PHARMACOLOGY,  
SCHOOL OF MEDICAL SCIENCES,  
THE UNIVERSITY OF SYDNEY

PHARMACOLOGY HONOURS PROJECTS FOR 2010

Science and Medical Science students with a sound record in pharmacology are encouraged to enrol in an Honours year in Pharmacology. An Honours degree in Pharmacology provides training in a wide range of scientific research methods, and is highly regarded by prospective employers in private industry, government and research institutions. Honours graduates benefit from wider employment possibilities, and also have the opportunity to proceed to a postgraduate degree (MSc or PhD). Students can elect to start their Honours year in second semester.

Pharmacology

We have strong research interests in the areas of central nervous system, medicinal chemistry, respiratory, cancer and clinical pharmacology, and receive research funding from the National Health and Medical Research Council and other health and industrial/pharmaceutical organisations. The Discipline is located on the main university campus on levels 1 and 2 of the Bosch Building (phone 02-9351-6958 level 2, Bosch Building or level 2 of the Blackburn Building, phone 02-9351-3819). Our fax number is 02-9351-3868.

We are well equipped for research and teaching, with good facilities for isolated tissue work, behavioural investigations, biochemical and molecular pharmacology, electro-physiological, ligand binding, microscopy, neurochemical and synthetic chemical studies, together with a mechanical and electrical workshop. There is also a new animal house facility in the Bosch Building.

Major items of equipment include nuclear magnetic resonance, atomic absorption and ultraviolet spectrometers, gas chromatograph-mass spectrometer, high performance liquid chromatographs, and beta and gamma radiation counters. There are on-line computers for anatomical, autoradiographical, behavioural, electrophysiological analyses and facilities for data and word processing. The Medical Library, housed on level 3 of the Bosch Building, is a comprehensive library with computer-assisted search facilities.
Eligibility for Pharmacology Honours

To qualify to enrol in Honours in 2010, the Faculty of Science requires:

(i) that students have qualified for the award of a pass degree; or be a pass graduate of the Faculty of Science; or be a pass graduate holding a Bachelor of Science degree or an equivalent qualification from another institution

(ii) that students have completed a minimum of 24 credit points of Senior units of study relating to the intended honours course (or equivalent at another institution).

(iii) that students have achieved credits in the relevant Senior Science units of study, and a SCIWAM of at least 65.

For students who do not meet these criteria, the Faculty of Science has a Graduate Diploma in Science. The Graduate Diploma in Science serves as an entry qualification for the degrees of Master of Science or Doctor of Philosophy. It consists of equivalent work to that carried out by candidates enrolled in the fourth year honours courses, and is normally available to candidates who may not be eligible to enrol in those courses. The normal duration of the degree is one year full time or two years part time and is fee-paying.

Application for Enrolment

You will need to complete two forms:-

• a Faculty of Science application form (see below) generally no later than Friday 30th October 2009 (international students) or Friday 26th November 2009 (local students) - please check the following website for updated details: http://www.science.usyd.edu.au/cstudent/ug/downloads/honours_info.pdf

• a Pharmacology application form available at the end of this document or from the website (http://www.usyd.edu.au/pharmacology) no later than 26th November 2009.

Faculty of Science application form

This form must also be submitted. Note that Faculty applications should be submitted no later than 30th October for international students or 26th November for local students for admission to Honours in semester 1, 2010

Current university of Sydney Students
Prospective Honours students currently enrolled in semester 2, 2009 in the Faculty of Science at the University of Sydney should look at:- http://www.science.usyd.edu.au/cstudent/ug/course/honours/index.shtml

Students from Other Universities in Australia
Prospective Honours students who have completed their degrees at other institutions, as well as Sydney students who have taken a break from their studies, should also examine the Faculty of Science website Honours information

International Students
International students, who are newly enrolling, should apply through the International Office http://www.usyd.edu.au/future_students/international_undergraduate/index.shtml
International students who are already students at the university should apply through BOTH the 1) International Office (above) and 2) through the Faculty of Science (with departmental signature) http://www.science.usyd.edu.au/cstudent/ug/course/honours/apply.shtml
Pharmacology application form
Prospective students should make their interest known to the relevant member of staff or the Fourth Year Coordinator and complete the Departmental application form, which is attached. Students are asked to list their project preferences (up to 5), and this list should include at least 3 project supervisors. These project preference forms should be submitted to us as early as possible and no later than 26th November 2009.

This should be given to Dr Jasmine Henderson (Honours co-ordinator) Room 211d Bosch, Phone 9036 9408, email jasmine@med.usyd.edu.au or Dr Rachel Codd (Honours sub-coordinator) Room 306 Blackburn Building, phone 9351 6738, email rcodd@med.usyd.edu.au

Honours selection:
A meeting to allocate students to projects is held soon after 3rd year results are available (early December). All students who have submitted an application to enrol in the Honours course (including those who apply to start in second semester) will be informed of our decision. The Faculty has a policy whereby notification of the outcome of your application will be made by the Faculty by early January 2009 for ‘main round’ offers. Applications for those starting in second semester will occur in April/May 2010.

The Pharmacology Honours course
(a) Aims
The aims of the course are to provide training in the performance of scientific research by introducing you to a particular area of research in pharmacology, and to provide experience in verbal and written presentation of the results of that research. The emphasis on presentation is to guide you in the preparation of material suitable for submission to professional journals, and as oral, poster and abstract communications to professional societies. The extensive use of personal computers is also encouraged in order to increase computer literacy with respect to scientific/technical data management and analysis, word processing, database searching and reference management.

(b) Structure
The course involves each student working on a research project under the close supervision of a senior member of staff. We will assign students to projects and supervisors on the basis of availability of staff, space and facilities, following consultations with prospective students and supervisors. The following timetable describes the course for students starting in first semester. The program for students who start in second semester is shown (in italics).
In April (*September*), you will submit a draft research proposal to the three members of staff who are assigned to mark your literature review and final thesis. They will provide comment on your proposed research plan.

In May (*October*), you will submit a literature survey which describes the background to your project and will make a ten minute oral presentation describing the background and proposed research plan.

Your main presentations will be in November (*June*), when you submit a thesis embodying the results and a critical discussion of your year’s work. The thesis has a page limit of 50 pages (including all illustrative and bibliographical material). Also in November (*June*), you will be present a 15 minute seminar on your research achievements during the year.

During the year you will need to attend the Pharmacology seminars which are held at 12-1pm on Wednesdays. These seminars may take the form of in-depth research seminars or broadly-based general interest topics related to pharmacology. You will also be required to attend a number of special workshops for Honours students and to prepare contributions for some of these. Some of these are integrated with other disciplines in the School of Medical Sciences in the Bosch New Investigators Workshops which also gives the opportunity to meet other students from both Pharmacology and other disciplines.

(c) **Assessment**

The grade of Honours is awarded by the Faculty of Science on the basis of your work during the year; First Class = 80+, Second Class Division I = 75 – 79, Second Class Division II = 70 - 75, or Third Class = 65 - 69. Your ability to undertake a research project successfully and to submit a well-written account of this work in the form of a thesis is of central importance to your Honours assessment.

The components for assessment are as follows:
- Research Proposal 5%
- Literature survey 15%
- 1st talk 10%
- Thesis 50%
- Final oral presentation 10%
- Performance assessment/logbook 10%

(d) **Prize**

*Dorothy Thorp Prize*. The Dorothy Thorp Prize is awarded for excellence in science communication by a student in the Honours course. All students will attend a workshop to discuss the importance of science communication to the media and general public. At the workshop sessions, you will be given scientific articles to use as the basis for writing a press release or scientific article to be read by the general public. Your submission will be judged by external judges with expertise in science communication. The Dorothy Thorp Prize will be awarded on the judges’ recommendation.

**Starting Date**

Your starting date will be decided by you and your Supervisor but will normally be no later than mid February 2010.
Research Interests

Honours projects offered are part of the research interests of the staff members and laboratories concerned, and the following pages give details of some of the research activities undertaken in Pharmacology. Fuller details of research, together with other information, is available on the web at http://www.usyd.edu.au/pharmacology

Please note that prospective students must contact the staff member concerned to discuss potential projects in detail.

It is possible that other projects will be available by arrangement with particular members of staff or collaborators. Such projects will be placed into a file on the Pharmacology website later in the year (by mid October). Please contact individual staff members to discuss updated details of projects.

Honours scholarships:
For outstanding students and award $6000. This will depend on undergraduate performance. Further information and the application form can be found at: http://www.science.usyd.edu.au/cstudent/ug/scholarships.shtml

PHARMACOLOGY HONOURS PROJECTS FOR 2010

Note- for more projects please check our website from mid-late October http://www.usyd.edu.au/pharmacology/

Respiratory Research Group projects

DR BRENT MCPARLAND
Senior Lecturer
Room 304/5 Blackburn Building (D06)
Smooth Muscle Mechanics Laboratory 228 Blackburn Building
Phone 9036 6477
Email brentmcparland@med.usyd.edu.au

Projects:
1) Glucocorticosteroids (GCs) are one of the major treatment options for asthma. GCs are thought to predominately work through a cytosolic receptor which then translocates to the nucleus where they can interact with DNA promoter regions. It is assumed that the receptors then move out from the nucleus back into the cytosol where they are available to interact with GCs again. To date we do not know how long it takes for the receptor to move back to the nucleus and whether at actually occurs in human airway cells. The aim of this project is to investigate the kinetic profile of the human corticosteroid receptor in airway smooth muscle.
2) The airway epithelium provides a “powerful” barrier to inhaled substances. This project will investigate the role of the barrier using pig airways obtained from a local abattoir (Picton 3 hr return trip). A driver’s license will be required for this project and good dissecting skills is essential.

3) Development of an in vitro breathing device using pressure feedback and computer programming. A background in programming (Labview) is desirable for this project.

Please call see me if you are interested in these project.

Can viruses stop \( \beta_2 \)-agonists from working?

**DR BRIAN OLIVER**  
Room 211C Bosch Building, tel 93512315.

**BACKGROUND**

**Asthma exacerbations cause substantial morbidity, mortality and health care costs.** Asthma exacerbations are characterised by worsening asthma symptoms and a fall in lung function, and contribute substantially to the cost and burden of asthma. In NSW alone there were 22,942 ED visits for asthma of which 42% were admitted to hospital in 2007\(^1\). The annual cost per person for hospital admissions can reach $23,766. In addition to the direct medical costs, the costs of absenteeism are thought to account for 50% of the total cost of treating asthma in Australia.

**Rhinovirus infection cause asthma exacerbations.** Viruses are identified in 80% of asthma exacerbations in children and 45-80% in adults \(^2\). Rhinovirus, which causes the majority of common colds, is responsible for at least half of asthma exacerbations.

**\( \beta_2 \)-agonist efficacy is reduced during viral exacerbations.** Under normal circumstances, asthmatic airway obstruction improves characteristically briskly in response to inhaled \( \beta_2 \)-adrenergic agonists (e.g., salbutamol), which are the most commonly used asthma therapy in most Western countries. Loss of response to \( \beta_2 \)-agonist is often the trigger for hospital presentation\(^4\), and may be life-threatening. During an exacerbation there is objective evidence that an impaired response to \( \beta_2 \)-agonists occurs\(^5\). We believe that the mechanisms by which viral exacerbations occur are distinct from those operating when asthma control is inadequate, since exacerbations can occur in otherwise well controlled asthmatics\(^5\).

**Surprisingly, given the importance of rhinovirus infections in acute exacerbations of asthma the mechanism by which rhinovirus induces an impaired response to \( \beta_2 \)-agonists is not known.**

**HYPOTHESIS**

The impaired response to short-acting \( \beta_2 \)-agonists which occurs with viral infections in asthmatic patients is due to \( \beta_2 \)-receptor dysfunction.

**PRELIMINARY DATA**

We have data which shows that factor(s) released from RV infected bronchial epithelial cells cause decreased \( \beta_2 \)-agonist-induced cAMP in airway smooth muscle. However there are several unanswered questions:

1) We also don’t know if the impaired \( \beta_2 \)-agonist-induced cAMP can be restored by the addition of more \( \beta_2 \)-agonist

2) We don’t know how quickly the factor is produced in rhinovirus infected epithelium

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[1]: mailto:brianol@usyd.edu.au
3) we don’t know if this phenomena is restricted to rhinovirus or is common to other viruses.

4) We don’t know if other causes of asthma exacerbations eg allergens also result in impaired β2-agonist-induced cAMP.

The aims of this project would be to choose 1 or 2 of the research ideas from the above list and investigate this for your honours. You would also evaluate weather current asthma therapeutics effect experimental outcomes. You would use an in vitro tissue culture model to investigate your aims. Typical techniques would include primary cell culture, real time PCR, FACS and western blotting.

**Does Tumstatin regulate inflammation asthma?**

**DR BRIAN OLIVER** brianol@usyd.edu.au,
**DR JANETTE BURGESS** janette@med.usyd.edu.au
Room 211C Bosch Building, tel 93512315.

Asthma is a complex and multi-factorial disease of the airways in which both inflammation and remodelling are important. Remodelling includes alterations in the extracellular matrix (ECM). Inflammation is largely treatable through the use of current therapeutics such as corticosteroids, however upon cessation of treatment inflammation reoccurs. We have discovered that an endogenous anti-inflammatory and antiangiogenic molecule, tumstatin, derived from the ECM, is absent from the airways of asthmatics.

Tumstatin is the non-collagenous (NC)-1 domain of the collagen IV α3 chain. Collagen IV, a major constituent of the basement membrane, exists in the ECM when any three of the six collagen IV α chains combine. We have identified the presence of the NC-1 domains of all six collagen IV α chains in non-asthmatic human lung sections, **however tumstatin was absent in all asthmatic lung sections irrespective of treatment, age and severity.**

ECM proteins are important in the regulation of the inflammatory process, with fragments of collagen having both pro- and anti-inflammatory properties. Whilst tumstatin is known as an angiogenic inhibitor, it also has anti-inflammatory properties which may be mediated via modulation of cytokines and/or chemokines produced by inflammatory cells.

**Hypothesis**

That the absence of tumstatin in the asthmatic airway is a major contributory factor to the underlying pathophysiological mechanism through which asthma occurs.

**Specific aims**

to determine if the lack of tumstatin leads to an enhanced inflammatory response in the asthmatic airway by a) directly altering the basal or stimulated release of inflammatory chemokines and cytokines (IL6, IL8, eotaxin, VEGF and Ang-1) from inflammatory cells.

**Methods**

In this project lymphocytes will be isolated from peripheral blood and human lung tissue. You will then use an in-vitro cell culture system to evaluate how these cells respond to tumstatin. This project will use the latest molecular biological techniques (eg siRNA, real time PCR, ELISA western blotting).

**Outcomes and Significance:** Airway inflammation, a cardinal characteristic of asthma, is usually well controlled by corticosteroids. However, this approach only controls the symptoms and not the underlying cause of the disease. Our novel observation that tumstatin, an antiinflammatory and antiangiogenic molecule is absent from asthmatic airways presents an opportunity for innovative ways of targeting inflammation in asthma.
Pulmonary lymphangioleiomyomatosis (LAM)

DR LYN MOIR
lmoir@usyd.edu.au
Room 222 Bosch Building, phone 9036 7693

Pulmonary lymphangioleiomyomatosis (LAM) is a progressive and usually fatal rare lung disease that affects almost exclusively young females and for which there is no treatment. The average age of onset for LAM disease is between 25 and 40 years of age. During the progression of the disease abnormal smooth muscle-like cells known as LAM cells invade the healthy lung tissue and obstruct the airways, blood and lymph vessels, preventing the lungs from functioning properly. Scientific research over the last 10 years has shown that LAM is associated with genetic mutations in the tuberous sclerosis genes, tuberous sclerosis complex 1 (TSC1) and TSC2. In particular, loss of function of TSC2 results in phenotypic manifestation of the disease. Dysfunction of TSC2 has been associated with altered cellular function including cell growth, migration and invasiveness. However, the cellular and molecular mechanisms of LAM disease are not well understood.

The aim of this study is to investigate the role of TSC2 in the enhanced cellular functions associated with LAM. By understanding the role of TSC2 we will enhance our knowledge of the basic mechanisms of LAM disease.

To investigate the aim you would use an in vitro tissue culture model. Other typical techniques include gel electrophoresis (Western blotting), flow cytometry, immunohistochemistry and real-time PCR.

Other types of projects available in Pharmacology

DR JONATHON ARNOLD
Senior Lecturer & Director of Cannabinoid Research Group
School of Medical Sciences (Pharmacology) and Bosch Institute
Phone: 9036 5361; Mobile: 0409744724
Email:arnie@med.usyd.edu.au; Web:http://www.usyd.edu.au/pharmacology/CRGweb

Role of ABC transporters in resistance to antipsychotic therapy and cannabinoid-antipsychotic drug interactions

Treatment-resistant schizophrenia is a major stumbling block in the clinical management of this disorder. Clozapine is the treatment of choice in patients whose positive symptoms are poorly managed by other antipsychotic drugs (APDs). Here we hypothesise that clozapine’s high efficacy is at least partly explained by its inability to bind and be transported by ABC transporters located at the barrier between the brain and the blood supply. The brain levels and consequent effectiveness of many other commonly prescribed APDs are strongly regulated by ABC transporters. For example, olanzapine and risperidone bind to such transporters that expel these drugs from the brain back into the blood. This action of ABC transporters reduces the brain levels of APDs and explains why patients are resistant to their therapeutic effects, in contrast to clozapine which is unaffected by ABC transport and is effective in treatment-resistant patients. Accordingly, one of the aims of this proposal is to
determine the extent to which commonly prescribed APDs are exported from the brain by different ABC transporters and how these transporters may cooperate in regulating the brain levels of APDs. In addition, we also aim to observe whether prolonged APD exposure alters the amount of ABC transporters found in the brain. This could explain the need to increase APD dose in some patients over time. The second dimension to the current proposal addresses the problem of cannabis use by schizophrenia patients. This provides cause for concern as little research has examined the effects of cannabis consumption on the effectiveness of APDs. My research group has recently shown that cannabis-like drugs affect ABC transporters. Therefore the simultaneous administration of cannabis and APDs may lead to a drug interaction due to their common effect on ABC transporters. To illustrate, long-term cannabis use may increase the amount of ABC transporters in the brain thereby decreasing the brain levels of APDs - the increased transporter number allows more of the APD to be pumped out of the brain. Our findings would justify closer inspection in the clinical population of the involvement of ABC transporters in APD treatment-resistance and cannabis-APD interactions which may ultimately help to reduce patient suffering and social/economic costs associated with schizophrenia.

DR RACHEL CODD
Lecturer
School of Medical Sciences (Pharmacology) and Bosch Institute
Blackburn Building D06: Room 306
Phone: 9351-6738; email rcodd@med.usyd.edu.au

Our group uses a chemical biology approach to access and characterise molecules (proteins, secondary metabolites) that provide platforms for drug design and drug discovery (antibiotics, anticancer agents, iron-overload treatments). Our principal interest lies in a class of molecules called siderophores (Greek for ‘iron carrier’), which are produced by pathogenic and non-pathogenic bacteria in order to sequester iron, which is an element fundamental for life. Hydroxamic acid-based siderophores have therapeutic applications for patients with beta-thalassemia who suffer from iron-overload disease. The metal-binding capacity of siderophores and siderophore mimics has exciting applications in the treatment of cancer and for the design of new antibiotics that exploit the regular bacterial iron-uptake pathway. We are also isolating siderophores from bacteria that reside under environmental extremes (‘extremophiles’). Students are invited to talk with me about projects that may be tailored to suit individual research interests.

Selective 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. The complexity of the structures of bleomycins and the related phelomycins prevents laboratory preparation; access to these compounds, therefore, relies on fermentation. Our laboratory is using an affinity-based capture technique for expediting access to biomedically relevant bacterial secondary metabolites. In this project, you will examine the potential of the technique to capture molecules that model the metal-binding region of bleomycins as a prelude to capturing bleomycins direct from bacterial culture. During the course of the project, new molecules, aside from bleomycins, may be discovered. 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. This project will suit a student with an interest in chemical biology, molecular biotechnology and/or microbiology.
Animal modelling of Parkinson’s disease
Parkinson’s disease (PD) characterised by symptoms such as bradykinesia, rigidity, tremor and postural instability. Pathologically there is loss of dopaminergic neurons in the substantia nigra pars compacta. Development of novel therapeutics relies upon preclinical studies using animal models of PD. In my laboratory, we are using the unilateral 6-hydroxydopamine (toxin-induced) model of PD as well as a 6-OHDA model incorporating thalamic degeneration. We have been testing antioxidants and glutamate antagonists to see if they reduce cell loss and have symptomatic benefits in these animal models of PD. We have also been collaborating with A/Prof Michael Kassiou (BMRI) and recently found that BZAD-01 (a selective NMDA NR2B antagonist) reduces cell loss when administered as a pretreatment prior to lesioning and is associated with improved symptoms. We have also found that low dose EGCG, a catechin found in green tea produces mild improvement in motor dysfunction. A project along these lines could be suited towards an Honours student.

1. How well can non-statistical machine learning techniques interpret data from microarray experiments?
Supervisor: Matthews
Micro-array experiments are increasing in number and complexity with an exponential rate. The analysis of resulting data has led to the evolution of new statistical techniques and exciting new applications of machine learning algorithms. This project will involve the use of the Weka suite of machine learning algorithms to re-examine downloaded micro-array data from published experiments. MLA will be used to re-evaluate the strength of association. This project provides the opportunity to learn about applied artificial intelligence, the nature of micro-array data from chip-based experiments and the development of new statistical techniques.

2. Is heart rate variability a biomarker for psychological stress associated with exam preparation?
Supervisor: Matthews, Associate Supervisors: Jelinek, McLachlan
The rate at which the human heart beats is constantly changing in order to adapt to the environment. A decrease in heart rate variability is thought to be associated with a decrease in physiological well being that accompanies a number of disease conditions. Many people report an increase in illness at the time of exams and the number of special consideration forms received by the university increases dramatically at this time. This project aims to assess stress levels in and out of exam time and correlate those values with levels of heart rate variability. If there are changes in heart rate variability associated with exam stress this will tell us not only about a new biomarker but also about the level of physiological trauma we subject ourselves to when taking a course at Sydney University.
Pharmacology of Old Age projects

A/PROF SARAH HILMER (shilmer@med.usyd.edu.au)
Head of Department, Clinical Pharmacology and Staff Specialist, Aged Care and Rehabilitation, Royal North Shore Hospital; Associate Professor, Sydney Medical School, University of Sydney.

DR SLADE MATTHEWS (sladem@med.usyd.edu.au)
Lecturer, Discipline of Pharmacology, Sydney Medical School, University of Sydney.

These projects are based predominantly at Royal North Shore Hospital in the Department of Clinical Pharmacology. Interested students should arrange to visit the Department and meet A/Prof Hilmer.

Optimisation of gentamicin dose for treatment of older hospital patients
Supervisor: Dr Slade Matthews, Co-supervisor Dr Sarah Hilmer

Background: Gentamicin is commonly used to treat gram negative infections (eg urinary tract infections) in older hospital inpatients. This antibiotic has a narrow therapeutic index. Accurate dosing must account for the effects of body composition and renal function, which may vary with frailty. A previous study in our laboratory suggests that in patients receiving prophylactic gentamicin (not septic) frailty is associated with a lower volume of distribution and impaired clearance of gentamicin, with possible implications for calculation of loading and maintenance doses. Sepsis itself may also impact on the pharmacokinetics of gentamicin.

Aims: Describe the pharmacokinetics of gentamicin in older hospital inpatients. Compare pharmacokinetics between frail and non-frail (robust) older patients. Consider implications for dosing of gentamicin in frail older hospital patients with sepsis.

Methods: Recruit older patients who are prescribed gentamicin to treat an infection. Assess weight, height, frailty and comorbidities. Collect blood to estimate renal function and to measure gentamicin levels and calculate its pharmacokinetics.

Isoniazid hepatotoxicity in old age
Supervisor: Dr Sarah Hilmer, Co-supervisor: Dr Slade Matthews

Background: Isoniazid is an antibiotic commonly used worldwide as part of the treatment of tuberculosis. Isoniazid is associated with liver toxicity. Epidemiologic data suggests that hepatotoxicity is more common in older people. This may be due to exposure to multiple hepatotoxins, pharmacokinetic or pharmacodynamic factors.

Aim: Investigate the risk of isoniazid hepatotoxicity with old age.

Methods: (1) Conduct a review of the medical records of patients treated with isoniazid in the chest clinic at RNSH. Describe the factors above that may contribute to hepatotoxicity and any clinical indicators of hepatotoxicity in this population. Compare these factors between different age groups. (2) Examine livers from young and old rats treated with toxic doses of isoniazid using histology and immunohistochemistry. Describe markers of injury and cell death in each age group.

A/PROF QIHAN DONG AND PROF PAUL SEALE

Fatty acid, Akt and prostate cancer
Contact: Dr Dong, room 394 Medicine (endocrinology) Blackburn Building D06, Ph 9515 5186; email qhd@med.usyd.edu.au

Co-supervisor: Prof Paul Seale, Head of Pharmacology, Room 301, Blackburn.

Prostate cancer is the second most commonly-diagnosed malignancy after skin cancer and second only to lung cancer in males in terms of cancer-related death in Australia. We have
established that an aberrant activation of the arachidonic acid (AA) pathway occurs in human prostate cancer tissue. This project aims to determine the relationship between AA and other key pathways (e.g. PI3K/Akt) in prostate cancer and therapeutic potential by targeting the AA pathway. Honours students will learn the techniques of molecular biology (qRT-PCR and Western), biochemistry (AA release) and cell biology (cell culture and immunostaining) to investigate the role of the AA pathway in the growth of prostate cancer cells.

A/PROF ROBERT VANDENBERG AND DR RENAE RYAN
Transporter Biology Group
Rm 223 Blackburn Building
Ph: 9351 6734
Email: rvan9242@mail.usyd.edu.au

Neurotransmitter transporters play many crucial roles in regulating the dynamics of neurotransmission. Our lab works on various aspects of glutamate and glycine transporter functions and we use a range of techniques to address questions such as: How do these proteins work? How do drugs interact with the transporters? How does the membrane environment influence transporter function? Research in the Transporter Biology group is supported by 2 NHMRC project grants.

Project 1: Molecular Basis for K+ coupling of Glutamate Transporters

Glutamate plays many vital roles in the central nervous system and it is important to tightly regulate glutamate concentrations to maintain dynamic signalling processes between neurones. Glutamate transport is coupled to the co-transport of 3 Na+, 1 H+ and the counter-transport of 1 K+, which is able to support a 10^6 fold gradient across the cell membrane. However, under ischaemic conditions following a stoke, the collapse of Na+ and K+ gradients reduces the concentrating capacity of the transporter and may lead to reverse transport and subsequent excitoxicity. In this project you will investigate the molecular basis for K+ counter-transport by glutamate transporters. The neutral amino acid transporter, ASCT, is closely related to the human glutamate transporters, but shows distinct differences. One such difference is that ASCT does not require K+ counter-transport. You will construct a series of chimeric transporters that are part glutamate transporter and part neutral amino acid transporter to identify domains of the transporter that are required for K+ coupling. The project will involve learning techniques in molecular biology, including PCR, DNA cloning, DNA sequencing and RNA transcription and also techniques in electrophysiology using Xenopus laevis oocytes.

Project 2: Characterization of Drug Binding sites on Glycine Transporters

Glycine is an unusual neurotransmitter in that it is both excitatory and inhibitory and a number of recent studies have suggested that inhibition of glycine transporter may be a very useful way of treating a variety of neurological disorders. Enhancement of excitatory neurotransmission by inhibition of the glycine transporter GLYT1 has recently been investigated as a potential antipsychotic therapy. Conversely, enhancement of inhibitory neurotransmission by inhibition of the glycine transporter GLYT2 shows particular promise in the development of novel analgesics in the treatment of chronic pain. This project will investigate the molecular basis for drug selectivity of GLYT1 and GLYT2 inhibitors so as to provide a detailed description of the three dimensional structure of the drug binding sites. This project will complement ongoing studies in the laboratory aimed at developing high affinity novel GLYT inhibitors as potential therapeutics. In this project you will learn molecular biology techniques such as PCR, site-directed mutagenesis and also techniques in electrophysiology using Xenopus laevis oocytes.

Prospective honours students should come and see Robert Vandenberg or Renae Ryan to discuss these projects in more detail.
Addiction and driving

Opioid treatment programs (OTPs) are a core clinical initiative of NSW Health, with over 20,000 people currently participating in treatment in NSW alone. The number of clients taking both methadone and buprenorphine long term is on the rise, along with concerns about adverse effects for these individuals and the community. In particular, the potential for opioid substitution therapies to impair cognitive and psychomotor functioning has implications on the driving ability of these patients. Nevertheless, very little is currently known about the effects of long-term opioid maintenance on driving. Furthermore, no studies have addressed the issue of pre-dosing influences (i.e. 22-24 hours after last dose = trough plasma levels) on driving, nor have the effects of poly-drug driving received much attention. The purpose of this project is to gain direct experimental evidence of the effect of buprenorphine and other commonly taken substances (alcohol and alprazolam) on driving performance using a state-of-the-art driving simulator.

A/PROF MICHAEL KASSIOU
Brain and Mind Research Institute
University of Sydney
Phone: 9351 0849
E-mail: mkassiou@med.usyd.edu.au

DRUG DISCOVERY / MEDICINAL CHEMISTRY / MOLECULAR IMAGING

My research group 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 rationale design of more efficacious treatments for diseases of the brain. In addition by using molecular imaging techniques within these fields we are able to better understand the living brain through in vivo studies. The following is a sample of what is offered and projects which can be tailored to specific student interests.

Medicinal chemistry of CNS active molecules

We have an extensive medicinal chemistry program evaluating structure-activity relationships of a number of molecules varying from polycyclic to heterocyclic scaffolds that interact with specific targets we think are involved in brain disease. The purpose of these studies is to identify lead molecules that can be further developed into drug candidates for the treatment of disease. These projects will involve the synthesis of a series a compounds that aid in the identification of structural motifs responsible for optimizing activity. Please inquire for specific details.
PHARMACOLOGY
Application for 4th Year Programme – 2010

Before you complete this form, you must discuss projects in which you are interested with the appropriate supervisor.
This form must be submitted to Pharmacology by 26 November 2009

I WISH TO APPLY FOR THE FOLLOWING COURSE IN 2010:
(please circle the appropriate course)

BSc (Hons) / BMedSc(Hons) / Graduate Diploma

Name: ____________________________________________

SID #: __________________________ Current Course: __________________________

Address: ____________________________________________
(for contact during vacation)

Telephone: __________________________
(for contact during vacation)

Home: __________________________
Mobile: __________________________
Email: __________________________

ACADEMIC RECORD:

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<th>YEAR</th>
<th>SUBJECT</th>
<th>GRADE / MARK</th>
<th>WAM (if known)</th>
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4TH YEAR PROJECT & SUPERVISOR (list 5 options in order of preference)

1. ____________________________________________
2. ____________________________________________
3. ____________________________________________
4. ____________________________________________
5. ____________________________________________