| **Monash Venom Group**  
Wayne Hodgson, Geoff Ibister | A pharmacological and biochemical examination of two Chinese snake venoms |
## Honour Projects 2019 – Off campus projects

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<th>LABS / SUPERVISOR(S)</th>
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<td><strong>Baker Heart &amp; Diabetes Institute</strong></td>
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<tr>
<td>Rebecca Ritchie, Helena Qin,</td>
<td>• Nitroxyll-based therapies to overcome diabetes-induced impairments in cardiac NO signalling</td>
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<tr>
<td>Barb Kemp-Harper</td>
<td>• Targeting inflammation in the cardiac complications of diabetes</td>
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<tr>
<td>Rebecca Ritchie, Miles De Blasio,</td>
<td>• Targeting altered cardiac glucose metabolism in the cardiac complications of diabetes</td>
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<tr>
<td>Helena Qin</td>
<td>• Combining drug and gene therapy approaches to limit diabetes-induced cardiac fibrosis</td>
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<tr>
<td>Rebecca Ritchie, Mitchel Tate</td>
<td>• Targeting inflammation and its resolution in the acute and chronic cardiac response to myocardial infarction</td>
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<tr>
<td>Rebecca Ritchie, Helena Qin</td>
<td>• Targeting the inflammasome to limit diabetic cardiac and vascular disease</td>
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<tr>
<td>Judy de Haan, Rebecca Ritchie, Arpeeta Sharma</td>
<td>• Antioxidant and anti-inflammatory effect of pomegranate polyphenols on diabetic cardiovascular disease.</td>
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<td>Geoff Head, Kristy Jackson</td>
<td>• Role of renal microrna 181A in hypertension in mice</td>
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<tr>
<td><strong>Drug Discovery Biology Theme</strong></td>
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<tr>
<td><strong>Monash Institute of Pharmaceutical Sciences</strong></td>
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<tr>
<td>Karen Gregory, Katie Leach</td>
<td>• Allosteric Modulation of class C GPCRs for CNS and metabolic disorders</td>
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<tr>
<td>Lynda Whiting, Denise Wootten</td>
<td>• The physiological relevance of GLP-1R dimerization and biased agonism</td>
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<tr>
<td>Elva Zhao, Denise Wootten</td>
<td>• The dynamics of ligand-GLP-1R-G protein coupling and its contribution to biased agonism</td>
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EVALUATION OF STUDENT APPROACHES TO LEARNING

Supervisors: Assoc Prof Elizabeth Davis  
Dr Klaudia Budzyn  
Dr Jennifer Irvine

Location: Pharmacology Education Research Initiative  
Department of Pharmacology  
Monash University, Clayton

Background: Our group aims to gain a better understanding of factors that influence student learning, particularly within undergraduate pharmacology units. The current trend in university teaching, is to move away from didactic teaching and instead engage students more in active learning via pre-class; in-class; and after-class activities. While there is evidence that active learning improves student performance in science, this is dependent on student engagement with their learning, including attendance and active participation in their classes. Student engagement, however, is influenced by motivation and experience of what has worked for them previously. As it is known that assessment drives learning, if students have been successful using a passive approach to learning, they may be reluctant to embrace active learning. In addition, the resources that are made available as learning tools, and the feedback they receive on their work can have an impact on how students engage with their studies. We therefore need to have a better understanding of how our students respond to different “modes” of teaching and how they use and value the resources we offer to support their learning. In particular, we want to know what they perceive as most useful and how they adapt their learning in response to different formats of teaching.

Projects:
- Factors that influence the engagement of students with their learning of pharmacology
- How do students engage with different formats of teaching
- Development and evaluation of web-based learning resources and activities to encourage active learning
- Evaluation of attitudes to, and use of assessment feedback

Techniques: These projects use a mixed methods approach, using both quantitative (e.g. surveys) and qualitative (e.g. focus groups, interviews and in-class observation) techniques.

Contacts:
Assoc Prof Elizabeth Davis  
Department of Pharmacology  
Monash University  
Phone: 9905 5755, Rm E123  
Elizabeth.Davis@monash.edu

Dr Klaudia Budzyn  
Department of Pharmacology  
Monash University  
Phone: 9905 4857, Rm E116c  
Klaudia.Budzyn@monash.edu

Dr Jennifer Irvine  
Department of Pharmacology  
Monash University  
Phone: 9905 5745, Rm E116c  
Jennifer.Irvine@monash.edu
INVESTIGATING NOVEL ANTI-FIBROTIC THERAPIES

Supervisors: A/Prof Chrishan Samuel, Dr Tracey Gaspari & Dr Anita Pinar
Location: Fibrosis Laboratory (Rms E101/E102)
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 abnormal wound healing to tissue injury, resulting in 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.

Aims:
The Fibrosis Lab aims to identify novel anti-fibrotic therapies (relaxin, stem cells, AT2 receptor agonists and combinations of these) that will more effectively prevent/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 enhance their therapeutic potential and abrogation of organ scarring.

Projects:
1. Signal transduction studies (in models of heart and kidney disease)
2. Head-to-head and combination therapy efficacy studies
3. Targeting inflammasome activity to treat fibrosis

Techniques:
Depending on the project involved, animal/cell culture models of (heart/kidney disease), blood pressure and functional measurements, matrix biology, protein biochemistry, molecular biology and/or histological techniques will be utilized.

Contacts:
A/Prof Chrishan Samuel, Dr Tracey Gaspari &
Dr Anita Pinar
Department of Pharmacology
Monash University
Phone: 9902 0152 / 9905 4762
chrishan.samuel@monash.edu
tracey.gaspari@monash.edu
anita.pinar@monash.edu
EXPLORING NOVEL SIGNALING MECHANISMS ASSOCIATED WITH INSULIN-REGULATED AMINOPEPTIDASE (IRAP)

Supervisors: Dr Tracey Gaspari & Professor Robert Widdop
Location: Integrative Cardiovascular Pharmacology Group
Department of Pharmacology
Clayton Campus
A/Prof Siew Yeen Chai, Dept Physiology
Clayton Campus

Background:
Cardiovascular diseases (CVDs) remain the world’s leading cause of morbidity and mortality, claiming 17 million deaths annually. Risk factors such as ageing, excessive acute (e.g. myocardial infarct) or chronic (e.g. hypertension) cardiac injury, lead to increased cardiac fibrosis, chronic heart failure and/or end organ damage. However there are few effective treatments currently available and thus there is an urgent need to identify new targets/treatment given our aging population. We have compelling evidence that IRAP is upregulated in cardiac tissue in pathophysiological states, although we do not know if this is a cause or consequence of disease.

Project aim:
The aim of this Honours project is to investigate signaling mechanisms in human cardiac fibroblasts, using this system as a surrogate in vitro fibrotic read-out to mimic in vivo conditions. This study will also aim to elucidate the underlying effects caused by IRAP inhibition using novel selective pharmacological inhibitors.

Techniques:
This project will involve a range of methodologies that will include predominantly cell culture work coupled with biochemical measurements and cell microscopy.

Contacts:
Dr Tracey Gaspari
Professor Robert Widdop
Department of Pharmacology
Monash University
Phone: 9905 4762, Rm E119
Tracey.Gaspari@monash.edu
Robert.Widdop@monash.edu
Background:
The main effector hormone of the renin angiotensin system (RAS) is angiotensin II which can stimulate both angiotensin AT1 receptors (AT1R) and AT2 receptors (AT2R). There is currently intense interest focusing on the AT2R cardiovascular function, although there are few selective AT2R ligands available to delineate such effects. We have a drug discovery program replacing natural amino acids in the Ang II molecule with synthetic amino acid derivatives that may act as lead compounds. Our preliminary data have identified a series of novel angiotensin peptide analogues that exhibit AT2R selectivity, based on in vitro binding.

Project aim:
The current projects will use novel ligands, together with clinically-used compounds, to assess the therapeutic potential of AT2R stimulation in two areas of huge unmet clinical need:
- the treatment of hypertensive heart disease (HHD)
- the treatment of diabetic nephropathy (DN)

Techniques:
This project will involve
- animal models of HHD or DN
- Ex vivo analysis of collagen markers (production and breakdown)
- Signaling assays (vasorelaxation, inflammatory, extracellular matrix, biomarkers)

These studies will pave the way for future novel therapies that are likely to be beneficial against organ fibrosis in a number of common disease settings.

Contact:
Prof Robert Widdop
Department of Pharmacology
Monash University
Robert.Widdop@monash.edu
TARGETING THE CCL18-CCR8 AXIS TO TREAT HYPERTENSION-ASSOCIATED END ORGAN DAMAGE

Supervisors: Dr Barbara Kemp-Harper, Prof Rob Widdop, Dr Brad Broughton

Location: Cardiovascular & Pulmonary Pharmacology Group
Department of Pharmacology
Monash University, Clayton

Background:
Hypertension is a major cause of heart failure, heart attacks and strokes. Associated with the development of hypertension is the accumulation of macrophages in the arterial wall leading to fibrosis and vascular stiffening of central elastic arteries (i.e. aorta, carotid artery). This results in a reduced capacity of these vessels to buffer pulse pressure leading to peripheral vascular and end-organ damage. Whilst current antihypertensives are effective at lowering blood pressure, they don’t necessarily target vascular stiffening and as such new therapeutic approaches are sought.

We have exciting new data to suggest that human macrophages release high concentrations of a chemokine, CCL18 which activates the G-protein coupled receptor, CCR8 leading to an elevation in blood pressure and associated end-organ damage. We hypothesise that pharmacological targeting of the CCL18-CCR8 axis will reverse hypertension and associated cardiovascular and renal fibrosis, and protect against end-organ damage.

Project aim:
The aim of this honours project is to assess the therapeutic utility of pharmacological targeting the CCL18-CCR8 axis to protect against hypertension and the associated end-organ damage. This study may lead to the development of more effective therapies for the treatment of hypertension and fibrosis in cardiovascular pathologies.

Techniques:
The project will utilize an angiotensin II-infusion model of hypertension in mice, and involve the measurement of blood pressure and ex vivo assays to assess vascular function (myography), detect inflammation (RT-PCR, superoxide detection), collagen generation (zymography, immunohistochemistry) and pro-fibrotic factors (ELISA).

Contacts:
Dr Barbara Kemp-Harper
Department of Pharmacology
Monash University
Phone: 9905 4674, Rm E117
Barbara.Kemp@monash.edu
USING AMNION STEM-DERIVED EXOSOMES TO IMPROVE STROKE OUTCOME

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

**Background:**  
Stroke is a debilitating disease that can cause permanent neurological damage, complications, and death. At present, there are very few treatment options available for patients, thus the development of new treatment options that limit the damage caused by stroke is vital. Our research group has exciting evidence that shows acute (1.5 h) post-stroke administration of amnion stem cell-derived exosomes minimises functional deficits and cerebral infarct damage in mice. However, the ideal therapeutic would be one that could improve functional outcomes and brain injury when administered several hours/days after a stroke.

**Project aim:**  
The aim of this project is to test whether delayed post-stroke treatment of amnion stem cell-derived exosomes can improve long-term stroke outcomes. *The findings of the proposed project are expected to show that delayed-exosome treatment can promote functional recovery via bolstering neural regenerative and reparative mechanisms.*

**Techniques:**  
Techniques that will be used during this project include performing stroke surgery on mice and treating them with exosomes, carrying out functional tests, and performing MRI and histochemical staining to measure cerebral infarct damage. Additionally, fluorescent labelling approaches will be used to track the distribution of exosomes and to identify regenerative and reparative mechanisms.

**Contacts:**  
Dr Brad Broughton  
Department of Pharmacology  
Monash University  
Phone: 9905 0915, Rm B113  
bradley.broughton@monash.edu
TARGETING THE CCL18-CCR8 AXIS TO TREAT PULMONARY HYPERTENSION

Supervisors: Dr Barbara Kemp-Harper¹, Dr Jane Bourke² & Dr Brad Broughton¹
Location: ¹Cardiovascular & Pulmonary Pharmacology Group
         ²Respiratory Pharmacology Group
         Department of Pharmacology
         Monash University, Clayton

Background:
Chronic hypoxia-induced pulmonary hypertension is a major cause of death and illness throughout the world. Whilst there has been advancement in the treatment of PH, current treatment is not optimal, and a range of different drug options is needed for better clinical management of PH. Our research group has recently demonstrated that the chemokine, CCL18, which activates the G-protein coupled receptor, CCR8, causes an elevation in systemic blood pressure and associated end-organ damage. Moreover, CCL18 has been found to increase in the lungs of patients with pulmonary disease. Therefore, we hypothesise that the CCL18-CCR8 axis contributes to the development of chronic hypoxia-induced pulmonary hypertension.

Project aim:
The aim of this Honours project is to assess the therapeutic utility of pharmacological targeting the CCL18-CCR8 axis to protect against chronic hypoxia-induced pulmonary hypertension. The outcomes of the proposed research are expected to advance our understanding of the role of CCL18-CCR8 axis in pulmonary arteries following chronic hypoxia and thus, lead to the development of a novel therapy for the treatment of pulmonary hypertension.

Techniques:
Techniques that will be used during this project include establishing a 4-week mouse model of chronic hypoxia-induced pulmonary hypertension, and involve the measurement of blood pressure and ex vivo assays to assess vascular function (myography, lung slice model), detect inflammation (RT-PCR, superoxide detection), collagen generation (zymography, immunohistochemistry) and pro-fibrotic factors (ELISA).

Contacts:
Dr Barbara Kemp-Harper
Department of Pharmacology
Monash University
Phone: 9905 4674, Rm E117
Barbara.Kemp@monash.edu
THE INS AND OUTS OF CALCIUM - NOVEL APPROACHES TO OPPOSE AIRWAY CONTRACTION IN COPD AND ASTHMA

Supervisors:  
Dr Jane Bourke¹  
A/Prof Chrishan Samuel²  
Dr Simon Royce³

Location:  
¹Respiratory Pharmacology/²Fibrosis  
Department of Pharmacology  
³Department of Medicine  
Central Clinical School  
Monash University

Background: The Respiratory Pharmacology and Fibrosis Laboratories are both interested in identifying improved therapeutic strategies for chronic lung diseases. This research project will examine how calcium, the key mediator driving airway contraction, may be dysregulated in asthma and COPD. To explore this, a unique technique to examine calcium signaling and airway contraction and relaxation in precision cut lung slices (PCLS) will be used.

In a preclinical model of COPD, Dr Bourke’s lab has shown that cigarette smoke exposure alters expression of the ryanodine receptor (RyR), leading to altered calcium release and impaired airway relaxation in vitro. With support from her collaborators A/Prof Chrishan Samuel and Dr Simon Royce, this project will define changes in calcium homeostasis and develop novel approaches to oppose airway contraction and promote relaxation to improve quality of life in people with asthma and COPD.

Project aims: This project will test the hypothesis that inflammation-induced changes in calcium homeostasis drive the airflow limitation and impaired bronchodilator reversibility in chronic lung diseases.

Specific aims to be tested may include (1) defining the influence of in vitro inflammation (with stimuli relevant to asthma or COPD) on calcium signaling, contraction and responses to current and novel dilators in mouse and human small airways in PCLS; (2) investigating the effects of in vivo inflammation (with cigarette smoke or allergen exposure in animal models, or disease status in airway smooth muscle (ASM) cells from COPD or asthma patients) on calcium signalling and airway/ASM function.

Techniques: This project will combine in vitro assays of reactivity using a novel lung slice technique (to visualise changes in small airway lumen area in situ), as well as biochemical and molecular assays such as immunohistochemistry, Westerns, RT-PCR, ELISAs etc (to measure mechanisms underlying altered reactivity).

Contacts:  
Dr Jane Bourke  
Pharmacology,  
Monash University  
Phone: 9905 5197  
jane.bourke@monash.edu

Dr Simon Royce  
Central Clinical School  
Monash University  
Phone: 9905 0913  
simon.royce@monash.edu

Airway contraction is driven by Ca²⁺ release and reuptake from SR stores
TRANSFORMING GROWTH FACTOR β - THE LINK BETWEEN FIBROSIS AND INCREASED AIRWAY CONTRACTION?

Supervisors: Dr Jane Bourke¹
Prof Phil Bardin/Dr Belinda Thomas²

Location: ¹Respiratory Pharmacology, Monash
²Hudson Institute
Baker Heart & Diabetes Institute

Background:
The Respiratory Pharmacology Laboratory focuses on characterising pathophysiological mechanisms in chronic lung diseases.

It is becoming increasingly clear that airway fibrosis and airway contraction are inextricably linked in diseases such as asthma. Increased collagen deposition in the airways is associated with more severe asthma and loss of responsiveness to bronchodilator therapy.

*In vitro*, contraction promotes the release of pro-fibrotic mediators such as TGF-β1 which are not only implicated in airway remodeling in asthma but can also increase the expression of contractile proteins in airway smooth muscle (ASM). This positive feedback is likely to promote airway narrowing, but its potential impact on bronchodilator sensitivity is less well defined.

In collaboration with Prof Phil Bardin and Dr Belinda Thomas at the Hudson Institute, this project will utilize a unique transgenic mouse model, where TGF-β is selectively induced in the airways when mice drink doxycycline-containing water. The planned experiments will try to tease out how this profibrotic cytokine impacts on airway contractile function and responses to dilator therapy.

Project aims: To characterize the role of TGF-β in regulation of airway fibrosis and airway reactivity to constrictors and dilators.

Techniques: This project will combine *in vitro* assessment of airway reactivity using a novel lung slice technique (to visualise changes in the lumen area of small intrapulmonary airways *in situ*), with cutting edge imaging techniques (to measure collagen deposition in the lungs) and biochemical and molecular assays such as Westerns, RT-PCR, ELISAs etc (to measure markers of fibrosis).

This project will be performed both in Dr Bourke’s laboratory on campus and in Prof Bardin’s laboratory at the Hudson.

Contacts:
Dr Jane Bourke
Pharmacology,
Monash University
Phone: 9905 5197
jane.bourke@monash.edu

Prof Phil Bardin & Dr Belinda Thomas
Hudson Institute
belinda.thomas@monash.edu
EXPLORING A NOVEL TREATMENT FOR PULMONARY HYPERTENSION

Supervisors: Dr Jane Bourke¹
Co-supervisors: Prof Rebecca Ritchie, Dr Helena Qin²
Location: ¹Respiratory Pharmacology, Monash
          ²Heart Failure Pharmacology, Baker Heart & Diabetes Institute

Background:

The Respiratory Pharmacology and Heart Failure Laboratories focus on identifying new strategies to prevent and treat chronic diseases that impair lung and myocardial function.

A/Prof Rebecca Ritchie and Dr Helena Qin have shown that the glucocorticoid-regulated protein annexin-A1 (ANX-A1) protects against inflammation-induced injury and impaired contractile function in cardiac muscle (Qin et al., 2013). In an exciting new collaboration with Dr Jane Bourke, they have now shown that a drug that acts at the same receptor as ANX-A1 possesses novel vasodilator properties and relaxes pulmonary arteries. These results suggest that synthetic ANX-A1 protein and related non-protein mimetics may represent an alternative or adjunct therapy for the treatment of pulmonary hypertension (PH).

Project aims:

This project will test the hypothesis that ANX-A1 mimetics cause relaxation of pulmonary arteries in a mouse model of PH.

Specific aims to be tested may include

(i) defining the efficacy of ANX-A1 mimetics relative to and in combination with existing pulmonary vasodilators in vitro;
(ii) exploring the mechanisms underlying protective actions of ANX-A1 mimetics; and/or
(iii) assessing ANX-A1-mediated effects on vascular relaxation in a mouse model of PH.

Techniques:

This project will combine in vitro assessment of vascular reactivity using a novel lung slice technique (to visualise changes in the lumen area of small intrapulmonary arteries in situ), standard organ bath techniques and myography (to measure changes in contractile force in larger arteries) as well as biochemical and molecular assays such as Westerns, RT-PCR, ELISAs etc (to measure receptor expression and changes in cytokines that contribute to PH).

This project will be performed largely in Dr Bourke’s laboratory on campus, but will also include components in Prof Ritchie’s laboratory at the Baker Institute in Prahran.

Contacts:

Dr Jane Bourke
Pharmacology, Monash University
Phone: 9905 5197
jane.bourke@monash.edu

Prof Rebecca Ritchie & Dr Helena Qin
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1392
rebecca.ritchie@bakeridi.edu.au
ChengxueHelena.Qin@bakeridi.edu.au
PHARmacological and biocheMical examination of two chinese snake venoms

Supervisors: Professor Wayne Hodgson  
Professor Geoff Isbister (University of Newcastle)

Location: Monash Venom Group  
Department of Pharmacology  
Monash University, Clayton

Background: The Chinese cobra (Naja atra) and sharp nosed pit viper (Deinagkistrodon acutus) are two medically important snakes found in China and surrounding countries. The Chinese cobra is from the family Elapidae (i.e. snakes with small, fixed front fangs) while the sharp nosed pit viper is from the family Viperidae (i.e. snakes with large mobile fangs). Both these species are highly venomous snakes responsible for considerable mortality and morbidity in the region. However, the venoms of these snakes has been poorly studied.

Project aim: The aim of this honours project is to undertake a details pharmacological and biochemical investigation of these venoms and, if possible, isolate and characterize key toxins. The efficacy of commercially available antivenoms against the activity of these venoms/toxins will also be investigated. The primary focus will be on (1) neurotoxicity, (2) cardiovascular activity and (3) pro-coagulant activity.

Techniques: This will involve the use of in vitro and in vivo assays including the chick biventer cervicis nerve-muscle preparation (i.e. a skeletal muscle), isolated blood vessels as well as anaesthetized rats. Blood coagulation studies and enzymatic assays will be carried out at the University of Newcastle (NSW) so students will need to be willing to spend 1-2 weeks in NSW (NB. this trip will be funded by the laboratory).

Contact:  
Professor Wayne Hodgson  
Deputy Dean, Education, Faculty of Medicine, Nursing & Health Sciences

Head, Monash Venom Group, Department of Pharmacology  
Monash University  
Phone: 99054861
wayne.hodgson@monash.edu
NITROXYL-BASED THERAPIES TO OVERCOME DIABETES-INDUCED IMPAIRMENTS IN CARDIAC NITRIC OXIDE SIGNALLING

Supervisors: Prof Rebecca Ritchie, Dr Helena Qin & Dr Barbara Kemp-Harper
Location: Heart Failure Pharmacology, Baker Heart & Diabetes Institute, Melbourne

Background:
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 T2D is a major research focus of the Heart Failure Pharmacology laboratory at the Baker. Ultimately, HNO-based strategies may offer new treatment options for cardiac disease, particularly T2D.

Project aim:
The aim of this Honours project is to determine the extent of NO resistance in T2D, and whether HNO can overcome this in the short- and longer-term. HNO may be superior to NO with respect to limiting diabetes-induced myocardial dysfunction and changes in cardiac structure, key characteristics of diabetes-induced HF.

Techniques:
It is anticipated that this will involve pre-clinical models of diabetic cardiac disease, isolated rodent hearts, assessment of cardiac and vascular function, biochemical techniques: Westerns, reactive oxygen species (ROS) detection, ELISA, real-time PCR, histology.

Contact:
Prof Rebecca Ritchie
Heart Failure Pharmacology
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1392
rebecca.ritchie@baker.edu.au
TARGETING INFLAMMATION IN THE CARDIAC COMPLICATIONS OF DIABETES

Supervisors: Prof Rebecca Ritchie, Dr Helena Qin & Dr Miles De Blasio
Location: Heart Failure Pharmacology, Baker Heart & Diabetes Institute, Melbourne

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

Project aim:
The aim of this Honours project is to investigate annexin-A1 cardioprotection for the cardiac complications of type 2 diabetes. It will test the hypothesis that 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.

Techniques:
It is anticipated that this will involve pre-clinical models of diabetic cardiac disease, assessment of cardiac function, biochemical techniques: Westerns, ELISA, real-time PCR, histology and 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 mimetics.

Contact:
Prof Rebecca Ritchie
Heart Failure Pharmacology
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1392
rebecca.ritchie@baker.edu.au
TARGETING ALTERED CARDIAC GLUCOSE METABOLISM IN THE CARDIAC COMPLICATIONS OF DIABETES

Supervisors: Prof Rebecca Ritchie & Dr Miles De Blasio
Location: Heart Failure Pharmacology, Baker Heart & Diabetes Institute, Melbourne

Background:
The increasing global prevalence of type 2 diabetes (T2D) and our aging population has given rise to an epidemic of heart failure (HF). Up to one-third of patients in clinical HF trials are diabetic, and diabetes is an independent predictor of poor outcome. Despite the higher rate of HF in these patients, no specific treatment for HF 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 HF. The Heart Failure Pharmacology laboratory has an established track record for identifying mechanisms of diabetes-induced HF (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 O-GlcNAc increases susceptibility of a range of proteins to O-GlcNAc modification, altering their 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 route of glucose metabolism impairs left ventricular (LV) function, and will focus in particular on O-GlcNAcylation of key components within the cardiomyocyte.

Project aim:
The aim of this Honours project is 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, and to investigate susceptibility of specific components within the cardiomyocyte to O-GlcNAcylation, and how this impacts on diabetes-induced HF.

Techniques:
It is anticipated that this will involve pre-clinical models of diabetic cardiac disease, gene delivery, drug treatment, assessment of cardiac function, biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence, ROS detection.

Contact:
Prof Rebecca Ritchie
Heart Failure Pharmacology
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1392
rebecca.ritchie@baker.edu.au
COMBINING DRUG AND GENE THERAPY APPROACHES TO LIMIT DIABETES-INDUCED CARDIAC FIBROSIS

Supervisors: Prof Rebecca Ritchie & Dr Mitchel Tate
Location: Heart Failure Pharmacology, Baker Heart & Diabetes Institute, Melbourne

Background:
Diabetes is Australia’s fastest growing chronic disease. Diabetes affects almost 2 million Australians, increasing heart failure (HF) risk and accelerating its onset. Two key structural changes in the diabetic heart are cardiac fibrosis and hypertrophy of cardiac myocytes, both of which contribute to the impaired cardiac function evident in the diabetic heart. Whether specifically targeting diabetes-induced cardiac fibrosis alone, or diabetes-induced cardiomyocyte hypertrophy alone, is sufficient to restore cardiac function in the context of diabetes, will be investigated. This project explores whether specifically limiting diabetes-induced cardiac fibrosis, using a cardiac-selective gene therapy approach to enhance a naturally-occurring antifibrotic mechanism, restores cardiac function in the context of type 2 diabetes (T2D) 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 HF, it is not known understood whether such approaches can restore cardiac function in the context of T2D over the longer-term in vivo. We will also 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 heart. Ultimately, such approaches may limit progression to HF and death in diabetes-affected patients.

Project aim:
The aim of this Honours project is to determine whether enhancing cardiac gene expression of regulators of cardiac fibrosis, cardiomyocyte hypertrophy, or their combination, protects cardiac function in the context of T2D in vivo.

Techniques:
It is anticipated that this will involve pre-clinical models of diabetic cardiac disease, gene delivery, drug treatment, assessment of cardiac function, biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence, ROS detection.

Contact:
Prof Rebecca Ritchie
Heart Failure Pharmacology
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1392
rebecca.ritchie@baker.edu.au
TARGETING INFLAMMATION IN THE ACUTE AND CHRONIC CARDIAC RESPONSE TO MYOCARDIAL INFARCTION

Supervisors: Dr Helena Qin & Prof Rebecca Ritchie
Location: Heart Failure Pharmacology, Baker Heart & Diabetes Institute, Melbourne

Background:
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 aim:
The aim of this Honours project may include determining whether cardiac gene delivery of annexin-A1 limits cardiac injury over the short- and longer-term, whether annexin-A1 as a therapeutic target remains effective in ageing, and investigation of the receptor signalling fingerprints downstream of annexin-A1 in cardiac cell types.

Techniques:
It is anticipated that this will involve in vitro and/or in vivo models of cardiac ischaemia, gene delivery, drug treatment, assessment of cardiac function and biochemical techniques: FPR signalling fingerprints, Westerns, ELISA, real-time PCR, histology, immunofluorescence.

Contact:
Dr Helena Qin
Heart Failure Pharmacology
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1374
ChengxueHelena.Qin@baker.edu.au
**TARGETING THE INFLAMMASOME TO LIMIT DIABETIC CARDIAC AND VASCULAR DISEASE:**

**Supervisors:** Assoc Prof Judy de Haan, Prof Rebecca Ritchie & Dr Arpeeta Sharma

**Location:** Oxidative Stress Laboratory and Heart Failure Pharmacology, Baker Heart and Diabetes Institute, Melbourne.

**Background:** Cardiovascular complications associated with Type 2 diabetes (T2D) lead to significant morbidity and mortality (heart attacks and stroke), for which standard treatment options are insufficient to halt or reduce this clinical burden. T2D affects almost 2 million Australians, and its prevalence is expected to increase with the growing obesity epidemic. Therefore, there is a strong clinical need to identify new pathways and targets for effective drug treatment. Recent evidence suggests that "sterile" inflammation plays a significant role via the NLRP3 inflammasome. This project will use a recently identified inhibitor of the NLRP3 inflammasome as well as IL-1β knockout mice to investigate whether inhibition of inflammasome activation and function lessens diabetic cardiovascular complications. The susceptibility of endothelial and cardiac cells to inflammasome-mediated injury will be assessed in iPSC-derived cardiac and endothelial human and mouse cells. Therefore, this project uses both pharmacological and genetic manipulations to address the role of this key component, the inflammasome, in diabetic cardiac and vascular complications.

**Project aim:** To lessen diabetic inflammation using both a pharmacological and genetic approach to improve diabetic cardiac and vascular complications.

**Techniques:**
It is anticipated that this project will involve pre-clinical mouse models of diabetic cardiac and vascular disease, assessment of vascular and cardiac function, derivation of iPSCs, biochemical techniques: Western blotting of key inflammasome components, reactive oxygen species (ROS) detection, ELISA, real-time PCR, histology.

**Contact:**
Assoc Prof Judy de Haan
Oxidative Stress Laboratory
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1520
judy.dehaan@baker.edu.au
ANTIOXIDANT AND ANTI-INFLAMMATORY EFFECT OF POMEGRANATE POLYPHENOLS ON DIABETIC CARDIOVASCULAR DISEASE

Supervisors: Assoc Prof Judy de Haan, Prof Rebecca Ritchie & Dr Arpeeta Sharma

Location: Oxidative Stress Laboratory and Heart Failure Pharmacology, Baker Heart and Diabetes Institute, Melbourne.

Background:
Oxidative stress and inflammation are two significant drivers of Diabetic Complications such as cardiovascular disease. Type 2 Diabetes affects almost 2 million Australians, and by 2040 it is predicted to increase to 642 million people globally. Despite available drugs to reduce high blood pressure, lower lipids and lessen blood glucose levels, individuals with Type 2 diabetes still develop debilitating complications. Thus, there is an urgent need for new drugs to lessen these complications. Recent evidence suggest that polyphenols extracted from pomegranate juice are potent antioxidant and anti-inflammatory agents. Limited studies show their benefits in improving insulin-resistance but the effect of these compounds on diabetic cardiovascular disease has not yet been explored. Therefore, mice will be made diabetic by high fat feeding together with administration of a β-islet cytotoxic drug, streptozotocin, and administered polyphenols for varying lengths of time. Thereafter, vascular lesions and cardiac function will be assessed. This project will also investigate the effect of these drugs on “sterile” inflammation in vitro by assessing NLRP3 inflammasome signalling in mouse bone marrow derived macrophages.

Project aim: The aim of this Honours project is to determine whether limiting oxidative stress and inflammation through the use of polyphenols derived from pomegranate juice, lessens cardiac and vascular injury sustained as a consequence of Type 2 diabetes. These aims will be undertaken in in vitro and in vivo type 2 diabetic models.

Techniques:
It is anticipated that this will involve pre-clinical models of diabetic cardiac and vascular disease, drug treatment, assessment of cardiac and vascular function, biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence, ROS detection.

Contact:
Assoc Prof Judy de Haan
Oxidative Stress Laboratory
Baker Heart & Diabetes Institute
75 Commercial Rd, Melbourne
Phone: 8532 1520
judy.dehaan@baker.edu.au
ROLE OF RENAL MICRON181A IN HYPERTENSION IN MICE

Supervisors: Prof. Geoff Head, Dr Kristy Jackson
Location: Neuropharmacology Laboratory
Baker Heart and Diabetes Institute
Commercial Rd, Prahran

Background:
We have shown that genetically hypertensive mice (BPH, Blood Pressure High) have hypertension due to an overactive sympathetic nervous system and renin angiotensin system compared with control mice (BPN, Blood Pressure Normal). These hypertensive mice also have elevated renal renin mRNA which is associated with low levels of its negative regulator, microRNA181a. Similarly, mice with global knockout of the mir181a gene (miR181a KO), also have elevated renal renin mRNA and elevated blood pressure compared with control C57Bl6 mice. We hypothesise that reduced levels of miR181a in the tubules of the kidneys results in elevated renin production causing activation of the intrarenal renin angiotensin system and hypertension.

Project aim:
Our aim is to investigate the effective of reintroducing/increasing mir181a in the kidney of mir181a KO and BPH/2J mice respectively. In this study, all mice will undergo telemetry surgery to enable us to measure blood pressure in conscious and unrestrained mice. Mice will have baseline measurements before undergoing surgery to deliver a virus to overexpress mir181a in the kidney. The blood pressure response will be measured following this intervention and kidney function will be measured using metabolic cages to collect urine and determine glomerular filtration rate. At the end of the experimental period kidneys will be removed and in situ hybridisation will be used to confirm the overexpression and localisation of the miR181a and real time quantitative PCR will be used to quantify mir181a and renin mRNA levels.

Techniques:
It is anticipated that this will involve the use of radiotelemetric measurement of blood pressure, qPCR analysis of microRNA and target RNA abundance and in situ hybridisation for localization of microRNA within the kidney in both miR181a knockout mice and spontaneously hypertensive mice.

Contacts:
Dr Kristy Jackson
Neuropharmacology laboratory
Baker Heart and Diabetes Institute
Phone: 03 85321390, Level 4, Lab1
Kristy.Jackson@baker.edu.au
ALLOSTERIC MODULATION OF CLASS C GPCRs FOR CNS AND METABOLIC DISORDERS

Supervisors: Dr Karen Gregory & Dr Katie Leach
Location: Class C GPCR Biology
Drug Discovery Biology
Monash University, Parkville

Background:
Our lab is interested in the biology and therapeutic potential of targeting Class C G protein-coupled receptors (GPCRs). We are predominantly focused on two class members: metabotropic glutamate receptor subtype 5 (mGlu5) and the calcium-sensing receptor (CaSR).

mGlu5 is an exciting new target for schizophrenia, Alzheimer's disease, autism spectrum disorders and depression, whereas modulators of the CaSR are already in the clinic for hyperparathyroidism and are putative therapeutics for osteoporosis, calcium handling disorders, asthma and idiopathic pulmonary arterial hypertension. We are pursuing a novel class of therapeutics, called allosteric modulators, to selectively target these receptors. To facilitate rational drug design and discovery efforts, a better understanding of the functional consequences and structural basis of allosteric modulation is needed.

Project aim:
Multiple projects are available to examine:
- the structural basis of Class C GPCR activation and allosteric modulation
- the influence of dimerisation on allosteric modulator pharmacology
- the impact of chronic vs acute exposure to allosteric modulators on mGlu5 & CaSR activity
- how different compounds influence receptor trafficking.

Techniques:
To test our hypotheses, we have access to a diverse allosteric modulator collection. Techniques applied may include molecular biology, high-throughput second messenger assays, primary neuronal culture, recombinant cell culture, protein chemistry, photoaffinity labelling, immunoblotting, computational modelling, medicinal chemistry and single cell imaging.

Contacts:
Dr Karen Gregory and Dr. Katie Leach
Department of Pharmacology and Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences
Monash University
Phone: 9903 9243, Rm 4.346
Building 4, Parkville
Karen.Gregory@monash.edu
Katie.Leach@monash.edu
THE PHYSIOLOGICAL RELEVANCE OF GLP-1R DIMERISATION AND BIASED AGONISM

Supervisors: Dr Lynda Whiting and Dr Denise Wootten
Location: Metabolic G protein-coupled receptor group
Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences
Monash University, Parkville

Background:
The glucagon-like peptide-1 receptor (GLP-1R) is a G protein-coupled receptor (GPCR) that is expressed in multiple tissues and is a validated drug target for treatment of type 2 diabetes. Approved GLP-1 peptide mimetics are effective in the clinic, however they have differing efficacies and side-effect profiles, and thus remain suboptimal. Biased agonism describes the ability of individual drugs targeting the same receptor to promote different profiles of signalling and regulation, with the potential to generate distinct physiological and pathophysiological outcomes. This phenomenon offers new opportunities for sculpting cellular responses with the promise of generating better and safer therapeutics. The GLP-1R receptor couples to both G protein-mediated and arrestin-mediated signalling pathways, with distinct ligands having different propensities to couple to each of these effectors. We have also identified that the GLP-1R oligomeric state is important for controlling biased agonism. However, substantial challenges remain in translating this knowledge for therapeutic benefit as little is known of the physiological and pathophysiological relevance of biased agonism and receptor dimerisation and this is a barrier for the design of novel drug candidates. Our group has identified key mutations within the GLP-1R that either (i) disrupt GLP-1R dimerisation, (ii) selectively disrupt G protein-mediated signalling or (iii) selectively disrupt arrestin-mediated. We have generated three transgenic mice that express these mutations to assess the importance of GLP-1R G-protein-mediated signalling, arrestin-mediated signalling and dimerisation for normal physiology and for targeting this receptor for the treatment of type 2 diabetes.

Project aim:
The aim of this honours project is to assess the physiological and pathophysiological relevance of biased agonism and dimerisation using a series of in vivo and ex vivo models.

Techniques:
This project will involve performing islet isolations from wildtype and transgenic mice fed chow and high-fat diets to assess glucose-stimulated insulin secretion, proliferation and apoptosis of these primary islets. Techniques to assess these endpoints will include homogenous time resolved fluorescence and flow cytometry. In vivo assessments will include monitoring food intake, energy expenditure and performing glucose and insulin tolerance tests, as well as measuring serum levels of key hormones and lipids associated with glucose regulation and diabetes (via ELISA, colourmetric and fluorescence-based assays). The project may also involve measurements of key proteins within islets via qPCR and western blotting.

Contacts: Dr Denise Wootten
Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences
Denise.wootten@monash.edu
THE DYNAMICS OF LIGAND-GLP-1R-G PROTEIN COUPLING AND ITS CONTRIBUTION TO BIASED AGONISM

Supervisors: Dr Elva Zhao and Dr Denise Wootten
Location: Metabolic G protein-coupled receptor group
Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences
Monash University, Parkville

Background:
The glucagon-like peptide-1 receptor (GLP-1R) is a class B G protein-coupled receptor (GPCR) that is expressed in multiple tissues in the body and is a major drug target for treatment of global health burdens, including type 2 diabetes and obesity. While GLP-1 peptide mimetics are approved for treatment of these diseases, they remain suboptimal with significant side-effect profiles. Biased agonism has gained attention in recent years as a novel mechanism for targeting GPCRs. This phenomenon describes the ability of individual ligands of a receptor to promote distinct functional outcomes and offers new opportunities for sculpting receptor signalling to target events leading to therapeutically beneficial effects, while avoiding signalling pathways that may lead to adverse side effect profiles. While this offers potential opportunities to develop better and safer therapeutics, exploitation of this phenomenon for rationale design of novel drugs requires an understanding of the molecular events that couple ligand binding to intracellular signalling. However, the molecular basis that directly links GLP-1R ligand engagement and receptor conformational changes with transducer (G protein or β-arrestin) activation remain unclear.

Project aim:
The aim of this honours project is to investigate the molecular mechanisms that contribute to GLP-1R biased agonism and allosteric signalling. This study will lead to a better understanding of GLP-1R biased agonism revealing molecular signatures induced in downstream effectors that are linked to different signalling profiles mediated by the GLP-1R

Techniques:
This project will use fluorescent ligand binding assays to assess ligand binding kinetics and a range of novel G protein and arrestin biosensors to assess ligand-induced effector coupling, effector conformational changes and effector activation. In addition, a variety of second messenger signalling end point assays will be assessed in a range of novel cell lines where distinct effectors have been depleted. Techniques will include cell culture techniques, bioluminescence resonance energy transfer (BRET), bioluminescence complementation assays (NanoBiT), a range of state-of-the-art cell signalling assays (including cAMP, ERK1/2 phosphorylation, calcium mobilisation. Mathematical modelling will be combined with pharmacological data to quantify ligand binding kinetics and signalling efficacy.

Contacts: Dr Elva Zhao or Dr Denise Wootten
Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences
Phone: 9903 9211,
Elva.Zhao@monash.edu or Denise.wootten@monash.edu