Honours in Pharmacology

Graduate Diploma in Pharmacology

2011

Projects and Program Information
Message from the Head of Discipline and Honours Coordinator

The Discipline of Pharmacology invites you to apply to undertake a research year in the fourth year of your studies (Honours or Graduate Diploma in Pharmacology). These programs are designed to give students a greater depth to their studies in biomedical science and to promote research-led inquiry and intellectual endeavour. Students who complete an Honours/Graduate Diploma year in Pharmacology will be equipped with a skill set that improves their employment prospects in industry or government and is a requirement for pursuing postgraduate studies in Pharmacology or related areas.

In the Discipline of Pharmacology at The University of Sydney, we have a group of dedicated academic staff who are conducting cutting-edge research across a variety of fields, including asthma pharmacology, cancer therapeutics, chemical biology, chronic inflammation and pain, clinical pharmacology, drug design and development, neuropharmacology, pharmacoinformatics, pharmacology of cannabis, and transporter biology. We have a changing staff profile, with several recent appointments having been made in frontier areas. Our most recent appointment is Professor Nigel Bunnett, who will join the Discipline in 2011 as an NHMRC Australia Fellow. This booklet is designed to provide further details about the Honours program and describes in some detail the projects on offer to students in 2011. We hope you’ll join us in 2011.

Please contact the Honours Coordinator (Dr Rachel Codd: rachel.codd@sydney.edu.au) with any further enquiries you may have.

I’m interested in Honours in Pharmacology - what do I do next?

Please join us for our Honours Information session, which is to be held on:

Monday 13 September at 12 noon in Bosch Lecture Theatre 2.

At this session, the Honours Coordinator will provide further details on the structure of the program and staff will give a snapshot of their research areas. After formal proceedings, you are warmly invited to a lunch in the Bosch precinct courtyard from 1:00 pm, where you will be able to talk with individual members of staff in whose projects you have an interest. You have about 2 months to reach a decision about which project/research group interests you the most, before submitting to the Honours Coordinator your Honours Preference Form (page 19 of this booklet), which is due on Friday 26 November 2010. Students can elect to start their Honours year in Semester 1 or Semester 2.

In addition to lodging your Honours Preference Form with Pharmacology, you must lodge an application for Honours through the Faculty of Science by Thursday 25 November 2010. Further information is available on the Faculty of Science URL: http://sydney.edu.au/science/fstudent/undergrad/course/honours/index.shtml

Am I eligible for Honours in Pharmacology?

All students with a sound record in Pharmacology are strongly encouraged to apply to the Honours Program. Students are required to have completed a major in the area relevant to Honours and have a Science Weighted Average Mark (SCIWAM) of at least 65. If you are uncertain about your eligibility, you should arrange to meet with the Honours Coordinator and have your academic transcript available for review. Further information is available from the Honours Coordinator and on the Faculty of Science URL: http://sydney.edu.au/science/fstudent/undergrad/course/honours/index.shtml

What will I do during my Honours year?

You will undertake a research project under the direct supervision of a member of staff, and as part of their research group. You will deliver two oral presentations to the Discipline (one in May/June (10%) and another in Oct/Nov (10%)), write a 15-page combined literature review and research proposal (May/June (15%)) and write a 50-page thesis detailing the aims, methods, results and discussion of your project (55%). Your supervisor will award you a mark (10%) that reflects your research dedication, competency and aptitude.
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<td>BKB: 307</td>
<td>Endogenous cannabinoid system, behavioural neuropharmacology</td>
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<td>Prof. Judy Black</td>
<td>WIMR</td>
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<td>Prof. Nigel Bunnett</td>
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<td>Chronic inflammation and pain</td>
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<td>Dr Janette Burgess</td>
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<td>Dr Heidi Fedorow</td>
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<td>A/Prof. Sarah Hilmer</td>
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<td>Dr Tina Hinton</td>
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<td>GABAergic neurotransmission in the CNS, schizophrenia</td>
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<td>Prof. Graham Johnston</td>
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<td>A/Prof. Renae Ryan</td>
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<td>Biophysics of membrane transport, glycine transport</td>
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<td>Mr Farid Sanai</td>
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<td>Prof. Paul Seale</td>
<td>BKB: 301B</td>
<td>Clinical pharmacology, asthma, corticosteroids</td>
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<tr>
<td>A/Prof. Robert Vandenberg</td>
<td>BKB: 223</td>
<td>Molecular biology, glutamate transport, electrophysiology</td>
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* To e-mail staff, the generic format is: firstname.familyname@sydney.edu.au.
For example: rachel.codd@sydney.edu.au.

* BKB = Blackburn building (D06), BSH = Bosch building (D05), BMRI = Brain & Mind Research Institute; WIMR = Woolcock Institute of Medical Research. RNSH = Royal North Shore Hospital. RPAH = Royal Prince Alfred Hospital.
NEW RECRUIT: Joining us in 2011

Professor Nigel BUNNETT
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My laboratory seeks to understand the fundamental mechanisms that underlie chronic inflammation and pain, from studies at the molecular, cellular and whole animal level. Inflammation and pain are essential for survival. Inflammation protects against infection and orchestrates healing, and pain allows avoidance of noxious and damaging stimuli. Inflammation and pain must be tightly controlled to ensure that responses are of an appropriate magnitude and duration. Dysregulated inflammation causes diseases (e.g. inflammatory bowel disease, pancreatitis, atherosclerosis, asthma, arthritis) that affect all systems and are a global cause of suffering. Chronic inflammation exacerbat

PROJECT 1
Endosomal Signalling of G Protein-Coupled Receptors (GPCRs): Mechanisms of Inflammation and Pain

This project examines the molecular mechanisms that regulate trafficking and signalling of neuropeptide receptors in endosomes. Studies will focus of GPCRs for neuropeptides that control inflammation and pain, including substance P, calcitonin gene-related peptide, and opioids. Experiments will examine the innovative concepts that receptors in endosomes signal by mechanisms that are distinct from those operating at the plasma membrane, and that these mechanisms convey sustained signals that underlie chronic inflammation and pain. Targeting these unique pathways may provide more selective therapies for inflammatory diseases. The figure illustrates proposed functions of endosomal signalling complexes.

TECHNIQUES
Molecular and cellular biology: receptor expression, mutagenesis, siRNA knockdown, signalling assays, protein-protein interaction assays, confocal microscopy.

PROJECT 2
Transient Receptor Potential (TRP) Ion Channels and G Protein-Coupled Receptors Signalling Complexes: Mechanisms of Inflammation and Pain

TRP channels and GPCRs expressed by nociceptive neurons are essential mediators of pain. Inflammatory agents that activate GPCRs cause pain by activating/sensitising TRP channels by mechanisms that are not fully understood. This project examines the concept that β-arrestins, cytosolic proteins that can interact with activated GPCRs and TRP channels, assembly GPCRs/TRP complexes at the plasma membrane that control the activity of nociceptive neurons. The project has the potential of discovering new mechanisms of inflammatory pain, with broad therapeutic implications. The figure shows a model of assembly of a complex of the bradykinin B2 receptor, TRPV4 and arrestin.

TECHNIQUES
Molecular and cellular biology: receptor and channel expression, mutagenesis, siRNA, signalling assays, proximity ligation assays, confocal microscopy, neuronal culture, patch clamp recordings of cultured neurons.
TECHNIQUES
Proteomics: gel electrophoresis, mass spectrometry. Imaging: whole animal optical imaging coupled to CT and MRI; 2-photon confocal imaging in the nervous system. Studies of experimentally-induced inflammation and pain in genetically-modified mice.

TECHNIQUES
Receptor localization and neuronal mapping by immunofluorescence and confocal microscopy; behavioural analysis of itch and pain; patch clamp recordings of cultured neurons; studies of genetically modified mice.

PUBLICATIONS.
PROJECT 1  AN ANIMAL MODEL OF GENE-ENVIRONMENT INTERACTION IN SCHIZOPHRENIA

Schizophrenia (SCZ) arises due to a complex interaction between genetic and environmental factors during early neurodevelopment, culminating with disease onset in late adolescence/early adulthood. This project aims to model in mice how genetic vulnerability interacts with environmental insults to disturb brain maturation subserving the development of SCZ symptoms. Our unique model focuses on a SCZ susceptibility gene, neuregulin 1 (Nrg1), and two environmental insults linked to SCZ, early life stress and adolescent cannabis use. In rodents such insults promote loss of dendritic spines and long-lasting behavioural deficits. This is significant as dendritic spines support excitatory synaptic connections which are less abundant in SCZ brain. The brains of SCZ patients show reduced N-methyl-D-aspartate receptor (NMDAR) levels, a key regulator of dendritic spine growth and maturation. Mice heterozygous for the Nrg1 gene (Nrg1 HET mice) provide a powerful model of SCZ as they have dysfunctional NMDAR and display a time-dependent expression of SCZ-related behaviour. We have data showing repeated adolescent stress exposure in these mice unmasks attention deficits earlier than in the absence of stress. Here we aim to examine whether this is subserved by a genetic vulnerability to stress-induced NMDAR dysfunction and loss of dendritic spines in key cognitive areas of the brain. Further, we will observe whether repeated environmental insults (e.g. prenatal stress and adolescent cannabinoid exposure) amplifies neurobehavioural deficits. Once our model has been developed, we will test whether we can restore NMDAR function and dendritic spine growth. Recombinant Nrg1 (rNrg1) and the atypical antipsychotic clozapine are effective in this regard, therefore they will be the drugs of choice tested in our model.

TECHNIQUES  knockout mice, behavioural analysis, western blotting, visualisation/quantification of dendritic morphology

PROJECT 2  ROLE OF ABC TRANSPORTERS IN CANNABIS-ANTIPSYCHOTIC DRUG INTERACTIONS

A quarter of schizophrenia patients use cannabis and there is little research examining the beneficial or harmful effects of cannabis use on antipsychotic drug therapy. This project aims to investigate whether cannabis use might alter the effectiveness of antipsychotic treatment in schizophrenia patients. Many antipsychotic drugs are substrates for ABC transporters. These transporters are localized at the blood brain barrier where they bind substrates drugs and transport them out of the brain back into the peripheral blood supply. Our work has shown acute cannabinoid exposure inhibits the transport function of the ABC transporters P-gp and BCRP. Therefore, cannabis-using schizophrenia patients may have increased CNS retention of antipsychotic drugs that would either assist in reducing schizophrenia symptoms and/or increase the incidence of side effects. An alternate mechanism whereby cannabis might affect the brain retention of antipsychotic drugs is by altering the expression of ABC transporters. Our preliminary data suggests that longer-term cannabinoid exposure increases P-gp expression at the blood brain barrier. Thus, chronic cannabinoid exposure may reduce brain levels of antipsychotic drugs. Taken together, this project will help illuminate a novel mechanism for cannabis-antipsychotic drug interactions.

TECHNIQUES  knockout mice, behavioural analysis, laser capture microdissection (LCM), qPCR, western blotting, analytical techniques (HPLC and GCMS)

PROJECT 3  DOES DIETING CAUSE CANNABINOID RE-INTOXICATION IN HUMANS?

The main psychoactive constituent of cannabis, THC, is stored in fat for significant periods of time which explains its long elimination half-life. We have recently demonstrated in THC-treated rats that dieting or stress, by promoting fat breakdown, cause THC to be released back into the blood. Accordingly, it is possible that individuals who have kicked their cannabis habit for some time, who decide to go on a diet, may experience a sufficient increase in THC blood levels causing them to be “spontaneously” intoxicated. This phenomenon we have termed “re-intoxication” and it has significant implications for cannabis-related medicolegal cases. This project aims to demonstrate cannabis re-intoxication in human users. Cannabis withdrawing patients will undergo 24 hours of dieting and we will measure whether this increases THC blood levels that correlates with neuropsychological impairment.

TECHNIQUES  human study, neuropsychological tests, analytical techniques (HPLC and GCMS)

Dr Janette BURGESS  
Respiratory Research Group  
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Janette Burgess is one of the international principal pioneers of the work on the extracellular matrix - its role in airway disease - its interaction with structural lung cells, and the potential for pharmacological intervention. Her particular area of expertise is the molecular and cellular biology of lung disease.

PROJECT 1  
Growth Factors Binding to Elastin in the Lung

Elastin, one of the essential proteins in the extracellular matrix in tissues such as arteries, lung and bladder, is composed of interlinked tropoelastin monomers associated with elastin binding proteins such as fibrillins and fibulins. Elastin fibres have been recognised as a reservoir for growth factors sequestered to the extracellular matrix (such as latent transforming growth factor (TGF) β binding proteins). The enmeshing of these growth factors may have important consequences for the behaviour of the cells in this region. How the interaction of growth factors with elastin in the extracellular matrix, and adjacent cells regulates new blood vessel formation is an important question to be answered.

TECHNIQUES  
tissue culture, ELISAs, protein-protein interaction analysis using QCM assays and immunofluorescence and confocal microscopy

PROJECT 2  
The Role of Fibulin 1 in Airway Fibrosis

Recently we have identified a component of the ECM, fibulin-1 which may play a critical role in airway wall remodelling. We now hypothesise that this protein is responsible for the fibrotic component of many lung diseases and therefore represents a target for therapeutic intervention. Accumulating in vivo and in vitro evidence shows that corticosteroids are ineffective in reversing or preventing fibrosis. Since fibulin-1 may play a crucial role in the development of airway fibrosis and aberrant wound repair, then finding ways of inhibiting its deposition or effects has the potential for development of novel therapies for fibrotic diseases.

TECHNIQUES  
tissue culture, ELISAs, immuno and histochemistry and confocal microscopy, real time PCR and signal transduction analysis

PUBLICATIONS.


Our research group is primarily focused on how chemotherapy drugs (currently used and new agents) alter the local and systemic inflammatory response. Our group has shown that inflammation impacts the pharmacological response to chemotherapy in terms of response and toxicity.

We conduct both clinical and preclinical investigations of the response and toxicity induced by chemotherapy drugs to further understand how to improve the treatment of patients with cancer. New drugs are also tested in our research group to limit the toxicity of the current anti-cancer treatments.

PROJECT 1 Investigation of the detoxification pathways for novel chelating agents

*Project co-supervised with Dr Rachel Codd*

Iron overload disease occurs as a secondary complication of blood diseases, such as β-thalassemia, that require treatment by 2-4 weekly blood transfusions. An excess of iron in the body leads to major organ damage and if left untreated is fatal. The current first-line therapy for iron overload (Desferal®) is not orally available and requires patients to endure an arduous subcutaneous or intravenous administration regime for up to 60 hours per week. The first widely available oral iron chelating agent is in the post-surveillance marketing phase - selected patient groups are not able to be treated with this agent.

Additional oral agents that are non toxic and able to selectively bind excess iron are sought. We have designed a series of chelating agents with characteristics (plasma stability, increased lipophilicity) that support the potential for oral administration. Relative to Desferal®, the new agents show lower cellular toxicity and improved cellular iron mobilisation.

To ensure that these drugs have good oral bioavailability this project will investigate the detoxification pathways (drug metabolism enzymes and transporters) for this series of compounds.

**TECHNIQUES** Synthesis, liver and intestinal microsomal preparation, enzyme kinetic assays, HPLC.

Projects in the Chemical Biology in Drug Discovery group sit at the interface of chemistry, biochemistry and microbiology - sometimes with a dash of biotechnology. We isolate compounds used to treat iron overload, infection and cancer and study function at a molecular level. Some projects use traditional chemical synthesis, and other projects use bacteria to produce compounds which we purify from culture using a specialist technique we designed in our group.

**PROJECT 1**  
**STRUCTURE-ACTIVITY RELATIONSHIPS OF DESFERRIOXAMINE B CONJUGATES**  
Desferrioxamine B ($R = H$, DFOB) is used in the treatment of $\beta$-thalassemia to ‘mop up’ excess Fe(III), which accumulates in patients as a result of their receiving frequent blood transfusions. We have made simple modifications to the structure of DFOB to produce new compounds ($R =$ polycyclic cage-based motifs) that have shown improved toxicity and cellular Fe mobilisation measures, compared to DFOB itself. We are now interested in gaining a molecular level understanding of the stability of the new compounds in biological matrices. In this project, you will prepare derivatives of DFOB ($R = H$; or polycyclic cage-based motifs), which vary in the number of amide groups and/or hydroxamic acid groups in the linear chain region and examine the stability of the compounds in plasma and artificial gastric juice.

**TECHNIQUES**  
Synthesis, characterisation and purification, stability studies, HPLC.

**PROJECT 2**  
**DESFERRIOXAMINE B CAPTURE: A NEW TECHNOLOGY**  
We have discovered a streamlined method for selectively capturing the natural metabolite, desferrioxamine B, direct from culture supernatant of *Streptomyces pilosus*. Desferrioxamine B (refer above) is a high-value trihydroxamic acid-based siderophore that binds Fe(III) with high affinity and is used in the treatment of $\beta$-thalassemia. In this project, you will compare the costly, multi-step method of isolating desferrioxamine B from bacterial culture currently used by industry with our single-step affinity technology.

**TECHNIQUES**  
Bacterial culture, affinity chromatography, optimisation, characterisation.

**PROJECT 3**  
**CAPTURE OF BLEOMYCINS FROM STREPTOMYCES VERTICILLUS**  
Bleomycins are a family of metal-dependant glycopeptide-based DNA-cleaving antibiotics produced by *Streptomyces verticillus*, which are used in combination therapy for the treatment of Hodgkin’s disease, head and neck cancer, certain lymphomas and testicular cancer. Bleomycins have complex structures (shown at right) and cannot be synthesized. Bleomycins used in the clinic are isolated from fermentation. Our laboratory is using an affinity-based capture technique for expediting access to biomedically relevant bacterial secondary metabolites. In this project, you will apply this technique to capture molecules that model the metal-binding region of bleomycins as a prelude to capturing bleomycins direct from bacterial culture. A successful outcome to this project will provide a rapid and high yielding route to bleomycins using green technology that will have significant advantages above current processing approaches.

**TECHNIQUES**  
Synthesis, bacterial culture, affinity chromatography, compound characterisation.

Sarah Hilmer leads a geriatric pharmacology research group based at Royal North Shore Hospital. We study pharmacology in ageing, aiming to improve the safety and efficacy of medicines for older people. Using basic experimental pharmacology, we study the hepatic disposition and hepatotoxicity of drugs in our Laboratory of Ageing and Pharmacology in the Kolling Institute. Our clinical pharmacology research measures risk and benefit of drugs in fit and frail older people. Pharmacology honours students are supervised by Dr Slade Matthews (slade.matthews@sydney.edu.au).

PROJECT 1  Pharmacokinetics and pharmacodynamics of fentanyl in old age and frailty

This project aims to improve our understanding of clinical pharmacology in old age and frailty. The target drug, fentanyl, is administered intravenously to patients undergoing upper gastrointestinal endoscopies and colonoscopies. It is a marker of hepatic blood flow and of CYP3A clearance. The student will recruit young, older robust and older frail participants, take 3-4 blood samples for measurement of fentanyl concentrations, and observe participants for respiratory depression. The student will use software to analyse the roles of age, frailty, sex, co-medications, co-morbidities and body composition on pharmacokinetics and pharmacodynamics of fentanyl.

TECHNIQUES  Clinical research (ethics, data collection, blood sampling), PK/PD analysis

PROJECT 2  Isoniazid hepatotoxicity in old age: prevalence and mechanisms

Isoniazid is an antibiotic commonly used to treat tuberculosis. Isoniazid therapy is associated with raised liver function tests in 10-20% of patients and rarely with idiosyncratic serious hepatotoxicity, for which metabolic risk factors have been identified. The risk of drug induced liver disease with isoniazid treatment increases in old age, despite a decrease in Phase I hepatic metabolism, which theoretically reduces formation of the toxic metabolite. This project involves a clinical audit of patients from a tuberculosis clinic to investigate the incidence and risk factors associated with isoniazid toxicity. It will also involve studies of livers from young and old rats treated with toxic doses of isoniazid to investigate the age-associated mechanisms of toxicity.

TECHNIQUES  Clinical audit, immunohistochemistry, western blot, biostatistics

PROJECT 3  Warfarin management in adverse outcomes in older people with atrial fibrillation.

Anticoagulation is indicated for people with atrial fibrillation to prevent stroke. However, adverse events such as ischaemic and haemorrhagic strokes are common in patients taking warfarin, especially in older people. This project investigates the role of warfarin management in these adverse events in patients aged >65 years with atrial fibrillation who have an ischaemic or haemorrhagic stroke. (1) Audit medical records, record whether patients were prescribed warfarin at the time of the stroke, and if so, the INR. (2) Prospective study of inpatients to investigate issues around warfarin management using validated tools. (3) Apply risk assessment tools to this population to investigate whether newer anticoagulants may be appropriate.

TECHNIQUES  Clinical audit and study (ethics, data collection), modelling, biostatistics

PUBLICATIONS.
Drug discovery research within my group is multidisciplinary and at the interface between chemistry and biology. The research is primarily concerned with the understanding of drug-protein and drug-binding site interactions in order to obtain structure-activity relationships of bioactive CNS molecules. This allows the rational design of more efficacious treatments for diseases of the brain. In addition by using molecular imaging within these fields we are able to better understand the living brain in normal and diseased states through in vivo studies.

PROJECT 1  P2X7 RECEPTOR LIGANDS IN THE TREATMENT OF DEPRESSION

Activation of P2X7 receptors (P2X7R) by ATP has been shown to stimulate the release of interleukin-1β (IL-1β) (1). Considering that IL-1β can induce behavioural changes that resemble depression and that P2X7R antagonists play an important role in modulating IL-1β, it could be hypothesized that blockade of P2X7R might result in antidepressant-like properties. This project will involve determining the ability of newly developed P2X7R molecules by our group in reducing IL-1β levels and the evaluation of lead molecules in rat antidepressant behavioural studies.

TECHNIQUES  Cell culture, in vitro functional assays, animal behaviour

PROJECT 2  MEDICINAL AGENTS FOR THE MICROGLIAL TRANSLOCATOR PROTEIN

The recognition that microglia activation is closely linked to the pathophysiology of brain disease has made the translocator protein (TSPO) (18 kDa) an important therapeutic (2). Recently we have identified molecules can be used to treat anxiety and other mood disorders. We have also identified that altering the position of the nitrogens as seen with the imidazopyridazines results in TSPO ligands with 2-5 times higher affinity. This project will involve investigation of the structure activity profile of both classes of compounds at both R1 and R2.

TECHNIQUES  In vitro binding, medicinal chemistry, molecular modelling

PROJECT 3  NICOTINIC LIGANDS FOR THE TREATMENT OF ALZHEIMER’S DISEASE

Nicotinic acetylcholine receptors (nAChRs) play an important role in complex brain functions, and in the pathogenesis of several brain disorders, such as Alzheimer’s disease. The design and synthesise of novel ligands containing 2 pharmacophoric units will allow interaction at multiple sites on this receptor. It is anticipated that these bivalent ligands will bind with co-operativity to enhance ligand affinity and nAChR subtype selectivity. These improved binding characteristics will be important for the development of effective therapeutics.

TECHNIQUES  Medicinal Chemistry

We are interested in the regulation of contractile activity of the vas deferens. This is of importance for the transport of spermatozoa from the testes to the urethra. We are currently exploring various regulatory mechanisms in eliciting rhythmic contractile activity including the involvement of interstitial cells of Cajal, the epithelium and the autonomic neurotransmitters ATP, noradrenaline and acetylcholine. There are three systems available in the laboratory to undertake functional studies: wire myography (project 1 below), pressure myography (project 2 below) and classic organ bath methodology (project 3 below). Experiments are conducted using rat, mouse and guinea-pig tissue. In 2011 we anticipate having access to human vas deferens obtained after vasectomy. The aim is to further our understanding of mechanisms of sperm transport in the vas deferens, which is critical to male fertility.

**Technique 1  Exploring contractility of the vas deferens using wire myography**

Wire myography is a technique used to investigate the function of tubular tissues such as the vas deferens. Using this technique it is possible to study exclusively the contractile activity of circular smooth muscle.

**Technique 2  Contractility of the vas deferens using pressure myography**

In pressure myography tissue is studied under near physiological conditions and permits studies on myogenic and neural regulatory mechanisms.

**Technique 3  Functional studies using a simple organ bath set-up**

We use traditional organ baths to study contractile activity of longitudinal smooth muscle of the vas deferens. This set-up is easy to learn, which is of value in determining tissue viability and sensitivity of preparations to various agents for use in the other systems described above.
Dr Slade MATTHEWS  
Pharmacoinformatics Laboratory  
Room 214, Blackburn Building  
slade.matthews@sydney.edu.au

The Pharmacoinformatics Laboratory uses computer technologies to uncover previously unknown relationships in biomedical data. Pharmacoinformatics incorporates the principles of computerised data management, machine learning techniques and complexity analysis in a pharmacology context. These techniques as well as applied statistics are used on a range of problems in this lab including clinical observational studies and laboratory based data driven studies.

PROJECT 1  IS HEART RATE VARIABILITY A BIOMARKER FOR PSYCHOLOGICAL STRESS ASSOCIATED WITH EXAM PREPARATION?

The rate at which the human heart beats is constantly changing. A decrease in heart rate variability is associated with a decrease in health. This project aims to assess stress levels in and out of exam time and correlate those with heart rate variability.

TECHNIQUES  Interpretation of ECG traces, use of questionnaire data, statistical analysis

PROJECT 2  CELLULAR AUTOMATA MODEL OF PROSTATE CANCER PROGRESSION

Cellular Automata (CA) uses simple rules to model interactions within complex systems. The CA will be built in the R mathematical program. The model cancer will then be compared to published cancer behaviour.

TECHNIQUES  Construction of artificial intelligence models

PROJECT 3  COMPUTER MODELLING OF DURATION-DEPENDENT ANTIGEN ABLATION THERAPY OUTCOMES IN PROSTATE CANCER

Despite a primary response rate of 80%-90% with hormonal ablation, almost all patients, in due course, advance to a state of androgen independence. The aim of this project is to produce a systematic review of current practice and to model length of androgen ablation on either side effect outcomes or its influence on new cancer relapse.

TECHNIQUES  Systematic review. Computer models. External supv.: Dr Craig McLachlan

PROJECT 4  BLOOD PRODUCTS and RESUSCITATION: TRENDS IN ICU's

A large international multi site clinical trial (NICE sugar study) for intensive glucose control was recently completed by the George Institute. Key publications for the NICE data set appeared in BMJ and New England Journal of Medicine. The study examined intensive care insulin therapy for 6000 patients and mortality outcomes. We are interested in exploring this data set with respect to ICU use of blood products. This will be contrasted to patients that received fluid therapy only or combinations with blood products.

TECHNIQUES  Data set provided in collaboration with George Institute. Exposure to design issues in clinical trials and data capture. External Supervisors: Dr Craig McLachlan, Colman Taylor

Dr Brent McPARLAND  
Smooth Muscle Mechanics Laboratory  
Room 304/5, Blackburn Building  
brent.mcparland@sydney.edu.au

The Smooth Muscle Mechanics Laboratory studies mechanics and mediators which influence narrowing of the airways in respiratory disease such as asthma and chronic obstructive lung disorders.

PROJECT 1  Compounds which inhibit agonist interaction with its target receptor.

The epithelium provides a barrier between the outside and the inside of the body. The epithelium has several mechanisms by which it provides a barrier to the external environment. Air can contain stimuli that potentially can provoke the airways to contract. Tight junctions between the epithelium restrict entry of external stimuli and it also secretes mediators which can modify the effect caused by external stimuli. This project will investigate whether charged molecules alter the interaction between contractile drugs and the receptor target. Our objective at the fundamental level is to shift the concentration-curve generated to a contractile agonist rightward so as to decrease its effective potency and thereby attenuate airway narrowing.

TECHNIQUES  Dissecting skills, organ bath experiments, histology; driver’s license essential.

PROJECT 2  Development of an in vitro breathing apparatus

People with asthma have airways that narrow excessively and the reason for this is not known. We believe that the mechanisms involved in airway relaxation may be impaired in asthma. Airways are relaxed by circulating adrenaline or by inhaled β2-agonists. Breathing itself can also relax the airways, since during breathing the smooth muscle within the airways stretch, which in turn decreases contractile power. To investigate the effect of stretch on airway narrowing, in vitro, an apparatus is required that can simulate the effect of breathing. For this project a mechanical breathing apparatus will be developed using a tube/segment of airway tissue in an organ bath. Breathing will be simulated by controlling the amount of fluid within the tissue using computer controlled motors and the feedback will be provided by a pressure transducer. The motion control program used will be Labview [http://www.ni.com/labview/].

TECHNIQUES  Computing skills (Labview), building/integrating equipment (2 direct current motors and specialised pressure transducer).

PROJECT 3  Discovering the elusive epithelial-derived hyperpolarising factor

The reason why the airways of asthmatics narrow excessively is not known. We believe that some mechanisms involved in airway relaxation may be impaired. The epithelial cells that line the airways appear to release mediators that can decrease contraction of the airway smooth muscle. This study will investigate how effective the epithelial-derived mediator(s) is/are at inhibiting the effect of contractile mediators such as histamine and acetylcholine. The effectiveness will be compared with other relaxing factors such as prostaglandin E2 and adrenergic agonists (adrenaline, isoprenaline, salbutamol).

TECHNIQUES  Dissecting skills, organ bath experiments, histology; driver’s license essential.

My research group is investigating why viruses cause exacerbations of airways diseases such as asthma and chronic obstructive airways disease (COPD). We have developed several in-vitro systems which enable us to mimic and assess what happens when a virus infects the airways. In our experiments we are able to use cells from people both with and without diseases to establish if they respond differently to virus infection.

PROJECT 1  Is rhinovirus-induced inflammation different in COPD?

Emerging evidence suggests that rhinovirus is a causative factor during exacerbations of chronic obstructive pulmonary disease (COPD). The prevalence of COPD continues to rise, currently affecting 3.5% of the Australian population. COPD is the 5th leading cause of death (4th worldwide) and costs $700 million annually in direct health care expenditure. COPD exacerbations result in approximately 50,000 hospitalisations annually in Australia, and are associated with a more rapid disease progression. It is therefore vital to better understand the role of viral infections in exacerbations of COPD. This project will establish if the host response to rhinovirus is different in COPD.

TECHNIQUES  Cell culture, qPCR, Western blotting, ELISA

PROJECT 2  What stops rhinovirus infections?

Following rhinovirus infection of the lungs a massive influx of inflammatory cells occurs. It is thought that the role of these inflammatory cells is to limit virus infection. However exactly how this occurs is not known. This project will assess the interaction that occurs between virally infected lung cells and inflammatory cells. You will determine if the presence of inflammatory cells up regulates innate immune mechanisms that aid in viral clearance, or conversely, determine if greater rhinovirus replication occurs in the presence of the inflammatory cells.

TECHNIQUES  Insert techniques In-vitro cell isolation and culture, virological assays, protein assays

PROJECT 3  Why do asthma therapeutics stop working when people have a cold?

Asthma exacerbations are characterised by worsening asthma symptoms and a fall in lung function. Exacerbations can be mild, however a large proportion are life threatening and require hospitalisation. In NSW alone there were 22,942 emergency department visits for asthma in 2007, of which 42% were admitted to hospital. Rhinovirus (RV), which causes the majority of common colds, is responsible for at least half of all asthma exacerbations. Whilst asthma medications, such as steroids and $\beta_2$ agonists, reduce the frequency of exacerbations they do not completely stop virus induced exacerbations from occurring. This project will determine the molecular events initiated by rhinovirus which result in impaired therapeutic action.

TECHNIQUES  Cell culture, immunoprecipitation, western blotting, fluorescence microscopy

Glutamate is the predominant excitatory neurotransmitter in the mammalian central nervous system and activates a wide range of receptors to mediate a complex array of functions. Extracellular glutamate concentrations are tightly controlled by a family of glutamate transporters expressed in both neurons and glia. The aim of our research is to develop a structural model for how glutamate transporters work, and in this way lay the foundations for a more rational approach to the development of drugs that are both transporter-specific and subtype selective. Such compounds will help to delineate the roles of different transporter subtypes in normal brain functions and also in various neuropathological conditions, such as ischemia following a stroke, Alzheimer’s disease and motor neurone disease.

**PROJECT 1  Understanding glutamate transporters using chimeras**

The glutamate transporter family is made up of proteins from several species and includes the human EAATs, the prokaryotic homologue GltPh, and also a human neutral amino acid transporter ASCT1. All of these proteins share significant amino acid homology and share some functional properties but also exhibit some differences. This project will exploit the similarities and differences between these 3 transporters by making chimeric transporters, which are part of one transporter and part of another. By making several different combinations we can begin to identify which parts of the protein are important for conferring differences between the different members of the glutamate transporter family.

**TECHNIQUES**  molecular biology; electrophysiology; radiolabelled uptake

**PROJECT 2  Identifying the role of a large extracellular loop of the EAATs**

The human EAATs share about 37% amino acid identity with GltPh, and the structure of GltPh appears to be a good model for the human glutamate transporters. An exception to this is that the EAATs contain a large extracellular loop (~80 amino acids in length) that does not exist in GltPh. We do not have any structural information about this loop and we don’t know how it interacts with the rest of the protein. The aim of this project is to understand the functional importance of this loop in the EAATs and how this region interacts with other parts of the transporter. Is this loop required for proper targeting and expression of the protein? Or is it required for substrate transport and/or ion coupling? This information will further our understanding of the mechanism of transport by the EAATs.

**TECHNIQUES**  molecular biology; electrophysiology recordings; protein localisation studies

**PUBLICATIONS.**
Ryan RM, Kortt NC, Sirivanta T, Vandenberg RJ (2010)
The position of an arginine residue influences substrate affinity and K(+) coupling in the human glutamate transporter, EAAT1. *Journal of Neurochemistry* (Epub 06/05/10).

Ryan RM, Compton EL, Mindell JA (2009)

Huang S, Ryan RM, Vandenberg RJ (2009)

Research in the Transporter Biology Group is focused on understanding the molecular basis for neurotransmitter transporter functions and how this can be manipulated by endogenous regulators and pharmacological agents. Glycine is an unusual neurotransmitter in that it acts on inhibitory glycine receptors and excitatory NMDA receptors. The Glycine Transporter GLYT1 regulates the concentrations of glycine at excitatory synapses, whilst a combination of GLYT1 and GLYT2 are required for regulation of glycine at inhibitory synapses. GLYT1 inhibitors are currently under trial for the treatment of schizophrenia, whilst GLYT2 inhibitors may have potential as analgesics in the treatment of chronic pain.

**PROJECT 1 Defining Drug Binding Sites on GLYT1**

Although a number of GLYT1 inhibitors are under clinical trials for the treatment of Schizophrenia, very little is known about their mechanism of inhibition of GLYT1 or how they interact with the transporter. In this project you will characterize the binding sites on GLYT1 for a series of novel GLYT1 inhibitors. Figure on right is of the drug, clomipramine bound to the leucine transporter, LeuT. Similar models will be generated for GLYT1 to identify drug binding sites. The models will be tested by site-directed mutagenesis combined with electrophysiology techniques.

**TECHNIQUES** Molecular biology, site-directed mutagenesis, electrophysiology, molecular modelling

**PROJECT 2 Identification of Na⁺ binding sites in GLYTs**

Glycine transport by GLYT1 is coupled to the co-transport of 2Na⁺ and 1Cl⁻, whereas glycine transport by GLYT2 is coupled to the co-transport of 3Na⁺ and 1Cl⁻. This difference in co-transported Na⁺ ions is responsible for differences in concentrating capacity between the two transporters. In this project you will investigate the molecular basis for Na⁺ coupling of glycine transporters by identifying amino acid residues that bind Na⁺ ions. A combination of site-directed mutagenesis, electrophysiology and molecular modelling will be used.

**TECHNIQUES** Molecular biology, site-directed mutagenesis, electrophysiology, molecular modelling

**PUBLICATIONS.**


Where are they now?

Honours is a fantastic year in itself, but is also a springboard to postgraduate studies and careers in industry and government. Shown in the Table below are the current positions of a selection of students who have completed Honours or a Graduate Diploma in Pharmacology.

<table>
<thead>
<tr>
<th>Name</th>
<th>Completed</th>
<th>Current Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phuoc Huynh</td>
<td>2010</td>
<td>PhD Candidate (Pharmacology, University of Sydney)</td>
</tr>
<tr>
<td>Carleen Fernandez</td>
<td>2010</td>
<td>PhD Candidate (Centenary Institute)</td>
</tr>
<tr>
<td>Vivian Liao</td>
<td>2010</td>
<td>Research Assistant (Chemical Biology Group)</td>
</tr>
<tr>
<td>Dmitry Goloskokov</td>
<td>2010</td>
<td>Laboratory Aide (Douglass Hanly Moir Pathology)</td>
</tr>
<tr>
<td>Lauren Brites</td>
<td>2009</td>
<td>Research Assistant (EnGeneIC)</td>
</tr>
<tr>
<td>Sai Krishnan</td>
<td>2009</td>
<td>PhD Candidate (Children’s Medical Research Institute)</td>
</tr>
<tr>
<td>Marietta Salim</td>
<td>2009</td>
<td>Research Assistant (Transporter Biology Group)</td>
</tr>
<tr>
<td>Areeg Hamdi</td>
<td>2009</td>
<td>Masters Candidate (Pharmacy, University of Sydney)</td>
</tr>
<tr>
<td>Steven Devenish</td>
<td>2008</td>
<td>PhD Candidate (Pharmacy, University of Sydney)</td>
</tr>
<tr>
<td>Nicholas Kortt</td>
<td>2008</td>
<td>Medicine (University of Notre Dame)</td>
</tr>
<tr>
<td>Phoebe Hone</td>
<td>2008</td>
<td>Research Assistant (Veterinary Science)</td>
</tr>
<tr>
<td>Cho Zin Soe</td>
<td>2007</td>
<td>PhD Candidate (Pharmacology, University of Sydney)</td>
</tr>
<tr>
<td>Jonathon Tobin</td>
<td>2007</td>
<td>Medicine (University of Wollongong)</td>
</tr>
<tr>
<td>Jessica Kermale</td>
<td>2007</td>
<td>PhD Candidate (Woolcock Institute of Medical Research)</td>
</tr>
<tr>
<td>Amelia Eddington</td>
<td>2007</td>
<td>PhD Candidate (Pharmacology, University of Sydney)</td>
</tr>
<tr>
<td>Alana Scarf</td>
<td>2007</td>
<td>PhD Candidate (Brain &amp; Mind Research Institute)</td>
</tr>
<tr>
<td>Chiu Chin Ng</td>
<td>2006</td>
<td>PhD Candidate (Pharmacology, University of Sydney)</td>
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<tr>
<td>Tim Bakas</td>
<td>2006</td>
<td>MPhil Candidate (Pharmacology, University of Sydney)</td>
</tr>
<tr>
<td>Brina Sheriff</td>
<td>2005</td>
<td>Poisons Information Centre</td>
</tr>
<tr>
<td>Nathan Gunasekaran</td>
<td>2005</td>
<td>PhD (University of Sydney), Medicine (University of Notre Dame)</td>
</tr>
</tbody>
</table>
Discipline of Pharmacology: Honours Preference Form (2011)

This form must be submitted to the Honours Coordinator by: Friday 26 November 2010

An application for Honours must be lodged at the Faculty of Science by: Thursday 25 November 2010.

I wish to apply for the following course in 2011 (circle choice):

BSc (Hons)  BSc Adv (Hons)  BMedSc (Hons)  Graduate Diploma

I intend starting my studies in (circle choice): Semester 1 or Semester 2.

STUDENT DETAILS:

First Name

Family Name

SID

E-mail

Postal address

Phone (home)

Phone (mobile)

STUDENT PREFERENCES:

Please list your preferences for an Honours supervisor (from 1st to 4th preference). You must provide 4 names.

1

2

3

4

STUDENT TRANSCRIPT:

Please attach your academic transcript (photocopy or original) to this application.

Return to: Dr Rachel Codd, Room 274 Blackburn Building (D06)