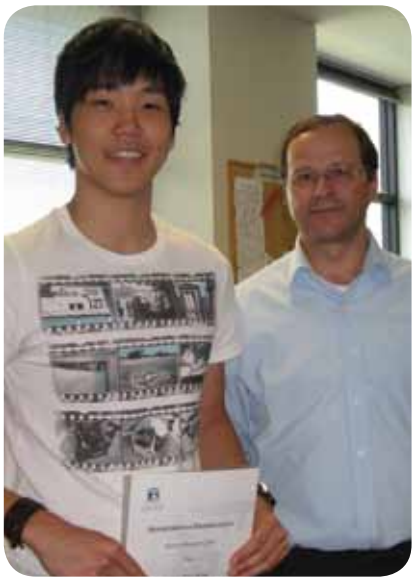
2013




PHARMACOLOGY

HONOURS & MSc (BHS)

PROJECT BOOKLET

Prospective Students

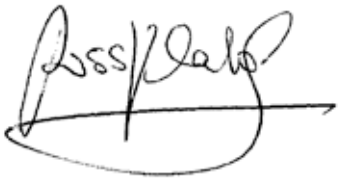
It is a great pleasure to introduce you to the projects that are on offer by the Department of Pharmacology for 2013. Most projects offered will be in our spacious, high quality research laboratories on the 8th and 9th floors of the Medical Building. The remainder will be conducted in affiliated Research Institutes with external supervisors and co-supervision by Department staff.

It is not a simple task to select a project, laboratory and supervisor. We suggest you talk to several potential supervisors, as well as to their current Honours or RHD students, to gain some appreciation of the research problems being addressed and the related techniques.

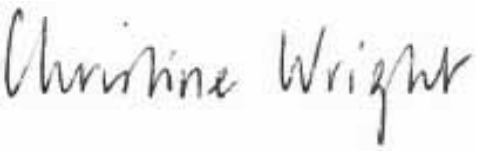
The Department of Pharmacology Honours & MSc (BHS) Course is directed at students with above average scientific ability. The courses are a transition from formal lectures and teaching, to self-directed learning and exploration of your own scientific problem. We will introduce you to skills in communication, data analysis and assessment of scientific papers. Your supervisor and laboratory staff will guide you through the challenges, strengthen your technical skills and introduce you to the excitement of research – its rewards and its disappointments. You will have the opportunity to use the latest in equipment and to share with RHD scholars their recent research experiences in the laboratory. The "Honours/Masters Experience" will require self-motivation and discipline, and you will learn a lot about your own problem-solving ability.

We hope you will join us in Pharmacology in 2013 for Honours or Masters. We aim to give you the best opportunity to 'have a go' at solving a research problem, teach you important skills for future employment in various biomedical vocations and provide a solid basis for those who want to go further in a research career.

Very best wishes for the next step in your journey!



Honours Co-ordinator



Associate Professor Christine Wright
MSc (BHS) Co-ordinator

Associate Professor James Ziogas
Head of Department

'Research is to see what others have seen - but to think what no-one has thought!'

Szent-Gyorgi

CONTENTS

ANAESTHESIA & PAIN MANAGEMENT UNIT

Supervisor: **Dr Jenny Callaway**
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Location: **Department of Pharmacology,**
Level 9, Room N922
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Co-Supervisors: **Prof Colin Royse &**
Dr Trisha Jenkins (RMIT)

www.pharmacology.unimelb.edu.au/research/Anaesthesia.html

Two projects are on offer for Honours.

It is remarkably common to experience loss of memory and concentration following surgery and anaesthesia. While this is more likely to be long-lasting and cause significant problems in people over the age of 65 years, it can and does happen in young patients. This phenomenon is now recognised and is referred to as Post-Operative Cognitive Dysfunction (POCD) and the cause is currently unknown. We are currently investigating the possibility that type of anaesthesia, age, and inflammation or infection may interact to cause POCD.

This project will involve considerable hands-on work in anaesthetised and conscious rats. The techniques involved will include surgery, blood sampling, memory testing methods as well as investigation of brain pathology and assessment of inflammatory markers using immunohistochemistry and biochemical assays. This exciting project will give the right student the opportunity to work within the pharmacology department in a research science laboratory as well as to interact with anaesthetists and surgeons with direct interest in POCD research.

ANTI-ALLERGIC THERAPEUTICS

Supervisor: **Dr Graham Mackay**
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Facsimile: **8344 0241**
Location: **Department of Pharmacology**
Level 8 Medical Building

www.pharmacology.unimelb.edu.au/research/GrahamLab.html

The following projects are offered as Honours only

NOVEL MAST CELL-DERIVED FACTORS AS REGULATORS OF AIRWAY CELL FUNCTION IN ASTHMA

Supervisors: **Dr Graham Mackay &**
Prof Alastair Stewart

In asthma, mast cells are observed in close proximity to smooth muscle cells within the airways suggesting that communication between these cells is an important aspect of the disease. We have identified novel factors that are released from mast cells that can trigger airway smooth muscle cells to release a number of potent cytokines1. However, it is unclear as to how these factors produce smooth muscle cell activation and if they also regulate the actions of other neighbouring cells such as airway epithelium.

In this project you will quantify the ability of a number of mast cell-derived factors to mediate airway smooth muscle and epithelial cell activation and analyse the ability of these factors to modulate the activity of known stimulators of these cells. You will also determine the pathways, and possible receptors, used by these novel factors to produce their effects.

Techniques to be used in the study likely include cell culture, flow cytometry, calcium analysis, Western blotting, quantitative PCR and ELISA.

Reference:

1) Xia YC, Harris T, Stewart AG, Mackay GA. Secreted Factors from Human Mast Cells Trigger Inflammatory Cytokine Production by Human Airway Smooth Muscle Cells. Int Arch Allergy Imunol. 2012; in press.

MS4A EXPRESSION AND FUNCTION IN ALLERGIC DISEASE AND ASTHMA

Supervisors: **Dr Graham Mackay &**
Dr Mark Hulett (La Trobe University)

The β-subunit of the high-affinity IgE receptor (FcεRIβ) belongs to a newly identified larger family of proteins termed 'membrane-spanning four domain proteins' (MS4A family)1. Genes for these proteins are located at chromosomal location 11q13, a region shown through genetic studies to be linked to allergy. Whilst the activity of FcεRIβ has been relatively well characterised many of the other MS4A proteins have been little studied.

We have recently demonstrated expression of MS4A proteins in airway epithelium in the lung. In this project you will examine the function of MS4A proteins in both lower and upper respiratory tract epithelial cells using continuous cell lines and primary cell cultures. You will moreover examine if expression of these MS4A proteins is modulated by factors associated with allergic disease, a feature that may contribute to disease pathology.

Techniques to be used in the study likely include cell culture, cell transfection, flow cytometry, immunohistochemistry, Western blotting, ELISA and quantitative PCR.

Reference:

1) Liang Y, Tedder TF. Identification of a CD20-, FcεRIβ-, and HTm4-related gene family: sixteen new MS4A family members expressed in human and mouse. Genomics. 2001;72:119-27.

BRAIN NEUROTRANSMITTERS IN SCHIZOPHRENIA & DEPRESSION

Supervisor: **A/Prof Maarten van den Buuse**
Email: **mvdbuuse@unimelb.edu.au**
Telephone: **903 56624**
Location: **Florey Institute of Neuroscience & Mental Health**
Melbourne Brain Centre
University of Melbourne

Pharmacology Supervisor: A/Prof Tony Hughes

The following projects are offered as Honours and MSc (BHS) projects. Up to one Honours and one Masters student position will be allocated.

These projects are aimed at students who are interested in schizophrenia, bipolar disorder and depression, genetically-modified mice, pre-clinical psychopharmacology and behavioural neuroscience. The project will be done at the new Melbourne Brain Centre, University of Melbourne.

NEURODEVELOPMENT AND SCHIZOPHRENIA AND DEPRESSION: ROLE OF REELIN

Supervisors: **A/Prof Maarten van den Buuse & Dr Laetitia Buret**

Schizophrenia and other mental illnesses are caused by an interaction of genetic and early neurodevelopmental factors, leading to altered expression of trophic factors in the brain and changes in synaptic density and neuronal activity. We use mice with reduced brain expression of the trophic factor, Reelin, to study the effect of stress or drug abuse during development on schizophrenia-like and depression-like behaviours in adulthood, including cognitive deficits. The focus of the project can either be on the neuropharmacology of behaviour, including antipsychotic and antidepressant drugs, or assessment of protein levels of relevant receptors or signalling factors in the brain by Western Blot.

ROLE OF OESTROGEN IN SCHIZOPHRENIA AND DEPRESSION

Supervisors: **A/Prof Maarten van den Buuse & Dr Rachel Hill**

There are gender differences in schizophrenia with respect to the age of first onset, symptom severity and treatment response. The reason for this difference is unclear but is often attributed to a 'protective' action of oestrogen and an opposite effect of high levels of testosterone. These effects are particularly relevant during puberty, when the brain undergoes extensive plastic changes and remodelling. This project will assess the modulatory effect of oestrogen and testosterone during puberty on behaviour in adulthood. The work will include the behavioural and molecular consequences of chronic administration of different clinically-used sex steroid hormone drugs in male and female rats or mice. Behavioural tests include locomotor hyperactivity, prepulse inhibition, social behaviour and cognitive testing. Neurochemical studies will focus on indices of the activity of brain dopamine and serotonin, receptor signalling pathways, and neuroplasticity factors in relevant brain areas.

CANNABIS AND METHAMPHETAMINE AS RISK FACTORS IN SCHIZOPHRENIA

Supervisors: **A/Prof Maarten van den Buuse, Dr. Rachel Hill & Ms Elizabeth Manning**

Abuse of cannabis or methamphetamine ('Ice') is a well known risk factor in the development of psychosis. However, it is unclear exactly how these drugs cause such effects. The work in this project will focus on the effects of chronic treatment of adolescent or young-adult mice with cannabinoid receptor agonists or methamphetamine. This could include mice with mutations in relevant brain signalling pathways, such as BDNF. Effects of the treatments will either be analyzed at the level of different behaviours with relevance to schizophrenia or by analysing indices of the activity of brain dopamine and serotonin, including receptor signalling and neuroplasticity factors in relevant brain areas. Particular emphasis will be on sex differences and developmental effects.

Selected references illustrating some of our work:

1. Van den Buuse M, Wischhof L, Lee RX, Martin S, Karl T (2009). Neuregulin 1 hypomorphic mutant mice: enhanced baseline locomotor activity but normal psychotropic drug-induced hyperlocomotion, prepulse inhibition regulation. International Journal of Neuropsychopharmacology 12, 1383-1393.
2. Choy KH, de Visser Y, Nichols NR, van den Buuse M (2008). Combined neonatal stress and young-adult glucocorticoid stimulation in rats reduce BDNF expression in hippocampus: effects on learning and memory. Hippocampus 18, 655-667.
3. Gogos A, Bogeski M, van den Buuse M (2008). Role of serotonin-1A receptors in the action of antipsychotic drugs: comparison of prepulse inhibition studies in mice and rats and relevance for human pharmacology. Behavioral Pharmacology 19, 548-561.
4. Klug M, van den Buuse (2012). Chronic cannabinoid treatment during young adulthood induces sex-specific behavioural deficits in maternally separated rats. Behavioural Brain Research 233, 305-313.
5. Hill R, Wu YW, Kwek P, van den Buuse M (2012). Modulatory effects of sex steroid hormones on brain-derived neurotrophic factor-tyrosine kinase B expression during adolescent development in C57Bl/6 mice. Journal of Neuroendocrinology 24, 774-788.

CARDIOVASCULAR THERAPEUTICS UNIT

Supervisor: **A/Prof Christine Wright**
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Telephone: **8344 8219**
Location: **Department of Pharmacology Cardiovascular Therapeutics Unit, Level 9 Room N906 Medical Building**
Co-Supervisor: **A/Prof Paul Soeding**

www.pharmacology.unimelb.edu.au/research/ctu.html

The following project is offered as Honours only

PULMONARY HYPERTENSION: ROLE OF ENDOTHELIN

An important area of pharmacological research is the development of new therapy directed at the pulmonary circulation. Patients with primary lung disease for example, can develop significant pulmonary hypertension with abnormal vasoconstriction and remodelling of the pulmonary vasculature. Disease can lead to severe breathlessness, heart failure and death. In some cases lung transplantation is indicated. Therapy for severe pulmonary arterial hypertension currently involves the use of one, or a combination of three pharmacological classes of drugs: endothelin (ET) receptor antagonists, phosphodiesterase type-5 inhibitors and/or prostacyclin analogues. Despite treatment however, the prognosis of these patients remains poor, with approximately one in two patients dying within the first five years after diagnosis.

Our research is directed at identifying whether new endothelin receptor antagonists acting on either ET-A or ET-B receptors, can selectively decrease pulmonary vascular tone and potentially optimise cardiopulmonary function. Endothelin is an important regulator of pulmonary vascular tone and in disease has a mitogenic action inducing cellular proliferation. Our laboratory has experience in characterizing vascular reactivity using both *in vitro* and *in vivo* preparations, and has established the use of human isolated tissue techniques. A unique collaboration exists with the Department of Cardiothoracic Surgery, Royal Melbourne Hospital, which enables researchers to obtain human vascular and right atrial tissue samples for experimentation. Secondly we have extensive experience with *in vivo* animal experimentation, and this expertise is well placed to investigate the cardioprotective action of new drugs. Pulmonary trunk banding for example, is an effective model of right heart failure, where surgical banding of the pulmonary trunk leads to pulmonary obstruction, increased right ventricular work and mass, and right heart failure. This model is used to study the effect of new drugs on right ventricular remodelling induced by pulmonary hypertension.

The project focuses on the effect of new drugs on pulmonary vascular reactivity and on right heart function. The study involves exposure to a number of experimental techniques:

- *in vitro* analytical pharmacology using myography: human and animal vessels.
- *in vivo* model of right heart failure: surgical implantation of flow probes and catheters, allowing haemodynamic measurements.
- Assessment of right heart function using echocardiography.

CELL SIGNALLING AND LUNG DISEASE

Supervisor: **A/Prof Steven Bozinovski**
Email: **bozis@unimelb.edu.au**
Telephone: **8344 4221**
Facsimile: **8344 0241**
Location: **Department of Pharmacology**
Level 8 North Medical Building

www.pharmacology.unimelb.edu.au/research/bozinovski.html

The following projects are offered as Honours only

HOW DOES SMOKE EXPOSURE WORSEN VIRAL AND BACTERIAL INFECTIONS

Co-Supervisor: Dr Desiree Anthony

Viral lung infections are known to predispose susceptible people to secondary bacterial infections that can be very serious or fatal but the underlying mechanism are obscure. Cigarette smoke exposure is known to alter immune responses to viral infections and is a major epidemiological risk factor for severe chest infection. Chronic smokers with a disease termed COPD are particularly susceptible to aggressive infectious events known as exacerbations.

Understanding why the immune system of COPD patients does not respond appropriately to infection is a central theme of our laboratory, as this will lead to better ways of treating this debilitating disease. Using immunological and molecular techniques, this project will investigate how smoke exposure alters viral responses and how this in turn promotes susceptibility to secondary bacterial transmission.

You will be trained in a wide suite of techniques including Quantitative PCR, cell and tissue culture, FACS analysis of cell populations; ELISA and Western blotting, *in vivo* disease models and viral culture.

IDENTIFYING MOLECULAR LINKS IN COPD (EMPHYSEMA) AND LUNG CANCER

Co-Supervisors: Prof Gary Anderson
Prof Louis Irving (Royal Melbourne Hospital)

Lung cancer is the #1 cause of cancer death worldwide killing more people each year than breast, colon, ovarian and skin cancer combined. Current treatments extend life by only a few months. COPD (Chronic Obstructive Pulmonary Disease / Emphysema) is the #4 cause of cause of all death worldwide and both diseases will continue to be a major health burden for decades to come. Intriguingly, COPD is also recognised to be major risk factor for lung cancer, and interestingly this can occur independently of smoking status, which implicates shared molecular pathways. This project will investigate novel molecular pathways in COPD very recently discovered in our laboratory and explore their significance in lung cancer susceptibility. A range of molecular and cell biology methods will be implemented including phenotyping of macrophage and myeloid lineages that may be important in tumour evasion and progression.

You will be trained in a wide suite of techniques including Quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; ELISA and Western blotting, in vivo disease models and viral culture.

An important part of this project is that your basic research will be translational i.e. linked in with the Lung Cancer Research effort at Royal Melbourne Hospital.

DEVELOPMENTAL NEUROSCIENCE & NEUROTRAUMA

Supervisor: **Prof NR Saunders**
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Telephone: **8344 5678**
Facsimile: **8344 0241**
Location: **Department of Pharmacology**
Level 9 Medical Building
Co-Supervisors: **A/Prof KM Dziegielewska**
Dr MD Habgood

www.pharmacology.unimelb.edu.au/research/DNNL.html

The following project is offered as Honours or MSc (BHS)

MECHANISM OF MACROMOLECULAR TRANSFER ACROSS CEREBROSPINAL FLUID/ BRAIN BARRIER DURING DEVELOPMENT

Studies of transfer mechanisms into developing brain across protective barriers (the blood brain and blood-cerebrospinal fluid, CSF barriers) demonstrated that tight junctions at these interfaces close off the intercellular transfer even at the earliest stages of brain development. Instead, the transfer appears to be across a small proportion of choroid plexus epithelial cells with uptake into the brain from the CSF, rather than across cerebral blood vessels. Recent studies showed that protein is transferred by a different mechanism but also across a small proportion of choroid plexus cells. The next stage of the work involves molecular characterisation of these transfer mechanisms during different stages of brain development.

In this project you will examine expression of several protein transporters in the CSF/brain barrier in normal and pathological conditions. The techniques involved range from whole animal physiology and dissection to molecular biology and detailed morphology.

Reference:

Liddelow et al, 2011. Eur J Neurosci. 33(3):391-400

Supervisor: **Dr Mark Habgood**
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Telephone: **8344 5741**
Facsimile: **8344 0241**
Location: **Department of Pharmacology**
Level 9 Medical Building
Co-Supervisor: **Prof NR Saunders**

The following project is offered as Honours or MSc(BHS)

SPINAL CORD INJURY

Spinal cord injuries are devastating for patients because they result in the sudden and permanent loss of motor, sensory and autonomic functions below the level of the injury. The extent of functional disability suffered by patients is determined both by the spinal level at which the injury occurs and the amount of tissue that is lost. Tissue damage after a spinal cord injury typically occurs in two phases: (1) initial mechanical damage that happens at the time of the injury followed by (2) ongoing secondary biochemical and cytotoxic damage in the hours and days after injury. Secondary damage is amenable to therapeutic interventions because this is tissue that had survived the initial impact, but is lost later. Methods for prolonging the survival of this 'at risk' tissue hold the best immediate prospects for limiting the amount of spinal cord tissue that is lost and thus the degree of spinal cord function that is lost. This pilot project will investigate the effectiveness of various neuroprotective treatments aimed at limiting the amount of secondary tissue loss after spinal injury. The techniques involved range from whole animal physiology and dissection to detailed morphology.

HEART FAILURE PHARMACOLOGY

Supervisors: A/Prof Rebecca Ritchie
Email: rebecca.ritchie@bakeridi.edu.au
Phone: 8532 1392
Location: Baker IDI & Diabetes Institute

Pharmacology Supervisor: Dr Jane Bourke

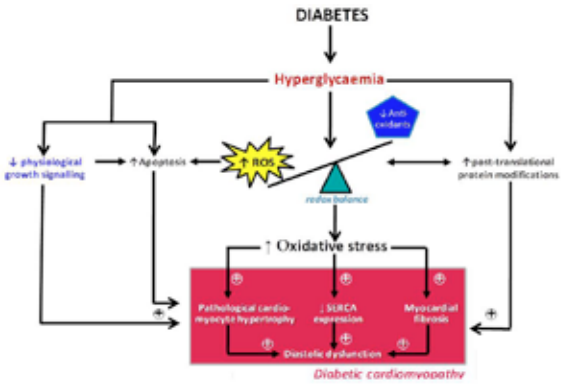
The following projects are offered as Honours or MSc (BHS)

NEW STRATEGIES TO RESCUE DIABETES-INDUCED CARDIAC DYSFUNCTION

Diabetes is Australia's fastest growing chronic disease; one million Australians have been diagnosed, with close to one million more yet to be identified. Most of these patients will eventually die from cardiovascular causes. As diabetes induces left ventricular (LV) dysfunction, this increases the risk of death from heart failure in affected patients. Patients with diabetes are 2.4-fold more likely to develop heart failure, even when adjusted for age and coronary artery disease. Onset of heart failure occurs at a younger age in diabetic patients, with heart failure prevalence increased five- to eight-fold in middle-aged patients.

New therapies for restoring cardiac function in the diabetic heart are thus highly desirable. In most forms of non-diabetic heart failure, systolic (contractile) dysfunction is the first and predominant functional abnormality. The aetiology of diabetic heart disease is distinct from other causes of LV dysfunction, as it is characterised initially by diastolic dysfunction, where relaxation of the cardiac muscle following contraction is prolonged. Diabetes-induced cardiac dysfunction is often exacerbated by underlying LV fibrosis (increased extracellular matrix deposition), hypertrophy (abnormal pathological growth) of cardiac myocytes, and excess generation of reactive oxygen species (ROS) such superoxide.

Our laboratory has demonstrated that antioxidant and/or ROS-suppressing approaches, as well as activation of cardioprotective signalling and negative regulators of LV hypertrophy, are beneficial for treating the cardiac complications of type 1 and type 2 diabetes in the intact heart.



We are now offering an exciting research project in 2013, exploring a novel potential therapeutic strategy for rescuing cardiac function and structure in the diabetic heart. This project will determine whether post-translational protein modifications induced by high glucose and implicated in insulin resistance play a causal role in the development of diabetic cardiomyopathy, and investigate whether pharmacological and/or gene-based strategies targeted at limiting these modifications can prevent diabetes-induced LV dysfunction and remodelling.

The scope of this project will be tailored depending on the student's abilities and interests, and is suitable for both Honours and Masters students. It will provide the opportunity for learning a range of techniques, including physiological (e.g. isolated rodent hearts ex vivo or in vivo models of diabetic cardiac disease, for assessing cardiac function and blood pressure) biochemical (Westerns, ROS detection, ELISA), molecular (real-time PCR, Northerns) and/or histological techniques. Ultimately, treatment strategies that may emerge from these studies may provide significant benefits alone or in combination with current standard care, to ultimately reduce progression to heart failure and death in diabetic patients.

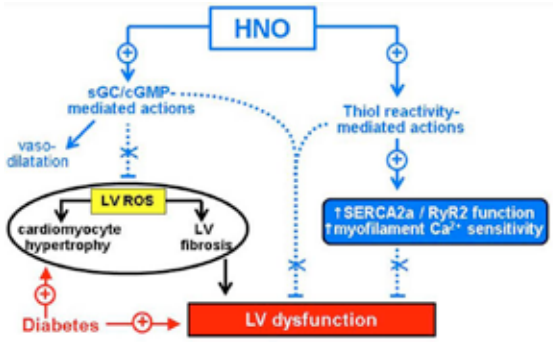
NITROXYL, A RELATIVE OF NO, IS A NATURALLY-OCCURRING CARDIOPROTECTIVE MOLECULE

The nitric oxide (NO•)/cGMP signalling system is as a powerful cardiac antihypertrophic mechanism. Nitroxyl (HNO), a novel redox sibling of NO•, has several therapeutic advantages for the treatment of cardiovascular diseases. We have shown that HNO prevents hypertrophy (abnormal pathological growth) and generation of superoxide in isolated cardiomyocytes. Excitingly, HNO also potentiates cardiac function, in contrast to NO•, via the cardiac calcium handling proteins, SERCA2a (sarcoplasmic reticulum Ca2+ATPase) and the ryanodine receptor RyR2. The activity and expression of these enzymes is abnormally affected in cardiac pathologies (LV hypertrophy, heart failure, diabetes), and together with the upregulation of ROS is recognised for as playing a causal role in the development of LV dysfunction. HNO thus is likely to be favourable for treating these cardiac pathologies.

We are now offering an exciting student research project in 2013, exploring whether HNO or related strategies represent novel pharmacotherapy for the prevention and treatment of myocardial dysfunction, induced by chronic LV hypertrophy, heart failure or diabetes. The project will examine whether the mechanisms by which HNO acutely enhances cardiac function in intact heart are different to those that prevent hypertrophy and elicit ROS suppression, and determine if acute or chronic HNO treatment is cardioprotective in isolated cardiomyocytes and the intact myocardium in vivo in settings of chronic cardiac impairment.

The scope of this project will be tailored depending on the student's abilities and interests. The scope of this

project will be tailored depending on the student's



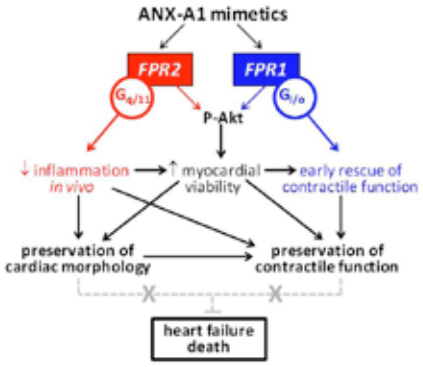
abilities and interests, and is suitable for both Honours and Masters students. It will provide the opportunity for learning a range of techniques, including cell culture (cardiomyocytes and/or cardiac fibroblasts), physiological/pharmacological (e.g. isolated rodent hearts ex vivo or in vivo models of cardiac disease, for assessing cardiac function and blood pressure) biochemical (Westerns, ROS detection, ELISA, real-time PCR) and/or histological techniques. The outcome of this project will be definitive information regarding the mechanism(s) and effectiveness of HNO-mediated rescue of myocardial dysfunction. Ultimately, HNO-based strategies may offer new treatment options for cardiac disease, either alone or on top of standard care.

TARGETING THE ANTI-INFLAMMATORY PROTEIN ANNEXIN-A1 FOR PROTECTION FROM MYOCARDIAL INFARCTION (HEART ATTACK)

Myocardial ischaemia, in which coronary blood flow is reduced, causes anginal chest pain, myocardial infarction (MI, also known as heart attack), and death. Myocardial infarction represents the major cause of death in Western societies, and in the next decade, this will expand to all corners of the world. The primary determinant of outcome from MI is the extent of cell death during and after ischaemia, from necrosis, apoptosis and/or autophagy. Restoration of blood flow (reperfusion) however is associated with the development of further cell death and impaired recovery of cardiac function, referred to as "reperfusion injury". Myocardial ischaemia-reperfusion induces an inflammatory response, with damage resulting from both infiltration of circulating inflammatory cells, as well as neutrophil-independent direct actions on myocardium and endothelium (including Ca2+ overload, ROS generation and impaired mitochondrial regulation all contributing mechanisms to cell death. In addition, there is incomplete recovery of LV function. Together these phenomena contribute to increased risk of ischaemic cardiomyopathy, heart failure and death. Novel treatment strategies that protect against multiple mechanisms of MI injury will have major clinical impact.

The therapeutic potential of the anti-inflammatory mediator annexin-A1 (ANX-A1) has been recognized in a range of systemic inflammatory disorders. Importantly, we have shown that ANX-A1 has powerful protective actions against cardiac injury and loss of LV contractile function. We are now offering an exciting student research project in 2013, exploring the potential for mimetics of ANX-A1 to represent potential new pharmacotherapy for treating cardiac inflammatory disorders such as ischaemia-reperfusion (I-R) injury. The project will test the hypothesis that ANX-A1 represents a novel modulator of myocardial viability and LV contractile function following ischaemia-reperfusion, and will seek to investigate the cardioprotective function of endogenous ANX-A1 in I-R injury, the receptors responsible for cardioprotection elicited by ANX-A1 and its mimetics, and examine the potential therapeutic opportunities offered by exogenous ANX-A1 mimetics after I-R injury in the intact heart.

The scope of this project will be tailored depending on the student's abilities and interests, and is suitable



for both Honours and Masters students. It will provide the opportunity for learning a range of techniques, including cell culture (cardiomyocytes), physiological/pharmacological (e.g. isolated rodent hearts ex vivo or in vivo models of ischaemic cardiac disease, for studying impact on cardiac function and structure) biochemical (Westerns, ROS detection, ELISA, real-time PCR) and/or histological techniques. These studies will provide insight into ANX-A1-mediated rescue of myocardial viability and function after I-R injury in the intact heart, and the mechanisms involved. Development of therapeutic strategies for treating myocardial infarction after an unplanned ischaemic event (while reperfusion injury is still evolving), alone or concurrent with standard care, will ultimately reduce progression to heart failure and death in affected patients.

IMMUNOPHARMACOLOGY & CANCER

Supervisor: **Prof Alastair Stewart**
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www.pharmacology.unimelb.edu.au/research/Immuno.html

The following projects are offered as Honours & MSc (BHS); depending on funding/ supervision commitments of up to 3 projects will be available.

GLUCOCORTICOID RESISTANCE IN LYMPHOCYTES

Location: **Pharmacology / WEHI / Peter MacCallum Cancer Centre**

Co-supervisors: **Ross Dickins/Ricky Johnstone**

The glucocorticoids are used palliatively in a wide variety of solid and other tumour types. In a few types of tumour, there is an additional chemotherapeutic effect, based on the promotion of apoptosis. Thus, glucocorticoids in the form of prednisolone are used as part of the CHOP therapeutic regimen in a variety of types of lymphoma (CHOP= cyclophosphamide, doxorubicin, vincristine and prednisolone). However, in some individuals there is intrinsic or acquired resistance to the glucocorticoid that reduces effectiveness of this regimen. There is evidence that the resistance is partly explained by increased expression of the 11β-hydroxy steroid dehydrogenase II (11βHSDII) enzyme that oxidise the 11 hydroxyl to a keto, thereby inactivating the glucocorticoid. Synthetic, 9-fluorinated glucocorticoids are much less sensitive to this effect, but still exhibit reduce responses in "resistant" cell lines, such as the MOLT4F (Sai et al., 2011).

Our laboratory has been interested in mechanisms of GC resistance in inflammatory cell types and has reviewed mechanisms (Keenan et al., 2012) including the description of an impact of TGF-β (Salem et al., 2012). We will test TGF-β pathways and related mechanisms to ascertain whether these play a role in the GC resistance that is not explained by increased 11βHSDII expression.

In this project, you will work collaboratively with 3 groups with complementary expertise in pharmacotherapy and lymphoma to explore mechanisms of steroid resistance using well-characterised cell lines. You will learn cell culture, western blotting, RT-qPCR and how to transfect cells. A number of functional assays will be used to characterise cell survival, apoptosis and proliferation.

References:

Keenan CR, Salem S, Fietz E, Gualano,R. & AG Stewart (2012). Glucocorticoid-resistant asthma and novel anti-inflammatory drugs. Drug Discovery Today http://dx.doi.org/10.1016/j.drudis.2012.05.011

Sai S, Nakagawa Y, Yamaguchi R., Suzuki M., Sakaguchi K, Okada S, Seckl JR, Chapman K. (2011). Expression of 11beta-hydroxysteroid dehydrogenase 2 contributes to glucocorticoid resistance in lymphoblastic leukemic cells. Leukemia Research, 35: 1644-1648.

Salem S, T Harris, J Mok Shiueh Lian, M Yuen Sin Li, CR Keenan, MJ Schuliga & AG Stewart (2012). Transforming growth factor-β impairs glucocorticoid activity in the A549 lung adenocarcinoma cell line. Br J Pharmacol. 166:2036-2048.

DETERMINANTS OF GLUCOCORTICOID RESPONSIVENESS

Co-supervisors: Dr Connie Xia & Dr Michael Schuliga

The high level of sensitivity of allergic inflammation to regulation by glucocorticoids underlies the therapeutic success of this class of drugs in most cases of asthma, hayfever and urticaria. However, there is a partial resistance to control of severe asthma by GCS. There is a more profound GCS resistance in COPD. A number of mechanisms for GCS-resistance have been advanced; including an upregulation of glucocorticoid receptor (GR) β, oxidative inactivation of histone deacetylase 2 (HDAC2) and our studies have suggested acquired resistance from extracellular matrix changes (collagen breakdown) signalling through integrins (Bonacci et al., 2006).

A In this project you will investigate the possible mechanisms of GCS-resistance that develop through chronic exposure to glucocorticoids. The project will involve: culture of the A549 and BEAS-2B cell lines and of normal and asthmatic-derived airway fibroblasts; measurement of gene expression changes by quantitative RT-PCR and Western blotting; use of live cell imaging to track the translocation of YFP-tagged wild-type and mutated GRs; use of reporter constructs and interventions using transient cell transfection and silencing RNA. Well-established pharmacological inhibitors will also be used in experiments designed to provide new insights into this important limitation on the effectiveness of GCS- in chronic inflammatory diseases.

B A separate, but related project will examine the mechanism of glucocorticoid resistance induced by viral infection using both human cell culture and mouse models. In this project you will learn to propagate viruses, infect airway epithelial cells and use techniques such as ELISA, western blotting and RT-qPCR to analyse glucocorticoid responses. Mice will be subjected to viral infection to examine the impact on gene expression responses to glucocorticoid treatment.

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

References

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Wong ZX, Jones JE, Anderson GP, Gualano RC. (2011). Oseltamivir treatment of mice before or after mild influenza infection reduced cellular and cytokine inflammation in the lung. Influenza Other Respi Viruses: 5(5): 343-50.

MECHANISMS THAT SOFTEN AIRWAY SMOOTH MUSCLE DURING REMODELLING

Location: **Departments of Pharmacology and Chemical Engineering**

Co-Supervisors: **Dr Xuehua Zhang, Department of Chemical Engineering; and Dr Shan Shan Kou, School of Physics**

In asthmatics the muscle cells shorten too quickly and too much in response to chemicals that have little effect on muscle from non-asthmatic patients. This muscle shortening can be reduced by bronchodilator drugs. However, over-use of the bronchodilator drugs can make them ineffective and in patients with severe asthma, the bronchodilators may not work well enough to provide adequate airflows.

Our current work is probing airway smooth muscle cells from humans using techniques of atomic force microscopy (Figure below) and 3D real-time phase imaging. These techniques have the unique capacity to probe structure and function of living cells on a nanometre scale (AFM) and assess rapid changes in refractive index (Phase imaging).

We have discovered that a growth factor protein called bFGF that is able to soften the muscle cells, preventing them from becoming rigid and from shortening. We are now investigating how this happens, because amongst all the signals that enable this response, we believe there will be some excellent drug targets with which to develop completely new and safer bronchodilator drugs.

ANNEXIN-1, LIPOXINS AND TUMOUR CELL FUNCTION

Co-Supervisor: **Dr Cameron Johnston, Peter MacCallum Cancer Centre**

The annexins are a large family of Calcium and phospholipid binding proteins with diverse biological activities (D'Acquisito et al., 2008). Annexin-1 has anti-inflammatory and inflammation-resolving activities, the latter being mediated through a G-protein coupled receptor, formyl peptide receptor 2 (FPR2) that is also activated by the lipid product, Lipoxin A.

Inflammation in tumours is regarded as a negative prognostic factor in many instances. On the other hand, activation of inflammation-resolving mechanisms in tumour environment may be expected to limit tumour growth and spread. We have identified a role for endogenous annexin-1 in modulating the proliferative activity of both the estrogen receptor (ER) positive and ER negative cell lines: MCF7 and MDA MB-231, respectively. We now wish to ascertain the role of the FPR2 receptor in and annexin-1, in a model of melanoma using the B16F10 line. This project will include initial characterisation of the effects of annexin-1 and FPR in vitro using cell culture techniques to assess cell growth survival and chemotherapy sensitivity. We will then examine melanoma growth (Konopka et al., 2001) in transgenic annexin-/- and FPR2 -/- mice.

The project will involve: culture cell lines, quantitative RT-PCR and Western blotting; isolation and analysis of exosomes shed by tumour epithelial cells; use of live cell imaging to track the translocation of GFP-tagged annexin-1; use of transient cell transfection and silencing RNA and in vivo tumour growth studies.

References

Khau T, Langenbach SY, Schuliga M, Harris T, Johnstone CN, Anderson RL, Stewart AG. (2011). Annexin-1 signals mitogen-stimulated breast tumor cell proliferation by activation of the formyl peptide receptors (FPRs) 1 and 2. FASEB J. 25:483-496.

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Sutherland, T.E., Schuliga, M., Harris, T., Eckhardt, B.L., Anderson, R.L., Quan, L. & Stewart, A.G. (2005). 2-methoxyestradiol is an estrogen receptor agonist that supports tumor growth in murine xenograft models of breast cancer. Clin Cancer Res, 11, 1722-32.

D'acquisto, F., Perretti, M. & Flower, R.J. (2008). Annexin-A1: a pivotal regulator of the innate and adaptive immune systems. Br J Pharmacol, 155, 152-69.

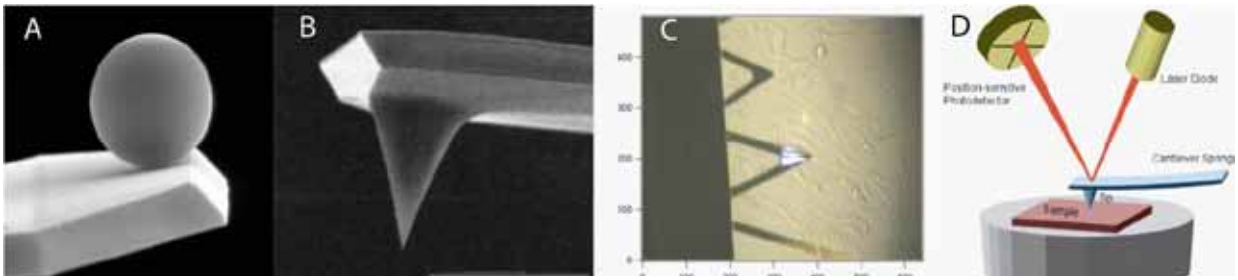

Figure: The AFM probes (A 5μm; B 20 nm) that will be used to map the tension in airway smooth muscle (C, ASM in culture with 20 nm probe [tip illuminated with LASER] engaged at ASM surface) and of the laser processes for tracking tip movement as the tip is advanced to probe ASM surface. AFM can provide high resolution, high accuracy measurements of sample stiffness in a physiological environment.

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The following projects are offered as Honours only

Chronic respiratory diseases such as asthma are a major unmet health need. Although asthma is treatable, there is no cure, and new improved therapies are required. Airway inflammation and tissue remodelling contribute to asthma, and our data supports the urokinase plasminogen activator (uPA) as being an important mediator of these processes. We have discovered that airway structural cells, including smooth muscle and fibroblast cells, convert plasminogen into plasmin in an uPA-dependent manner1. Furthermore, plasmin stimulates these cells to proliferate and express cytokines, by interacting with annexin A2. Plasminogen is a serum protein that extravasates into the airway wall during asthma exacerbations, and its conversion into the pro-inflammatory plasmin is expected to have an important role in airway pathophysiology.

THE EFFECT OF PLASMINOGEN ON AIRWAY EPITHELIAL CELL FUNCTION

The objective of this study will be to demonstrate the conversion of plasminogen into plasmin by human airway epithelial cells. The roles of uPA and annexin A2 in this process will be investigated. Furthermore, the effects of plasmin on cell function, including cytokine production, wound repair responses and changes in cell phenotype (ie epithelial mesenchymal trans-differentiation or EMT) will be characterised.

THE EFFECT OF PLASMINOGEN ON PROSTAGLANDIN E2 PRODUCTION BY AIRWAY SMOOTH MUSCLE CELLS

The objective of this study will be to characterise, using primary cultures of human airway smooth muscle cells (ASM), the effect of plasminogen on the production of the pro-inflammatory mediator, prostaglandin E2 (PGE2). The effect of both plasminogen and plasmin on COX-2 gene expression and PGE2 formation will be assayed. Furthermore, the role of PGE2 in mediating the effects of plasmin on airway smooth muscle cell function (ie cytokine production, collagen remodelling and cell proliferation) will be examined using the COX-2 inhibitor, indomethacin, and antagonists of PGE2 receptors (ie the E prostanoid receptor 2 or EP2).

Methods:

Students will culture either airway epithelial (project 1) or smooth muscle (project 2) cells for their investigations. Plasmin formation will be measured by a fluorometric assay. The roles of uPA and annexin A2 will be examined by knock down of the mRNA encoding these proteins. PGE2 and cytokine levels will be measured by radio-immunoassays (RIA) and enzyme-linked immunosorbent assays (ELISA) respectively. Gene expression of COX-2 will be evaluated by real time PCR to measure levels of COX-2 mRNA. EMT will be measured by changes in cell morphology using microscopy and by increases in the expression of mesenchymal cell-specific proteins such as alpha-smooth muscle actin (α-SMA).

References

1 Schuliga M, Harris T, Stewart AG. (2011) Plasminogen activation by airway smooth muscle is regulated by type I collagen. Am J Respir Cell Mol Biol 44: 831-9

LUNG REGENERATION

The broad interest of the Lung Regeneration Laboratory is to characterize epithelial and mesenchymal stem cells in the normal and diseased lung, including chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and cancer. Our long-term goal is to identify factors regulating lung stem cells as a prerequisite to the development of therapeutic strategies to attenuate lung disease and regenerate the injured lung.

This work addresses an area of utmost importance in human health with more than half a billion people worldwide struggling each year for life and breath due to chronic respiratory diseases. Successful completion of this project will help us to understand the mechanisms involved in regulating lung epithelial stem cells which will ultimately inform the development of stem cell targeted therapies to enhance the regenerative capacity of the lung. Equally, this research will provide critical insight into the role of perturbed epithelial stem cell regulation in lung epithelial remodeling, a major clinical manifestation of chronic asthma and COPD, and in the initiation, propagation and metastasis of lung cancers.

The following project is offered as Honours or MSc (BHS)

www.pharmacology.unimelb.edu.au/research/lungregen.html

IMMUNOREGULATION OF LUNG EPITHELIAL REGENERATION

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The central hypothesis to be tested in this proposal is that inflammation in the lung following injury or disease plays an important role in regulating lung epithelial stem cell behaviour. This project will investigate the role of innate and adaptive immune responses in the resolution of lung injury and regeneration of the respiratory epithelium in well-characterised mouse models of allergen and toxin-induced lung disease. This project will involve cutting edge research using flow cytometry-based cell sorting strategies, three-dimensional cell culture and molecular biology techniques to determine how different immune cell subsets (i.e. macrophages, natural killer cells and T cells) interact with epithelial stem cells and their microenvironment to regulate their regenerative potential. Cell culture analysis of the proliferation, self-renewal and lineage specificity of lung stem cells at various stages of injury and repair will provide valuable insights into the role of inflammatory cells in regeneration of the lung in chronic respiratory diseases, including asthma, chronic obstructive pulmonary disease and lung cancer. regeneration and repair of lung epithelial cell lineages. Immunophenotypic and molecular cell lineage tracing techniques, and clonal stem/progenitor cell assays, will be used to measure the regenerative potential of repopulating cells and analyse their ability to give rise to descendent cell lineages. Successful completion of this project will provide data informing translational studies aimed at developing cellular therapies for intractable lung diseases.

NEUROPEPTIDE RECEPTOR

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http://www.florey.edu.au/about-florey/our-people/staff-directory/17/ross-bathgate

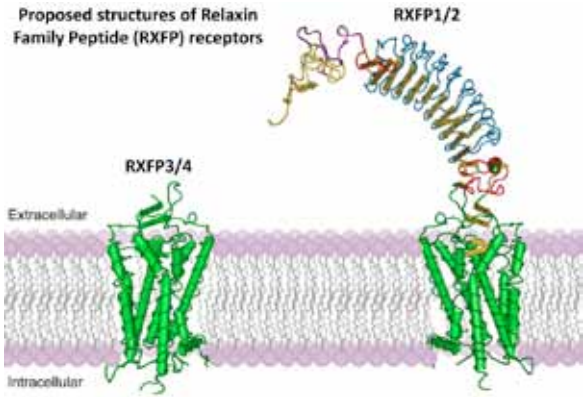
The following projects are offered as Honours or MSc (BHS)

STUDIES ON NOVEL G-PROTEIN COUPLED RECEPTORS

My research focuses on the relaxin peptide family and their G-protein coupled receptors RXFP1-4. The peptides relaxin, relaxin-3, insulin-like peptide 3 (INSL3) and INSL5 have numerous essential biological roles. Relaxin is a hormone and growth factor that induces its effects by regulating collagen turnover, stimulating tissue growth and angiogenesis and inducing blood vessel dilatation. It is currently being used in a Phase III clinical trial for the treatment of acute heart failure being performed by Novartis. INSL3 is essential for germ cell maturation and drugs targeting its receptor RXFP2 have considerable potential as fertility regulators in both males and females. INSL5 is a gut hormone that has potential roles in fat and glucose metabolism and we are working with Takeda Cambridge to develop compounds targeting its receptor RXFP4 which may be useful for treating obesity and/or diabetes. Relaxin-3 is a specific neuropeptide which has potential roles in regulating behaviours which are perturbed in mental illnesses including anxiety, depression, sleep disorders, and memory deficits. Hence drugs targeting the relaxin-3 receptor RXFP3 may be potential therapeutics to treat these mental illnesses. We are working with pharmaceutical industry partners (eg. Takeda and Novartis) to determine the biological roles of the peptides and to develop drugs targeting their receptors.

Receptor projects:

The receptors for these peptides are all G-protein coupled receptors (GPCRs) which are the largest class of cell surface signaling molecules and major drug targets. The receptors for relaxin and INSL3, RXFP1 and RXFP2 are leucine rich-repeat containing GPCRs with large extracellular domains (see figure). Relaxin-3 and INSL5 interact with unrelated receptors RXFP3 and RXFP4 which are more like classic peptide GPCRs and lack a large ectodomain. We are using various molecular and pharmacological techniques to map the native ligand binding sites of these receptors and determine the mechanisms of receptor activation as well their cell signalling characteristics. A complete understanding of the mechanism of ligand binding and activation is required to design drugs targeting these receptors.



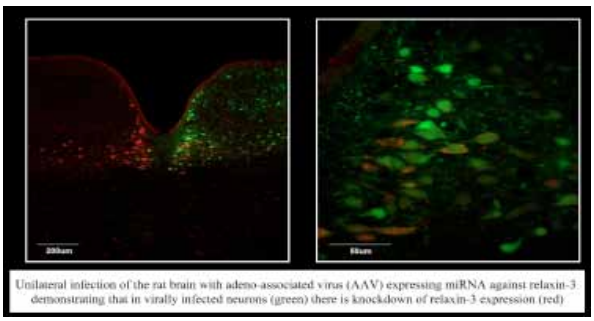
Furthermore in collaboration with Dr Daniel Scott and A/Prof Paul Gooley we are utilizing various biochemical techniques to study the receptor structures. GPCRs are the largest single class of drug targets in the human body, but they are difficult to study with molecular detail because they are unstable when removed from the cell membrane. The ability to probe these receptors using biochemical and structural approaches would enhance our understanding of how they function and lead to the discovery and optimisation of novel therapeutics. We are therefore studying ligand interactions with receptor domains using soluble protein constructs and NMR. Additionally, we are one of the only laboratories in the world using protein engineering techniques to generate stabilised GPCRs that can be readily applied to standard biochemical methods after they have been removed from the cell membrane. We are using these stabilised receptors to probe the structure and dynamics of GPCRs with X-ray crystallography and NMR as well as protein interaction analysis and screening to investigate how these receptors bind to natural ligands and drugs.

ADENO-ASSOCIATED VIRUS MEDIATED MODULATION OF NEUROPEPTIDE FUNCTION IN BRAIN

(Collaboration with A/Prof Andrew Gundlach, Florey Neuroscience Institutes)

Mental illness is a large and increasing health and economic burden in Australia and worldwide and more research is urgently required to identify new and innovative therapies. In this regard, GPCR neuropeptide receptors may be better therapeutic targets than receptors for the 'primary' transmitters (amino acids and monoamines), as they offer reduced side-effects, due to their modulatory actions. Studies by our group have shown that relaxin-3 has potential roles in regulating behaviours which are perturbed in mental illnesses including anxiety, depression, sleep disorders and memory deficits. We utilize viral gene transfer to transduce specific neuronal populations allowing the chronic modulation of neuropeptide or neuropeptide receptor function by either gene silencing or by overexpression of peptide agonists or antagonists in adult animals thus avoiding potential compensation that can occur in knockout animals.

We have successfully employed adeno-associated viral (AAV) driven gene silencing to ablate the expression of the neuropeptide relaxin-3 at its site of production, the nucleus incertus. Co-expression of EmGFP simultaneously confirmed injection sites and labelled tranduced neurons (see figure). Additionally, we have utilized AAV and lentiviral particles overexpressing a relaxin-3 agonist to modulate feeding and arousal in rat models. This research will determine if targeting the RXFP3 receptor will be effective for the treatment of mental illnesses such as anxiety, depression, sleep disorders, and memory deficits. We have intellectual property (IP) and commercial links in the area that will facilitate therapeutic opportunities.



Unilateral infection of the rat brain with adeno-associated virus (AAV) expressing miRNA against relaxin-3 demonstrating that in virally infected neurons (green) there is knockdown of relaxin-3 expression (red)

Projects overview

Honours and Masters projects are available on both these topics. Candidates will undergo training in various techniques including molecular cloning, site-directed mutagenesis, cell biology, cell signalling, protein chemistry, protein engineering, fluorescence activated cell sorting (FACS), confocal microscopy, viral expression and animal behavioural phenotyping.

Recent Publications:

1. Bathgate RAD, et al., (2006) International union of pharmacology (IUPHAR); Recommendations for the nomenclature of receptors for relaxin family peptides. Pharmacological Reviews 58: 7-31.
2. Scott DJ, Rosengren KJ and Bathgate RAD (2012) Determining the factors that govern INSL3 binding specificity to RXFP2. Molecular Endocrinology. in press
3. Callander GE, Ganella DE, Ma S, Wimmer V, Gundlach AL, Thomas WG, Bathgate RAD (2012) Silencing Relaxin-3 in Nucleus Incertus of Adult Rodents: a Viral Vector-based Approach to Investigate Neuropeptide Function. Plos One. 7 (8): e42300
4. Callander GE, Thomas WG and Bathgate RAD (2009) Prolonged RXFP1 and RXFP2 signaling can be explained by poor internalization and a lack of β-arrestin recruitment. American Journal of Physiology, Cell Physiology 296: C1058-66
5. Hossain MA, et al., and Bathgate RAD (2008) The A-chain of human relaxin family peptides has distinct roles in the binding and activation of the different relaxin family peptide receptors. Journal of Biological Chemistry 283: 17287 - 17297.
6. Yan Y, et al., and Bathgate RAD (2008) Identification of the N-linked Glycosylation Sites of the Human Relaxin Receptor and the Effect of Glycosylation on Receptor Function. Biochemistry 47: 6953-6968
7. Scott D, Layfield S, Hsueh A, Tregear GW and Bathgate RAD (2006) Characterization of novel splice variants of LGR7 and LGR8 reveals that receptor signaling is mediated by their unique LDLa modules. Journal of Biological Chemistry 281: 34942-34954.

NEUROPHARMACOLOGY

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The following projects are offered as Honours or MSc (BHS)

INNATE IMMUNITY AND CHRONIC NEURODEGENERATION – A FOCUS ON ALZHEIMER'S DISEASE

A major new area of research in our laboratory is the role that the innate immune system plays in the progression of neural injury. It is now appreciated that the central nervous system (CNS) does exhibit features of inflammation, and in response to injury, infection or disease, resident CNS cells generate inflammatory mediators, including proinflammatory cytokines, prostaglandins, free radicals and complement, which in turn induce chemokines and adhesion molecules, recruit immune cells, and activate glial cells. Activation of the innate immune system is an important component of this inflammatory response. The innate immune system uses a newly discovered family of receptors to transducer its' signal called the Toll-like receptors (TLRs). The roll that the TLR's play in the progression and response to neural in jury is an exciting and emerging field of research. The molecular mechanisms that are influenced by the TLRs comprise new targets for therapeutic intervention into acute neurological conditions such as stroke and neurotrauma and chronic neurological diseases such as Alzheimer's disease.

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

OXIDATIVE STRESS AND NEURAL INJURY

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

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

THE ROLE OF NEUROINFLAMMATION IN PARKINSON'S DISEASE.

Parkinson's disease (PD) is a progressive neurological disease that is characterized by the loss of dopaminergic neurons, primarily in the substantia nigra. The loss of these neurons leads to a motor handicap, associated depression, pain and general decreased quality of life. The mechanism for the loss of the dopaminergic neurons is unknown although it is hypothesised that protein mis-folding, oxidative stress and neuroinflammation may contribute to the cell death. We hypothesise that the neuroinflammatory response triggers deleterious events (e.g., oxidative stress and cytokine-receptor-mediated apoptosis), potentiating dopaminergic cell death and contributing to disease progression. This project proposes to study the molecular and cellular events associated with neuro-inflammation in an animal model of PD. A multi disciplinary approach using an in vivo mouse model of PD coupled with in vitro studies to investigate the specific molecular pathways involved will investigate the role that neuro-inflammation plays in the progression of PD.

Skill acquisition: The techniques involved in this project entail a mouse model of PD, immunohistochemistry, primary neural cell culture, ELISA, DNA cloning, siRNA and Western analysis and data analysis.

UNDERSTANDING TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) represents the major cause of death in young individuals in industrialised countries. Despite the improvement of neurosurgical procedures as well as critical care management, morbidity and mortality are still high and approximately 25% of these patients remain with permanent disabilities becoming a familiar, social and economic burden for society. A better understanding of events occurring in the brain after traumatic brain injury is essential to identify ways to limit the damage and ultimately improve the outcome. The advent of microarray technology has given the researcher the ability to potentially identify the regulation of thousands of genes and enables a broad assessment of gene changes after traumatic brain injury. With the backing of the Victorian Trauma Foundation we have undertaken a microarray study to determine a temporal profile of gene changes in the brain after TBI. This data is being used to understand the molecular pathways that are changed in the brain after TBI.

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

PATHOGENESIS OF CHRONIC LUNG DISEASES

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The following project is offered as Honours or MSc (BHS)

ROLES OF SAA IN THE WASTING ASSOCIATED WITH COPD

Chronic obstructive pulmonary disease (COPD; emphysema) is a debilitating disease characterised by progressive airflow limitation. Patients with COPD often suffer from severe muscle wasting, which increases their risk of death and reduces quality of life. An increase in systemic inflammation (including C-reactive protein, serum amyloid A and various cytokines) is thought to contribute to the wasting associated with COPD. Serum amyloid A (SAA) is an acute phase protein produced by the liver in response to infection. Our laboratory demonstrated that circulating SAA is markedly elevated in COPD patients during an exacerbation (a worsening of disease associated with infection). The increase in circulating SAA level may contribute to the skeletal muscle wasting associated with COPD. Therefore, the goal of this project is to determine if SAA can alter the proliferation and differentiation of skeletal muscle cells (C2C12 murine cell line). A major focus of this project will be to identify whether SAA alters the signalling of proteins important for skeletal muscle homeostasis.

You will be trained in a wide suite of techniques including Quantitative PCR, cell culture, FACS analysis of cell populations; ELISA and Western blotting and in vivo disease models.

PEPTIDE DRUG DISCOVERY

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www.pharmacology.unimelb.edu.au/research/DrugDesignLab.html

The following projects are offered as Honours only.

EXAMINATION OF LOW MOLECULAR WEIGHT MIMETICS OF BDNF AS REGULATORS OF MYELINATION

Co-Supervisors: **Dr Simon Murray &**
Dr Junhua Xiao

Myelination of axons is vital for the correct functioning of the peripheral and central nervous systems. Furthermore, demyelinating diseases, such as multiple sclerosis, constitute a major unmet medical need.

With our collaborators Simon Murray and Junhua Xia at the Melbourne Brain Centre, we have recently demonstrated that small peptide mimetics of the protein brain-derived neurotrophic factor (BDNF) act promote peripheral (Schwann cell) myelination. The compounds offer a unique opportunity to unravel the complex mechanisms through which BDNF signals myelination.

In 2013, we will offer Honours projects looking at:

- New generation p75 mimetics as potential drugs to promote peripheral myelination.
- The examination of selective trkB peptide mimetics as potential regulators of central myelination.

Depending on the project and interests of the student, the project will involve:

- Computer-aided molecular design techniques.
- Synthesis, purification and characterisation of synthetic peptides.
- Organic synthesis of non-peptide peptide mimetics.
- Characterisation of peptide ligand-receptor interactions.
- Examination of myelination mechanisms in vitro.

Depending on the nature of the projects, we will have the capacity to offer either or both of these projects in 2013.

DEVELOPMENT OF NOVEL ANALOGUES OF RELAXIN FAMILY PEPTIDES

Co-Supervisor: **A/Prof Ross Bathgate**

The relaxin family of peptide hormones – including H2 and H3 relaxin, and the insulin-like peptides INSL-3 4, 5 and 6 – modulate a very wide range of physiological effects throughout the multiple body systems. As a consequence, the therapeutic potential of these compounds is formidable. However, this potential remains largely untapped, due to the poor drug-like behaviour of the relxain family peptide.

In our on-going collaborations with Ross Bathgate's Neuropeptides Division of the Florey Institute, we will offer the following Honours projects on 2013:

- Investigations into the metabolic stability of H2-relaxin.
- Design, synthesis and characterisation of peptide analogues of INSL5 as novel regulators of appetite.

Depending on the project and interests of the student, the project will involve:

- Computer-aided molecular design techniques.
- Synthesis, purification and characterisation of synthetic peptides.
- Examination of the pharmacological actions of relaxin family peptides by a variety of complementary in vitro techniques
- Studies relating to the metabolic stability and characterisation of products of proteolysis.

We will likely be able to offer one project in this area in 2013.

RESPIRATORY PHARMACOLOGY

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The following project is offered as Honours or MSc (BHS)

ANNEXIN-A1 MIMETICS TARGET AIRWAY HYPERRESPONSIVENESS IN ASTHMA

Co-Supervisor: **A/Prof Rebecca Ritchie**
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Asthma is characterised by chronic inflammation and airway hyperresponsiveness (AHR), whereby airways contract too easily and too much. The ability of anti-inflammatory glucocorticoids to reduce the severity and frequency of asthma attacks is limited by steroid resistance in many patients. Excessive airway contraction in severe asthma, particularly in small airways, may also be relatively insensitive to bronchodilation in response to β2-adrenoceptor agonists. This highlights a pressing need to identify novel strategies to overcome inflammation-induced changes in airway reactivity that fail to respond to current asthma therapy.

A/Prof Rebecca Ritchie has shown that the glucocorticoid-regulated protein annexin-A1 (ANX-A1) protects against inflammation-induced injury and impaired contractile function in cardiac muscle. We now propose that synthetic ANX-A1 protein and non-protein mimetics represent a novel alternative to overcome the limitations of steroids in asthma treatment.

This project will test the hypothesis that ANX-A1 mimetics inhibit inflammation, reduce AHR and preserve bronchodilator sensitivity in steroid-resistant asthma. Specific aims to be tested may include (i) defining the efficacy of ANX-A1 mimetics relative to steroids on inflammation-induced changes in airway reactivity in vitro; (ii) exploring the mechanisms underlying protective actions of ANX-A1 mimetics; and/or (iii) assessing ANX-A1-mediated effects on chronic inflammation, AHR and impaired bronchodilator sensitivity in vivo.

These studies may provide insights into mechanisms whereby ANX-A1 mimetics, but not steroids, minimise alterations in reactivity in inflamed airways in asthma to support their rapid clinical evaluation and improve quality of life in patients with poorly-controlled asthma.

This project will be performed largely in Dr Bourke's laboratory on campus, but may also include a component in A/Prof Ritchie's laboratory at the Baker IDI Heart and Diabetes Institute in Prahran.

ADIPOKINES AND AIRWAY REACTIVITY – EXPLORING LINKS BETWEEN OBESITY AND ASTHMA

Supervisors: **Dr Jane Bourke &**
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There is accumulating epidemiological evidence of a causal link between obesity and asthma. Longitudinal studies indicate the risk of developing asthma increases with increasing body weight; the reasons for this are unknown.

Obesity alters the levels of circulating adipokines (including leptin, adiponectin, resistin, IL-6, TNF-α), factors produced and released by white adipose tissue. Adipokines can have either pro- or anti-inflammatory properties and have been strongly associated with the development of cardiovascular disease. More recently, many adipokines have also been implicated in the inflammation and airway hyperresponsiveness seen in animal models of asthma. However, it is unclear whether adipokines have a direct effect on airway smooth muscle.

The goal of this project is to determine if adipokines induce changes in the reactivity of airway smooth muscle. To achieve this goal, you will measure the direct effects of adipokines on large and small airways, using tracheal and lung slice preparations respectively. You will also determine if adipokines can modulate changes in airway inflammation and smooth muscle reactivity induced by pro-inflammatory cytokines associated with asthma. Positive findings will be translated to animal models of inflammation or allergic airways disease to evaluate whether the regulation of airway function by adipokines may provide a novel therapeutic approach for obesity-related asthma.

TECHNIQUES FOR PROJECTS 1 & 2

The scope of these projects will be tailored depending on the student's abilities and interests, and would be suitable for either Honours or Masters students. They will provide opportunities to learn a range of techniques, including the application of models of inflammation, obesity and allergic airways disease. Changes in airway structure and function will be assessed using standard organ bath and lung slice techniques, biochemical and molecular assays (Westerns, ROS detection, ELISA, real-time PCR) and histological techniques.

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The following project is offered as Honours only

ROLE OF INTERLEUKIN-17 IN LUNG DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a major incurable global health burden and will become the third largest cause of death in the world by 2020. It is currently believed that an exaggerated inflammatory response to inhaled irritants, in particular cigarette smoke, causes progressive airflow limitation. This inflammation involves the production of various cytokines and chemokines, induction of various proteases, oxidative stress, small airway fibrosis, mucus hypersecretion and emphysema. Patients with COPD are also prone to respiratory infections (commonly called acute exacerbations of COPD - AECOPD) that cause an accelerated decline in lung function, hospitalisation and even death. These respiratory infections consist of bacteria and viruses that get into the lungs of people with COPD. Interleukin-17 (IL-17) is a newly discovered cytokine that has rapidly emerged as a major player in lung disease. In this project you will investigate whether IL-17 contributes to COPD and AECOPD. The significance of this will be that IL-17 may be a novel target that can be exploited therapeutically to treat COPD and acute exacerbations of COPD.

Skill acquisition: In vivo disease models, FACS analysis of cell populations, quantitative PCR, histology, virus and cell culture, ELISA, zymography and Western blotting.

2013 COURSE OUTLINE

BSc & BBiomedSci HONOURS

PHRM40002 ADVANCED TOPICS IN PHARMACOLOGY (SEMESTER 1) 12.5 PTS

Manuscript Evaluation Examination	30%
Theory Project	70%

BIOM40001 INTRODUCTION TO BIOMEDICAL RESEARCH (SEMESTER 1) 12.5 PTS

2 Assignments	50% each

PHRM40001 + 40006 RESEARCH PROJECT 75 PTS

Oral Research Presentation I & II	15%
Literature Review	10%
Research Thesis	75%

Note: After each assessment, you will be given a grade on the LMS.

H1	80% +
H2A	75-79%
H2B	70-74%
H3	65-69%
F	Below 65%

MSc (BHS)

This is a 2 year degree comprising a 125pts research project and 75 pts of coursework subjects. However, it is expected that students will enrol in both PHRM40002 and BIOM40001 subjects in their first semester.

For details of the prerequisites and coursework subjects, see the handbook entry.

MSc (BHS) Handbook is available on the following website:

https://handbook.unimelb.edu.au/view/2012/MC-SCIBHS

HOW TO APPLY

If you wish to be considered for Honours or MSc (BHS) in 2013, and you would like to undertake your project and coursework in a MDHS Department or affiliated institute, you will need to carry out **THE FOLLOWING STEPS:**

HOW TO APPLY FOR HONOURS:

STEP 1

Decide which Supervisor(s) and Project(s) you wish to apply for. To do this you must speak to potential supervisors prior to submitting your application for entry to the Honours course.

Applicants who have NOT made contact with each potential Supervisor prior to listing their project preferences will not be considered for entry to the course.

STEP 2

Lodge an online application by mid November at:

http://sc.mdhs.unimelb.edu.au/how-apply

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

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

1. Current and previous University of Melbourne applicants (Local and International) must select the "RETURNING APPLICANTS, CURRENT STUDENTS AND PREVIOUS STUDENTS" option.
2. Non-University of Melbourne applicants must select the "FIRST TIME APPLICANTS" option.

STEP 3

Once you have contacted potential research supervisors (Step 1) and submitted your online application (Step 2), you will be issued with a password for the Honours Application and Tracking System (HATS). This system allows you to submit up to ten (10) research project preferences online.

Please note that HATS is only available to On-Time applicants for Start Year entry.

Late Applicants (i.e. Those applying after the Application Closing Date in mid November) must complete Step 3 by submitting a hard copy "Late Application – Project Preference Form".

Late applications will be assessed in January as part of the Round 2 selection process.

The "Late Application – Project Preference Form" is made available on the MDHS Honours "How to Apply" web page after the Application Closing Date, but only allows applicants to list a maximum of three (3) project preferences.

Students applying for Mid Year entry must contact potential supervisors from the departments offering mid-year entry (Step 1), submit an online application for entry to the course (Step 2) and submit a hard copy "Mid Year Project Preference Form". The Mid Year form can be obtained by contacting the Student Advisor (Honours) at the MDHS Student Centre.

How you will know the outcome of your application

Round 1 offer letters are sent to applicants via post and email around the 21 of December. It is the responsibility of applicants to ensure their contact details and mailing address are correct and up to date, as offer packs will be sent to the address provided in the original course application, unless other arrangements have been made in advance.

Students who meet the minimum entry requirements for entry to MDHS Honours but do not receive an offer in Round 1 will be considered for a place in Round 2, along with Late Applicants.

Students who do not meet the entry requirements or are not successful in obtaining a place in the course will be advised in writing by the end of January.

HOW TO APPLY FOR MSc (BHS):

1 Before you apply you need to find a potential supervisor. The supervisor has to agree to take on the student and a project needs to be identified with the approval of the Department Coordinator. To find a potential supervisor and project please refer to our Project Booklet or visit our Research Web page and then contact the Laboratory Head of the Research Laboratory you are interested in.

2. Once you have a potential supervisor and project, applications are made through the Melbourne Graduate School of Science on the following website:

http://graduate.science.unimelb.edu.au/apply.php.

The MSc (BHS) is a different degree to BSc Honours and applications are handled independently.

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