

THE UNIVERSITY OF  
**SYDNEY**

# Honours in Pharmacology

## Graduate Diploma in Pharmacology

2012

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Projects and Program Information

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## Message from the Head of Discipline and Honours Coordinator



**Professor Robert Vandenberg**  
Head of Discipline

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.



**Dr Rachel Codd**  
Honours  
Coordinator

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. This booklet is designed to provide further details about the Honours program and describes in some detail the projects on offer to students in 2012. We hope you'll join us.

Please contact the Honours Coordinator (Dr Rachel Codd: [rachel.codd@sydney.edu.au](mailto: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:

**Friday 23 September at 12 noon in Bosch Lecture Theatre 1.**

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 20 of this booklet), which is due on **Wednesday 30 November 2011**. 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 **Wednesday 30 November 2011**. 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.

## Academic staff

Name <sup>a</sup>	Location <sup>b</sup>	Research Area
Dr Jonathon Arnold	BKB: 307	Endogenous cannabinoid system, behavioural neuropharmacology
Dr Elena Bagley	BKB: W326	Synaptic physiology/plasticity, synaptic function/dysfunction, brain disorders
Prof. Judy Black	WIMR	Asthma pharmacology, smooth muscle culture, inflammation
A/Prof Janette Burgess	WIMR	Asthma, angiogenesis, molecular biology, gene discovery
Dr Kellie Charles	BKB: 306	Cancer pharmacology, tumour-immune cell interactions
Prof MacDonald Christie	BKB: W326	Cellular/molecular neuropharmacology, pain pathways and pain therapeutics
Dr Rachel Codd	BKB: 274	Chemical biology and medicinal chemistry, metals in biology
Dr Heidi Fedorow	BKB: 211f	Parkinson's disease and neurodegenerative disorders
A/Prof Sarah Hilmer	RNSH: W11c	Geriatric medicine and clinical pharmacology
Dr Tina Hinton	BKB: 294	GABAergic neurotransmission in the CNS, schizophrenia
Prof. Michael Kassiou	BMRI	Drug design and medicinal chemistry, CNS active compounds
Dr Hilary Lloyd	BKB: 219	Neurotransmitter release mechanisms, neuroprotection
Dr Slade Matthews	BKB: 214	Machine learning in biomedicine
Dr Brent McParland	BKB: 304	Asthma pharmacology, human bronchus, smooth muscle
Dr Lenka Munoz	BKB: TBA	Glioblastoma, p38 MAPK inhibitors, medicinal chemistry
Dr Brian Oliver	WIMR	Respiratory pharmacology
A/Prof. Renae Ryan	BKB: 212	Biophysics of membrane transport, glycine transport
Prof. Paul Seale	BKB: 301B	Clinical pharmacology, asthma, corticosteroids
Dr Margaret Sunde	BKB: TBA	Protein biophysics, protein misfolding, amyloid fibril formation and structure
Prof. Robert Vandenberg	BKB: 223	Molecular biology, glutamate transport, electrophysiology

<sup>a</sup> To e-mail staff, the generic format is: [firstname.familyname@sydney.edu.au](mailto:firstname.familyname@sydney.edu.au).

For example: [rachel.codd@sydney.edu.au](mailto:rachel.codd@sydney.edu.au).

<sup>b</sup> 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.

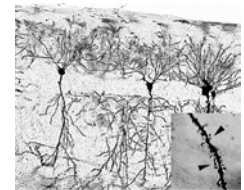
**Dr Jonathon ARNOLD**  
**Cannabinoid Research Group**  
Room 307, Blackburn Building  
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The Cannabinoid Research Group led by Dr Jonathon Arnold conducts a diverse array of research on the pharmacology of cannabis, the most widely used illegal drug in the world.

## 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.

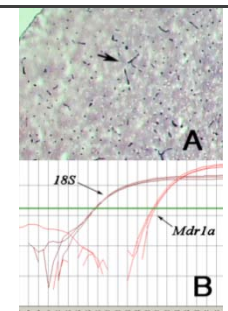


Hippocampal CA1 pyramidal neurons and dendritic spines stained in our lab

**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 substrate 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.



A) Rat blood brain barrier microvessels. B) Amplification plot for *Mdr1a* mRNA and 18S rRNA from microvessels.

**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.



This research was covered in the *New Scientist* and the *Sun Herald*.

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

**PUBLICATIONS.** Carson, D, Hunt, G, Guastella, A, Barber, L, Cornish, J, Arnold, J, Boucher, A, McGregor, I (accepted 9/6/2010) Systemically administered oxytocin decreases methamphetamine activation of the subthalamic nucleus and accumbens core and stimulates oxytocinergic neurons in the hypothalamus *Addiction Biology*. Long, L, Chesworth, R, Arnold, J, Karl, T (accepted 23/5/10) A follow up study: Acute behavioural effects of  $\Delta^9$ THC in female heterozygous Neuregulin 1 transmembrane domain mutant mice. *Psychopharmacology (Berl)*. Long, LE, Chesworth, R, Huang, XF, McGregor, IS, Arnold, JC, Karl, T (2009) A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. *Int J Neuropsychopharmacol*: 1-16. Gunasekaran, N, Long, LE, Dawson, BL, Hansen, GH, Richardson, DP, Li, KM, Arnold, JC, McGregor, IS (2009) Reintoxication: the release of fat-stored Delta(9)-tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *Br J Pharmacol* 158(5): 1330-1337.

**Dr Elena Bagley**  
**Synaptic Physiology and Plasticity**  
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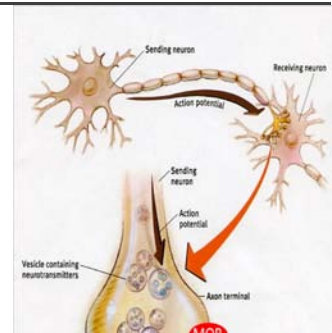


Our research group is interested in normal synaptic function and synapse dysfunction. Synaptic dysfunction is emerging as a key player in many brain disorders. We use patch-clamp electrophysiology in brain slices, immunohistochemistry and biochemical assays to study synaptic properties and synaptic plasticity that may participate in physiological or pathophysiological processes. These honours projects focus on how endogenously released opioid peptides alter synaptic function and plasticity in the amygdala.

Fear and anxiety are adaptive responses that allow animals to defend themselves against harm. Neural circuits in the amygdala are key for fear memory acquisition and storage but also for reducing the fear response (extinction). Extinction of the fear response relies on a special group of GABAergic interneurons in the amygdala, the intercalated cells.

### PROJECT 1 Do opioids inhibit cortical glutamate release onto amygdala neurons?

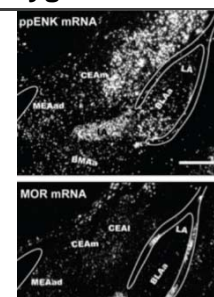
The intercalated cells can be activated by glutamatergic inputs/synapses from the cortex and from the basolateral amygdala. When activated these cells inhibit the amygdala output neurons and reduce the expression of the fear response. Intercalated neurons express very high levels of the  $\mu$ -opioid receptor (MOR) and the endogenous opioid ligand enkephalin. We are interested in whether endogenous opioids modulate intercalated cell activity. This project will study whether the glutamatergic inputs from the cortex are inhibited by opioids.



**TECHNIQUES** In vitro patch-clamp electrophysiology

### PROJECT 2 Does stress change endogenous opioid expression in the amygdala?

Enkephalins are endogenous opioids that are strongly expressed in the amygdala and are thought to be involved in several aspects of fear. Mice deficient in the enkephalin precursor, preproenkephalin, are highly anxious and aggressive. Intercalated neurons (IA in figure) express very high levels of the  $\mu$ -opioid receptor (MOR) and the endogenous opioid ligand enkephalin. Stress or anxiety may change enkephalin expression in the amygdala. This project will determine whether a stressful experience alters enkephalin expression in the intercalated cells.



**TECHNIQUES** Immunohistochemistry, biochemistry

#### PUBLICATIONS.

Bagley EE, Hacker J, Chefer V.I., Chieng B.C. McNally G.P., Shippenberg T.S. & Christie M.J. GAT-1 transporter currents excite GABAergic neurons to produce opioid withdrawal behaviour. Accepted Aug 17<sup>th</sup> 2011 Nature Neuroscience,  
Thomas CG, Krupp JJ, Bagley EE, Bauzon R, Heinemann SF, Vissel B, Westbrook GL. (2006) Probing NMDA receptor desensitization with the substituted-cysteine accessibility method. Mol Pharmacol.  
Bagley EE, Chieng BC, Christie MJ, Connor M. (2005) Opioid tolerance in periaqueductal gray neurons isolated from mice chronically treated with morphine. Brit J Pharmacol. 2005 Sep;146(1):68-76.  
Hack SP, Bagley EE, Chieng BC, Christie MJ. (2005) Induction of delta-opioid receptor function in the midbrain after chronic morphine treatment. J Neurosci. 25:3192-8.  
Bagley EE, Gerke MB, Vaughan CW, Hack SP, Christie MJ. (2005) GABA transporter currents activated by protein kinase A excite midbrain neurons during opioid withdrawal. Neuron. 45:433-45.

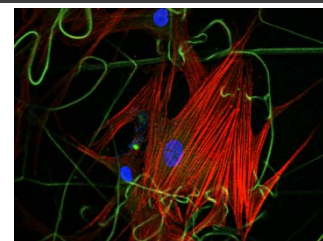
**Assoc Prof Janette BURGESS**  
***Respiratory Research Group***  
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Janette Burgess is one of the international principal pioneers of the work on the extracellular matrix - its role in airway disease - its interaction with structural lung cells, and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

## PROJECT 1 Elastin in the Lung

Airway remodelling, including alterations in the extracellular matrix, is a characteristic feature of persistent asthma that is resistant to modification by current therapies. One of these alterations is a distinct fragmentation of elastin. These elastic fibres are needed to maintain airway elasticity but recently have been ascribed a role in regulating the behaviour of the resident airway cells. We want to learn whether cells from asthmatic and nonasthmatic donors have differences in their ability to synthesize elastin and the content of the resulting matrices. In addition, we will assess the functional characteristics of the resultant matrices with a focus to on how they pertain to the regulation of airway remodeling.



Airway smooth muscle cell interacting with elastin fibres

**TECHNIQUES** tissue culture, ELISAs, cell proliferation and migration and immunofluorescence and confocal microscopy

## PUBLICATIONS.

1. Justine Y Lau, Brian G Oliver, Melissa Baraket, Emma L Beckett, Nicole G Hansbro, Lyn M Moir, Steve D Wilton, Carolyn Williams, Paul S Foster, Philip M Hansbro, Judith L Black, **Janette K Burgess** (2010). Fibulin-1 is increased in asthma - a novel mediator of airway remodelling? PLoS ONE 5(10): e13360 doi:10.1371/journal.pone.0013360
2. **Janette K. Burgess**, Qi Ge, Maree H. Poniris, Sarah Boustany, Stephen M Twigg, Judith L. Black and Peter R.A. Johnson 2006 Connective tissue growth factor and vascular endothelial growth factor from airway smooth muscle interact with the extracellular matrix. American Journal of Physiology- Lung Cellular and Molecular Physiology, DOI, 10.1152/ajplung.00287.2005, Vol 290:(1)L153-L161.
3. \*Peter R.A. Johnson, \***Janette K Burgess**, Qi Ge, Maree Poniris, Sarah Boustany, Stephen Twigg and Judith L. Black (\*These authors contributed equally) 2006 Connective tissue growth factor induces extracellular matrix in asthmatic airway smooth muscle American Journal of Respiratory and Critical Care Medicine, Vol 173 (1):32-41.
4. **Burgess JK**, Oliver BG, Poniris MH, Ge Q, Boustany S, Cox N, Moir LM, Johnson PRA and Black JL. 2006 A phosphodiesterase 4 inhibitor inhibits matrix protein deposition in airways in vitro. Journal of Allergy and Clinical Immunology, Sep;118(3):649-57. Epub 2006 Jul 20 Editor's Choice article.
5. **Janette K Burgess**, Sarah Boustany, Lyn M Moir, Markus Weckmann, Justine Y Lau, Karryn Grafton, Melissa Baraket, Philip M Hansbro, Nicole G Hansbro, Paul S Foster, Judith L Black, Brian G Oliver (2010). Reduction of Tumstatin in asthmatic airways contributes to angiogenesis, inflammation and hyperresponsiveness. Am J Resp Crit Care Med 181:106-115

**Dr Kellie CHARLES**  
**Cancer Therapeutics Group**  
Room 306, Blackburn Building  
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*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.*

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### **PROJECT 1     Investigation of drug metabolism gene SNPs on chemotherapy response**

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The response to chemotherapy differs widely between individuals. Differences in drug metabolism, in particular detoxification enzymes, are important to overall systemic exposure and response to chemotherapy. Single nucleotide polymorphisms (SNP) in drug metabolising enzymes genes play a large role in determining the enzymatic activity.

This project will investigate the role of SNPs in the drug metabolism pathways of FEC (5-fluorouracil, epirubicin and cyclophosphamide) combination therapy in blood samples isolated from cancer patients. Genotypic expression status will be correlated with drug pharmacokinetics and response, toxicity or survival.

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**TECHNIQUES**     DNA isolation, PCR, Taqman Real-time PCR, biostatistics

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**PUBLICATIONS.** Morgan, E., Goralski, K., Piquette-Miller, M., Renton, K., Robertson, G., Chaluvadi, M., Charles, K., Clarke, S., Kacevska, M., Liddle, C., Richardson, T., Sharma, R., Sinal, C. Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. *Drug Metabolism and Disposition*. 2008; 36:205-216. Charles, K., Rivory, L., Brown, S., Liddle, C., Clarke, S., Robertson, G. Transcriptional repression of hepatic cytochrome P450 3A4 gene in the presence of cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2006; 12:7492-7. Charles, K., Rivory, L., Stockler, M., Beale, P., Beith, J., Boyer, M., Clarke, S. Predicting the toxicity of weekly docetaxel in advanced cancer. *Clinical pharmacokinetics*. 2006; 45:611-22.

**Dr Rachel CODD**  
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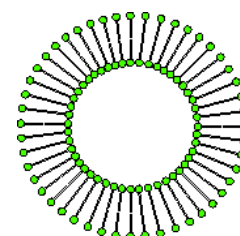
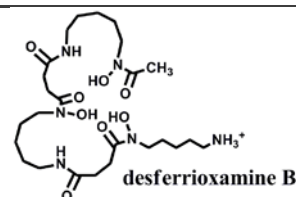


*Projects in the Chemical Biology in Drug Discovery group sit at the interface of chemistry, biochemistry and microbiology - sometimes with a dash of biotechnology. We isolate compounds used to treat iron overload, infection and cancer and study function at a molecular level. Some projects use traditional 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 LIPOSOMES AS A DELIVERY OR ANALYTICAL PLATFORM IN IRON OVERLOAD

*Project co-supervised with A/Prof Renae Ryan*

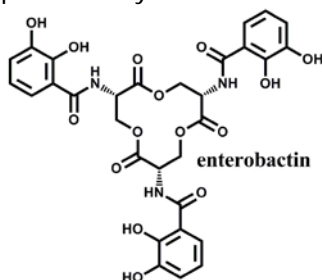
About 350 people in Australia have life-threatening blood disorders that require a blood transfusion every 3-4 weeks to survive. Frequent blood transfusions causes iron to accumulate which if left untreated can lead to major organ damage. To achieve iron balance, patients are treated daily with compounds that form complexes with Fe(III) that are able to be excreted. Desferrioxamine B (at right) binds Fe(III) strongly, but is not orally active and has a difficult-to-tolerate administration regimen. New orally active agents in clinical use have varied efficacy and toxicity profiles. Efforts to design new iron-overload compounds and to assess *in vitro* efficacy are ongoing. In this project you will design a liposome-based assay that predicts the ability of known and new Fe(III)-binding compounds designed in our laboratory to traverse the cell membrane to access intracellular iron stores. New studies of improved delivery or administration of desferrioxamine B will also be studied.



**TECHNIQUES** Liposome assembly, assay design, biochemistry, synthesis/characterisation (optional).

## PROJECT 2 CATECHOL CAPTURE VIA IMMOBILISED METAL AFFINITY CHROMATOGRAPHY

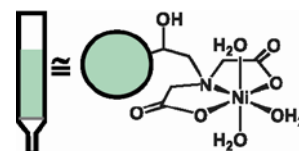
Siderophores are low-molecular-weight organic compounds that bind Fe(III) with high affinity and are produced by bacteria to acquire essential iron from the environment or host. The ability to bind Fe(III) and other transition metal ions confers value upon siderophores as therapeutic agents for iron overload and as metallo-enzyme inhibitors. Siderophores are structurally diverse and have been classified into three families: hydroxamic acids, catechols and hydroxycarboxylic acids. We have shown that immobilised metal affinity chromatography captures hydroxamic acid-based siderophores from bacterial culture. In this project, you will determine the utility of the method towards capturing catechol-based siderophores and mixtures of siderophores from different classes. Our target siderophore (enterobactin) has the highest binding towards Fe(III) of any known molecule.



**TECHNIQUES** Immobilised metal affinity chromatography, biodiscovery, characterisation.

## PROJECT 3 INFORMING THE MECHANISM OF AFFINITY-BASED HYDROXAMATE CAPTURE

We have discovered that immobilised metal affinity chromatography captures high-value hydroxamic acid-based siderophores from bacterial culture. In this project you will examine the relationship between the denticity of the immobilised chelate (iminodiacetic acid, nitriloacetic acid) upon the efficacy of capturing bi-, tetra- and hexa-dentate hydroxamic acids. You will prepare heteroleptic coordination compounds to inform the binding stoichiometry.



**TECHNIQUES** Immobilised metal affinity chromatography, optimisation, coordination chemistry

**PUBLICATIONS.** Liu, J.; Obando, D.; Schipanski, L. G.; Groebler, L. K.; Witting, P. K.; Kalinowski, D. S.; Richardson, D. R.; Codd, R. Conjugates of Desferrioxamine B (DFOB) with Derivatives of Adamantane or with Orally Available Chelators as Potential Agents for Treating Iron Overload. *J. Med. Chem.* 2010, 53, 1370-1382. Braich, N.; Codd, R. Immobilized Metal Affinity Chromatography for the Capture of Hydroxamate-Containing Siderophores and Other Fe(III)-binding Metabolites from Bacterial Culture Supernatants. *Analyst* 2008, 133, 877-880. Codd, R. Traversing the Coordination Chemistry and Chemical Biology of Hydroxamic Acids. *Coord. Chem. Rev.* 2008, 252, 1387-1408.

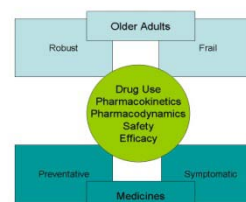
**A/Professor Sarah HILMER**  
**Northern Clinical School**  
Royal North Shore Hospital  
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*Sarah Hilmer leads a geriatric pharmacology research group based at Royal North Shore Hospital. We study pharmacology in ageing, aiming to improve the safety 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 co-supervised by Dr Slade Matthews ([slade.matthews@sydney.edu.au](mailto:slade.matthews@sydney.edu.au)) and Professor Peter Carroll ([peter.carroll@sydney.edu.au](mailto:peter.carroll@sydney.edu.au)), with associate supervisor Dr Danijela Gnjidic ([danijela.gnjidic@sydney.edu.au](mailto:danjela.gnjidic@sydney.edu.au)).*

### PROJECT 1 Clinical pharmacology of preventative and symptomatic medicines in frail older patients with osteoporotic fractures

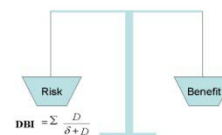
There are changes in all aspects of clinical pharmacology with old age and frailty. This project will describe and compare drug use, pharmacokinetics, efficacy and safety of preventative medicines (treatments for osteoporosis) and symptomatic medicines (analgesics) in a cohort of robust and frail older inpatients with osteoporotic fractures. The student will recruit patients and collect information on sociodemographics, diagnoses and medicines. Patients will be assessed for frailty, pain relief and adverse events. Blood samples will be collected for paracetamol pharmacokinetic analyses in a subgroup. Results will inform therapeutic guidelines for older patients.



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

### PROJECT 2 Drug Burden Index vs polypharmacy as a risk assessment tool in hospital patients

Polypharmacy (taking increasing numbers of medicines) is associated with an increased risk of adverse drug events. However, medicine dose and action are also likely to be important predictors of outcomes. The Drug Burden Index (DBI) is a pharmacologic tool that measures a person's total exposure to medicines with anticholinergic and sedative effects based on principles of dose response and maximal effect. DBI is associated with functional decline and falls in older people living in the community more strongly than polypharmacy. This study aims to assess the associations of polypharmacy and DBI with adverse drug events in older patients admitted to hospital. The student will recruit older inpatients, and collect and analyse information on sociodemographics, diagnoses, medicines, function and frailty.



**TECHNIQUES** Clinical research (ethics, data collection), biostatistics

#### PUBLICATIONS.

Perera V, Bajorek B, Matthews S, Hilmer SN. The Impact of Frailty on the Utilization of Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Age and Ageing* 2009 38(2):156-62.

Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, Windham BG, Harris TP, Hanlon JT, Rubin SM, Shorr RI, Bauer DC, Abernethy DR. A drug burden index to define the functional burden of medications in older people. *Archives of Internal Medicine* 2007; 167: 781-7.

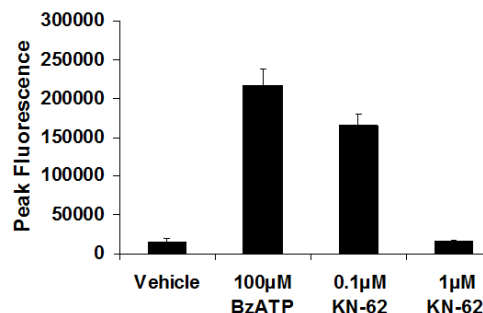
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Drug discovery research within my group is multidisciplinary and at the interface between chemistry and biology. The research is primarily concerned with the understanding of drug-protein and drug-binding site interactions in order to obtain structure-activity relationships of bioactive CNS molecules. This allows the rational design of more efficacious treatments for diseases of the brain.

### PROJECT 1 P2X<sub>7</sub> RECEPTOR LIGANDS IN THE TREATMENT OF DEPRESSION

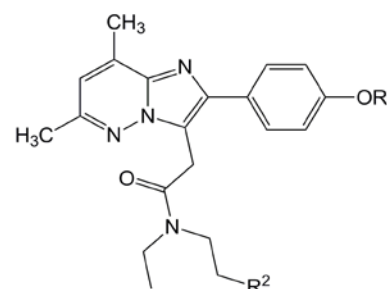
Activation of P2X<sub>7</sub> receptors (P2X<sub>7</sub>R) by ATP stimulates the release of interleukin-1 $\beta$  (IL-1 $\beta$ ) (1), inducing behavioural changes that resemble depression. It is hypothesised that blockade of P2X<sub>7</sub>Rs might result in antidepressant-like properties. This project will determine the ability of P2X<sub>7</sub>R molecules, newly developed by our group, to reduce IL-1 $\beta$  levels and the evaluation of lead molecules in rodent antidepressant behavioural studies.



**TECHNIQUES** Cell culture, in vitro functional assays, animal behaviour

### PROJECT 2 MEDICINAL AGENTS FOR THE MICROGLIAL TRANSLOCATOR PROTEIN

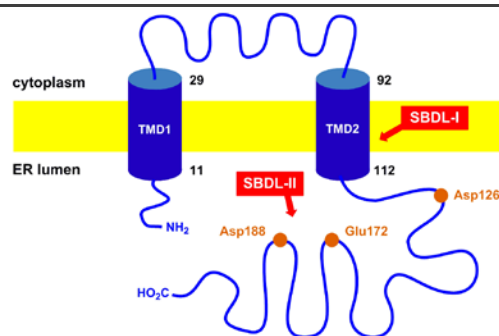
The recognition that microglial activation is closely linked to the pathophysiology of brain disease has made the translocator protein (TSPO) (18 kDa) an important therapeutic (2). Recently we have identified molecules can be used to treat anxiety and other mood disorders. We have also identified that altering the position of the nitrogens in the heterocyclic core profoundly affects both TSPO binding and functional activity. This project will involve investigation of the structure-activity profile of imidazopyridazines at both R<sup>1</sup> and R<sup>2</sup>.



**TECHNIQUES** In vitro binding, medicinal chemistry, molecular modelling

### PROJECT 3 SIGMA LIGANDS AS NEUROPROTECTIVE AGENTS IN BRAIN DISEASE

During brain injury, microglia become activated and migrate to areas of degenerating neurons. These microglia release proinflammatory cytokines and reactive oxygen species causing additional neuronal death. Microglia express high levels of sigma receptors, however, the function of these receptors in microglia and how they may affect the activation of these cells remain poorly understood. This project will evaluate the ability of a library of sigma ligands attenuate the release of nitric oxide and cytokines.



**TECHNIQUES** Cell culture, cell based assays, ELISA

**PUBLICATIONS.** (1) Gunosewoyo H, Coster MJ, Bennett MR, Kassiou M. (2009) Purinergic P2X<sub>7</sub> receptor antagonists: Chemistry and fundamentals of biological screening. *Bioorg. Med. Chem.* 17, 4861-4865. (2) Scarf AM, Ittner LM, Kassiou M (2009) The translocator protein (18 kDa): Central nervous system disease and drug design. *J. Med. Chem.* 52, 581-592.

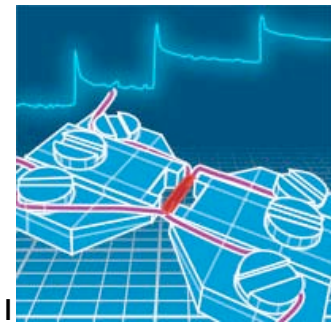
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*We are interested in the regulation of contractile activity of the vas deferens. This is of importance for the transport of spermatozoa from the testes to the urethra. We are currently exploring various regulatory mechanisms in eliciting rhythmic 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 2012 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.



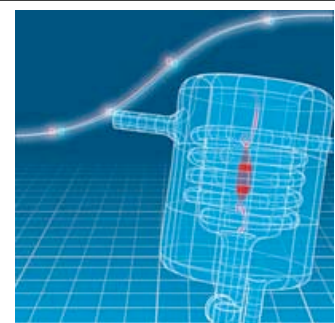
### Technique 2 Contractility of the vas deferens using pressure myography

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.



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*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

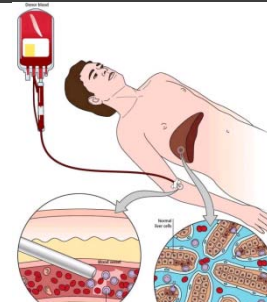
Cellular Automata (CA) uses simple rules to model interactions within complex systems. The CA will be built in the R mathematical program. The model cancer will then be compared to published cancer behaviour.



**TECHNIQUES** Construction of artificial intelligence models

### PROJECT 3 GAMMA GLOBULIN BIOMARKER-DOSE EFFICACY STUDY

It is possible to measure gamma globulin in the serum in various clinical states? We aim to measure pre and post gamma globulin administration levels. Dosages of Gamma Globulin are suspected to be elevated for 3-4 weeks following a specific single dose, in some conditions the elevated response is less than 5 days. Are elevated levels of gamma globulin are dosage dependent? Gamma Globulin Drives Th2-inducing T cells and stimulates IL-4. Measurement of IL-4 as a biomarker for gamma globulin dose-dependent changes in IL-4. This work aims to improve the efficient use of precious/rare blood-derived resources in the Australian Community.



**TECHNIQUES** Data Analysis and Laboratory Based Techniques at Australian Red Cross Laboratories.  
External supv.: Dr Hugh Capper, Dr Craig McLachlan

#### RECENT STUDENT PUBLICATIONS.

1. S. J. Mitchell, S. N. Hilmer, B. P. Murnion, S. Matthews. (2010) Hepatotoxicity of therapeutic short-course paracetamol in hospital inpatients: impact of ageing and frailty. *Journal of Clinical Pharmacy and Therapeutics*
2. Sarah N Hilmer, Kim Tran, Patrick Rubie, Jason Wright, Danijela Gnjidic, Sarah J Mitchell, Slade Matthews, Peter R Carroll (2010) Gentamicin Pharmacokinetics in Old Age and Frailty. *British Journal of Clinical Pharmacology*
3. McLachan CS, Taylor CB, Li Y, Willenberg L, Matthews S, Glass P, Myburgh J. (2010) Severe falciparum malaria patients transferred "late" to a high level ICU in India represents a difficult research capture point to comment on predictors of mortality and related organ dysfunction. *Singapore Medical Journal* 51(9): 752-3.
4. Craig S. McLachlan, PhD, MPH, Ryan Ocsan, MSc, Ian Spence, PhD, Brett Hambly, MD, PhD, Slade Matthews, PhD, Lexin Wang, MD, PhD, and Herbert F. Jelinek, PhD. (2010) Increased total heart rate variability and enhanced cardiac vagal autonomic activity in healthy humans with sinus bradycardia. *Proc (Bayl Univ Med Cent)* 23(3):1-3.
5. Perera, V., Bajorek, B., Matthews, S. and Hilmer, S. (2009) The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age and Ageing* 38: 156-162.
6. Sarah J Mitchell, Bridin P Murnion, Slade T Matthews, Sarah N Hilmer (2009) Compliance with Paracetamol Prescribing Policies at a Sydney Hospital. *Journal of Pharmacy Practice and Research* 39 (2): 124-129.

## Dr Brent McPARLAND

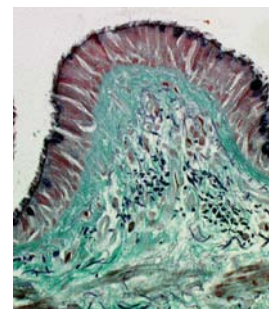
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- 1) Asthma and chronic obstructive lung disorders
- 2) Lyme Disease (Dr Ann Mitrovic: [annmit@pharmacol.usyd.edu.au](mailto:annmit@pharmacol.usyd.edu.au))

### PROJECT 1 Inhibiting airway contraction

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** Surgical skills, organ bath experiments, histology

### PROJECT 2 Discovering whether Lyme disease causing bacteria are harboured by Australian ticks

The current stance by the Australian Government is that ticks in Australia do not harbour the Lyme Disease causing bacteria, *Borrelia burgdorferi* (BB). It is our mission to use specifically designed primers to identify whether BB or some other similar species/strains are found within ticks from Australia. The methods of importance for this project centre around gene-based technologies such as primer design, PCR and sequence analysis; powerful tools for any biology-based research. Proteins will be gel separated and identified using western blotting.

George Negus report: [http://www.youtube.com/watch?v=JbGFleV\\_FaQ](http://www.youtube.com/watch?v=JbGFleV_FaQ)

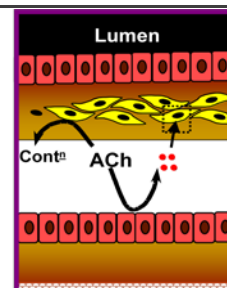
Lyme Disease Foundation WWW: <http://karlmcmanus.org/>



**TECHNIQUES** Surgical skills, tick identification, gene and protein-based technologies

### 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 E<sub>2</sub> and adrenergic agonists (adrenaline, isoprenaline, salbutamol).



**TECHNIQUES** Dissecting skills, organ bath experiments, histology;

**PUBLICATIONS.** P. D. Paré, P. T. Macklem, C. Y. Seow, B. E. McParland. Chapter 32: Mechanics of airway narrowing. Book: "Physiological basis of airway disease", edited by Q. Hamid, J. Martin and J. Shannon. 1<sup>st</sup> Ed. BC Decker, 2005. Trian T, Ge Q, Moir LM, Burgess JK, Kuo C, King NJ, Reddel HK, Black JL, Oliver BG and McParland, BE. Rhinovirus-induced Exacerbations of Asthma - How is the B2-adrenoceptor Implicated? *Am J Respir Cell Mol Biol* 2009. Chapman DG, Berend N, King GG, McParland BE, Salome CM. Deep inspirations protect against airway closure in nonasthmatic subjects. *J Appl Physiol* 2009; 107(2):564-9. Cooper PR, McParland BE, Mitchell HW, Noble PB, Politi AZ, Ressmeyer AR and West AR. Airway mechanics and methods used to visualize smooth muscle dynamics in vitro. *Pulm Pharmacol Ther* 2009; 22(5):398-406.

**Dr Lenka MUNOZ**

***Molecular Innovations in Glioblastoma Therapy***

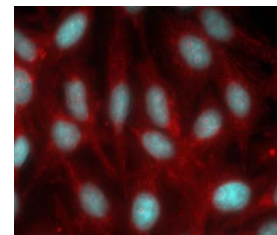
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Glioblastoma (GBM) is a fatal brain tumour of glial origin and my goal is to contribute to the development of better GBM treatments by targeting the inflammatory tumour microenvironment. Our current research is directed towards better understanding of the inflammation-cancer axis in GBM pathophysiology and development of novel p38 MAPK inhibitors that may find utility as anti-neuroinflammatory agents in GBM therapy. We aim to achieve this through dynamic integration of molecular pharmacology, cell biology and medicinal chemistry.

**PROJECT 1 Testing novel p38 MAPK inhibitors in brain tumour stem cells**

Brain Tumour Stem Cells (BTSCs) are a subpopulation of GBM cells that display much greater tumorigenic potential than non-stem GBM cells and thereby more closely resemble the genotypic and phenotypic characteristics of the original GBM and recapitulate many of its properties in vitro. Furthermore, the stem-like cells are most likely the cells of origin for tumour relapse as they exhibit a poor response to therapy. This project will examine anti-inflammatory and anti-invasion efficacy of novel p38 MAPK inhibitors in BTSCs in order to minimise the development of a therapeutic for which GBM could be resistant.

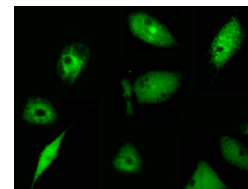


Glioblastoma cells

**TECHNIQUES** cell culture, immunoblotting, ELISA, migration and invasion assays

**PROJECT 2 Investigation of HMGB-1 induced inflammation**

In our current work we are using lipopolysaccharide (LPS) as a glial activator to induce inflammatory response. LPS, an exogenous ligand of Toll-like receptor 4 (TLR4), is widely used for studying inflammation associated with CNS disorders; however, it is not a GBM-relevant physiological stimulus. This project will investigate an inflammatory response of primary human microglia induced by an endogenous TLR4 ligand, the high-mobility group box-1 protein (HMGB-1), and establish a novel GBM-relevant inflammatory model.

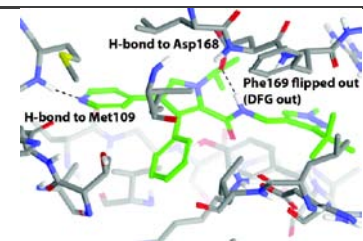


Microglia cells

**TECHNIQUES** cell culture, immunoblotting, ELISA, Bio-Plex bead-based immunoassays

**PROJECT 3 Development of novel p38 MAPK inhibitors targeting the inactive kinase conformation**

The majority of p38 MAPK inhibitors target the active conformation of the kinase where ATP binding affinity is high, and so suffer the disadvantage of unfavourable ATP-binding competition, in part explaining the clinical failure of these inhibitors. Conversely, inactive p38 MAPK binds ATP with low affinity, and thus intracellular ATP does not compromise the binding of inhibitors. This project involves design and synthesis of novel p38 MAPK inhibitors targeting the inactive conformation of the kinase. Pharmacological evaluation of novel agents will include in-vitro kinase binding assays and microglia-based inflammatory assays. *Co-supervisor: Prof. Michael Kassiou, BMRI*



Docking into the ATP and DFG-out pockets of inactive p38 MAPK

**TECHNIQUES** medicinal chemistry, FP binding assay, cell-based inflammation assays

**PUBLICATIONS.** 1. Yeung YT, Bryce NS, Adams S, Braidy N, Konayagi M, McDonald KL, Teo C, Watterson DM, Guillemin G, Grewal T and Munoz L. p38 MAPK inhibitors attenuate pro-inflammatory cytokine production and invasiveness of human glioblastoma cells. *Br J Cancer*, subm.; 2. Munoz L, Selig R, Yeung YT, Peifer C, Hauser D, Laufer S. Fluorescence polarisation binding assay to develop inhibitors of inactive p38 $\alpha$  mitogen-activated protein kinase. *Anal Biochem* 401 (2010) 125 - 133; 3. Munoz L, Ammit AJ. Targeting p38 MAPK pathway for the treatment of Alzheimer's disease. *Neuropharmacology* 58 (2010) 561 - 568; 4. Munoz L, Ralay Ranaivo H, Roy SM, Hu W, Craft JM, McNamara LK, Wing Chico L, van Eldik LJ and Watterson DM. A novel p38 MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer's disease mouse model. *J Neuroinflammation* 2007, 4:21

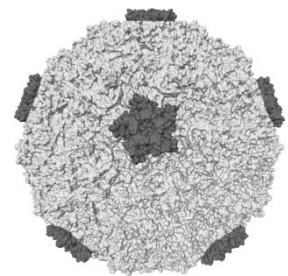
**Dr Brian OLIVER**  
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My research group investigates the reasons why viruses induce exacerbations of airways diseases such as asthma and chronic obstructive airways disease (COPD). We have developed several in-vitro systems which enable us to mimic and assess what happens when a virus infects the airways.

### PROJECT 1 Is rhinovirus-induced inflammation different in COPD?

The prevalence of COPD continues to rise, currently affecting 3.5% of the Australian population, causing significant mortality (4th leading cause of death worldwide) and morbidity. Exacerbations of COPD result in approximately 50,000 hospitalisations annually in Australia, and are associated with a more rapid disease progression. Until recently exacerbations were thought to be caused by only bacteria; however viruses are now emerging as important precipitants, with up to 50% of exacerbations being caused by viruses. It is therefore vital to better understand the role of viral infections in exacerbations of COPD. This project will establish if the innate immune response to rhinovirus is: 1) intrinsically different in lung cells from people with COPD, and 2) impaired by current therapeutic regimes.



rhinovirus

**TECHNIQUES** Cell culture, virus assays, qPCR, Western blotting, ELISA

### PROJECT 2 Is airway fibrosis caused by viral infections treatable

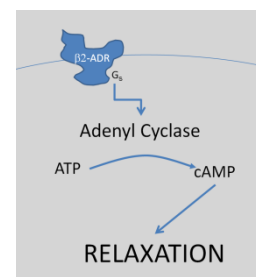
In COPD fibrosis of the small airways results causes majority of respiratory airflow limitation (the reason why patient with COPD find it difficult to breath). In our previous research (Kuo et al AJPLCMP 2011 and Krimmer et al ACRCCM 2011) we have found that rhinovirus and cigarette smoke can directly induce airway fibrosis. In this project you would examine if there is any synergy between rhinovirus and cigarette smoke, and also examine if novel respiratory treatments such as ultra long acting  $\beta_2$ -agonists and or PDE inhibitors are capable of inhibiting the development of fibrosis.



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

### PROJECT 3 How does rhinovirus desensitize the $\beta_2$ -adrenoceptor?

During virus-induced asthma exacerbations bronchodilators such as  $\beta_2$ -agonists do not work as well as they do at other time. *In-vitro* we have shown that this is due to desensitisation of the  $\beta_2$ -adrenoceptor (AR). The  $\beta_2$ -AR is a G coupled protein receptor, and its expression upon the cell surface is regulated by multiple mechanisms. In this project you will treat human airway smooth muscle cells with a variety of inflammatory factors known to be induced by rhinovirus, and then examine if they affect  $\beta_2$ -AR function. We assess  $\beta_2$ -AR function by measuring the response to  $\beta_2$ -agonist, for example the amount of cAMP induced, the phosphorylation of down-stream targets such as vasodilator-stimulated phosphoprotein and the amount of cAMP responsive genes activated.



**TECHNIQUES** Cell culture, qPCR, western blotting, ELISA, fluorescence microscopy

**PUBLICATIONS.** Oliver BG, et al Increased proinflammatory responses from asthmatic human airway smooth muscle cells in response to rhinovirus infection. *Resp Res* 7:71, 2006. , Oliver BG, et al: Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax* 63: 519-525, 2008. TRIAN T et al. Rhinovirus-induced Exacerbations of Asthma - How is the  $\beta_2$ -adrenoceptor Implicated *AJRCMB* 2009.

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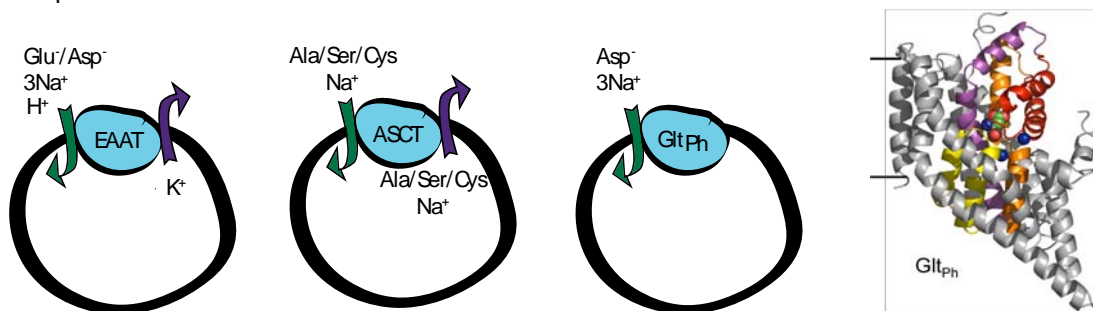
Glutamate is the predominant excitatory neurotransmitter in the mammalian central nervous system and activates a wide range of receptors to mediate a complex array of functions. Extracellular glutamate concentrations are tightly controlled by a family of glutamate transporters expressed in both neurons 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, motor neurone disease and obsessive compulsive disorder.

### PROJECT 1 Understanding the mechanism of transport by the glutamate transporter family using chimeras and site-directed mutagenesis

The glutamate transporter family is made up of proteins from several species and includes the human glutamate transporters (EAATs) and neutral amino acid transporters (ASCTs), and a prokaryotic aspartate transporter  $\text{Glt}_{\text{ph}}$ . All of these transporters share significant amino acid homology and share some functional properties but also exhibit some differences. For example, the EAATs are secondary active transporters of acidic amino acids while the ASCTs are electroneutral exchangers of neutral amino acids (see figure below).

The aim of this project is to exploit the similarities and differences between these 3 transporters by making chimeric transporters and performing site-directed mutagenesis to identify the molecular determinants for substrate selectivity and ion-coupling in the glutamate transporter family.

Glutamate transporter dysfunction has been implicated in disease states such as ischemia following a stroke, Alzheimer's disease and obsessive compulsive disorder. The expression of the neutral amino acid transporter ASCT2 is known to be upregulated in some prostate, breast and skin cancers. Through a better understanding of the mechanism of these transporters we can develop compounds that may have therapeutic benefits in these disease states.



**TECHNIQUES** molecular biology (including site-directed mutagenesis and the generation of chimeric transporters); electrophysiology; protein purification; reconstitution of protein into liposomes, radiolabelled uptake; molecular modelling

#### PUBLICATIONS.

Bailey C, Ryan RM, Thoeng A, Ng C, King K, Vanslambrouck J, Auray-Blais C, Vandenberg RJ, Broer S, Rasko J (2011) Loss-of-function mutations in the glutamate transporter SLC1A1 cause human dicarboxylic aminoaciduria. *Journal of Clinical Investigation* 121, 446-453.

Ryan RM, Kortt NC, Sirivanta T, Vandenberg RJ (2010) The position of an arginine residue influences substrate affinity and K<sup>(+)</sup> coupling in the human glutamate transporter, EAAT1. *Journal of Neurochemistry* 114, 565-75.

Ryan RM, Compton EL, Mindell JA (2009) Functional characterization of a Na<sup>+</sup>-dependent aspartate transporter from *Pyrococcus horikoshii*. *The Journal of Biological Chemistry* 284, 17540-17548.

Boudker O, Ryan RM, Yernool D, Shimamoto, K and Gouaux E (2007) Coupling substrate and ion binding to extracellular gate of a sodium-dependent aspartate transporter. *Nature* 445, 387-393.

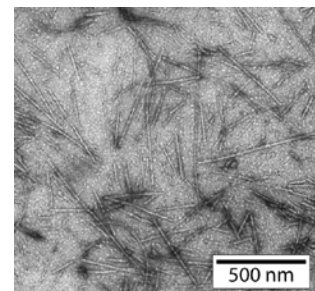
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*Protein misfolding and the formation of stable, fibrillar protein deposits known as amyloid fibrils are associated with many diseases. The process of misfolding and aggregation that leads to fibril formation can disrupt proteostasis in the cell. Amyloid protein fibrils that have similar structural features but which have essential biological functions have recently been identified in mammals and many different microorganisms. In these cases the amyloid self-assembly is advantageous to the organism. The Sunde lab uses a range of molecular biology, protein chemistry and structural techniques to study the formation and structure of amyloid fibrils, both from disease states and from Nature.*

### PROJECT 1 Amyloid fibril formation by atrial natriuretic factor

Atrial natriuretic factor (ANF) is an amyloidogenic peptide hormone that plays a key role in the regulation of water and salt homeostasis. It is responsible for maintenance of blood volume and pressure. ANF is the peptide that forms amyloid fibrils in Isolated Atrial Amyloidosis (IAA), a condition associated with atrial fibrillation. In this project you will characterise the formation of amyloid fibrils by ANF and determine whether the pro-form of ANF is protective against amyloid formation. You will test the effect of the small heat-shock protein alphaB-crystallin, a chaperone that is highly expressed in the heart, on the rate of formation of ANF amyloid.

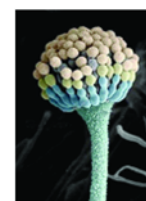


Electron micrograph of ANF amyloid fibrils

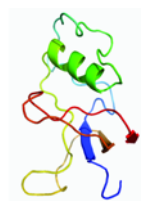
**TECHNIQUES** Molecular biology, protein expression and purification, fibril formation assays and fluorescence studies

### PROJECT 2 The role of functional amyloid fibrils in infection of hosts

The fungus *Aspergillus fumigatus* causes invasive aspergillosis in immune-compromised patients. The spores of this fungus are coated in a layer of amyloid fibrils formed by the fungal hydrophobin protein RodA. This amyloid layer appears to protect the spores from recognition by the human immune system. In addition, a second hydrophobin RodB is expressed when the fungal hyphae invade cells. In this project you will characterise the structure of amyloid fibrils formed by the proteins RodA and RodB. You will identify cellular components that may interact with the monomeric and fibrillar forms of RodA and RodB in the lung during infection.



*A. fumigatus* spores



Homology model of RodA protein

**TECHNIQUES** Protein expression and purification, amyloid assembly assays, protein:protein interaction studies, proteomics

#### PUBLICATIONS.

- Sunde, M., Kwan, A.H., Templeton, M.D., Beever, R.E. & Mackay, J.P. Structural analysis of hydrophobins. *Micron* 39, 773-84 (2008).  
Morris, V.K. Ren, Q., Macindoe, I., Kwan, A., Byrne, N. and Sunde, M. Recruitment of class I hydrophobins to the air:water interface initiates a multi-step process of functional amyloid formation. *J. Biol. Chem.* 286(2011).  
Chiti, F. and Dobson, C.M (2006) Protein Misfolding, Functional Amyloid and Human Disease. *Ann. Rev. Biochem.*, 75, 333-366  
Aimanianda, V. et al. Surface hydrophobin prevents immune recognition of airborne fungal spores. *Nature* 460, 1117-21 (2009).

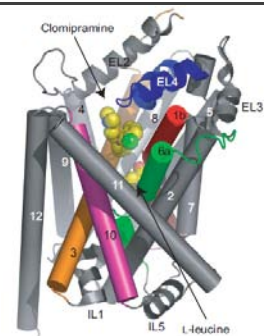
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Research in the Transporter Biology Group is focused on understanding the molecular basis for neurotransmitter transporter functions and how this can be manipulated by endogenous regulators and pharmacological agents. Glycine is an unusual neurotransmitter 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 being developed for the treatment of schizophrenia, whilst GLYT2 inhibitors may have potential as analgesics in the treatment of chronic pain.

### PROJECT 1 Novel Antipsychotics

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 to the 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.

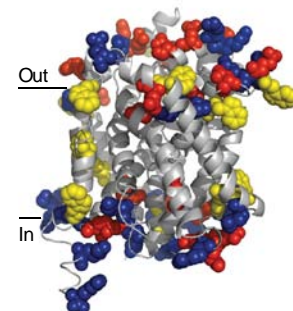


**TECHNIQUES** Molecular biology, site-directed mutagenesis, electrophysiology, molecular modelling

### PROJECT 2 Lipid Inhibitors of GlyT2

The Transporter Biology Group has identified two novel lipids that inhibit GlyT2 which have potential for use as analgesics. This project will investigate the mechanism of inhibition and also how endogenous cell membrane lipids influence the function of GlyT2. Figure to the right shows the exterior surface of GlyT2 with potential lipid binding sites highlighted in blue, red and yellow.

A number of research directions and techniques are possible with both of these projects. Students are encouraged to discuss these projects with Professor Vandenberg so that the style of the project can be tailored to the student's interests.



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

#### PUBLICATIONS.

Amelia Edington, Audra McKinzie, Aaron J. Reynolds, Michael Kassiou, Renae M. Ryan and Robert J. Vandenberg (2009) Extracellular Loops 2 and 4 of GLYT2 are Required for NAGly Inhibition of Glycine Transport *Journal of Biological Chemistry* 284:36424-36430

Robert J. Vandenberg, Kim Shaddick and Pengchu Ju (2007) Molecular basis for substrate discrimination by glycine transporters *The Journal of Biological Chemistry* 282, 14447-14453

Amy Wiles, Rhonda-Jo Pearlman, Mari Rosvall, Karin R. Aubrey K and Robert J. Vandenberg (2006) N-Arachidonyl-glycine inhibits the glycine transporters, GLYT2a. *Journal of Neurochemistry* 99, 781-786

Karin A Aubrey and Robert J. Vandenberg. (2001) N[3-(4-fluorophenyl)-3-(4'-phenylphenoxy)propylsarcosine (NFPS) is a selective persistent inhibitor of glycine transport. *British Journal of Pharmacology* 134, 1429-1436

## 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.

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



## Discipline of Pharmacology: Honours Preference Form (2012)

This form must be submitted to the Honours Coordinator by: **Wednesday 30 November 2011**  
An application for Honours must be lodged at the Faculty of Science by: **Wednesday 30 November 2011**.

I wish to apply for the following course in 2012 (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 (University of  
Sydney Account)

.....

Postal address

.....

Phone (home)

.....

Phone (mobile)

.....

### STUDENT PREFERENCES:

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

1

.....

2

.....

3

.....

4

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### STUDENT TRANSCRIPT:

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

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

