Honours and Master of Science (BHS) PROJECTS 2012

Bachelor of Biomedicine and Bachelor of Science (Degree with Honours)

Medical Research — Bench to Bedside

Affiliations:
The Royal Melbourne Hospital, The Royal Women’s Hospital, NorthWest Academic Centre, National Ageing Research Institute (NARI), The Walter and Eliza Hall Institute of Medical Research (WEHI), The Peter MacCallum Institute, The Burnet Institute – Centre for Population Health, Ludwig Institute for Cancer Research, CSIRO Materials Science & Engineering, Florey Neuroscience Institute
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218. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effect - also offered as MSci

219. Pharmacogenetics: do mutations in CYP 2C19 alter the clinical effectiveness of clopidogrel in patients with cerebrovascular disease?
220. A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy - also offered as MSci

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2011/12 KEY DATES

ENTRY REQUIREMENTS

COURSE WORK

HOW TO APPLY

RMH/WH ACADEMIC CENTRE DEPARTMENT LINKS:
AGEING

1. **A model of epileptogenesis in Alzheimer’s disease - also offered as MSci**
   
   **Supervisors:** Professor Patrick Kwan, Professor Terence O’Brien  
   **Project Site:** Department of Medicine (RMH)  
   **Contact:** Professor Patrick Kwan, E: Patrick.kwan@unimelb.edu.au  
   Professor Terence O’Brien E: obrrientj@unimelb.edu.au

   **Laboratory Overview:** The project will be carried out at the Department of Medicine through the RMH/WH Academic Centre.

   **Project Overview:** Epilepsy is most likely to develop in old age. One of the most important risk factors in this age group is pre-existing neurogenerative disorders, particularly Alzheimer’s disease (AD). The pathomechanisms underpinning the increased risk, whether recurrent seizures might exacerbate the pathological process of AD, and how antiepileptic drug therapy might further contribute to cognitive decline in these patients have not been well studied. A specific model for epileptogenesis in AD is an essential tool to address these important questions, but none has been developed so far.

   In the present project, we aim to establish and perform pilot experiments to characterise such a model by applying a widely employed model of focal epilepsy, namely the electrical kindling model, to a transgenic mouse model of AD. Epileptogenic factors in AD will be determined. It is hypothesised that (1) mutant mice are more sensitive to epileptogenesis by kindling compared with wildtype mice; (2) sensitivity of kindling correlates with the volume of amyloid plaques in the mutant mice.

   **Research plan:** Epilepsy will be induced (i.e. epileptogenesis) in mutant and wild-type mice by rapid amygdala kindling (RAK). Mutant and wild-type stimulated mice will be compared for sensitivity to acute seizures and to hippocampal epileptogenesis. The animals will also be compared for primary histological endpoints characteristically found in human TLE, and Aβ amyloid plaques in mutant mice will be measured.

   **Acquired skills** will include small animal handling, neurosurgery, amygdala kindling, EEG recordings and analysis, post-mortem processing, and immunocytochemistry.

2. **Targeting Tau phosphorylation to treat and prevent acquired epilepsy, neurodegeneration and neuropsychiatric disease following a brain injury - also offered as MSci**

   **Supervisors:** Dr Sandy Shultz, Professor Terence O’Brien, Associate Professor Chris Hovens, Dr. Nigel Jones, Dr. Dennis Velakoulis.  
   **Project Site:** Departments of Medicine, Surgery and Psychiatry, The Royal Melbourne Hospital, University of Melbourne  
   **Contact:** Dr Sandy Shultz E: sandy.shultz@unimelb.edu.au

   **Project Description:** This project will advance an entirely novel approach to the treatment of traumatic brain injury, seizures and epileptogenesis, and the associated neurodegenerative changes. This approach involves the inhibition of pathological hyperphosphorylation of the Tau protein via enhancing PP2A activity.

   Our work to date has demonstrated that treatment with sodium selenate specifically enhances the activity of the Tau protein phosphatase, PP2A leading to inhibition of the pathological hyperphosphorylation of Tau. Strongly supporting a role for pathological Tau in epilepsy we have found that sodium selenate is effective in suppressing induced seizures in a variety of rodent models. The proposed study will extend this line of translational research to establish:

   1. That treatment with sodium selenate is effective at inhibiting neurological deficits, epileptogenesis, and neurodegeneration following a model of traumatic brain injury in the rat (fluid percussion brain injury).
   2. Treatment with sodium selenate will mitigate the increased tissue expression of total and phospho-tau following a traumatic brain injury, with and without the development of epilepsy.
The outcomes of this project will advance the pre-clinical development of this approach, building on a sound basic science rational and strong preliminary data. Selenate has already been demonstrated to be safe and well tolerated in a 6 month Phase I trial in humans with prostate cancer, meaning a positive result from these studies has the potential to be expediently translated into clinical studies. In addition this project has relevance for epilepsy secondary to sporadic neurodegenerative conditions such as Alzheimer’s disease.

Skills: Small animal handling, neurosurgery (electrode implantations and fluid percussion injury), rat electroencephalography recordings, rat behavioral testing, brain perfusion and fixation, brain histological techniques, drug administration and in-vivo small animal MRI acquisition and analysis.

National Ageing Research Institute (NARI)

NARI is an independent, NHMRC accredited, Medical Research Institute located in Parkville. The central mission of the organisation is to be a centre of excellence in Australia for medical, psychological and social research into all aspects of ageing and thereby improve the health and quality of life for older people. The Institute conducts a full array of research activity, from the basic biology of ageing through clinical research programs and public health/service evaluation research. Within the Clinical Research laboratory there are existing programs examining dementia and memory function, painful diseases common in older persons (e.g. osteoarthritis), falls and balance, depression and disability as well as the study of better measurement techniques (psychometric and physiological) for use in older adults. We have a number of Honours, Masters, PhD and DPsych students working in these areas of research and are currently seeking new students to study within the broad areas of neurophysiology and psychophysiology of pain. Scholarships may be available to a limited number of applicants. Some examples of current and available projects are listed below:

3. Exploring nutrition needs of older people with chronic illness and their carers
   Supervisors: Dr Irene Blackberry and Dr Briony Dow
   Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
   Contact: Dr Irene Blackberry T: 8344 3373 E: i.blackberry@unimelb.edu.au
             Dr Briony Dow T: 8387 2639 E: b.dow@nari.unimelb.edu.au

   Nutrition plays a major role in health outcomes among older people particularly those with chronic illness. There are many older people with chronic illness who currently live at home with and being dependent on their carers to provide adequate nutritional needs for them. Few studies overseas suggested that malnutrition is quite common among both older people with chronic illness and their carers at home. Additionally, studies on carers identified that carers had lack of nutrition support and information. This project aims to explore nutritional status, needs and knowledge among older people with chronic illness and their carers at home. Carers and care recipients will be interviewed regarding their nutrition knowledge and needs, as well as completing two nutrition questionnaires to assess their risk of malnutrition. Findings will be used to develop strategies to meet nutritional needs and provide nutritional support for this group of older people.

   The project offers students an opportunity to develop communication skills with research participants, as well as research skills including literature review, quantitative and qualitative data analysis, and epidemiological study skills.

4. Vitamin D to help with Bone and Muscle Health - also offered as MSci
   Supervisors: A/Professor Cassandra Szoeke, Professor John Wark, Professor Lorraine Dennerstein, Professor David Ames
   Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
   Contact: A/Professor Cassandra Szoeke T:61 3 8387 2224 F: 61 3 9387 9384 E: cszoeke@unimelb.edu.au
             Women’s Healthy Ageing Project (WHAP), National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

   Vitamin D is made in the skin, a process that requires sun exposure, ingestion in the diet or being taken as a nutritional supplement. Adequate levels of vitamin D are essential for healthy bones and muscle function, and are important for other aspects of health. Severe vitamin D deficiency causes obvious and serious bone and muscle disease. The effects of mild to moderate deficiency are less clear-cut, but may include bone fragility, muscle weakness and a propensity to fall over. In Australia, mild to moderate vitamin D deficiency is relatively common in the adult population, but the health consequences of this deficiency in apparently healthy adults are poorly understood. It is also not clear below which blood vitamin D level health problems may arise. The purpose of this project is to investigate the consequences of mild to moderate vitamin D deficiency (blood already collected) examining Bone Mineral densities (BMD) (already collected) and...
Balance data (already collected) in healthy women from the internationally re-known Melbourne Women’s Healthy Ageing Project (&MWMHP).

Opportunities:-

i) Internationally re-known cohort and Research Team each with international recognition. (Prof, J Wark, Prof L Dennerstein, Prof D Ames, Dr C Szoeke)

ii) Already have measures collected (no hard yards and thesis easily achievable in time frame)

iii) Publication within one year

iv) Treatment potential with commercial opportunities – candidate with experience in media and interest in commercialisation preferred.

5. **Lifestyle Factors for healthy Ageing - also offered as MSci**

   **Supervisors:** A/Professor Cassandra Szoeke, Professor David Ames

   **Project Site:** National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.

   **Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384

   E: cszoeke@unimelb.edu.au

   Women’s Healthy Ageing Project (WHAP), National Ageing Research Institute (NARI), 34-54 Poplar Rd, Parkville, 3052.

   **Project description:** Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. For example smoking, alcohol consumption and a lack of physical activity have been linked to an increased rate of cognitive impairment and cardiovascular diseases. Studies investigating lifestyle factors have been limited by cohort sampling bias, cross sectional designs, short follow-ups and small sample sizes. Furthermore the frequency and intensity of lifestyle alteration is still not defined. In this project we examine a 20 year longitudinal dataset to determine the influence of lifestyle (i.e. alcohol consumption, smoking, diet and physical activity) on cognitive performance and health.

   **Major benefits from this study are:-**

   1. Internationally re-known cohort Melbourne’s Women Midlife Health Project (MWMHP)
   2. Research Team each with international recognition
   3. Publication within one year
   4. Rich database with lifestyle data from mid-life and spanning over 20 years

6. **Depression and Anxiety in Healthy Women: A Longitudinal Study - also offered as MSci**

   **Supervisor:** A/Professor Cassandra Szoeke, Professor David Ames, Professor Lorraine Dennerstein

   **Project Site:** National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.

   **Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384

   E: cszoeke@unimelb.edu.au / Cassandra.szoeke@mh.org.au

   Women’s Healthy Ageing Project (WHAP), National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

   **Project description:** The Australian population is ageing at a dramatic rate and mental disorders in old-age are and often unrecognised and under-treated. The top 5 factors with the greatest negative impact on healthy ageing are cognitive decline, depression, cardiovascular disease and malignancy. They are responsible for high rates of illness and mortality as well as significant dependence on social and government support. There is high rate of the presence of a physical illness and anxiety or depression, which reflects an intimate relationship between physical and mental health. There exists a limited amount of research which examines depression and anxiety in elderly people, particularly in Australia. There is also a lack of earlier Australian study data which examines factors that predict depression and anxiety accrual in ageing. These predictors of aging outcome are of extreme importance as it is this knowledge, which promises to significantly reduce the personal, economic and social burden of ageing in our community.

   This study therefore aims to examine the prevalence and incidence of depression and anxiety and physical illness as women move from middle age into old age. It will also seek to identify protective factors that contribute to healthy ageing and will examine the relationship between depression and physical illness.

   **Major benefits from this study are:-**

   1. Internationally re-known cohort Melbourne’s Women Midlife Health Project (MWMHP)
   2. Research Team each with international recognition
   3. Publication within one year
   4. Ability to analyse the factors that contribute to depression and anxiety in old age, as well as to identify the change of incidence and prevalence of depression as the women age
7. Early detection and prevention of age associated diseases using imaging - also offered as MSc
Supervisor: Professor Patricia Desmond, A/Professor Cassandra Szoeke
Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
Contact: A/Professor Cassandra Szoeke  T: 61 3 8387 2224  F: 61 3 9387 9384
E: c.szoeke@unimelb.edu.au / Cassandra.szoeke@mh.org.au
Women’s Healthy Ageing Project (WHAP), National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Project description: Australia’s population is ageing at a dramatic rate with about two million people aged over 70 years at present. As populations age, the disabilities of the oldest age groups become increasingly important. Studies have identified cardiovascular diseases to be the most prevalent chronic disease in the elderly, followed by cognitive impairment. Identifying the at-risk population for these illnesses is an important step towards developing treatment and prevention strategies. An aim of this study is to examine emerging measures for identifying early at risk populations in an epidemiologically sampled cohort of women. These measures include the use of Magnetic Resonance Imaging (MRI) neuroimaging quantifying the accrual of white matter hyperintensities (WMH) as a measure of cerebrovascular disease (CVD). It has been found that white matter hyperintensity volume could predict 1-year cognitive decline, and therefore should be considered as a variable of interest in AD trials.

Major benefits from this study are:-
1. Internationally re-known cohort Melbourne’s Women Midlife Health Project (MWMHP)
2. Research Team each with international recognition
3. Publication within one year
4. Treatment potential with commercial opportunities

8. Comparison of event-related potentials (ERP) responses using two different auditory stimulus models in healthy young adults and healthy elderly adults
Supervisor: Dr Bruce Barber
Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
Contact: Dr Bruce Barber T: 8387 2618/0423 292 792 E: b.barber@nari.unimelb.edu.au

Event-related potentials (ERP) have a role in evaluating aspects of brain function underlying perception, attention and cognition. The ERP P300 is a response that occurs approximately 300 milliseconds after a stimulus has been presented. It is regarded as an index of short term memory processing. Typically the P300 response is elicited using the standard tone/oddball stimulus paradigm. A different stimulus model recommended for cognitively impaired populations uses just a single tone stimulus. It is used in such populations because it is a simpler, more accessible task that elicits ERP wave forms even in the absence of an overt response to stimuli such as a button press. However, the ERP response to the single tone stimulus has some, as yet, unquantitated differences to that of the standard tone/oddball stimulus model. This study will make a direct comparison of the ERP responses to the standard tone/oddball and the single tone stimulus models to in a group of healthy young adults and a group of cognitively intact, healthy elderly persons. The study will provide quantitative evaluation of the amplitude, latency and topographic distribution of the ERP sequence in response to the two stimulus models.

The results will contribute to the on-going development of ERP as an objective measure of treatment-related changes in cognitive processing – an essential tool for use in the evaluation of a range of interventions with potential use in the management of symptoms of dementia.

The student will gain expertise in ethics applications, recruiting healthy participants, study design and electroencephalographic recording and analysis methods.

9. The needs of stroke survivors and primary care physicians in rural communities
Supervisors: Dr Jacques Joubert and Professor David Ames
Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
Contact: Tel: +61 3 8387 2305 or +61 0419 780 448
Email: jacquesjoubert@bigpond.com.au

Stroke is the second leading cause of death in developing countries and the leading cause of disability. Rural and remote populations are disadvantaged in access to high quality, timely evidence based healthcare. With a rapidly increasing ageing population worldwide, finding strategies to reduce the burden of stroke on society, are increasingly important. NARI currently supports a large clinical research project in secondary stroke prevention aimed at the primary care level and based in designated metropolitan divisions of general practice. The investigators have performed pilot research in rural Victoria to better understand the needs of stroke survivors and primary care physicians in rural divisions and to potentially advise on effective translation of evidence based models of care into the rural sector.
Using the data from the pilot ‘NEEDS’ study, this study seeks to determine the feasibility of conducting a large multi-center randomized controlled research study across multiple practice divisions and amongst culturally diverse populations in both rural and remote regions of Australia.

Students will have the opportunity to develop skills including, conceptualization, generation of research questions and hypotheses, literature review, both quantitative and qualitative data analysis, and reporting and interview techniques.

**ALCOHOL**

10. **Drinking choices of high risk drinkers**  
   **Supervisors:** Michael Livingston, Turning Point Alcohol and Drug Centre; Professor Robin Room, CHS  
   **Project Site:** Possibly Turning Point Alcohol and Drug Centre- to be confirmed  
   **Contact:** Michael Livingston, T: 8413 8413 E: michael@turningpoint.org.au  
   Risky alcohol consumption is a major risk factor for illness and disease in Australian society. In Victoria, rates of alcohol-related harms have increased significantly in the last decade, with particular increases in acute harms (e.g. emergency department presentations, violence) amongst young adults. This study will attempt to describe and analyse the drinking choices made by high-risk drinkers aged between 16 and 24 years. Using data from a population survey of 5000 young adults, differences in consumption choices between young people drinking in low-risk, risky and very high risk (e.g. 20+ drinks in a session) ways will be analysed to determine whether particular beverages or particular settings are linked to high-risk drinking behaviours.  
   **Skill acquisition:** Survey analysis; Multivariate statistical methods; Public health approaches to alcohol

11. **GENACIS: culture of home brew drinking in Victoria/Australia - also offered as MSci**  
   **Supervisor:** Jason Ferris, Turning Point Alcohol and Drug Centre; Professor Robin Room, CHS  
   **Project Site:** Possibly Turning Point Alcohol and Drug Centre- to be confirmed  
   **Contact:** Jason Ferris, T: 8413 8413 E: jasonf@turningpoint.org.au  
   Prior to the early 1970’s home brew alcohol in Australia was prohibited. In 1972 this restriction was limited. The culture of home brewing in Australia has been growing. This research should document this burdening culture of home brewing in Australia, the impact of this on the ‘unrecorded consumption of alcohol’. The research can also undertake secondary analysis of GENACIS (Australia) to reflect the ‘current’ culture of home brew consumption.  
   **Skill acquisition:** Literature review, secondary data analysis; multivariate statistical methods; Public health approaches to alcohol

12. **Youth and alcohol: the road travelled in the health system using linkage data between ambulatory attendance, emergency department and hospital admissions - also offered as MSci**  
   **Supervisor:** Jason Ferris & Belinda Lloyd, Turning Point Alcohol and Drug Centre  
   **Project site:** Possibly Turning Point Alcohol and Drug Centre- to be confirmed  
   **Contact:** Jason Ferris, T: 8413 8413 E: jasonf@turningpoint.org.au  
   With the growing social culture of binge drinking in youth it is not surprising to see a strong presence of youth being picked up in ambulatory attendance as well as ED and hospital admissions. Using data from a linkage project the research will explore the transitional pathway of youth how have been capture by ambulance attendance data. The research will provide a literature of the burgeon behaviour of heavy episodic risky drinking in youth and illustrate the impact of this in the health system.  
   **Skill acquisition:** Literature review, secondary data analysis; multivariate statistical methods; (possible multilevel analysis of repeat cases), public health approaches to alcohol, costing models

13. **Media reporting on alcohol in Victoria since 2007 - also offered as MSci**  
   **Supervisor:** Paul Dietze, Robin Room  
   **Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
   **Contact:** Paul Dietze E: Hpauld@burnet.edu.au  
   From 2007 onwards there has been a dramatic increase in the amount of media reporting on alcohol and alcohol-related issues in the Victorian community. The aim of this project will be to document and analyse the content of this media reporting with a view to describing the main issues examined and better understand the place of key players (eg alcohol industry, researchers, government) and their role in the media portrayal of alcohol
14. **Why do some people with hepatitis C continue to drink? - also offered as MSci**

**Supervisor/s:** Peter Higgs, Margaret Hellard  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Peter Higgs E: peterh@burnet.edu.au; Margaret Hellard E: Hellard@burnet.edu.au

Whereas injecting drug use is the most significant risk factor for acquiring hepatitis C (HCV) in the developed world, once infected with HCV, alcohol use is the strongest known modifiable determinant of HCV disease progression. Alcohol consumption has been found to raise the viral load and accelerate hepatic fibrosis in the context of HCV infection, and heavy alcohol consumption is a risk factor for premature death from HCV. Moreover, as well as impacting on liver disease progression, heavy alcohol use may influence the likelihood of successful HCV treatment.

The proposed project involves in-depth interviews with up to 25 consenting participants living with HCV from the Melbourne Injecting Cohort Study (MIX). Interviews will address alcohol use and other related exposures and outcomes, including participants’ alcohol consumption prior to and after HCV diagnosis, any medical advice regarding alcohol consumption they may have received, advice from peers with HCV regarding alcohol consumption, perception of alcohol consumption practices amongst peers with HCV, participants’ understanding of the relationship between alcohol-related and injecting drug use-related behaviours, clinical symptoms and other effects of HCV on relationships and self-perception, current self management strategies for living with HCV.

*Note: this project is also listed under Injecting Drug Use*

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**ARTHITIS AND INFLAMMATION RESEARCH**

**Arthritis and Inflammation Research Centre**

The Arthritis and Inflammation Centre is headed by Professor John Hamilton who leads a team of scientists that focuses on inflammation-associated diseases, including arthritis, host pathogen interaction and cancer. The pathology of most diseases involve some degree of inflammation with macrophages often being the major cell type; as a result the Centre focuses primarily on macrophage biology and the effects of macrophage-associated inflammation on other cell types such as stem cells.

We employ a variety of techniques and strategies including gene-based strategies (for example, micro-array technology) to understand disease causation, protein-based strategies (including proteomics, immunoprecipitation, cell transfection) to study the cellular signal transduction pathways associated with disease, and mouse models and clinical material to analyse disease in vivo.

Key components of the biology involve an analysis of how macrophage lineage cells are altered during inflammatory disease, how at a molecular level these cells survive, proliferate, differentiate or are activated, and how to down-regulate the cellular functions aberrant in disease. There is some emphasis on growth factor biology/biochemistry and on signal transduction pathways implicated strongly in human arthritis, cancer and stem cell biology.

15. **The role of urokinase plasminogen activator (u-PA) and its receptor (u-PAR) in arthritis and inflammation**

**Supervisor:** Dr Andrew Cook  
**Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
**Contact:** Dr Andrew Cook T: 8344 3290 Email: adcook@unimelb.edu.au

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the population. Fibrin deposition, cell migration, and tissue destruction and remodeling are key components in the pathology of RA joints. The plasminogen activators (PAs), urokinase (u-PA) and tissue-type (t-PA), which converts plasminogen to plasmin, are implicated in these processes; however their precise roles in such processes, particularly for u-PA and its receptor (u-PAR), have yet to be defined. In this project you will study the role of u-PA and the u-PAR, in inflammation and arthritis using mice genetically altered mice such that u-PA or u-PAR have been rendered inactive. In particular, the effect of u-PA on cell migration to an inflammatory site, on tissue destruction and remodeling, and in activating/suppressing other key cytokines/proteases (eg metalloproteinases (MMPs)) involved in these processes will be studied.

**Skill acquisition:** experience with animal models of human disease, measurement of inflammatory mediator mRNAs by real time-PCR and their concentrations by ELISA, and the use of FACS and immunohistochemistry to study cell populations.
16. **The role of granulocyte macrophage colony stimulating factor (GM-CSF) in arthritis and inflammation**
   Supervisor: Dr Andrew Cook  
   Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   Contact: Dr Andrew Cook  
   T: 8344 3290  
   Email: adcook@unimelb.edu.au

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the population. We have shown that GM-CSF is important for the development of several models of inflammation and arthritis. Furthermore, blockade of GM-CSF is effective at reducing arthritis severity. Phase 1 clinical trials are now underway in human rheumatoid arthritis. However, we still do not completely understand how GM-CSF is acting during inflammation and arthritis. In this project you will study the role of GM-CSF in inflammation and arthritis, and in particular, its role in monocyte/macrophage survival and activation.

**Skill acquisition:** experience with animal models of human disease, measurement of inflammatory mediator mRNAs by real time-PCR and their concentrations by ELISA, and the use of FACS and immunohistochemistry to study cell populations.

17. **The role of inflammation in mesenchymal stem cell differentiation**
   Supervisor: Dr Derek Lacey and Prof John Hamilton  
   Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   Contact: Dr Derek Lacey  
   T: 8344 3292  
   Email: dlacey@unimelb.edu.au

Mesenchymal stem cells (MSC) have been shown to differentiate into osteoblasts, adipocytes, myocytes and aid in the tissues repair. In the context of chronic inflammatory conditions like rheumatoid arthritis, chronic obstructive pulmonary disease and crohn’s disease, MSC are unable to repair their target tissue for unknown reasons. In this study we propose to determine the mechanisms by which MSC are prevented from undergoing differentiation and tissue repair in the presence of inflammation. Specifically, the project will be examining the signalling pathways involved in blocking MSC differentiation into osteoblasts in the presence of inflammatory mediators. In this project you will be isolating adult mesenchymal stem cells from mice and using a stem cell line to determine the effects of inflammation on stem cell biology.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis; immuno-affinity purification of proteins, SDS-PAGE and Western blotting.

18. **The role of Wnts in Arthritis**
   Supervisor: Dr Derek Lacey, Dr Andrew Cook and Prof John Hamilton  
   Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   Contact: Dr Derek Lacey  
   T: 8344 3292  
   Email: dlacey@unimelb.edu.au

Wnts are a family of proteins important in development. Through a microarray screen of macrophage populations we have also found that Wnts are expressed by inflammatory macrophages. Macrophages are key cells involved in the destruction joints during rheumatoid arthritis. This project will investigate the expression of Wnts in patient’s tissue samples and in an inflammatory model of arthritis and determine if targeting Wnts would be a beneficial treatment for arthritis. In this project you will be cutting tissue sections and measuring the expression of Wnts. You will be inducing an murine model of arthritis and measuring a number of clinical parameters and collecting and processing tissue and measuring Wnt expression by histology, real-time PCR, western blotting and FACS analysis.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting.

19. **The role of a novel therapeutic target in Arthritis**
   Supervisor: Dr Derek Lacey, Dr Andrew Cook and Prof John Hamilton  
   Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   Contact: Dr Derek Lacey  
   T: 8344 3292  
   Email: dlacey@unimelb.edu.au

Through a proteomic screen of inflammatory macrophages we have identified a novel potential therapeutic target for the treatment of arthritis. Macrophages are key cells involved in the destruction joints during rheumatoid arthritis. This project will investigate the expression of this target in patient’s tissue samples and in an inflammatory model of arthritis and determine if targeting this protein would be a beneficial treatment for arthritis. In this project you will be cutting...
tissue sections and measuring the expression of this novel protein. You will be inducing a murine model of arthritis and measuring a number of clinical parameters and collecting and processing tissue and measuring protein expression by histology, real-time PCR, western blotting and FACS analysis.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting

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20. **The role of Wnts in Macrophages**

   **Supervisor:** Dr Derek Lacey, A/Prof Glen Scholz and Prof John Hamilton  
   **Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   **Contact:** Dr Derek Lacey  T: 8344 3292  Email: dlacey@unimelb.edu.au

Wnts are a family of proteins important in development. Through a microarray screen of macrophage populations we have also found that Wnts are expressed by inflammatory macrophages. Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. This project will investigate the expression of Wnts in macrophages under various inflammatory conditions. You will also overexpress Wnts in a macrophage cell line to determine its role in macrophage function. In this project you will be culturing cell lines and primary cells and measuring the expression of Wnts. You will be cloning a Wnt protein and transfecting cell lines and measuring Wnt expression by histology, real-time PCR, western blotting and FACS analysis.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting

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21. **The role of a novel therapeutic target in Macrophages**

   **Supervisor:** Dr Derek Lacey, A/Prof Glen Scholz and Prof John Hamilton  
   **Project Site:** Arthritis Research and Inflammation Centre, Department of Medicine (RMH), University of Melbourne  
   **Contact:** Dr Derek Lacey  T: 8344 3292  Email: dlacey@unimelb.edu.au

Through a proteomic screen of inflammatory macrophages we have identified a novel potential therapeutic target for the treatment of arthritis. Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. This project will investigate the expression of this novel protein in macrophages under various inflammatory conditions. You will also overexpress this protein in a macrophage cell line to determine its role in macrophage function. In this project you will be culturing cell lines and primary cells and measuring the expression of this protein. You will be cloning this novel therapeutic target protein and transfecting cell lines and measuring its expression by histology, real-time PCR, western blotting and FACS analysis.

**Skill acquisition:** a variety of molecular and cell biological, and biochemical techniques, such as PCR and cloning of recombinant DNA; tissue culture, and FACS analysis, SDS-PAGE and Western blotting

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22. **Retinal Vascular Calibre and Cardiovascular Disease in Patients with Autoimmune Disease**

   **Supervisor:** Dr Sharon Van Doornum  
   **Project Site:** Department of Medicine (RMH)  
   **Contact:** Dr Sharon Van Doornum  T: 8344 3144  E: svd@unimelb.edu.au

Patients with auto-immune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are at increased risk of morbidity and mortality due to cardiovascular disease. It may be that chronic high levels of systemic inflammation initiates and/or accelerates atherosclerosis in patients with autoimmune disease resulting in excess cardiovascular events in these patients. Control of inflammation, along with early detection of cardiovascular disease, are likely to be the keys to reducing the high mortality in patients with autoimmune disease. However, despite this knowledge, predicting persons at risk of cardiovascular disease remains problematic. Thus, there is significant interest in developing new methods that may assist in identifying persons with autoimmune disease who are at higher risk of cardiovascular disease.

Two novel and promising methods of early detection of cardiovascular disease are examination of the retinal microcirculation and measurement of arterial stiffness. Application of these techniques in this patient population may be used not only predict cardiovascular disease, but also to gain valuable insights into the role of inflammation in the pathogenesis of vascular disease.

In this study you will investigate the prevalence of retinal vascular abnormalities in a cohort of patients with autoimmune disease, compare this with age and gender matched population controls, and correlate the findings with measures of disease activity, cardiovascular risk factors and arterial stiffness.
The project offers students an opportunity to develop research skills including literature review, effective communication with patients (recruitment, informed consent, clinical assessment), quantitative and qualitative data analysis and epidemiological study skills.

ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The lung disease research group will be offering projects in the molecular pathogenesis of COPD (chronic obstructive pulmonary disease), a group of diseases that will be the number 3 killer world-wide by 2010 and in severe asthma, a major health problem in Australia in 2007 and lung cancer, now the most common cause of cancer death world-wide.

All of the projects on offer here are based on mouse disease models but form part of larger translation research programs involving patients with lung disease.

23. **Src kinases, lung inflammation and lung cancer**

   **Supervisors:** A/Prof Margaret Hibbs (Monash University) and Professor Gary Anderson, Department of Pharmacology, University of Melbourne

   **Project Site:** Department of Pharmacology, University of Melbourne

   **Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

   Lung cancer is now the most common cause of cancer death in the world. We have discovered that mutations in Src kinases cause lung cancer even though the mutated kinases are not themselves expressed in lung tissue. Deregulated inflammation seems to be the underlying problem. This project will study exactly how inflammation causes lung cancer.

   **Skill acquisition:** In vivo disease models, quantitative PCR, cell culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, immune regulation and transduction biochemistry.

   *This project is also listed under Cancer*

24. **Elucidation of signaling pathway involved in IL-11 induced TH2 inflammation in the lung**

   **Supervisor(s):** A/Prof Mathias Ernst and Prof. Gary Anderson

   **Project Site:** Department of Pharmacology, University of Melbourne

   **Contact:** Prof Gary Anderson T: +61-3-8344-8602 E: gpa@unimelb.edu.au

   **Project (including aims):** Asthma is a debilitating disease that results in extensive matrix remodelling in the lung and immunologically is characterised by the induction of a T cell-driven inflammatory response (Th2 response). This immune response is characterized by the production of factors including the cytokines IL-4 and IL-13. Recent data has shown that the cytokine IL-11, which is produced by a variety of cells in response to inflammatory stimuli, is one of the prime inducers of matrix remodelling and a Th2 response in the lung. Of therapeutic interest is that genetic deletion of the IL-11 receptor as well as inhibition of IL-11 significantly reduced the Th2 response and IL-13 production, and this resulted in a reduction in mucin secretion and inflammatory cells. The project aims therefore to further elucidate mechanisms involved in immune regulation by IL-11 in the lung by using a comprehensive and unique range of existing genetically modified mutant mice, which would be important in developing possible novel avenues of treatment.

   **Skill Acquisition:** In vivo disease models, analysis and genetic complementation of knock-in mouse strains, real-time PCR analysis, histopathological staining of paraformaldehyde and frozen tissue sections, fluorescence activated cell sorting (FACS) analysis, cytokine determination by ELISA, western blotting.

25. **T cell memory in Src mutant mice with viral lung infections**

   **Supervisors:** A/Prof Margaret Hibbs (Monash University), Professor Gary Anderson

   **Project Site:** Department of Pharmacology, University of Melbourne

   **Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

   COPD (chronic obstructive lung disease) patients are particularly susceptible to chest infections, particularly by virus. Respiratory failure after such viral respiratory tract infections is one of the main causes of death of COPD patients but nothing at all is understood as to why they are unusually sensitive to infection. We have created a new genetic model of COPD by mutating kinases that control macrophages and dendritic cells. This project will use this new COPD model and two mouse-adapted lung viruses, RSV and influenza, together with a range of molecular and cell biology methods to identify the inflammatory pathways that are most unregulated in COPD when viruses infect the lungs. A major focus will be to understand why CD8+ cell anti-viral memory, which should normally protect from infection, does not work efficiently.

   **Skill acquisition:** In vivo disease models, viral culture and characterisation lung function measurement, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; basic T cell immunology, ELISA and Western blotting.
26. **Regulatory T cells and myeloid suppressor cells in asthma and COPD**

**Supervisors:** A/Prof Margaret Hibbs, Dr Steve Bozinovski and Professor Gary Anderson

**Project Site:** Department of Pharmacology, University of Melbourne

**Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

Regulatory T cells (Tregs) are a newly discovered set of cells that limit immune responses in order to prevent tissue damage. Myeloid suppressor cells dampen inflammation but promote cancer. There is now a suspicion that Tregs and MSC may be defective in some common inflammatory diseases. In your project you will determine whether Tregs work properly in animal models of asthma and COPD.

**Skill acquisition:** In vivo disease models, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, immune regulation and transduction biochemistry.

27. **Stem cell strategies to cure pulmonary alveolar proteinosis (PAP)**

**Supervisors:** Dr Steve Bozinovski and Professor Gary Anderson

**Project Site:** Department of Pharmacology, University of Melbourne

**Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

Alveolar proteinosis a rare and often fatal disease caused by antibodies against the blood growth factor GM-CSF which arise spontaneously for unknown reasons. In this project you will use a novel stem cell strategy to develop a curative treatment for this orphan disease.

**Skill acquisition:** In vivo disease models, zymography, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, 1D & 2D gels for protein pattern analysis, advanced proteomics (SELDI-ToF, MS/MS), ELISA and Western blotting.

28. **Skeletal muscle failure in COPD**

**Supervisors:** Dr Michelle Hanson and Professor Gary Anderson

**Project Site:** Department of Pharmacology, University of Melbourne

**Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

Patients with COPD often suffer from severe muscle wasting. The cause of this is unknown but wasting is known to increase the risk of death from the disease. Reversing wasting might therefore be a major advance in COPD treatment. In this project you will use advanced gene and protein profiling methods to find new disease pathways that might help stop or reverse wasting. Protein pattern analysis, advanced proteomics (SELDI-ToF, MS/MS).

29. **Inflammation resolving lipids in experimental models of very severe lung inflammation**

**Supervisors:** Professor Gary Anderson, A/Prof Margaret Hibbs, Dr Steve Bozinovski and Professor Bruce Levy, (Harvard Medical School, Boston USA)

**Project Site:** Department of Pharmacology, University of Melbourne

**Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

Inflammation of the lung normally heals completely after injury but in chronic lung disease this does not occur. In this project you will test whether the production and action of newly discovered naturally produced lipids that normally turn off inflammation is defective in chronic inflammatory lung disease.

**Skill acquisition:** In vivo disease models, zymography, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, 1D & 2D gels for protein pattern analysis, advanced proteomics (SELDI-ToF, MS/MS), ELISA and Western blotting.

30. **TH17 cells in lung disease**

**Supervisors:** Professor Gary Anderson and A/Prof Margaret Hibbs

**Project Site:** Department of Pharmacology, University of Melbourne

**Contact:** Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

IL-17 is a newly discovered cytokine that has rapidly emerged as a major player in lung disease. In this project you will determine why IL-17 is so strongly up-regulated in genetic models of severely lung disease.

**Skill acquisition:** In vivo disease models, zymography, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, 1D & 2D gels for protein pattern analysis, advanced proteomics (SELDI-ToF, MS/MS), ELISA and Western blotting.
31. **Novel molecular mechanisms of tumour evasion in COPD (emphysema) and lung cancer**  
**Supervisor:** Dr Steve Bozinovski  
**Co-Supervisor/s:** Dr Ross Vlahos, Professor Gary Anderson  
**Project Site:** Department of Pharmacology, University of Melbourne  
**Contact:** E: bozis@unimelb.edu.au, T: 8344 4221, F: 8344 0241  
**Project Description:** COPD (Chronic Obstructive Pulmonary Disease / Emphysema) and lung cancer are leading causes of death worldwide and will continue to be a major health burden for decades to come. COPD is also recognised to be a major risk factor for lung cancer, and interestingly this can occur independently of smoking status, which implicates shared molecular pathways. Myeloid Suppressor cells are thought to contribute to tumour evasion by impairing the actions of cytotoxic T cells. This project will investigate known molecular pathways in COPD previously described in our laboratory and explore their significance in lung cancer susceptibility. A range of molecular and cell biology methods will be implemented including phenotyping of macrophage lineages defective in COPD and the characterisation of myeloid cell populations important in tumour evasion in relevant disease models.  
**Skill acquisition:** Quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; basic T cell immunology, ELISA and Western blotting, In vivo disease models and viral culture.

32. **Role of anti-oxidants in COPD (emphysema)**  
**Supervisor:** Dr Ross Vlahos  
**Co-Supervisors:** Dr Steven Bozinovski & Prof Gary Anderson  
**Contact:** E: rossv@unimelb.edu.au, T: 8344-4221, F: 8344-0241  
**Project Site:** Dept of Pharmacology, Level 8, N814  
**Project Description:** Chronic Obstructive Pulmonary Disease (COPD or emphysema) is a major incurable global health burden and will become the third largest cause of death in the world by 2020. It is currently believed that an exaggerated inflammatory response to inhaled irritants, in particular cigarette smoke, causes progressive airflow limitation. This inflammation involves oxidative stress, the production of various cytokines and chemokines, induction of various proteases, small airway fibrosis, mucus hypersecretion and emphysema. Patients with COPD are also prone to respiratory infections (commonly called acute exacerbations of COPD - AECOPD) that cause an accelerated decline in lung function, hospitalisation and even death. These respiratory infections consist of bacteria and viruses that get into the lungs of people with COPD. We have developed mouse models of AECOPD that replicate the features of human disease. Oxidative stress plays a major role in COPD and AECOPD because cigarette smoke contains more than 1014 oxidants per puff, many of which are relatively long-lived. These oxidants give rise to Reactive Oxygen Species (ROS), which are a family of highly reactive molecules that are generated enzymatically by various cells in the lung in response to a variety of chemical and physical agents. However, the normal lung has developed defences to ROS-mediated damage, which include the anti-oxidant enzymes NADPH oxidase-2 (Nox-2) and glutathione peroxidise-1 (gpx-1). In this project you will investigate whether Nox-2 and gpx-1 ameliorates experimental AECOPD in a murine model of the disease. This will be achieved by using mice deficient in these anti-oxidant enzymes and pharmacological interventions. The significance of this will be that anti-oxidants such as Nox-2 and gpx-1 may be used to treat exacerbations of COPD.  
**Skill acquisition:** In vivo disease models, FACS analysis of cell populations, quantitative PCR, lung function measurement, histology, virus and cell culture, ELISA, zymography and Western blotting.

**LUNG REGENERATION LABORATORY**

The most significant impediment to the delivery of cell therapies for intractable respiratory diseases is the lack of knowledge about the precise identity and spatial location of regenerative stem cells in the adult lung, and the way in which lung stem and progenitor cell compartments are regulated by growth factors, stromal cells and extracellular matrix proteins which comprise their microenvironment.  

The broad aim of the Lung Regeneration Laboratory is to characterize epithelial and mesenchymal stem cells in the normal and diseased lung (including chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and cancer) in order to understand how lung stem cell compartments maintain the normal lung, and contribute to lung disease, injury and repair.  

In 2010, we will be offering two honours projects aimed at determining the biological and pathophysiological behaviour of endogenous lung stem cells in respiratory diseases, including asthma, chronic obstructive pulmonary disease and lung cancer. These projects will involve cutting edge research using flow cytometry-based cell separative strategies, novel three-dimensional cell culture assays, in vivo transplantation and molecular biology techniques.

33. **The role of adult lung stem cells in lung injury and repair**  
**Supervisor:** A/Professor Ivan Bertoncello  
**Co-Supervisor:** Dr Jonathan McQualter (jlmcq@unimelb.edu.au)
Project Site: Department of Pharmacology, Level 8 (N808), Medical Building,
Contact: E: ivanb@unimelb.edu.au T: 8344 6992 F: 8344 0241

Project Description: The central hypothesis to be tested in this proposal is that disruption of the epithelial-mesenchymal trophic unit during chronic respiratory disease and lung cancer results in unbalanced signalling in lung stem cells leading to a disturbed (pathologic) regenerative process. This project will analyse the temporal pattern of depletion and recovery of lung epithelial stem cells following lung injury in transgenic mouse models of lung disease. Cell culture analysis of the proliferation, self-renewal and lineage specificity of lung stem cells at various stages of injury and repair will provide valuable insights into the role in endogenous epithelial stem cells in injury and repair of the adult lung.

34. The role of the HGF/Met signalling in regulating adult lung stem cells

Supervisor: Dr Jonathan McQualter
Co-Supervisor: A/Professor Ivan Bertoncello (ivanb@unimelb.edu.au)
Project Site: Department of Pharmacology, Level 8 (N808), Medical Building
Contact: E: jlmcq@unimelb.edu.au T: 8344 8509 F: 8344 0241

Project Description: Recently we have identified a population of multipotent adult lung stem cells and developed new culture systems to assess their proliferative and differentiative potential. Using this assay, we have shown that hepatocyte growth factor (HGF) in co-operation with fibroblast growth factor (FGF-10) is essential for lung stem cell growth. This project will characterize the intracellular signalling pathways downstream of the HGF receptor tyrosine kinase (Met) that are fundamental to the survival, proliferation, and differentiation of lung epithelial stem cells in health and disease. Completion of this project will provide fresh insight into the previously unexplored role of HGF/Met signalling in regulating distinct cellular processes of adult lung stem cells in health and disease, ultimately leading to the identification of novel therapeutic targets for preventing aberrant stem cell growth (i.e. cancer and epithelial remodelling) and promoting epithelial regeneration.

35. Characterisation of the lung epithelial stem cell niche

Supervisor: A/Professor Ivan Bertoncello
Project Site: Department of Pharmacology, Level 8 (N808), Medical Building
Contact: A/Professor Ivan Bertoncello E: ivanb@unimelb.edu.au T: 8344 6992 F: 8344 0241

Project Description: The interaction of lung epithelial stem cells with mesenchymal stromal cells which comprise their niche is a critical factor regulating their regenerative potential. However, the stromal cell lineages involved in this process are ill-defined. This project will use flow cytometric analysis and sorting, and cell culture assays, to determine how different lung stromal cell types interact with specific growth factors and matrix proteins to regulate lung epithelial stem and progenitor cell proliferation and differentiation.

BEHAVIOURAL HEALTH

36. Investigating the use of Social Networking sites for health promotion to identify key strategies for success in engaging users - also offered as MSci

Supervisor/s: Rachel-Sacks Davis, Alisa Pedrana, Mark Stoové
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Mark Stoové E: stoove@burnet.edu.au

In recent years online social networking sites (SNS) have grown rapidly in popularity. The popularity of these sites, along with their interactive functions, offers a novel environment in which to deliver health promotion messages. We recently conducted a review of SNS to assess their use for sexual health promotion purposes. We found that, although many organisations involved in sexual health promotion have begun to use these websites, there has been very little formal study and evaluation of them. We identified a number of organisations that appear to be using SNS more effectively than others but we were unable to further investigate the strategies that these organisations used.

This Honours project will aim to identify strategies for success in this growing area. More specifically, the findings from this study will help us better understand the content, features and approaches that successfully encourage social engagement within a SNS health promotion context. Methods will include interviewing organisations with active health promotion activities on SNS and conducting an independent comparative evaluation of these sites. Quantitative and qualitative research will be used for the latter; and the project will involve novel online recruitment methods.
37. **Analysis of sexual risk behaviours reported by men who have sex with both men and women in Lao PDR - also offered as MSci**  
*Supervisor/s*: Mark Stoové, Caroline van Gemert  
*Project Site*: Burnet Institute, 85 Commercial Road, Melbourne  
*Contact*: Mark Stoove E: stoove@burnet.edu.au  

In 2010, the Burnet Institute, in collaboration with the Vientiane Capital Committee for the Control of AIDS and the Centre for HIV, AIDS and STIs in the Lao PDR, conducted a study exploring the sexual networks of men who have sex with men and women in Lao PDR. This study utilised a sampling technique called respondent driven sampling, which combines “snowball sampling” (getting individuals to refer those they know, these individuals in turn refer those they know and so on) with a mathematical model that weights the sample to compensate for the non-random sampling strategy used. An opportunity exists for detailed quantitative analysis of data collected using software specifically designed for analysis of data collected by driven sampling data to complement broader analyses of this data (note that prior experience using this software is not required). This project will focus on describing and comparing the risk behaviours reported among these men, their sexual networks and how these outcomes might potentially influence the transmission of sexually transmitted infections.

38. **Structural and environmental impacts on women’s relationships with their children following imprisonment - also offered as MSci**  
*Supervisor/s*: Rebecca Winter, Stuart Kinner, Mark Stoové  
*Project Site*: Burnet Institute, 85 Commercial Road, Melbourne  
*Contact*: Mark Stoove E: stoove@burnet.edu.au; Stuart Kinner E: kinner@burnet.edu.au  

Connection with family, particularly dependent children, is often a key factor in the psychological and social welfare of women in prison and those transitioning from prison to the community. This project will examine structural and environmental factors such as the operation of the Victorian criminal justice and welfare systems and the way these factors impact on women’s relationships with their children. The study will involve a desktop review of key policy documents and other ‘grey literature’ and interviews with key informants to identify systemic barriers and enablers to maintaining connection with children, and how these ultimately impact on the in contact with the criminal justice system.

**BIOLOGY — BONE**

39. **Bone health in children and young people with epilepsy treated with anti-epileptic drugs (AEDs) - also offered as MSci**  
*Supervisors*: Professor John Wark, Dr Peter Simm, Professor George Werther, Dr Sandra Petty  
*Project Site*: Department of Medicine (RMH)  
*Contact*: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au  

**Background:** Epilepsy and the use of anti-epileptic drugs (AEDs) are known to be associated with low bone mass and the risk of bone disease. In most patients, AED therapy once initiated is taken for many years if not for life. Moreover, it is well-established that AED therapy is a major cause of bone fractures in our community. However, there are still limited data concerning bone problems in children and adolescents taking these medications. We propose a novel study to explore their bone health looking at a number of measures, including analysing bone geometry and bone strength, which have not been described previously in this cohort. We will also follow these patients’ growth and development as well as their bone mass accrual and the number of fractures and other injuries that they sustain. These data will give great insight into the effects of epilepsy and its treatment on bone health and lead to improved management of bone health issues in young patients taking AEDs. The findings also will help us to establish a clinical model for the management of bone health in these patients.

Students undertaking this project will gain substantial experience in clinical study design, data collection and management, data analysis and interpretation, as well as translational aspects of biomedical research.

40. **Hallux valgus: is it by nature or by nurture? A twin study**  
*Supervisor*: Professor John Wark,  
*Project Site*: Department of Medicine (RMH)  
*Contact*: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au  

**Background:** Hallux valgus, also referred to as a “bunion”, is a common condition that may be considered to represent osteoarthritis of the first metatarso-phalangeal joint. Prevalence rates range from 5 to 37%, with the largest study reporting a prevalence of 28%. Hallux valgus has a significant impact on society, being associated with significantly lower
score health-related quality of life. Hallux valgus also affects balance and gait patterns, independently increasing the risk of falls in older people. Many people with hallux valgus undergo surgical correction of the deformity.

Despite the considerable burden on society, little is known about risk factors for hallux valgus. Between 58 and 90% of people with hallux valgus report a familial tendency. However, the heritability of the condition has not been established. A classical twin study provides a powerful approach to addressing this important issue and will be performed utilizing an existing cohort of adult female twins involved in long-term studies of bone health.

This novel project will provide students with substantial experience in clinical study design and implementation, an understanding of genetic epidemiology and twin studies, and the analysis and interpretation of twin data.

41. Understanding bone loss and the risk of fractures in patients treated for diabetes-related foot complications: a prospective study

**Supervisor:** Professor John Wark, Dr Paul Wraight, Ms Sue Kantor.

**Project Site:** Department of Medicine (RMH)

**Contact:**
- Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au
- Dr Paul Wraight E: Paul.Wraight@mh.org.au

**Background:** Foot disorders are a major cause of morbidity and hospitalization in patients with diabetes, with aetiological factors including vascular insufficiency, neuropathy and predisposition to infection. These patients also appear to be at increased risk of fractures in the affected feet, adding to their morbidity and disability. Therefore, it is proposed that individuals managed for diabetes-related foot complications are more likely to develop significant bone mineral loss causing increased fracture risk during the course of their treatment. Aspects of their therapy (e.g., pressure off-loading) are likely to contribute to this risk. Falls (which predispose to fractures) also are more prevalent in individuals prone to developing foot complications; poor calcium intake, vitamin D deficiency (from reduced outside activities) and other factors also may contribute to bone loss.

**Aim:** This project has three main objectives:

1) To determine whether individuals with diabetes-related foot complications are at an increased risk of bone loss, with a corresponding increase in morbidity/fractures.
2) If an association is identified between diabetes-related foot complications and bone loss, to identify contributing factors for this bone loss.
3) To develop a risk stratification tool in order to identify those individuals who are at highest risk of developing significant bone loss/morbidity/fractures. This study may lead to improved outcomes in diabetic patients with this important cause of morbidity, poor quality of life and high health care costs.

**Method:** It is proposed to recruit 50 consecutive patients under the care of the RMH Diabetic Foot Unit to assess bone mineral measures during the management of their diabetes-related foot complications. Regional bone mineral density will be measured using dual energy Xray absorptiometry and peripheral quantitative computed tomography in all patients on entry to the study and at 6 months. Patients will be assessed for known and putative risk factors for both local and systemic bone mineral loss including features which may be novel to the management of their foot complication. Students undertaking this novel project will gain substantial experience in the design and implementation of an original clinical research study, in patient recruitment, and data collection, management, analysis and interpretation.

42. Enhancing fracture risk prediction in osteoporosis - also offered as MSci

**Supervisors:** Professor John Wark, Ms Sue Kantor and Dr Andrew Briggs

**Project Site:** Department of Medicine (RMH), University of Melbourne, Parkville Campus

**Contact:**
- Prof. John Wark: jdwark@unimelb.edu.au;
- Ms Susan Kantor: skantor@unimelb.edu.au;
- Dr Andrew Briggs: A.Briggs@curtin.edu.au

**Background:** Osteoporosis is a common condition where bones are fragile leading to fractures, predominately of hip, spine, forearm and ribs. Dual energy Xray absorptiometry (DXA) performed using anteroposterior projection scanning of the spine is the current method of choice for estimating vertebral fracture risk in a clinical setting, but has limitations in predictive value. Our preliminary data suggest that lateral projection DXA using subregions of the lumbar vertebral bodies as regions of interest provides superior fracture risk prediction and could be a major advance in clinical assessment of osteoporosis.

**Aims and Methods:** This project will involve recruiting and evaluating several patient groups using this novel approach to osteoporosis assessment. Once validated, this methodology will allow more reliable identification of patients at high fracture risk. The ultimate aim is to refine diagnostic methods for the improved care of osteoporosis patients.
43. **Validation of bone density testing in women of south Asian background** - also offered as MSci  
**Supervisors:** Professor John Wark, Dr Ashwini Kale and Sue Kantor  
**Project Site:** Department of Medicine (RMH), University of Melbourne, Parkville Campus  
**Contact:**  
Prof. John Wark: jdwark@unimelb.edu.au;  
Ms Susan Kantor: skantor@unimelb.edu.au;  
Dr Ashwini Kale: akale@unimelb.edu.au  

**Background:** Osteoporosis is a common condition where bones are fragile leading to fractures, predominately of hip, spine, forearm and ribs. Osteoporotic fracture incidence varies widely in different countries and ethnic groups, potentially related to genetic, nutritional, environmental and lifestyle factors. Bone density measurement by dual energy Xray absorptiometry (DXA) is currently the most useful way of assessing bone strength and an individual’s fracture risk. However, normal ranges for bone density vary between ethnic groups and measurements of bone density have mostly been done in white or western people. Bone density in people of south Asian background typically has been interpreted using reference data taken from white people. This may not provide an accurate reflection of true fracture risk in this population.

**Aims and Methods:** This project will involve recruiting and evaluating bone density by DXA in females of south Asian background and above the age of 30 years, and comparing their bone density values to Caucasian Australian females. Peak bone density will be estimated and age-ethnicity-specific bone density reference curves for women of south Asian background will be constructed. Ultimately, this study will allow for appropriate estimation of fracture risk in this section of the Australian population.

44. **Assessing the clinical usefulness of peripheral quantitative CT in fracture prediction** - also offered as MSci  
**Supervisors:** Professor John Wark, Ms Sue Kantor  
**Project Site:** Department of Medicine (RMH), Parkville Campus  
**Contact:**  
Prof. John Wark: jdwark@unimelb.edu.au;  
Ms Susan Kantor: skantor@unimelb.edu.au  

**Background:** Bone density measurement by dual energy Xray absorptiometry (DXA) is currently the most useful way of assessing bone strength and an individual’s fracture risk. However, at a population level, most low trauma fractures occur in people who have DXA bone density values below the young normal range but above the range defined as osteoporosis (so-called “osteopenia”). While DXA has a number of attractive attributes, it is not able to assess bone biomechanical indices nor to selectively measure the density of trabecular and cortical bone. These bone properties contribute to the risk of fracture and can be assessed using peripheral quantitative computed tomography (peripheral QCT).

**Aims and Methods:** This project will involve recruiting patients who have sustained low trauma fractures despite not having osteoporosis by conventional DXA criteria, and assessing measures of fracture risk determined using pQCT. The contribution of this new technique to the specific diagnosis of osteoporosis will be evaluated and potentially a better understanding of the pathogenesis of low-trauma fractures will be obtained.

45. **Improving the bone outcomes for patients with diabetes-related foot problems**  
**Supervisors:** Dr Paul Wraight, Professor John Wark and Ms Sue Kantor  
**Project Site:** Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Department of Medicine, University of Melbourne, Parkville Campus  
**Contact:**  
Dr Paul Wraight: Paul.Wraight@mh.org.au;  
Prof. John Wark: jdwark@unimelb.edu.au;  
Ms Susan Kantor: skantor@unimelb.edu.au  

**Background:** Foot complications are a major cause of disability, hospitalization and cost in patients with diabetes. Individuals managed for diabetes-related foot complications may be more likely to develop significant bone mineral loss thus contributing to an increased fracture risk during the course of their treatment. Not only do these individuals share similar risk factors to the general population but aspects of their therapy are likely to be further contributing to this risk. For example, all individuals are managed with pressure off loading devices for varying lengths of time and this treatment not only reduces weight-bearing exercise but also increases the risk of mechanical falls. Mechanical falls are known to be more prevalent in individuals prone to developing foot complications, with our own data demonstrating that 30% of all patients had a fall in the 12 months prior to developing a foot complication. It is likely that poor calcium intake and low vitamin D levels (from reduced outside activities) also contribute to bone loss.

Further contributing factors are likely and these may include the presence of infection (with 20-25% of individuals having
pedal osteomyelitis), prolonged hospitalisations, co-existence of other diseases (including diabetes itself) and medications

**Aims and Methods:** This project will involve recruiting a cohort of patients managed by the Royal Melbourne Diabetic Foot Unit to assess the impact of diabetic foot problems and their management on measures of bone health and to determine risk factors for poor bone outcomes in these patients. A risk stratification tool will be developed to help identify those individuals who are at highest risk of developing significant bone loss/morbidity/fractures. The ultimate aim is to improve outcomes for this group of high-risk patients.

46. **Do balance deficits in patients chronically taking anti-epileptic medications reflect neurodegeneration of the cerebellum** - *also offered as MSci*

**Supervisors:** Professor Terence O’Brien, Professor John Wark, Professor Keith Hill and Professor Patricia Desmond.

**Project Site:** Departments of Medicine and Radiology, The Royal Melbourne Hospital, University of Melbourne, National Ageing Research Institute.

**Contact:** Prof Terence O’Brien: obrientj@unimelb.edu.au; Prof. John Wark: jdwork@unimelb.edu.au; Prof. Keith Hill: keith.hill@nh.org.au; Prof. Patricia Desmond: PatriciaDesmond@mh.org.au.

**Background:** Anti-epileptic medications are taken chronically by many people of all ages, for epilepsy and for a range of other high prevalence medical conditions. The adverse effects of the chronic use of these medications on bone and fracture risk is well recognised, but only recently has the negative impact of these medications on balance performance been documented by our group and others. Using a matched twin-sibling pair design we found that worse performance on several sway measures for AED users with longer duration of AED use. The association between chronic AED use, particularly with phenytoin, and cerebellar atrophy has long been recognised, but this has not previously been correlated with measures of balance function.

**Aims of Project:** To investigate whether the magnitude of cerebellar volume on MRI, compared with a matched twin or sibling control, is associated with the severity of quantitative measures of balance dysfunction.

**Methods:** 35 AED use-discordant twin or sibling pairs have had a detailed falls and balance assessment. The T1-weighted volumetric MRI images on these patients will be used to quantitatively measure cerebellar, cerebral and brainstem volumes. The relative cerebellar volume will be compared between the AED user and their matched twin/sibling pair for the study population using the powerful discordant twin/sibling pair approach. The within pair difference in cerebellar volumes will then be correlated with that of the within pair difference for the balance measurements.

**Skills:** MRI image analysis, balance assessment interpretation, clinical pharmacology and statistical analysis of data.

47. **Foot and ankle fractures in men** - *also offered as MSci*

**Supervisors:** Associate Professor Julie Pasco, Dr Sharon Brennan

**Project Sites:** Shared: 1) NorthWest Academic Centre, Department of Medicine, University of Melbourne, Sunshine Hospital, and 2) Barwon Epidemiology and Biostatistics Unit, Deakin University, Barwon Health, Geelong

**Contact:** Assoc Prof Julie Pasco T: 5226 7393 E: juliep@barwonhealth.org.au, Dr Sharon Brennan T: 5226 7915 E: sbrannen@unimelb.edu.au

Foot and ankle fractures are among the most common nonvertebral fractures but little is known about their epidemiology or risk factors. This is surprising given that foot/ankle fractures have a poor prognosis and can have a substantial impact on quality of life. Furthermore, as lower extremity fracture patients often have comorbid conditions, treatment can be complex. This project fulfills a major public health goal to identify specific risk factors and methods to prevent occurrence of lower extremity fractures. The aim of the study is to identify risk factors for foot and ankle fractures in men and determine the incidence of these fractures in the community. In this study, fracture cases will be identified from radiology reports and compared with controls from men enrolled in the GOS. Assessments include bone mineral density, heel ultrasound, anthropometry, body composition, blood pressure, diet, alcohol consumption, medication use and cause of fracture. Logistic regression will be used to determine risk factors for foot/ankle fractures.

48. **Fractures in young children: Informing Policy** - *also offered as MSci*

**Supervisors:** Associate Professor Julie Pasco, Dr Sharon Brennan

**Project Sites:** Shared: 1) NorthWest Academic Centre, Department of Medicine, University of Melbourne, Sunshine Hospital, and 2) Barwon Epidemiology and Biostatistics Unit, Deakin University, Barwon Health, Geelong

**Contact:** Assoc Prof Julie Pasco T: 5226 7393 E: juliep@barwonhealth.org.au, Dr Sharon Brennan T: 5226 7915 E: sbrannen@unimelb.edu.au

This project will involve recruiting a cohort of patients managed by the Royal Melbourne Diabetic Foot Unit to assess the impact of diabetic foot problems and their management on measures of bone health and to determine risk factors for poor bone outcomes in these patients. A risk stratification tool will be developed to help identify those individuals who are at highest risk of developing significant bone loss/morbidity/fractures. The ultimate aim is to improve outcomes for this group of high-risk patients.
During the last decade there have been major reviews of children’s safety in Victoria, in terms of legislation, and broad policy and practice frameworks. This innovative, cost-effective study will be the first to determine patterns of annual fracture incidence in southeastern Victoria for all children aged 10 years and under, over a period spanning 1994-2010. The identification of fracture patterns in children, and whether these patterns correspond with changes to children’s health, wellbeing and safety legislation and policies, will provide important, cost-effective information to children’s welfare groups, providing evidence for future intervention and changes to policy for the benefit of Victorian children. Incident fractures will be identified at all skeletal sites for children aged 5 years and under for 1994 to 2009 from radiological reports for the Barwon Statistical Division, Victoria. Changes to Acts and legislation for the protection of children over this time period will be identified from policy databases and grey literature, and mapped against fracture incidence.

**49. Asthma and the risk of fracture in children** - also offered as MSci

**Supervisors:** Associate Professor Julie Pasco, Dr Sharon Brennan

**Project Sites:** Shared: 1) NorthWest Academic Centre, Department of Medicine, University of Melbourne, Sunshine Hospital, and 2) Barwon Epidemiology and Biostatistics Unit, Deakin University, Barwon Health, Geelong

**Contact:** Assoc Prof Julie Pasco T: 5226 7393 E: juliep@barwonhealth.org.au, Dr Sharon Brennan T: 5226 7915 E: sbrennan@unimelb.edu.au

This is a collaborative project between the GOS and Dr Peter Vuillermin, Paediatrician. There are a number of reasons children with asthma may be more susceptible to fracture, which include the use of beta agonists and corticosteroid medications, differences in activity levels and the disease process itself. The aim is to compare fracture rates in children with asthma with fracture rates of their peers. In 2005, the Geelong Childhood Asthma Study identified a community-based sample of primary school aged children with asthma. Fracture rates for this sample will be determined over the following years and compared with rates from the general community of primary school aged children as defined by the GOS. This project will provide the opportunity to develop skills in epidemiological methodology, abstracting and comparing data from existing large databases and analysing data using rate ratio analysis. This project presents the opportunity to utilize good quality data from two large community-based projects to generate clinically useful information.

**BIOLOGY —WOMEN’S HEALTH**

**50. The young female health initiative (YFHI)** - also offered as MSci

**Supervisors:** Professor John Wark, Professor Suzanne Garland, Dr Ashley Fletcher and Dr Yeshe Fenner

**Project Site:** Department of Medicine (RMH), University of Melbourne, Department of Microbiology and Infectious Diseases, RWH, Parkville Campus

**Contact:** Prof. John Wark: jdwark@unimelb.edu.au; Prof Suzanne Garland: Suzanne.Garland@thewomens.org.au; Dr Yeshe Fenner: yeshe.fenner@mcri.edu.au

**Background:** Behaviours and lifestyle choices of adolescents and young adults have far-reaching consequences for future well-being, quality of life and productivity. Women drive health behaviours in our society, making it critical to understand the factors shaping health and lifestyle in young women, and how to intervene effectively during the critical ages of 16-25 years when health patterns are established that shape future health trajectories. Risk factors for many diseases tend to cluster yet few studies have examined interlinkages between different health domains, nor harnessed novel information and communications technologies (ICT) for health surveillance and intervention.

**Aims of project:** This study is a pilot for a larger project that will comprehensively examine young women’s health and wellbeing. In this pilot study we aim to: 1) gather a broad array of questionnaire and biological/physical data on physical and mental health and socioecological factors in a sample of young women using novel ICT methods 2) assess levels of compliance and participation; data quality; and acceptability of study procedures; and 3) establish a youth-friendly study protocol for a large cohort study. We will also be running additional pilot studies to develop and validate web- and mobile-based information and communication technologies for data collection, health promotion and intervention.

**Methods:** 200 Victorian females aged 16-25 years, will be recruited using a novel web-based method via Facebook that was successfully piloted in a recent study. Participants will be invited to complete an online health-related survey (administered in different styles and modes to assess acceptance and feasibility) and visit a study site for a physical examination, collection of blood, and scans of bone density and body composition. Novel remote, ICT-based measurement methods also will be evaluated and used. Examples include techniques to assess physical activity, mood and diet. These will be applied in the study of determinants of obesity and associated disease risk.
Outcomes: Our results will provide an important understanding of the acceptability and feasibility of examining multiple health domains using ICT based methods in this demographic; and will inform the design of a large cohort study, aiming to have a far-reaching positive impact on women’s health and wellbeing.

Honours Opportunities: This project offers the opportunity to be involved in various components of this exciting project:

- Pilot study to gather online questionnaire and various biological data on aspects of health areas including:
  - bone and joint health
  - obesity and metabolic health
  - cardiovascular health
  - nutrition, physical activity, and health-related behaviour
  - sexual and reproductive health
  - mental health
- Pilot studies using mobile communication technology to investigate the relationship between:
  - physical activity, mood and mental health in young women
  - diet, sleep and mood in young women

Honours students involved in this study may gain in experience in: collecting and testing samples; communication with participants (recruitment, clinical assessment); analysis of large physical and questionnaire datasets; literature review; and preparation of reports and publications.

51. **VACCINE – Monitoring the Effectiveness of the Vaccine for Cervical Cancer**

**Supervisors:** Professor Suzanne Garland, Professor John Wark, Dr Yasmin Jayasinghe, A/Professor Sepehr Tabrizi and Dr Yeshe Fenner

**Location:** Department of Microbiology and Infectious Diseases, RWH, Parkville Campus

**Contact:** Prof Suzanne Garland: Suzanne.Garland@thewomens.org.au; Prof. John Wark: jdwark@unimelb.edu.au; Dr Yasmin Jayasinghe: Yasmin.Jayasinghe@thewomens.org.au; A/Prof Sepehr Tabrizi: sepehr.tabrizi@thewomens.org.au; Dr Yeshe Fenner: yeshe.fenner@gmail.com

**Background:** Australians are world leaders in the prevention of cervical cancer. In Australia, between 1991 and 2005, the incidence of cervical cancer in women of all ages decreased from 12.7 to 6.9 per 100,000 due to screening. In 2007 Australia became the first country to implement a fully funded national population-based cervical cancer vaccination program. The World Health Organisation (WHO) recommends that the impact of this vaccination program be monitored.

**Aims and Method:** The VACCINE Study will measure the effectiveness of the Australian cervical cancer vaccine programme in two complementary sub-studies. In over 1,500 18-25 year old females recruited through Facebook from the general population, we will determine the current prevalence of vaccine-type Human Papillomavirus (HPV) infection along with demographic and clinical correlates of genital HPV infection. In 500 consecutive CIN3 biopsies we will determine the current proportion of CIN3 biopsies that contain vaccine-type HPV DNA in a sample of young women in Victoria.

**Outcomes** will be compared with baseline pre-vaccine estimates from both the Australian and international literature.

This project gives students substantial experience in study design, data collection and management, data analysis and interpretation, as well as translational aspects of biomedical research.

52. **A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy - also offered as MSci**

**Supervisors:** Professor Terence O’Brien and Professor Frank Vajda, Epilepsy and Neuropharmacology Group, The Department of Medicine: The Royal Melbourne Hospital, Associate Professor Les Sheffield, The Murdoch Children’s Research Institute

**Project Site:** The Department of Medicine (RMH)

**Contacts:** Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au
Professor Frank Vajda E: vajda@netspace.net.au
A/Professor Les Sheffield E: les.sheffield@ghsv.org.au, The Murdoch Childrens Research Institute.

It is long been recognised that women with epilepsy who become pregnant while taking an anti-epileptic drug (AED) have an increased risk of having a foetus or infant with a birth defect (BD). This is particular high for valproate. Despite the increased risk associated with taking AED in pregnancy, most women with epilepsy who become pregnant, or plan to do so in the near future, cannot simply cease the drugs because of the risk to the health and safety of the mother and child.
of uncontrolled seizures. The development of methods that would allow the prediction that a specific drug would be associated with a higher risk of a birth defect in a particular woman would be of great potential benefit. There is evidence from family and twin studies that genetic factors may play a role in determining predisposing an individual to having a child with an AED associated birth defect. The Australian Register of Anti-epileptic Drugs in Pregnancy has been established in an attempt to obtain more accurate information about the risks of specific AEDs. This is a prospective, voluntary, telephone interview based study that enrolls pregnant women with epilepsy, prior to the outcome of the pregnancy being known, and follows the outcomes of their pregnancies. The study has been running since July 1999, and to date has enrolled more than 1600 pregnant women.

This study will attempt to identify genetic markers that predict the risk of valproate-induced birth defects. Participants will be identified through the Australian Registry of Anti-epileptic drugs in pregnancy. Women with epilepsy who were taking an AED in the first trimester, and their partners, will be offered enrollment. Two types of genetic tests will be performed:

1. A case-control genetic association studies comparing genetic information from mothers and infants taking a valproate AED during the first trimester with those who were taking the same valproate but did not have a child with a birth defect
2. A transmission disequilibrium test (TDT), design will be also be employed. This test looks for significant disequilibrium in the transmission of the allele of interest in the patient with a characteristic of interest. It therefore eliminates any potential sources of bias between the affected patients and non-affected controls, which may occur in case-control association studies. Blood for genetic analysis would be taken from the mother, father and child.

This project is also listed under Pharmacogenetics and Personalised Medicine

53. Endometriosis
   Project Leaders: Prof Peter Rogers and Dr Jane Girling
   Project Site: Department of Obstetrics & Gynaecology, Royal Women’s Hospital
   Contact: Prof Peter Rogers E: parogers@unimelb.edu.au or Dr Jane Girling E: jgirling@unimelb.edu.au

Endometriosis is a disease where endometrial tissue grows outside the uterus, most commonly on the organs and tissues of the peritoneal cavity. It can cause severe pain, and is associated with peritoneal inflammation, fibrosis and adhesions. It has been estimated that 8-10% of women in their reproductive years suffer from endometriosis. Endometriosis is a complex disease with a genetic basis, which is difficult to study. In this project, we will develop studies to examine the function of genes identified as playing a role in endometriosis

54. Growth and development of uterine fibroids
   Project Leaders: Prof Peter Rogers, Dr Marina Zaitseva and Prof Martha Hickey
   Project Site: Department of Obstetrics & Gynaecology, Royal Women’s Hospital
   Contact: Prof Peter Rogers E: parogers@unimelb.edu.au or Dr Marina Zaitseva E: zaitseva@unimelb.edu.au

Uterine fibroids are benign tumours of the smooth muscle of the uterus, and are the most common tumours in women. Fibroids are the commonest cause of hysterectomy in women today, with an estimated annual direct healthcare cost in the USA of 2 billion dollars. This project will build on extensive molecular profiling and protein work undertaken on fibroids over the past several years. A new two-cell model has been created involving both uterine smooth muscle cells and uterine fibroblasts in the development of fibroids. This project will utilise molecular and protein techniques using human tissues to better understand the processes that lead to the development and continued growth of uterine fibroids.

55. Investigation of novel placental specific genes in pregnancies complicated by pre-eclampsia and fetal growth restriction
   Supervisors: Dr Clare Whitehead, Dr Tu’uhevaha Kaitu’u-Lino and A/Prof Stephen Tong
   Project Site: Department of Obstetrics and Gynaecology, University of Melbourne at the Mercy Hospital for Women
   Contact: Dr Tu’uhevaha Kaitu’u-Lino T: 8458 4355 E: t.klino@unimelb.edu.au

Project description: Pre-eclampsia affects 10% of pregnancies and results in the deaths of approximately 50,000 pregnant women each year worldwide. Despite the global health burden of pre-eclampsia, the pathophysiology of the disease remains unclear, and therefore treatment options are limited. The only cure is delivery of the baby, but if the baby is severely premature, it too may die. Furthermore, the baby may fail to grow properly in the womb (fetal growth restriction-FGR), putting it at risk of dying in-utero (a stillbirth) or suffering long term disability if it survives. There are genes and proteins in the placenta that are different in pregnancies complicated by pre-eclampsia and FGR, which may
play a role in the development of the disease. The aim of this project is to improve our understanding of the roles of these genes in the development of preeclampsia.

56. **An in vivo model to assess the usefulness of phytophenols as therapeutic agents in the management of preterm birth**

**Supervisors:** Dr. Martha Lappas, Dr. Ratana Lim, Dr. Tuuhevaha Kaituu-Lino  
**Project Site:** Department of Obstetrics & Gynaecology, University of Melbourne located at the Mercy Hospital for Women  
**Contact:** Dr Martha Lappas T: 8458 4370 E: mlappas@unimelb.edu.au

**Project description:** The single most important complication contributing to poor pregnancy and neonatal outcome is premature birth. Intrauterine infection is a common trigger for preterm birth and is also a risk factor for the subsequent development of neurodevelopmental abnormalities in the neonate. Bacterial lipopolysaccharide (LPS) activates pro-inflammatory signalling pathways, which are implicated in both preterm delivery and antenatal brain injury. In our *in vitro* studies, phytophenols such as those found in turmeric, nuts and fruits, reduce LPS-induced pro-inflammatory reactions. In this project, we will use a mouse model of infection-associated preterm labour to determine whether the administration of phytophenols can (1) inhibit inflammatory mediators *in vivo*; (2) delay LPS-induced preterm delivery; and (3) improve neonatal outcome in the presence of intrauterine inflammation.

57. **Investigation of the transmission dynamics of S. aureus in mother/baby dyads in relation to the development of mastitis**

**Supervisors:** A/Prof. Sepehr Tabrizi and Dr. Meabh Cullinane  
**Project Site:** Dept of Microbiology and Infectious Diseases, Royal Women’s Hospital, C/- Bio 21 Institute  
**Contact:** E: Sepehr.tabrizi@thewomens.org.au and M.Cullinane@latrobe.edu.au

Over 80% of Australian women initiate breastfeeding and some of these women can develop an infection known as mastitis. Mastitis is an acute, debilitating infection that can occur in up to 20% of Australian breastfeeding women. This infection causes a red, painful breast combined with fever, 75% of such symptoms occurring in the first eight weeks postpartum. Research suggests that S. aureus is the predominant cause of mastitis. However, there has been a lack of research into the development of mastitis in breastfeeding mothers, or whether transmission of micro-organisms between mother and infant during breastfeeding plays a role in the development of mastitis. The CASTLE study (Candida and Staphylococcus Transmission, Longitudinal Evaluation) is investigating the role of S. aureus in the pathogenesis of breast pain and infection among breastfeeding women. 360 pregnant women have been recruited before birth and followed until 8 weeks postpartum. Swabs and breast milk samples have been collected at defined time points and cultivated for S. aureus. S. aureus isolated from mothers and infants have been stored. This project will use the S. aureus isolates obtained from the CASTLE study to further investigate the dynamics of S. aureus transmission between mother/baby dyads in the early weeks postpartum using random amplification of polymorphic DNA (RAPD) profiling. This will help determine the role of infant colonisation with S. aureus in relation to the timing of maternal mastitis. In addition, this analysis will determine whether specific RAPD types may be responsible for the development of mastitis.

**CANCER**

58. **Validation of candidate genes involved in the progression of gastric cancer**

**Supervisors:** A/Professor Alex Boussioutas. Co-supervisor: Dr Rita Busuttil  
**Project Site:** Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne  
**Contact:** A/Professor Alex Boussioutas T: +61 03 9656 1287 E: alexb@unimelb.edu.au  
Dr Rita Busuttil T: +61 03 9656 1287 E: Rita.Busuttil@petermac.org

Gastric cancer (GC) is the fourth most common cancer globally and in many western countries is usually only diagnosed at advanced stage giving patients a 5-year survival rate of less than 20%. GC has distinct premalignant stages that have significant propensity to progress. The premalignant cascade consists of easily identifiable histological stages from chronic atrophic gastritis (ChG), intestinal metaplasia (IM) and dysplasia. The progression through these stages, particularly IM, takes years, offering a large window of opportunity to intervene. However not all patients with IM will progress and selection of patients for high-risk surveillance would reduce the burden of unnecessary screening, patient anxiety and improve outcomes due to early detection of disease.

Relatively little is known about the key genetic events leading to IM. Our laboratory is currently in the process of completing the first comprehensive analysis of IM in the world and seeks to identify candidate genes involved in the progression of IM to GC that can be used to reliably predict the progression to GC in humans by using a genomics based approach. Identification of such genes offers an opportunity to study the molecular mechanisms involved and pinpoint
targets for prevention and therapy. The aim of this project is validate these candidate genes using an independent data set and then characterizing these genes using functional assays and animal models.

We are looking for motivated students (both Honours and PhD students) to strengthen our group. The project will use broad range techniques including bioinformatics, cell culture, animal models and molecular biology.

59. **Role of the Tumour Microenvironment in Gastric Cancer**

**Supervisors:** A/Professor Alex Boussioutas. Co-supervisor: Dr Rita Busuttil

**Project Site:** Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne

**Contact:** A/Professor Alex Boussioutas T: +61 03 9656 1287 E: alexb@unimelb.edu.au
Dr Rita Busuttil T: +61 03 9656 1287 E: Rita.Busuttil@petermac.org

Gastric cancer (GC) is the fourth most common cancer globally and 7th in incidence in Australia. It has a poor survival rate which can be attributed to the advanced stage at diagnosis in most patients. The molecular and cellular mechanisms underlying the development of GC are not well described.

Traditionally cancer research involved studying the cancer cell itself. More recently, there has been growing interest in studying the normal cells and molecules which surround the cancer cell. This tumour microenvironment consists of a variety of stromal cell types including cells such as fibroblasts. It is believed that the dynamic communication between tumour cells and the surrounding cell types may play a major role in cancer initiation, progression and establishment of metastatic disease. The aim of this project is to investigate tumour-stromal interactions in gastric cancer utilizing established and primary cell lines. Once the molecular pathways by which a tumour cell progresses has been elucidated it is possible that these processes could be exploited in the development of novel therapeutics.

This project will use a broad range of techniques such as live cell microscopy, cell culture techniques and siRNA to interrogate the function of gene products that influence tumour-stroma communication.

Our previous genomic experiments has provided us with a number of exciting candidate genes that may be involved in this interaction. This is novel research that may have a major benefit to our understanding of cancer and improve patient outcomes.

60. **Innovative method to target ovarian cancer stem/progenitor cells**

**Supervisors:** Dr Nuzhat Ahmed, Prof Jock Findlay (Women’s Cancer Research Centre, Royal Women’s Hospital & Department of Obstetrics & Gynaecology, University of Melbourne)

**Project Site:** Work will be conducted at the laboratories of the Royal Women’s Hospitals

**Contact:** Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. T: 8345 3734 E: Nuzhat.Ahmed@thewomens.org.au

**Aims/Hypothesis: H**

**Hypotheses:** Combination chemotherapy (cisplatin and paclitaxel) imposes on residual tumours cancer stem cell-like phenotype resulting in chemoresistant recurrent tumour mass. Targeting cancer stem cell-like markers will provide an opportunity for overcoming chemoresistance and consequently recurrence.

**Specific aim-** To use RNA aptamers against two currently identified cancer stem cell markers (EpCAM and CD44) to assess the inhibition/reversal of chemoresistance.

**Background/Rationale:** Epithelial ovarian cancer is the 5th most frequent cause of death in women worldwide, resulting in over 16,000 deaths in United States and 900 in Australia annually. These distressing statistics are due to the asymptomatic nature of the cancer, with patients usually presenting at a late stage. The hurdle faced by current therapies aimed towards treating ovarian cancer is chemotherapy resistance, resulting in relapse and death within a short time frame. Hence, novel approaches are needed to sensitize the tumour population which survives current therapies. Combination of platinum and taxol based drugs is the current standard regimen of chemotherapy after debulking surgery in advanced stage ovarian cancer patients. A diverse array of resistance mechanisms for these drugs has been described but none of these have been useful as a therapeutic target in a clinical setting. Recent results in our laboratory suggest that a distinct population of tumour cells isolated from the ovaries and ascites (tumour fluid) of advanced-stage ovarian cancer patients survive platinum and taxol treatment. These cells have up regulation of a series of cancer stem cell-like markers (CD44, EpCAM, CD133, CD117, Oct4 and Nanog). Hence, an effective cancer stem cell treatment is urgently required to sensitize chemotherapy treated residual cells. In this study we will evaluate the effect of RNA aptamers that binds to EpCAM and CD44 to facilitate a method of sensitizing chemoresistant cells.

**Outcomes/Benefits:** An effective cancer stem cell targeting system is urgently required to eradicate cancer/recurrence.

This project will use OVCA 433 as a model ovarian cancer cell line which will be treated in vitro with chemotherapeutic drugs to facilitate the expression of stem cell markers CD44 and EpCAM. These cells will be treated with cell surface aptamers against CD44 and EpCAM in the presence and absence of chemotherapy. The cells will be assessed for chemo-sensitization, alterations in signalling pathways and assessment of proteins which are involved with chemo-resistance. Techniques used will be MTT and {\textsuperscript{3}}H-Thymidine uptake assays, Western blot, immunofluorescence and
q-PCR. Successful completion of the project may provide a model for the development of novel targeted agents which may suppress cancer/recurrence. This will also provide a platform for a graduate student to understand the basics of clinical research. Results from this project will be published in biochemical/cancer journals and presented at a national or international conference.

61. Understanding peritoneal metastasis in the context of tumour recurrence in ovarian cancer

Supervisors: Dr Nuzhat Ahmed, Prof Jock Findlay (Women’s Cancer Research Centre, Royal Women’s Hospital & Department of Obstetrics & Gynaecology, University of Melbourne)

Project Site: Work will be conducted at the laboratories of the Royal Women’s Hospitals

Contact: Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. T: 8345 3734

E: Nuzhat.Ahmed@thewomens.org.au

Aims/Hypothesis: Hypotheses- Peritoneal tumour cellular aggregates (PTCs) surviving in ascites undergo epithelial to mesenchymal transition (EMT) in response to chemotherapy treatment. The regulation of EMT-associated molecules in response to drug treatment is crucial for maintaining the survival and invasiveness of PTCs for secondary growth (recurrence); and suppression of ovarian cancer growth in the peritoneum may be achieved by targeting drug induced EMT associated molecules.

The specific aims of the project are: (i) to characterize the EMT status in ovarian PTCs isolated from ascites of cancer patients in response to chemotherapy; and (ii) to suppress the growth of PTCs by targeting EMT associated molecules that are up regulated in response to chemotherapy.

Background/Rationale: The development of peritoneal metastases is a major clinical issue in the prognosis and management of ovarian cancer. A significant proportion of ovarian cancer cells in peritoneal ascites exist as PTCs with the capacity to metastasize to local organs. The pathology of localized metastasis includes attachment of shed PTCs in the peritoneum onto mesothelial-lined spaces resulting in tumour masses as a secondary growth. In most cases it is difficult to completely eradicate PTCs during debulking surgery. These free floating PTCs survive chemotherapy treatment and are a major source of recurrence which kills 80% of ovarian cancer patients treated with first line of chemotherapy. Hence, a comprehensive understanding of ascites tumour biology and its response to chemotherapy is needed to combat ovarian cancer dissemination/recurrence.

Outcomes/Benefits: Understanding the processes of growth/survival and the response of ascites PTCs to chemotherapy is essential for the clinical management of ovarian cancer patients. The project will involve isolating PTCs from ascites of cancer patients and using Western blot, quantitative PCR and immunofluorescence to identify novel proteins of interest. Successful completion of the project may provide a model of suppressing peritoneal dissemination of ovarian carcinoma. This will also provide a platform for a graduate student to understand the basics of clinical research. Results from this project will be published in biochemical/cancer journals and presented at a national or international conference.

Human ethics application (HEC #09/09) has been approved by the Royal Women’s Hospital Human Ethics Committee.

62. Characterization of cross-talk between tumour and stromal cells in inducing metastasis and resistance to chemotherapy in ovarian cancer

Supervisors: Dr Nuzhat Ahmed, Prof Jock Findlay (Women’s Cancer Research Centre, Royal Women’s Hospital & Department of Obstetrics & Gynaecology, University of Melbourne)

Project Site: Work will be conducted at the laboratories of the Royal Women’s Hospitals

Contact: Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. T: 8345 3734

E: Nuzhat.Ahmed@thewomens.org.au

Aims/Hypothesis: Hypotheses- Peritoneal dissemination of ovarian cancer is dictated by the extent of invasiveness in the tumour cells of ascites that survive as peritoneal tumour aggregates (PTCs), and is largely dependent on the biological changes induced by the surrounding stroma. We further hypothesize that identification of cross talk between tumour PTCs and stroma will successfully identify potential molecules involved in the predisposition of the tumour cells to metastasise locally as well as respond to chemotherapy.

Specific aims- (i) To determine whether cancer associated fibroblasts (CAFs isolated fresh from ascites) can alter the spheroid forming and invasive ability of ovarian cancer cell lines in vitro; & (ii) to determine if CAFs can alter the response of ovarian cancer cell lines to chemotherapy.

Background/Rationale: About 75% of ovarian cancer patients are diagnosed at an advanced-stage as symptoms are non specific and diagnosis delayed until the tumour has metastasized to the surrounding abdominal peritoneum and omentum. This type of peritoneal dissemination is almost unique to ovarian cancer and occurs due to the exfoliation of transformed ovarian surface epithelial cells. In the peritoneal cavity transformed cells disseminate as single cells or PTCs influenced by the flow of peritoneal tumour fluid or ascites. The unique biology of tumour cell exfoliation from the surface of the ovary, survival as single cells or as PTCs in the peritoneum, predisposition to peritoneal organs and innate
resistance to chemotherapy suggests that ovarian cancer PTCs possess distinct traits which enables them to self renew and adapt to the changing local environment. In animal models of cancer, normal epithelial cells have been shown to become malignant when surrounded by tumour-derived fibroblasts but not normal fibroblasts. These results signal the need to study the biological alterations induced by stroma on ascites tumours cells of ovarian cancer.

**Outcomes/Benefits:** This proposal represents a novel model of ovarian cancer progression where the inherent traits in ascites PTCs will be compared in the presence and absence of associated stroma. PTCs and stromal cells will be isolated from the ascites of ovarian cancer patients and evaluation of the biological alterations induced by the associated stroma that result in enhancing the metastasising capacity of ascites PTCs will be assessed by biological methods such as Western blot, quantitative PCR and immunofluorescence. The identification of these changes/molecules may lead to the development of novel prognostic indicators.

Human ethics application (HEC#09/09) has been approved by the Royal Women’s Hospital Human Ethics Committee.

**63. Elucidating the role of mesenchymal stem cells in promoting metastasis of ovarian cancer cells**

**Supervisors:** Dr Nuzhat Ahmed (Women’s Cancer Research Centre, RWH), Dr Bill Kalionis (Pregnancy Research Centre, RWH)

**Project Site:** Work will be conducted at the laboratories of the Royal Women’s Hospitals

**Contact:** Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. T: 8345 3734 E: Nuzhat.Ahmed@thewomens.org.au

**Hypothesis:** Mesenchymal stem cells (MSC) residing in ovarian stroma or in non-ovarian tissues can promote ovarian cancer metastasis.

**Specific aims:** (i) To determine whether MSC derived from ascites of ovarian cancer patients or those derived from human placenta can alter the growth, invasive and ovcaosphere forming abilities of ovarian cancer cell lines in vitro; & (ii) to determine if MSC can alter the response of ovarian cancer cell lines to chemotherapy.

**Background/Rationale:** MSC within tumour stroma are derived from the resident tissue or from the circulation or recruited from tissues not related to the tumour. Few recent reports have shown MSC to promote cancer metastasis by initiating paracrine signalling or through enriching the population of ‘tumour initiating cells’ commonly known as ‘cancer stem cells’. About 75% of ovarian cancer patients diagnosed at an advanced-stage have peritoneal dissemination in the form of ascites containing single cells and tumour cellular aggregates. Recent data in our laboratory suggests that MSC forms an important component of ascites of ovarian cancer patients. This warrants the need to study the biological alterations (phenotype) induced by MSC on the growth, invasiveness and response to chemotherapy in ovarian cancer cell lines in vitro.

**Outcomes/Benefits:** This proposal will compare the inherent traits and chemotherapy response of ovarian cancer cells in the presence and absence of MSC. MSC will be isolated from the ascites of ovarian cancer patients as well as from the placenta of women undergoing caesarean section. Differences in the biological phenotype of ovarian cancer cells in the presence and absence of MSC will be assessed by methods such as Western blot, quantitative PCR, immunofluorescence, flow cytometry, MTT and ³H-thymidine uptake assays. The identification of these changes/molecules may lead to the development of novel therapeutic targets either independently or by inhibiting the effects of MSC on ovarian cancer cells.

Human ethics application (HEC#09/09) has been approved by the Royal Women’s Hospital Human Ethics Committee.

**64. Synchrotron radiotherapy for the treatment of cancer**

**Project leaders:** Prof Peter Rogers, Dr Yuqing Yang, Dr Premila Paiva and Dr Jeff Crosbie

**Project Site:** Department of Obstetrics & Gynaecology, Royal Women’s Hospital and Australian Synchrotron Facility, Clayton

**Contact:** Prof Peter Rogers E: parogers@unimelb.edu.au or Dr Yuqing Yang E: Yuqing.Yang@unimelb.edu.au

The synchrotron produces near-parallel X-ray beams that are up to ten billion times more intense than those currently used for radiotherapy in the treatment of cancer. Synchrotron radiation provides novel opportunities for segmenting the beam into narrow microbeams in order to treat tumours. Normal tissues appear to be resistant to arrays of microbeam radiation, with survival following doses up to a hundred times greater than with conventional radiation. Conversely, tumours can be readily destroyed using microbeam radiation, although the molecular and cellular mechanisms behind this susceptibility are currently unknown. The prospective student will gain experience with cutting-edge molecular biology techniques and will utilise the Australian Synchrotron to investigate the mechanisms that underpin the response of normal and tumour cells to microbeam radiation.
65. **TGF- signalling and cancer development**  
*Supervisors:* Dr. Hong-Jian Zhu (and Dr. Rodney Luwor, Bo Wang, Catherine Winbanks)  
*Project Site:* Cancer Signalling Laboratory, Department of Surgery (5th Floor, Clinical Sciences Building, The Royal Melbourne Hospital)  
*Contact:* Dr. Hong-Jian Zhu T: 8344 3025 E: hongjian@unimelb.edu.au; Dr. Rodney Luwor E: rluwor@unimelb.edu.au  
*Project Outline:* Traditionally, key-lock or on-off models dominate the molecular understanding of cellular signalling and disease development, with most studies focusing on linear molecular signalling cascades. With the advent of large scale molecular techniques such as proteomics and microarrays, cross-talk between signalling networks has been implicated to play critical roles in cancer development. It challenges the physiological validity of the switch on-off model. Our lab, using molecular, cellular and gene targeted animal models as well as human patient samples, has established that the moderation of signalling sensitivity by other pathways, rather than a black-white switch on-off, specifically of the TGF-$\beta$ (Transforming Growth Factor-$\beta$) signalling pathways determines cancer progression. These findings have been published in top-ranking biomedical journals including *Nature Medicine* (11:845-52, 2005). Given the medical significance, current works in our lab are supported by 4 NHMRC and 1 Cancer Council grants totalling more than $2 million. This lab aims to understand the molecular fundamentals of TGF-$\beta$ signalling mis-regulation and its causation effect on early tumor development and late tumor invasion and metastasis. In particular, we focus on the few major oncogenic molecular pathways' cross-talk with TGF-$\beta$ signalling in various stages and types of cancer development. Concurrently, we are also devising strategies utilizing our unique molecular insights to convert tumor-causing signalling to directly tumor-killing.  

The following projects are designed for students to participate in forefront cancer research and to achieve excellent novel results in a relative short time frame (9-10 months).  

- **Project A:** Converting oncogene signalling to tumor killing in brain cancer  
- **Project B:** Stat3 mediated impairment of TGF - signalling in head&neck and breast cancer  
- **Project C:** Targeting TGF - signalling expansion in brain tumor invasion  
- **Project D:** Regulation of TGF - signaling by Wnt pathway in the development of colon cancer  

*Techniques to be used:* Cell culture, reporter assays (gene expression), adeno viral work, molecular biology, Western and Northern blotting (protein and mRNA respectively), thymidine assays (cell proliferation), real-time PCR, immunofluorescence and immunohistochemistry, siRNA (gene silencing), animal imaging.  

*Preferred background and quality of student:* biochemistry, pathology, medical sciences; good nature as a person, passionate and dedication in research, perseverance in problem solving.

66. **Circulating endothelial cells as biomarkers for prostate cancer**  
*Supervisor:* Dr. Chris Hovens  
*Project Site:* Department of Surgery, 5th Floor, Clinical Sciences Building, RMH, and Prostate Cancer Epworth Hospital, Richmond  
*Contact:* Dr. Chris Hovens T: 9342 7703/4 E: chovens@unimelb.edu.au  

The development of a vascular network (angiogenesis) is essential for all solid tumours. Numerous studies have underscored the importance of angiogenesis in the development and progression of prostate cancer. The significant contribution of bone marrow progenitor cells to the vascularisation of a number of different tumour types has recently been recognised. Following angiogenic stimuli, a pool of haematopoietic progenitor cells can become mobilized and contribute to the vascularization and growth of certain primary tumours. These cells are detectable in the circulation as Circulating Endothelial Cells. Significantly, it has recently been shown that these same cells are crucial for setting up a pre-metastatic niche at distinct organ sites where tumour metastasis is prevalent. We propose to determine whether measuring bone marrow endothelial cell recruitment to tumours may be of benefit in stratifying the risks of progression and metastases in patients with prostate cancer, and possible response to treatment.  

*Benefits to student:* Molecular and clinical research in the one project, multi-collaborative project encompassing basic research and clinical interaction  

*Requirements for students:* Dedicated, passionate and committed. Must have done well academically.

67. **Molecular Profiling of Prostate Cancer**  
*Supervisors:* A/Prof Chris Hovens and Dr Niall Corcoran  
*Project Site:* Department of Surgery (RMH), 5th Floor, Clinical Sciences Building and Prostate Cancer Epworth Hospital, Richmond  
*Contact:* A/Prof Chris Hovens T: 9342 7703/4 E: chovens@unimelb.edu.au  

*Project description:* With over 20,000 diagnoses per year, Australian men have the highest rate of prostate cancer in the world. Currently our research team are addressing some of the most important clinical questions today in prostate...
cancer management using genomics and proteomics experimental designs. We have access to human tissue samples taken from men undergoing surgery together with the clinical informatics that indicate their outcomes, therefore this project will have high clinical relevance and impact.

The aim of the project is to analyse RNA and DNA from specific groups of prostate cancer patients and with the use of whole genome microarrays, next-generation sequencing and other technologies, find distinguishing molecular markers that can predict prostate cancer behaviour.

Research students will work within a team of experienced scientists and have access to scientific expertise and equipment through our department, associated institutions and existing collaborations with leading urologists. Our commitment to academic excellence and links with the Australasian Prostate Cancer Conference, one of the largest urology meetings in the region, ensure additional exposure to publication and presentation opportunities for the motivated researcher.

Benefits to student: Molecular and clinical research in the one project, multi-collaborative project encompassing basic research and clinical interaction.

Requirements for students: Dedicated, passionate and committed. Must have done well academically.

68. **Targeting TAG-72 as a Therapeutic and Imaging Strategy in Prostate Cancer**

Supervisors: Dr Rodney Luwor and Dr Niall Corcoran

Project Site: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building and Prostate Cancer Epworth Hospital, Richmond

Contact: A/Prof Chris Hovens T: 9342 7703/4 E: chovens@unimelb.edu.au

Project Description: Prostate cancer accounts for the premature deaths of over 3000 Australian men annually. To date, no biological marker exists that can accurately predict a patient’s outcome at an early, curable stage. The lethality of prostate cancer is intimately associated with cancer metastasis, and our ability to detect and treat metastatic disease at an early stage is lacking. One biotechnology group has developed an antibody that can be loaded with either cytotoxic drugs or imaging markers. Given the right cancer antigens, this particular antibody may possess a dual role in the detection and treatment of metastatic disease by enabling targeted imaging and therapy. The antibody binds to TAG-72, an oncofetal antigen widely expressed in a number of adenocarcinomas including prostate cancer. We have recently shown the expression of TAG-72 in human prostate cancer, making this a clinically relevant cancer antigen. In this project we will explore the concept of using TAG-72 as a therapeutic and imaging agent in prostate cancer. Using orthotopic mouse xenograft models of prostate cancer, we will aim to show that TAG-72 can be successfully targeted to tumour cells. This will provide us with an early sensitive detection of metastatic spread using in vivo imaging, in addition to treating the metastatic prostate cancer with the drug loaded TAG-72 antibody.

Benefits to student: Molecular and clinical research in the one project, multi-collaborative project encompassing basic research and clinical interaction.

Requirements for students: Dedicated, passionate and committed. Must have done well academically.

69. **Stat3-mediates Resistance to EGFR targeted therapy in Cancer - also offered as MSci**

Supervisors: Dr Rodney Luwor

Location: Dept of Surgery, Level 5, Clinical Sciences Building, Royal Melbourne Hospital

Contact: Dr Rodney Luwor T: 9342-7703, E: rluwor@unimelb.edu.au

During physiological processes the intracellular protein Signal Transducer and Activator of Transcription 3 (Stat3) is activated by many growth factors and cytokines (e.g. EGF, IL-6, IL-11...etc) resulting in transcription of many genes involved in a multitude of cellular processes. However, uncontrolled or un-attenuated Stat3 phosphorylation and activation results in cancer initiation, progression and metastasis of many tumour types. Therefore, understanding how Stat3 is regulated or controlled within the cell is pivotal for cancer biology and may allow greater scope for therapeutic intervention into Stat3-driven tumourigenesis. Recently, we have shown that many colon cancer cell lines are resistant to a clinically approved anti-EGFR monoclonal antibody, Cetuximab. However, blocking Stat3 activation could re-sensitize these tumour cells to the growth inhibitory effects of cetuximab. Therefore we hypothesise that activation of Stat3 provides an alternative mechanism for resistance to EGFR targeted therapy and targeting IL-6, IL-11 or Stat3 can overcome this resistance. This honours project seeks to explore this clinically relevant yet incomplete field of cancer biology and therapy.

Specifically the Related Honours Projects available are:

1: Determining the extent of Stat3 mediated resistance to EGFR targeted therapy in a large set of colon cancer cell lines;
2: Examining the efficacy of IL-6 and IL-11 antagonists in combination with Cetuximab;
3: Examining the role of a phosphatase that regulates Stat3 phosphorylation in Cancer

**Skills acquisition:** Cell biology techniques including Cell transfections, western blotting, immunofluorescence staining and confocal microscopy, luciferase reporter assays, RT-PCR and potentially animal handling and injecting.
70. The role of the Eph/Ephrin signaling system in the progression of colon cancer - also offered as MSci
Supervisors: Dr Paul Senior & Professor Steven Chan
Project Site: North-West Academic Centre, WCHRE Building Sunshine Hospital, St Albans.
Contact: Dr. Paul Senior T: 83958228 E: psenior@unimelb.edu.au

The Eph/Ephrin family of receptors and ligands are major regulators of development and are coming to be recognised as important in tissue homeostasis including in the normal colonic epithelium. Loss of expression of several Eph receptors and increased expression of others are linked to poor prognosis in colon cancer. We are interested in understanding the mechanisms by which these receptors influence invasion and metastatic spread in colon cancer. The project involves modulating the expression of Eph receptors in colon cancer cell lines using both over-expression and gene knock down methods. Then utilising these cells to study the effects on invasion, cell migration and receptor ligand interaction using in vitro models together with in vivo experiments using models of metastatic spread.

Acquired skills will include small animal handling, surgery, fluorescent microscopy, cell culture, QPCR, protein & DNA electrophoresis Western blotting.

71. Generation of stable Stat3 reporter cell line for use in HTCS assay
Supervisors: Dr Michael Buchert, A/Prof Matthias Ernst (Ludwig Institute)
Project Site: Ludwig Institute for Cancer Research
Contact: Dr Michael Buchert T: 03 9341 3155 E: michael.buchert@ludwig.edu.au; A/Prof Matthias Ernst E: matthias.ernst@ludwig.edu.au

Multiple studies in the past few years have provided compelling evidence for the critical role of aberrant activation of a DNA binding protein called Signal Transducer and Activator of Transcription 3 (STAT3) in many human malignancies of hematological and epithelial origin. Thus, it is now generally accepted that STAT3 is one of the critical players in human cancer of the gastrointestinal tract, skin, breast and others and represents a valid target for novel anticancer drug design. Our laboratory has a longstanding track record in investigating the role played by STAT3 with seminal findings published in top class journals (Nature Medicine, Cancer Cell etc). We have developed a form of gp130 which is constitutively active and therefore always mediates STAT3 homodimerisation and associated activation of target genes. We also have constructed a STAT3-responsive, synthetic target gene that encodes a firefly luciferase (ff-luc) reporter protein whose light-emitting activity (referred to as bioluminescence, see figure) is easily measurable and directly proportional to the extent of STAT3 activation, and we have constitutively active renilla luciferase (ren-luc) constructs that do not require STAT3 activation. We now propose to exploit these reagents to establish a cell-based high-throughput chemical screening (HTCS) assay, which will allow the screening of complex small molecule libraries to identify compounds that selectively interfere with the process of STAT3 activation. This approach will therefore lead to the identification of lead compounds that mediate STAT3 inhibition.

Skill acquisition: The successful BSc honours student will be using a combination of molecular and biochemical techniques such DNA cloning, DNA transfection, PCR, Dual Luciferase assays, Western blotting, tissue culture etc.

72. The role of Epigenetics in Gastrointestinal Pathologies
Supervisor: Dr Michael Buchert (Ludwig Institute)
Project Site: Ludwig Institute for Cancer Research
Contact: T: 03 9341 3155 E: michael.buchert@ludwig.edu.au

Epigenetics is one of the fastest growing research areas in biomedicine. Studies have demonstrated that changes in the epigenome are not only common in cancer, but are also involved in the pathogenesis of a variety of noncancerous diseases such as chronic inflammation. Here, we propose to study the contribution of epigenetic modifications (e.g. DNA hypermethylation) to different gastrointestinal pathologies, such as acute and chronic inflammation, intestinal and gastric tumourigenesis using a range of in-house, genetically modified, mouse strains, established inflammation and mutagenesis protocols and state of the art analysis equipment.

Skill acquisition: The successful BSc honours student will be using a combination of molecular and biochemical techniques such as quantitative real-time PCR, histology, immuno-histochemistry, Western blotting, FACS analysis on biological samples derived from genetically engineered mice.

73. Examining the connection between U12-type mRNA splicing, development and cancer - also offered as MSci
Supervisors: Dr Yeliz Boglev and Assoc Prof. Joan Heath
Project site: Ludwig Institute for Cancer Research-Parkville Branch
Contact: Dr Yeliz Boglev: E: yeliz.boglev@ludwig.edu.au; T: 93413155; Assoc Prof. Joan Heath: E: joan.heath@ludwig.edu.au; T: 93413155

RMH Academic Centre Honours Projects 2012
**Description:** As a result of the detailed genetic and morphological characterisation of a zebrafish mutant, we have identified a gene, known as *RNA-binding region containing protein 3 (rnpc3)* that is indispensable for a stage in development when intestinal epithelial cells are highly proliferative. Previous studies have established that this gene encodes a protein, Rnpc3/65K involved in a specialised form of mRNA splicing. Specifically, Rnpc3 is a component of the minor class or U12-type spliceosome that catalyses the removal of a minor class of introns, called U12-type introns, from pre-mRNA molecules. U12-type introns are rare but are highly conserved in the plant and animal kingdoms. There are approximately 700 U12-type introns in the human genome (out of a total of >20,000 introns). Interestingly, these introns are not randomly distributed throughout the genome, but are found in “information processing genes”. Intriguingly, they are a feature of some tumour suppressor genes and oncogenes.

Because many of the behaviours of developing cells and tissues (eg. proliferation, cell migration and angiogenesis) are recapitulated by cancer cells, we believe that genes that play a role in intestinal development may also contribute to the development of cancer. To explore the possibility that Rnpc3 is required for the correct expression of tumour suppressor genes, we recently generated conditional and global *rnpc3* knockout mice. Using these mice, we aim to determine whether impaired U12-type splicing contributes to colon tumourigenesis.

This Honours project will entail analysis of *rnpc3* expression and function in our new mouse models. The specific aims are to determine: (i) the spatiotemporal patterns of *rnpc3* expression during normal mouse embryonic development and (ii) whether impaired Rnpc3 activity increases cancer susceptibility in tumour-prone mutant mice. The project will provide opportunities to become skilled in a variety of biochemical and molecular biology techniques, including in-situ hybridisation, immunohistochemistry, real-time PCR and histology.

**74. Characterization of the role of Th17 cell populations in gastrointestinal cancer**

**Supervisors:** Dr Tracy Putoczki, A/Professor Matthias Ernst, Ludwig Institute

**Project Site:** Ludwig Institute for Cancer Research

**Contact:** Dr Tracy Putoczki  T: 9341 3155  E: Tracy.Putoczki@Ludwig.edu.au
A/Prof Matthias Ernst  T: 9341 3155  E: Matthias.Ernst@Ludwig.edu.au

**Project (including aims):** Recently, the classical T helper-cell paradigm was challenged by the discovery of a new T-helper cell lineage, coined Th17. These cells have been implicated in a growing list of autoimmune disorders including psoriasis, arthritis, and multiple sclerosis and most recently they have been associated with cancer development. In contrast, regulatory T-cells (Tregs) are involved in managing appropriate immune responses to pathogen invasion and tissue damage. The role of this cell population in inflammation-associated cancer progression is not well understood. This project will explore the contribution of Th17 and Treg cell populations to gastrointestinal cancer development. We have a number of animal models of inflammation-associated gastrointestinal cancer which will be used in conjunction with a range of cellular biology methods to understand how these cells participate in the inflammation associated with cancer.

**Skill Acquisition:** In vivo disease models, analysis of genetic knock-in and knock-out mouse strains, histology, quantitative PCR, cell culture, FACs analysis, Elisa, Western blotting.

**75. Using a new mouse model to understand colitis**

**Supervisors:** Dr Tracy Putoczki, A/Professor Matthias Ernst, Ludwig Institute for Cancer Research

**Project Site:** Ludwig Institute for Cancer Research

**Contact:** Dr Tracy Putoczki  T: 9341 3155  E: Tracy.Putoczki@Ludwig.edu.au
A/Prof Matthias Ernst  T: 9341 3155  E: Matthias.Ernst@Ludwig.edu.au

**Project (including aims):** We have generated a novel transgenic mouse model in which a molecule called signal transducer and activator of transcription (Stat3), which utilizes gp130 receptor signalling, is constitutively expressed in a tissue specific and ligand independent manner. Stat3 has been demonstrated to provide a tissue protective function in inflammatory bowel disease (IBD), such as acute colitis, through activation of downstream target genes. However in a situation of chronic inflammation, Stat3 is associated with colon cancer development. The balance of Stat3 signalling is believed to be beneficial or deleterious for these diseases is not understood. In the first instance, this project will review the functionality of the DNA constructs used to generate the mouse model. In addition, this project will utilize the novel transgenic mouse described in a variety of models of IBD to fully characterize and further understand the role of Stat3 in colitis. Visualization of disease will be aided by the use compound mutant mice in which the transgenic mouse is crossed with a mouse expressing a luciferase reporter construct that will allow for in vivo imaging of the colonic epithelium using statement of the art equipment.

**Skill Acquisition:** In vivo disease models, in vivo animal imaging, analysis of transgenic and genetic knock-in and knock-out mouse strains, histology, quantitative PCR, Western blotting, molecular biology including vector design and recombinant DNA techniques.
76. **What role do T-cells play in colitis?**

**Supervisors:** Dr Tracy Putoczki, A/Professor Matthias Ernst, Ludwig Institute for Cancer Research  
**Project Site:** Ludwig Institute for Cancer Research  
**Contact:** Dr Tracy Putoczki T: 9341 3155 E: Tracy.Putoczki@Ludwig.edu.au  
A/Prof Matthias Ernst T: 9341 3155 E: Matthias.Ernst@Ludwig.edu.au  

**Project** (including aims): Individuals affected by chronic inflammatory diseases such as inflammatory bowel disease (IBD) are highly susceptible to developing colonic cancers. IBD refers to chronic diseases that cause inflammation of the intestine: ulcerative colitis (UC) and Crohn’s disease (CD). These diseases affect approximately 1% of Australians and lead to significant pain and discomfort for which there is no current cure. This project will utilize a mouse model for CD, referred to as the CD45 T-cell transfer model to establish the role different T-cells populations play in colitis and ultimately the role they may play in cancer development. The project will take advantage of a number of established knock-in and knock-out mouse models for numerous genes involved in T-cell development that also have suspected roles in cancer.

**Skill Acquisition:** In vivo disease models, analysis of transgenic and genetic knock-in and knock-out mouse strains, histology, quantitative PCR, cell culture, FACs analysis and Western blotting.

77. **Exploiting non-oncogene addiction for therapeutic purposes in a preclinical mouse model of gastric tumourigenesis**

**Supervisors:** A/Professor Matthias Ernst, Dr Tracy Putoczki (Ludwig Institute for Cancer Research)  
**Project Site:** Ludwig Institute for Cancer Research  
**Contact:** A/Prof Matthias Ernst T: 9341 3155 E: Matthias.Ernst@Ludwig.edu.au  
Dr Tracy Putoczki T: 9341 3155 E: Tracy.Putoczki@Ludwig.edu.au  

**Project:** Cancers of the gastrointestinal tract are often associated with chronic inflammation and represent a major health burden. These malignancies commonly show aberrant activation of the latent transcription factor Stat3 that promotes proliferation, cell survival and angiogenesis. Our previously developed the gp130<sup>F/F</sup> knockin mutant mouse provides a clinically relevant, fully penetrant preclinical mouse model for inflammation-associated intestinal-type gastric cancer, in which neoplastic disease shares many histological hallmarks with the human malignancies and is dependent on interleukin-6 cytokine family-mediated Stat3 hyperactivation. While therapeutic interference with this signaling axis shows some beneficial effect on tumour burden in gp130<sup>F/F</sup> mice, this project takes advantage of an emerging finding that non-mutated proteins and their associated pathways, often become rate limiting for neoplastic growth (referred to as “non-oncogene addiction”). This project will test the efficacy of pre-clinical drugs to target such pathways and explore whether they provide potential therapeutic value for the treatment of Stat3- and/or inflammation-dependent solid tumours.


**Skill Acquisition:** In vivo disease models, analysis of genetic knock-in and knock-out mouse strains, histology, quantitative PCR, cell culture, FACs analysis, Elisa, Western blotting.

78. **Investigation of novel tumour suppressor gene and oncogene candidates for colorectal cancer - also offered as MSci**

**Supervisors:** Dr Anuratha Sakthianandeswaren, Dr Nicholas Fleming, Dr Niroshani Pathirage, Dr Oliver Sieber  
**Project Site:** Ludwig Institute for Cancer Research  
**Contact:** Dr Oliver Sieber, T: 03 9341 3168, E: oliver.sieber@ludwig.edu.au  

Cancer is a genetic disease caused by (epi-) mutations in tumour suppressor genes, oncogenes and mutator genes. In our laboratory, we have performed comprehensive genome-wide profiling studies to identify novel genetic lesions in tumors from over 800 colorectal cancer patients. This project will further explore a number of selected cancer gene candidates identified to date, by performing detailed analyses of somatic mutations and loss of heterozygosity, mRNA and protein expression and basic functional assays in colon cancer cell lines. This work will provide the opportunity to gain experience in the field of cancer genetics and translational research.

**Skill acquisition:** The successful BSc honours student will acquire competence in a number of molecular biology techniques including cell culture, PCR, gene expression analysis, high-resolution melting curve analysis, DNA sequencing and protein detection techniques. Three placements are available.
LUDWIG INSTITUTE FOR CANCER RESEARCH MELBOURNE–AUSTIN BRANCH:-

The Tumour Targeting Laboratory:
The Tumour Targeting Laboratory research has focused on the development and preclinical characterization of targeting strategies to tumours with recombinant antibodies and signalling inhibitors for diagnostic and therapeutic applications. Current studies are investigating the enhancement of antibody immune function, the mechanisms of antibody-antigen binding and intracellular movement through cancer cells, and the generation of custom designed constructs through genetic engineering. Our laboratories also support clinical trials through the preparation of radiolabelled reagents for administration to patients and the analysis of patient sera samples for pharmacokinetic and immunological response data. Collaborations with the Austin Hospital's Departments of Nuclear Medicine and Anatomical Pathology facilitate biodistribution analyses and immunohistochemical studies, respectively. As part of the LICR's global Antibody Targeting Program, Phase I trials in colon, breast, lung, melanoma, glioma and renal cell cancers examining the safety, biodistribution and pharmacokinetics of recombinant antibodies have been conducted.

79. Fc engineering of the anti-LewisY hu3S193 antibody for optimal payload delivery

Supervisors: Prof. Andrew Scott, Dr Ingrid Burvenich, Ludwig Institute for Cancer Research, Austin Health, Lvl 6, Harold Stokes Building, 145-163 Studley Road, Heidelberg, VIC, 3084.

Project Site: Ludwig Institute for Cancer Research, Tumour Targeting Laboratory, Austin Health

Contact: Dr Ingrid Burvenich F: 03 9496 5762; email: ingrid.burvenich@ludwig.edu.au
Prof. Andrew Scott, F: 03 9496 5876, email: andrew.scott@ludwig.edu.au

We completed a first-in-man Phase I trial of hu3S193 (anti-LewisY (LeY) humanised antibody) in patients with LeY expressing tumours. A key finding from our clinical studies of hu3S193 has been the long half-life (t1/2) in vivo of the hu3S193 IgG1, which while optimal for therapeutic immune effector function, restricts the ability to use hu3S193 as a diagnostic, or for therapeutic payload delivery to cancer cells (eg isotopes/toxins). The pharmacokinetics of intact IgG is known to be strongly influenced by Fc binding to the neonatal receptor, FcRn. The LeY research project involves the design and engineering of novel humanised IgG constructs with improved pharmacokinetics for optimal payload delivery. The project will provide the student with a sound introduction to the use of antibodies in cancer diagnosis and therapy, and experiences in molecular biology, pharmacokinetics and imaging.

Techniques: Transient expression in Freestyle 293 cells, protein purification using HiTrap columns, in vitro quality controls (eg SDS-PAGE, HPLC (High Performance Liquid Chromatography), BioCore and FACS (Fluorescence Activating Cell Sorting)), in vivo analysis of radiolabelled (131I/111In-CHX-A“-DTPA-) mutant antibodies in A431 tumour-bearing mice (eg biodistribution studies, blood clearance, single photon emission computed tomography (SPECT) or positron emission tomography (PET)).

The Oncogenic Transcription Laboratory:
Located at the Austin Hospital, the Oncogenic Transcription Laboratory has a strong interest in colon cancer and developing new treatment strategies for patients with this disease. The laboratory focuses on epigenetic mechanisms of gene regulation in cancer, and in determining the efficacy of epigenome-modifying agents, particularly HDAC inhibitors, as anti-cancer agents. The laboratory also focuses on the development and application of high throughput genomic technologies to understand the mechanisms of drug action, and for predicting likelihood of response of colon cancer patients to existing and novel chemotherapeutic and biological agents. Through strong links with GI Oncologists in the Austin/Ludwig Joint Oncology Unit, the laboratory seeks to translate its findings to the clinic, and serves as a resource through which GI Oncologists can test and develop novel treatment concepts.

80. Role of stress response genes in colorectal cancer cell proliferation and chemotherapeutic drug sensitivity

Supervisors: Dr Anderly C. Chueh and A/Prof John M. Mariadason

Project Site: Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg

Contact: Dr Anderly C. Chueh, T: 9496 5814, E: anderly.chueh@ludwig.edu.au
A/Prof John M. Mariadason, T: 9496 3068, E: john.mariadason@ludwig.edu.au
http://www.ludwig.edu.au/austin/research/oncogenic-transcription-lab.htm

Colon cancer is one of the leading causes of cancer related deaths in Australia, and new treatment strategies for this disease are urgently needed. Histone deacetylase inhibitors (HDACi) are an emerging class of cancer therapeutics that induce apoptosis of colon cancer cells through epigenetic mechanisms. We have previously identified colon cancer cell lines that are highly sensitive and resistant to HDAC inhibitors. The goal of this Honours project is to identify molecular markers which can predict sensitivity to HDAC inhibitors, by comparing the epigenome of colon tumours sensitive and resistant to this drug. Findings from this study may help guide future clinical trials of this drug by identifying colon cancer patients likely to respond to this treatment.
81. **Investigating the mechanism of DUSP5 gene regulation in colon cancer**

**Supervisors:** A/Professor John Mariadason, Dr Lars Tögel

**Project Site:** Oncogenic Transcription Laboratory, Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg

**Contact:** A/Professor John Mariadason T: 61 3 9496 3068, E: john.mariadason@ludwig.edu.au

Dr Lars Tögel, T: 61 3 9496 5928 E: lars.togel@ludwig.edu.au

Colon cancer is driven by hyper-activation of the Wnt/β-catenin and the Ras/MAPK/ERK signalling pathways, which drive uncontrolled cell proliferation. The dual-specificity phosphatase 5 (DUSP5) gene is a negative regulator of the Ras/MAPK/ERK signalling and therefore a putative tumour suppressor. We have demonstrated that the Wnt/β-catenin pathway represses DUSP5 expression, thus identifying a novel mechanism of cross talk between these two pathways. However, the mechanism by which Wnt/β-catenin represses DUSP5 is unknown. The aim of this honours project is to determine the transcriptional mechanisms that regulate DUSP5 gene expression. The project will provide the student with insight into the signalling pathways that drive colon cancer, and the molecular mechanisms by which gene expression is controlled.

82. **Role of chromosomal passenger complex genes in mitotic checkpoint control of colorectal cancer and chemotherapeutic drug actions**

**Supervisors:** Dr Anderly C. Chueh and A/Prof John M. Mariadason

**Project Site:** Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg

**Contact:** Dr Anderly C. Chueh, T: 9496 5814, E: anderly.chueh@ludwig.edu.au
A/Prof John M. Mariadason, T: 9496 3068, E: john.mariadason@ludwig.edu.au

http://www.ludwig.edu.au/austin/research/oncogenic-transcription-lab.htm

Colorectal cancer is one of the most characterized tumour types in term of the underlying genetic aberrations and can be broadly separated into two major molecular subtypes: diploid tumours with microsatellite instability (MIN) and aneuploid tumours with chromosomal instability (CIN). While the genetic mutations that leads to the microsatellite instable phenotype is well characterized, the cause of chromosomal instability (CIN) phenotype is relatively unknown. We have recently demonstrated that a novel class of targeted therapeutics known as histone deacetylase inhibitors (HDACi), preferentially induce G2-M arrest in tumour cell lines that exhibit the MIN, compared to the CIN phenotype. The goal of this Honours project is to investigate potential mechanisms by which CIN tumours escape activation of the mitotic checkpoint in response to HDACi treatment, by comparing the gene expression changes induced by HDACi in MIN vs CIN tumour cell lines. Findings from this study are designed to enhance our understanding of the mechanism of action of this novel class of cancer therapeutics.

**CARDIOLOGY**

**CORONARY IMAGING GROUP @ NORTHERN HEALTH**

**Head of Research Group:** Associate Professor Peter Barlis

**Laboratory/Group Location:** The Northern Hospital, 185 Cooper Street, Epping

**What we do:**

The coronary imaging group, established by A/Prof Barlis, studies the application of novel imaging techniques to study coronary artery disease in humans. Peter is a Cardiologist that has pioneered the introduction of this imaging method, called optical coherence tomography (OCT) and introduced it into Australia in 2009. Coronary OCT uses near-infrared light within an imaging wire that is passed into the coronary arteries during angiography. OCT has a resolution of 15 microns seeing this modality dubbed ‘virtual histology’. The group focuses on the analysis of OCT data gained during invasive imaging of patients with known or suspected heart disease and provides unique information on atherosclerotic plaque and in the characterisation of the metallic devices called stents that are used to prop open blocked arteries. The research builds on established post-mortem data of vulnerable plaque and the importance of ruptured thin-cap fibrous atheroma (TCFA) in causing acute coronary syndromes (and even death) and uses OCT to detect these markers in-vivo. The group is also actively leading a number of national and international clinical trials using OCT to assess optimal stent expansion and tissue converge for next generation coronary stents used to open diseased arteries.

83. **Quantitative and qualitative analysis of atherosclerotic plaque and stents using coronary optical coherence tomography**

**Supervisor:** A/Professor Peter Barlis

**Project Site:** The Northern Hospital, 185 Cooper St., Epping
**Description of project:** Optical coherence tomography provides a highly detailed assessment of the coronary arterial wall and has brought the imaging resolution down to nearly cellular level. It offers ten times the resolution of ultrasound-based techniques and has been applied to the assessment of vulnerable plaque and stents in patients with coronary artery disease. It is known that vulnerable plaques with TCFA thickness <65 microns are more likely to rupture, leading to acute coronary syndrome or death. Up until recently, the detailed assessment of such plaques has relied on post mortem examination. The project will involve offline analysis of OCT images obtained from patients with heart disease. An OCT software package will be used to analyse the plaque characteristics and divide these based on their optical properties into fibrous, lipid-rich or calcified plaques. This data will be correlated to clinical data to identify possible predictors for unstable plaque. Patients who have lesions treated using coronary stents will have OCT imaging also performed. Pullback images through the stented segment will be analysed to examine stent geometry, sizing, extent of expansion within the vessel wall and tissue coverage occurring within the stent over time.

**Techniques to be used:** The project will use proprietary computer software to analyse OCT data.

**MOLECULAR GENETICS @ NORTHERN HEALTH**

Head of Research Group: Professor Judy Savige  
Laboratory/Group Location: The Northern Hospital, 185 Cooper Street, Epping

**What we do:**
We use eye photographs to predict heart disease; molecular genetics

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**84. Eye changes to predict heart disease**

**Supervisor:** Professor Judy Savige  
**Project Site:** The Northern Hospital, 185 Cooper St., Epping  
**Contact:** Professor Judy Savige T: 03 8405 8823 E: judy.savige@nh.org.au

Taking retinal photos of patients in the hospital and correlating vessel changes with risk of heart attacks.

**Techniques to be used:** Retinal photos, grading and simple statistics.

*Note: this project is also listed under Ophthalmology*

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**85. β-adrenergic activation: a double-edged sword for cardiac angiogenesis**

**Supervisors:** A/Professor Xiao-Jun Du, Dr Qi Xu, Dr Peter Kistler  
**Project Site:** Experimental Cardiology Laboratory, Baker IDI Heart and Diabetes Institute  
**Contact:** A/Professor Xiao-Jun Du. T : 61 03 8532 1267 E : xiao-jun.du@bakeridi.edu.au

Heart failure (HF) is a major cause of morbidity and mortality among older adults constituting a significant burden on health-care systems. The underlying mechanism of HF is incompletely understood. It has been well recognized that activation of stress-related nerve system, sympathetic nerve system (SNS) and its responding receptors, β-adrenergic receptors (β-AR), are important for the heart to respond to physiological stress. However, tonic and chronic activation of β-AR contributes significantly to symptom worsening and progression of cardiac dysfunction and chamber dilatation leading to HF. Angiogenesis, a physiological process involving the growth of new blood vessels from pre-existing vessels, is key factor crucially involved in the preserving of cardiac function and developing cardiac hypertrophy and its impairment leads to HF. Whereas both events, tonic/chronic β-AR activation and impaired cardiac angiogenesis, are well known to be
important factors in heart disease development and progression, the connection between them and how they synergistically contribute to the progression of HF remain unknown.

We have recently revealed, for the first time, that β-AR possesses the potential to both promote and suppress cardiac angiogenesis. We hypothesize that β-AR regulates cardiac angiogenesis oppositely via coupling to diverse signalling cascades, which is responsible for a new mechanism directing heart to either maintained cardiac function or transition towards HF. In this research plan, we aim to: first, understand the opposing roles of β-AR on cardiac angiogenesis and signalling molecules implicated; second, determine how β-AR affect cardiac function via its regulation on cardiac angiogenesis. These studies will be done both in vitro on cultured cardiomyocytes and on a few models in vivo. A range of methods will be used to evaluate the degree of cardiac angiogenesis carefully, as well as the angiogenic factors and key signalling pathways involved. The planned studies will generate valuable data addressing specific signalling pathways involved in the bi-directional modulation of cardiac angiogenesis. Furthermore, the outcomes of these studies could indicate potential therapeutic targets by which we could modulate cardiac angiogenesis to halt or reverse the progression of HF.

This project is suitable for candidate pursuing honorary or PhD degree. The research works will be conducted at Baker IDI Institute localized at Alfred Medicine, Research and Education Precinct (AMREP) in Prahran.

CEREBROVASCULAR

86. Ocular motor studies in the assessment of mild cognitive deficit in patients with microvascular cerebral disease - also offered as MSci

Supervisors: A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan
Project site: Dept of Neurology, Royal Melbourne Hospital, City Campus
Contact: Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au.
T: 9342 8448

Laboratory overview: the project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.

Project overview: The ocular motor system is the first motor system to develop in humans. Generation of movement involves planning, reflex movements, integration of sensory information with ongoing activity and inhibition of unwanted movement. Conservation of neural resources predicts that where possible, established circuitry and neural systems are used by like systems. There is evidence that attentional and inhibitory processes develop with the establishment of ocular motor control and subsequently these networks are utilized by somatic motor systems. The circuitry involved in attentional processes, inhibitory processes and working memory ramify widely throughout the cerebral hemispheres and is well defined. As such, ocular motor recordings, using conventional video oculography, may prove uniquely sensitive to systems abnormalities produced by multi lesion disease such as occurs with microvascular disease in hypertension and diabetes. In this pilot study we aim to establish the sensitivity of such recordings in a range of patients with microvascular disease, compared with conventional neuropsychological studies, and compare them with age matched control studies.

Acquired skills: Understanding of cognitive function testing; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

Note: this project is also listed under Motor Control

COLORECTAL MEDICINE AND GENETICS

87. Bioinformatics in colorectal cancer genetics and prevention - also offered as MSci

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics
Project Site: Royal Melbourne Hospital, Parkville
Contact: Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

The Department manages a large registry of people at high risk of colorectal cancer, principally based on family history. The surveillance histories of 3000 registrants have been documented and related to their assessed level of risk. This database is now linked through the Australian BioGrid database initiative with the familial cancer database. Advanced front end enquiry facilities have been developed by BioGrid allowing data linkage and searching to be done with facility, and results displayed. A collaboration with the eHealth division of the CSIRO p-Health flagship furthers enhances our capacity to explore this dataset, including through after merging with a similar dataset housed at Flinders University. The
The project is now poised to deliver important information on differential surveillance outcomes across a range of familial and personal risk groups. Examples of hypotheses being explored locally are: What is the risk to children whose both parents have colorectal cancer? What is the yield of faecal occult blood testing done between scheduled colonoscopies in high risk patients? What are the molecular characteristics of cancers and advanced adenomas occurring during surveillance? Do patients with serrated adenomas have high risk for metachronous advanced adenomas and cancers? What are the surveillance outcomes from mismatch repair gene carriers, by gene type and mutation location?

88. **The Human Variome Project (HVP) and familial bowel cancer - also offered as MSci**

**Supervisors:** Professor Finlay Macrae, Head, Colorectal Medicine and Genetics, Professor Richard Cotton, Director, Genomic Disorders Research Institute, University of Melbourne  
**Project Site:** Dept of Colorectal Medicine and Genetics, RMH; or GDRC, Alan Gilbert Building, Uni of Melb.  
**Contact:** Tel: 61 3 9347 0788 E: Finlay.macrae@mh.org.au

This important project forms a component of the HVP, which aims to document all DNA variants across all genes in man. The International Society for Gastrointestinal Hereditary Tumours is well advanced in formulating processes for the vision, with committees of experts world wide working on different aspects. A range of Honours and higher degree opportunities are available within the HVP and InSIGHT's engagement with the HVP. Its aims to position itself as a lead locus for the HVP

89. **Confocal endomicroscopy - also offered as MSci**

**Supervisor:** Professor Finlay Macrae, Head, Colorectal Medicine and Genetics  
**Project Site:** Royal Melbourne Hospital, Parkville  
**Contact:** Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

**Aim:** To assess distribution of disease in patients with known or historical microscopic colitis, Inclusion: Clinical need for colonoscopy in patients with known microscopic colitis Dysplasia in Ulcerative colitis and Barrett’s Oesophagus Intervention: Confocal Endomicroscopy.  
Correlation with conventional histology; diagnostic accuracy compared with random biopsy protocols

90. **Biogrid and IBD data basing - also offered as MSci**

**Supervisor:** Professor Finlay Macrae, Head, Colorectal Medicine and Genetics  
**Project Site:** Royal Melbourne Hospital, Parkville  
**Contact:** Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

The development of a common database for recording clinical management and outcomes for IBD clinics in Melbourne is being coordinated through the Department of Colorectal and Genetics. This project will bring students into close contact with the management of IBD, and working alongside a dedicated team of doctors and nurses focusing on IBD. The project will lead to linkage with other similar databases through the Australian BioGrid. [http://www.biogrid.org.au](http://www.biogrid.org.au)

91. **Capsule Colonoscopy as a Screen for Colorectal Cancer - also offered as MSci**

**Supervisor:** Professor Finlay Macrae, Head, Colorectal Medicine and Genetics  
**Project Site:** Royal Melbourne Hospital, Parkville  
**Contact:** Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

Capsule Colonoscopy is being introduced into Australia late in 2010. After ingestion of the device, the colon is visualized through a wireless capsule CCD device which transmits images to a receiver worn by the patient. The Department will be the Australian lead in the first two Capsule Colonoscopy projects. One is testing its capability on comparison with colonoscopy in an average risk population, and the other will tests its capacity in clinical scenarios where colonoscopy is relatively contraindicated or has failed. Assistance in performing the procedures and documenting the results of the project will be the core of this project.

92. **Dietary prevention of adenomas in familial adenomatous polyposis - also offered as MSci**

**Supervisor:** Professor Finlay Macrae, Head, Dr Suresh Sivanesan  
**Project Site:** Royal Melbourne Hospital, Royal Brisbane, Royal Adelaide and Sir Charles Gardiner Hospitals  
**Contact:** Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

This is a randomised controlled trial of a new resistant starch preparation capable of releasing large quantities of butyrate for chemoprevention in the colon. The trial will measure adenoma formation of FAP patients through their regular surveillance, comparing activity with placebo study agents. In partnership with CSIRO.
93. **Structure and folding of Aβ peptide familial mutants in Alzheimer’s disease**

**Co-Supervisors:** Dr Stewart Nuttall; Dr Lance Macaulay; Dr Victor Streltsov.

**Project Site:** CSIRO MSE and Preventative Health Flagship, 343 Royal Pde, Parkville.

**Contacts:**
- Dr Stewart Nuttall E: Stewart.Nuttall@csiro.au T: 03 96627324
- Dr Lance Macaulay E: Lance.Macaulay@csiro.au T: 03 96627335
- Dr Victor Streltsov E: Victor.Streltsov@csiro.au T: 03 96627311

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by the presence of misfolded protein depositions or amyloid plaques, which consist predominantly of amyloid β-peptide (Aβ). Frustratingly, obtaining structural data at an atomic resolution for Aβ has been well-nigh impossible, due in part to the propensity of the peptide to form amyloidal fibrils and aggregates, rather than crystal-like lattices. However, we have recently protein-engineered and obtained crystal structures of the P3 (amylogenic) region of Aβ peptide constrained within a protein scaffold.

This project will analyse Alzheimer’s disease familial mutants within the context of our protein engineered constructs, and poses the question: can we relate the familial mutant phenotype to the molecular structure of the Aβ peptide? The project is ideally suited to a candidate with an interest in protein chemistry and structure-based analysis.

**Skill acquisition:** Diverse molecular biology and protein chemistry techniques, including DNA cloning, and protein expression and purification. Instruction in protein crystallography (crystal growth and preliminary x-ray structure solution) will be provided.

94. **Using an *in vitro* model of the blood-brain barrier to study amyloid-β efflux and influx**

**Supervisors:** Dr Julie Nigro; Dr Lance Macaulay; Dr. Jose Varghese

**Project Site:** CSIRO MSE and Preventative Health Flagship, 343 Royal Pde, Parkville.

**Contacts:**
- Dr Julie Nigro: E: Julie.Nigro@csiro.au T: 03 96627216
- Dr Lance Macaulay: E: Lance.Macaulay@csiro.au; T: 03 96627335
- Dr Jose Varghese: E: Jose.Varghese@csiro.au; T: 03 96627277

We are developing a model of the blood-brain barrier to study the influx and efflux of amyloid β, a peptide which can misfold and aggregate in the brain and is implicated in the pathogenesis of Alzheimer’s disease. The blood-brain barrier (BBB) is a selective permeable membrane separating the brain from blood molecules. The restrictive characteristics of the BBB can be attributed to the endothelial cells that form the intima layer of the microvessels. These endothelial cells are different to other endothelial cells in the body because they are joined by tight junctions of high electrical resistance providing an effective barrier against paracellular movement of molecules. Other cell types present in the brain contribute to the tight junction properties of the BBB. Astrocytes and pericytes have foot processes which are located close to the endothelial cells and regulate the integrity and function of the endothelial cells.

This project involves recreating the BBB *in vitro* using the cell types important in the BBB, i.e. brain microvascular endothelial cells, astrocytes and pericytes. The cells will be characterised by immunofluorescence and Western blot. Isolated cell types of the BBB will be assembled in a two-dimensional transwell system. Electrical resistance measurements and permeability studies will be done to determine the quality and efficacy of the *in vitro* BBB. The transport of synthetic or natural amyloid-β peptide will be studied using the *in vitro* BBB. The expression of efflux (p-glycoprotein) and influx transporters of amyloid-β (lipoprotein related protein-1 and the receptor for advanced glycation end-products) will be monitored by Western blot.

The student will be trained in primary cell isolation and cell characterisation using immunofluorescence microscopy and Western blot.

**DERMATOLOGY**

95. **Assessment of the Digital Dermoscopic diagnosis and Histological diagnosis of Melanoma with Skin type association**

**Supervisor:** Dr. George Varigos, Professor Mohammad Aldeen

**Project Site:** Department of Medicine/Dermatology, University of Melbourne.

**Contact:** Dr George Varigos E: george.varigos@mh.org.au

Melanoma is a common cancer and we have a regular Melanoma Clinic. Cases are seen and documented for skin type and vitamin D.

- Dermoscopic photos are taken of moles and melanoma.
Digital analysis of these photos using our Image analysis system has been developed with joint studies with the University of Melbourne Electrical Engineering Dept Professor A Mohammad.

Identifying from our cohort of patient photos relevant for analysis, from the histories of patients and archived samples held by the Department of Pathology at Royal Melbourne Hospital (pending ethics approval).

Histological reports of staining and microscopy to examine samples for various hallmark features of Melanoma.

Retrospectively from histories of patients photos will be collected and skin type measures collected with other features and Melanoma type.

Prospectively patients samples will be collected who have Photos as routine and their dermocope images obtained and digitally analysed.

The accuracy of the digital image and histological result will be compared with both groups studied.

Attendances at clinics 2.5 days per week, melanoma and pathology meetings as well as statistical analysis will be needed. Good skills in clinical assessments will be obtained during the year.

### ELECTROPHYSIOLOGY

#### 96. Epilepsy and Fracture Risk – Cellular electrophysiology

**Supervisors:** Dr. Sandra Petty, Prof. Eleanor Mackie, Dr Chris French.

**Project collaborators:** Dr. Elisa Hill and Dr. Marian Todaro.

**Project Site:** The Department of Medicine (RMH), The Royal Melbourne Hospital

**Contacts:** Dr. Sandra Petty T: 83443262 E: pettys@unimelb.edu.au ; Dr Chris French E: crf@hfbg1.net / french@unimelb.edu.au; T: 9035 6376; Prof. Eleanor Mackie T: 8344 7357 E: ejmackie@unimelb.edu.au ; Dr Elisa Hill E: elhill@unimelb.edu.au

Patients with epilepsy are known to have a doubled fracture risk. The reasons for this are likely multifactorial, including reduced bone density in some patients, the mechanics of seizures and increased falls risk. Whether there are dual effects of anti-epileptic medications (AEDs) which reduce the risk of seizures in the CNS, but may produce side effects in other tissues such as bones requires investigation.

In this project, electrophysiological responses of bone cells to a range of AEDs will be investigated. Direct effects on osteoclast lineage cells will be assessed, and identification of surface channels present on each cell type will be established by PCR.

Skills acquired will include literature review in bone, epilepsy fields, examining pharmacology of AEDs and surface ion channels, PCR, cell culture, cell differentiation and whole cell electrophysiology (patch clamping).

#### 97. Epilepsy and Fracture Risk – Bone Cell Electrophysiology

**Co-Supervisors:** Dr. Sandra Petty, Prof. Eleanor Mackie, Dr. Chris French

**Project collaborators:** Dr. Elisa Hill and Dr. Marian Todaro.

**Project Site:** The Department of Medicine (RMH), The Royal Melbourne Hospital

**Contacts:** Dr. Sandra Petty T: 83443262 E: pettys@unimelb.edu.au ; Dr Chris French E: crf@hfbg1.net / french@unimelb.edu.au; T: 9035 6376; Prof. Eleanor Mackie T: 8344 7357 E: ejmackie@unimelb.edu.au ; Dr Elisa Hill E: elhill@unimelb.edu.au

Patients with epilepsy are known to have a doubled fracture risk. The reasons for this are likely multifactorial, including reduced bone density in some patients, the mechanics of seizures and increased falls risk. Whether there are dual effects of anti-epileptic medications (AEDs) which reduce the risk of seizures in the CNS, but may produce side effects in other tissues such as bones requires investigation.

In this project, electrophysiological responses of bone cells to a range of AEDs will be investigated. Direct effects on osteoblasts and osteocyte-like cells will be assessed in cell culture. Identification of surface channels present on each cell type will be established by PCR.

Skills acquired will include literature review in bone, epilepsy fields, examining pharmacology of AEDs and surface ion channels, PCR, cell culture, cell differentiation and whole cell electrophysiology (patch clamping).
98. Investigating inhibitory synaptic function in a mouse model of Autism - also offered as MSci

Supervisors: Dr Elisa Hill & Professor Terence O’Brien.
Project Site: Department of Medicine, University of Melbourne
Contact: Phone: 8344 3261 Email: elhill@unimelb.edu.au
Prof Terence O’Brien: obrientj@unimelb.edu.au

Aim of Project: This project involves the study of altered inhibitory synaptic function in the NL3 mouse model of Autism Spectrum Disorder. Specifically, the project will investigate:

i. electrophysiological characteristics of 2 interneuron subtypes, and
ii. the effect of the NL3 mutation on endogenous cannabinoid pathways in brain slices.

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder characterised by impairments in social interactions, communication, and repetitive behaviour. Up to 30% of ASD patients also experience seizures, suggesting alterations in neuronal network function. While the cause of ASD is unknown, an imbalance of excitation and inhibition in brain circuitry has been proposed as an underlying mechanism. NL3 mice express a mutation in the Neuregulin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex.

In order to investigate mechanisms underlying the observed increase in synaptic inhibition, this project will compare the functional properties of neuronal subtypes in the NL3 and Wild Type control mice. Specifically, this project will focus on action potential firing and network characteristics of Fast Spiking (FS) and Regular Spiking Non Pyramidal (RSNP) neurons. FS neurons are strong candidates for influencing synaptic inhibition as they play an important role in modulating cortical networks via their synapses onto pyramidal cell bodies. In contrast, RSNPs (expressing somatostatin) synapse preferentially at dendritic locations. Altered network inhibition will be further assessed in these mice by pharmacological modulation of the endogenous cannabinoid pathway.

Skills: Characterisation of cortical inhibitory neurons using patch clamp electrophysiology in acute slices, and biocytin histochemistry in fixed slices for cellular morphology.

99. How do Anti-Epileptic Drugs Work? - also offered as MSci

Supervisor: Dr Chris French
Project Collaborators – Prof T O’Brien, Prof D Williams
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
Website: http://sites.google.com/a/hfbg1.net/crf_lab/

Despite many years of use and research, it is still not clear how even some of the oldest forms of anti-epileptic drugs work. That which is known is generally based on the effects of these compounds on single neurons, rather than examining how activity of the whole inter-connected neural network of the mammalian CNS is modulated. This project involves studying the effects of AED’s at several levels of organization of the CNS – single channel (voltage-gated sodium, potassium and calcium channels), single neuron, principal neuron/interneuron dynamics, as well as glial cell effects. Patch clamp techniques are used for recording dissociated neuron and neurons in the intact brain slice, and these observations will be extended with high-speed calcium imaging with conventional microscopy as well as multiphoton techniques. This projects affords excellent opportunities for skill development in electrophysiology, pharmacology, advanced microscopy and computational neuroscience.

100. How do Antipsychotic Drugs Trigger Seizures? - also offered as MSci

Supervisor: Dr Chris French
Project Collaborators – Prof T O’Brien, Prof D Williams
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
Website: http://sites.google.com/a/hfbg1.net/crf_lab/

The treatment of psychosis and schizophrenia has been greatly improved with the use of anti-psychotic drugs such as chlorpromazine, haloperidol and newer drugs such as clozapine. One significant side effect of these drugs is that they tend to lower the threshold for epileptic seizures to occur. The aim of this project is to quantify enhanced seizure activity with this type of drug using the in vitro brain slice technique. Seizure provocation threshold, synaptic transmission and single neuron properties will be assessed using rat hippocampal brain slices after acute application of these drugs.

101. Multi-Electrode Recording in the Rat Brain - also offered as MSci

Supervisor: Dr Chris French
Project Collaborators – Prof T O’Brien, Dr P O’Brien
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au
Website: http://sites.google.com/a/hfbg1.net/crf_lab/
Although immense advances have occurred in recording electrical signals from the CNS, these observations tend to be of single cells in a matrix of many millions of neurons and hence give very limited information about how the whole highly interconnected network functions. One solution to this problem is to use banks of tetrodes, bundles of four 10-20 micron diameter electrodes to record many cells simultaneously, either from a single region or from different parts of the brain. Up to 32 electrodes can be implanted with our system, and sophisticated spike detection and analysis algorithms are available to organize the complex multiple signals recorded. This recording technique can also be easily adapted to exploring epileptiform discharges in models of both focal and generalised epilepsy (including drug effects), which will be the main aim of this project. This project provides opportunity to learn cutting-edge electrophysiological and computing analysis techniques for assessment of function of the mammalian nervous system.

EPILEPSY AND NEUROPHARMACOLOGY

102. Modelling Epilepsy and Epilepsy Drug Effects–Computational Neuroscience Project

Supervisor: Dr Chris French
Project Site: Department of Medicine, MBC Neurosciences Building, Parkville
Contact: Dr Chris French T: 9035 6376 E: frenchc@unimelb.edu.au

It is unclear how large scale electrical oscillations in the CNS are produced with epileptic seizures. Simple hyperexcitability of individual ion channel types and abnormalities of synaptic transmission are undoubtedly important. However, at the network level, recurrent excitation and inhibition from interneurons must be crucial, and may explain why some anti epileptic drugs (AED’s) produce paradoxical exacerbation of seizures. This project involves modelling small networks (initially just 2 neurons) to examine the dynamics of seizure production, as well as how certain anti-epileptic drugs suppress or occasionally exacerbate network oscillations. This modelling involves incorporating novel experimental data from this laboratory on normal and drug affected ion channel mechanisms, as well as the effect of glial (supporting cells) cell interactions. The program “Neuron” will be mainly used for the simulations. Some programming experience is necessary, but the modelling language is relatively simple. This project provides an opportunity to gain an in-depth understanding of ion channel kinetics and non-linear behaviour of individual neurons and networks, with a strong clinical relevance.

103. Expression of efflux multidrug transporters in temporal lobe as a biomarker for outcome after surgery for pharmaco-resistant temporal lobe epilepsy - also offered as MSci

Supervisors: Professor Patrick Kwan, Professor Terence O’Brien, Professor Mark Cook
Project Site: Department of Medicine/Dept of Neurology, Royal Melbourne Hospital
Contact: Professor Patrick Kwan E: Patrick.kwan@unimelb.edu.au; Professor Terence O’Brien: E: obrientj@unimelb.edu.au

Laboratory Overview: The project will be carried out at the Department of Medicine through the RMH Academic Centre.

Project Overview: Anterior temporal lobectomy is recommended for selected candidates with drug-resistant temporal lobe epilepsy (TLE). However, pharmacoresistant seizures recur in approximately one third of patients postsurgery, and no reliable clinical predictive factor has been identified.

It is hypothesised that expression of efflux drug transporters, notably P-glycoprotein, in the epileptogenic temporal neocortex might be one such marker. P-glycoprotein, encoded by the ABCB1 gene, is the “prototype” multidrug transporter belonging to the superfamily of ATP-binding cassette (ABC) proteins that extrude substrates from the cell against the concentration gradient. These proteins have been extensively studied in oncology because of their putative role in multidrug resistance to cancer chemotherapy. In the normal brain, P-glycoprotein is expressed at a basal physiologic level in capillary endothelial cells where it “pumps” a broad range of xenobiotics from intracellular space back to the capillary lumen, thereby maintaining the integrity of the blood-brain barrier and reducing the cerebral accumulation of substrate drugs. In a range of epileptogenic brain pathologies, upregulation of P-glycoprotein and other ABC multidrug transporters have been reproducibly demonstrated. In a previous study of paraffinized temporal lobe tissues resected from drug-resistant TLE patients who underwent surgery at RMH, we showed that those with recurrent seizures postsurgery had higher expression of P-glycoprotein (1).

The present project aims to confirm the novel findings by other expression techniques for more quantitative profiling, including quantification of mRNA or protein expression, using fresh frozen brain tissues.

Research plan
The project will study fresh human brain tissues frozen upon resection from patients with pharmaco-resistant TLE and stored at the biobank at RMH, SVH and the Chinese University of Hong Kong. mRNA and protein levels of P-glycoprotein and other efflux transporters will be quantified. Their levels will be correlated with postsurgery outcome of the patients.
Acquired skills will include molecular biology techniques such as mRNA and protein extraction, quantitative RT-PCR, western blotting.

Reference

104. Development and validation of clinical assessment tools for population genetic studies of epilepsy in rural China - also offered as MSci
Supervisor: Professor Patrick Kwan
Project Site: Department of Medicine (RMH)
Contact: Professor Patrick Kwan, Departments of Medicine and Neurology, E: patrick.kwan@unimelb.edu.au

Background: Affecting 50 million people worldwide with 80% living in resource poor countries, epilepsy is the most common serious neurological disorder and a major global public health issue. Understanding the genetic risk factors predisposing to epilepsy and drug resistance can help doctors find better treatment and potentially preventive therapy, but patients in developing countries are often excluded from such research because of lack of expertise and sophisticated investigation technologies to classify the different types of epilepsy. This research aims to develop the necessary infrastructure for conducting large scale genetics research in rural China through the development and validation of clinical assessment tools for accurate phenotyping and building genetics research capacity, including research logistics, network and personnel training.

Research Plan: This is part of a larger project funded by the US NINDS and Fogarty International Center (1R21NS069223) to develop and validate clinical assessment tools for population genetic studies of epilepsy in rural China. Approximately 2,000 patients with epilepsy have been recruited from rural areas of four provinces in China (Figure). In stage 1, rural primary care doctors performed phenotyping of seizure types and epilepsy syndromes using questionnaires in 600 patients. Patients attended the provincial hospitals for independent phenotyping by the gold standard, consisting of neurologist assessment, EEG and brain MRI. In stage 2, 1,400 patients were phenotyped by rural doctors only. All patients provided blood samples for DNA extraction. This honours project will analyse the clinical data to determine the validity of the questionnaires in phenotyping by comparing with the gold standard.

Acquired skills: Biostatistics, bioinformatics, clinical phenotyping.

Figure: Map of China showing study sites in 4 provinces: Ningxia, Shanxi, Henan, Hebei (red boxes).

105. Does a novel mutation in the rat Cav3.2 T-type Ca2+ channel gene increase burst firing of neurons in vivo in a rat model of genetic absence epilepsy? - also offered as MSci
Supervisors: Dr. Kim Powell, Professor Terence O’Brien
Project Site: The Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au
Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au

Voltage-gated calcium (Ca2+) channels are believed to play a critical role in the generation of the hypersynchronous oscillatory thalamocortical activity that underlies absence seizures. Mutations in the Ca3.2 T-type Ca2+ channel gene have been reported in patients with childhood absence epilepsy (CAE) patients. Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are widely used model of absence epilepsy. In this model, Ca3.2 mRNA expression and T-type Ca2+ currents are elevated in the reticular nucleus of the thalamus (nRT), and we have shown similar elevations in the cortex. An increasing body of evidence, including from our laboratory, indicates that the seizures in GAERS originate focally in the
somatosensory cortex. It is also known that the thalamus plays a critical role in allowing the seizures to occur, the basis of which is pathological oscillatory thalamocortical activity. Together this data implicates the Ca\textsubscript{3.2} channel in the pathogenesis of this disease although whether functional abnormalities in the channel play a causative role in absence epilepsy is unknown. Linking an absence phenotype to a mutation in this channel would provide a priori case for a causative role. To this end we have identified that GAERS carry a homozygous single nucleotide missense mutation in a highly conserved region the III-IV linker domain of the Ca\textsubscript{3.2} T-Type Ca\textsuperscript{2+} gene (R1584P).

Importantly, with our Canadian collaborators, we have shown that this mutation is dependent upon exonic splicing for its functional consequences to be expressed in-vitro (i.e. its requires the presence of exon 25 [Ca\textsubscript{3.2} (+25)] to produce significantly faster recovery from channel inactivation and greater charge transference during high frequency bursts). This gain-of-function mutation, the first reported in the GAERS polygenic animal model, has a novel mechanism of action.

The current project will attempt to link this novel mutation with a cellular epileptic phenotype in-vivo. For these in vivo studies adult male F2 progeny of both NEC (non-epileptic control rats)xGAERS and GAERSxNEC double-cross matings who are homozygous (+/+1) for the R1584P mutation will be compared to those who do not carry the mutation (-/-). Single-cell juxtacellular recordings of cortical neurons and extracellular field recordings will be made in vivo, under neurolept anaesthesia, along with EEG recording of the related sensorimotor cortex. Neuronal firing patterns in the somatosensory cortex and reticular thalamus, between and during seizures, will be compared between animals with and without the mutation. Variables to be examined will include: the firing rate, the burst firing percentage, the number of action potentials per burst and the intraburst firing rate. The location of the recorded cells will be confirmed at the end of each experiment by juxtacellular labelling with neurobiotin.

106. Evaluation of Dynamin Inhibitors as Novel Therapies for Epilepsy - also offered as MSci

Supervisors: Prof. Terence J. O’Brien, Professor Phil Robinson and Dr. Nigel Jones.

Project Site: The Department of Medicine, Melbourne, and the Department of Physiology, Children’s Medical Research Institute, Sydney.

Contact: Prof Terence J. O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au
Professor Phil Robinson E: probinson@cmri.com.au
Dr. Nigel Jones T: 9035 6402 E: nciones@unimelb.edu.au

Background: The group of Phil Robinson at the CMRI have discovered the principle that dynamin modulators can control synaptic transmission. Consequently, they have engineered the first generation of small molecule dynamin inhibitors and have preliminary evidence for their effectiveness as anticonvulsant drug candidates using in vivo models. The GTPase activity of the enzyme dynamin is a novel molecular target for epilepsy. Blocking dynamin produces inhibition of neuronal synaptic vesicle endocytosis (SVE) and reduced synaptic transmission. The common feature of all anti-epileptic drugs (AEDs) is a reduction in synaptic transmission. For most AEDs the mechanistic basis of this reduction is uncertain. In a 2006 publication in Nature Neuroscience Professor Robinson’s group showed that inhibition of SVE by blocking dynamin leads to an activity-dependent run-down in synaptic transmission. The unique aspect of this discovery is the lack of effect on acute or brief bursts of synaptic transmission - being inhibited only after high or prolonged stimulation. We propose that molecules based on SVE inhibition would reflect a new and better AED design, especially in those cases where sufferers fail to respond to or tolerate conventional treatments. SVE inhibition has the unique ability to block sustained neuronal burst firing, as occurs during an epileptic seizure, while allowing normal neuronal transmission to occur under most physiological situations. By targeting only neurons experiencing prolonged or unusually high frequency stimulation, such drugs may have fewer effects in the absence of a seizure thus reducing the risk of many of the side-effects associated with AED therapy.

This project would test one or more of these candidate dynamin inhibitor treatments for anti-epileptic and anti-epileptogenic effects in “true” epilepsy models of generalized genetic (i.e. GAERS) and acquired focal epilepsy (post-status epilepticus and electrical amygdala kindling) to provide data predictive of efficacy for human epilepsies.

Skills: Small animal handling and neurosurgery (electrode implantations), rat electroencephalography recordings, brain perfusion and fixation, brain histological techniques, drug administration and neuropharmacological principles.

107. Post traumatic brain injury and epilepsy onset: Imaging the brain to investigate neural circuits and appropriate therapy interventions - also offered as MSci

Supervisor/s: Dr Sandy Shultz, Professor Terence O’Brien, Dr Damian Myers, Prof Rod Hicks, and Dr Nigel Jones

Project Site: Department of Medicine (RMH), MBC Neurosciences Building Parkville, and the Centre for Molecular Imaging, The Peter MacCallum Cancer Institute

Email Dr Sandy Shultz E: sandy.shultz@unimelb.edu.au

Closed-head traumatic brain injury (TBI) is a common condition that has dramatic and often long-lasting impacts on the patient and their family. The annual incidence of significant TBI in developed countries has been estimated to be 1/1000.
One of the dramatic and disabling long-term consequences of TBI is the development of post-traumatic epilepsy (PTE), which occurs in up to 25% of patients with moderate to severe injuries. With penetrating brain injuries the incidence is over 50%.

Epilepsy is defined as the occurrence of recurrent unprovoked seizures and is a prevalent neurological disorder as it affects up to 3% of the population in a lifetime and 0.5-1% at any one time. PTE often has severe morbidity and is difficult to treat as the seizures that develop are highly refractory complex partial seizures.

There is a lack of information about the mechanisms underlying the late epileptic, neurocognitive and neuropsychiatric changes occurring post-TBI. Neuronal plasticity occurring after TBI may explain the altered neuronal circuitry that, potentially, involves multiple cellular processes including neuronal death, axonal sprouting with formation of aberrant circuitry, neurogenesis and altered circuit connectivity caused by both axonal and dendritic plasticity.

The neural changes that occur during the onset and development of PTE are poorly understood so this project has been designed to investigate structural changes that occur in the cortex, hippocampus, and white matter, key structures of the brain neural network circuitry.

Several projects are available that will study TBI in the rat using the fluid percussion injury model. Techniques involved in these projects include small animal MRI and diffusion tensor imaging (DTI), video-EEG monitoring and histological techniques to investigate neural network changes associated with seizure onset after head trauma, and the study of neurocognitive and neurobehavioural testing to study the consequences of TBI.

The following projects have been designed to investigate the progressive neurological changes that occur post-TBI. The long-term aim is to investigate potential therapies that may protect the neural circuitry immediately after injury. To date, no effective neuroprotective strategies that have significant, long-term, benefits have been developed to treat TBI and PTE.

**Project 1:** A study of the neurocognitive and neurobehvioural changes that occur after closed-head traumatic brain injury in the rat (fluid percussion injury);

**Project 2:** Structural changes in the brain monitored by DTI and MRI after closed-head traumatic brain injury;

**Project 3:** Post-traumatic brain injury and neurogenesis: Tracking neurological changes in post-traumatic brain injury using advanced fluorescence imaging techniques

These projects will be conducted through the Department of Medicine at the Royal Melbourne Hospital and imaging will be performed at both the Howard Florey Institute and the Centre for Molecular Imaging at the Peter MacCallum Cancer Institute.

**108. Investigations into the role of neuropeptide y in a genetic rat model of absence epilepsy - also offered as MSci**

**Supervisor:** Prof Margaret Morris, Prof Terence J O’Brien, Dr Kim Powell  
**Project Site:** Department of Medicine and Department of Pharmacology, University of New South Wales.  
**Contact:** Prof Terence J O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au  
Professor Margaret Morris E: m.morris@unsw.edu.au

Absence epilepsy is one of the most common idiopathic generalised epilepsy syndromes. The underlying neurophysiological correlate of absence epilepsy is a pathological activation of rhythmic thalamocortical activity. However, the underlying aetiology for this disorder is still unknown.

There is increasing evidence that neuropeptide Y has a role in modulating seizures in acquired focal epilepsies, however there has been little investigation of its possible role in generalised epilepsy syndromes.

This study will investigate the effect of intracerebral microinfusions of neuropeptide Y into selected intracerebral thalamocortical brain regions on the number and total duration of absence seizure in the Genetic Absence Epilepsy Rats of Strasbourg (GAERS) model. Absence seizures will be quantified on the basis of the SWDs recorded on EEG for 90 minutes following the infusion. The effect of infusion antagonists and agonists of various neuropeptide Y receptors will also be evaluated.

The second stage of the project will investigate the effect of enhancing NPY expression focally in selected thalamocortical using a recombinant adenovirus viral vector.

**Skills:** Small animal handling and neurosurgery (electrode implantations, microinjection catheter implantations), rat electroencephalography recordings, brain perfusion, fixation and histological preparation, immunohistochemistry.
109. Antiepileptic drugs and effects on bone health - also offered as MSci

Supervisor: Dr Damian Myers, Dr Andrew Stevenson, Professor John Wark, and Professor Terence O’Brien.

Project Site: Department of Medicine, The Royal Melbourne Hospital.

Contact: Dr Damian Myers T: 8344 6449/0401 766608 E: damianem@unimelb.edu.au

Dr Andrew Stevenson E: andrew.stevenson@csiro.au

Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Recent clinical studies have confirmed that long-term administration of antiepileptic drug (AED) therapies affect bone mineral density (BMD) and increase risk of bone fracture. Epilepsy is a common neurological disorder typically requiring life-long treatment with neuroactive drugs such as carbamazepine and valproate. The problem of AED-associated bone disease must be addressed. Our research group has developed a model to study AED-induced changes in bone and the emphasis of this project will involve the use of bone protective therapies to overcome the AED-induced bone loss.

The common aim of the projects listed below is to determine whether the loss of bone associated with anti-epilepsy therapies can be prevented by the administration of bone protective therapies. The two protective agents to be tested are bisphosphonate and parathyroid hormone (PTH).

**Project 1: AED–induced changes in bone macrostructure, microstructure and bone strength: AIM:** To image and quantify, in *in vivo* longitudinal studies, the effects of anti-epilepsy drugs on bone using peripheral quantitative computed tomography (pQCT) (for changes in bone macrostructure & strength) and phase-contrast X-ray imaging (PCI tomography to assess bone microarchitecture at high resolution). The two interventions, bisphosphonate and PTH will be assessed on bone parameters; images will be acquired at 8, 16 and 24 weeks.

**Project 2: AED–induced changes in measures of bone turnover: AIM:** To measure biochemical markers of bone turnover and key metabolic factors in the serum (vitamin D, PTH, osteocalcin, calcium) in our model of AED-induced bone loss and to determine whether the interventions, bisphosphonate or PTH, affect the biochemical outcomes.

**Project 3: AED–induced changes in macro- and micro-architectural features of bone: AIM:** To assess whether the bone-protective agents, bisphosphonate or PTH, inhibit bone remodelling after treatment with the AED. Microarchitectural changes to bone will be imaged using phase-contrast X-ray (PCX) imaging and tomography. These techniques provide high resolution images (in micron range) using X-ray projection-based techniques. These projects involve collaborations with other institutes.

This work will be conducted in the Department of Medicine at the Royal Melbourne Hospital and advanced imaging techniques will be performed in collaboration with the CSIRO Materials Science and Engineering division in Clayton.

110. Investigation of the role of Y receptors in the seizure suppression effect of valproate in a rat model of genetic generalised epilepsy - also offered as MSci

Supervisor: Prof. Terence O’Brien and Prof. Margaret Morris, Dr Kim Powell

Project Site: The Department of Medicine, The Royal Melbourne Hospital and The Department of Pharmacology, The University of New South Wales.

Contact: Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au

Prof. Margaret Morris: E: m.morris@unsw.edu.au

Description: Valproate is the drug of choice for treatment of primary generalised epilepsy, but its mechanisms of action is still uncertain. There is a delayed onset of maximal effect following commencement of valproate treatment, suggesting that upregulation of a secondary messenger may be involved in its anti-epileptic action. Recent work has demonstrated that chronic valproate administration in rats results in upregulation of expression of neuropeptide Y (NPY) in brain regions critical to the generation of generalised seizures. We have evidence that NPY has powerful seizure suppression effects in the genetic absence epilepsy rats from Strasbourg (GAERS), a genetic rat model of absence epilepsy, predominantly via effects on the Y2 receptor subtype. This project will investigate if the anti-seizure effects of NPY are mediated through NPY related mechanisms, and if so identify the receptors mediating this effect. A positive outcome of the study may lead to new drugs that more specifically target the epilepsy reducing some of the common undesirable side effects of valproate.

Skills: Small animal handling and neurosurgery (electrode/cannula implantations), rat electroencephalography recordings, drug administration, brain perfusion and fixation, brain histology, immunohistochemistry, stereological neuronal cell counting and analysis techniques.

111. Sodium Channels in Epilepsy - also offered as MSci

Supervisors: Dr Chris French, Prof Terence O’Brien

Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville

Contact: Dr Chris French T: 9035 6376 E: frenchc@unimelb.edu.au
Laboratory Overview. The O’Brien Laboratory in the Department of Medicine, University of Melbourne, has a wide range of research activities related to the neurological disorder epilepsy. Projects include molecular biological studies, in vivo and in vitro electrophysiology, advanced imaging techniques, animal behaviour models, pharmacogenomics as well as comprehensive clinical

Project Overview. The project will be to study voltage-gated sodium channels, membrane proteins that are the basis of almost all electrical signaling in the nervous system, and so of the greatest significance in normal function, as well as disease states including epilepsy. Properties of normal channels in rat brain cells and cloned channels in tissue culture will be studied, as well as the effects of common anti-epileptic drugs (AED’s). We are particularly interested in examining how minor genetic variations impact on AED action. Opportunities for mathematical modeling and computational simulations of nerve cell activity are also available.

The project thus offers a very wide range of possibilities for advanced skill acquisition, including molecular biological techniques, patch-clamping and computational neuroscience. Several publications are anticipated. Additionally, a very high priority is placed on basic research skill acquisition, including experimental design and analysis, statistical techniques, familiarity with common molecular biological methods, as well as public presentation of research findings.

112. Epigenetic regulation of gene expression in epilepsy

Supervisors: Dr Nigel Jones, Dr Kim Powell
Project Site: Department of Medicine, MBC Neurosciences Building, Parkville.
Contact: Dr. Nigel Jones  T: 9035 6402  E: ncjones@unimelb.edu.au
Dr. Kim Powell  T: 9035 6394  E: kpowell@unimelb.edu.au

Background: Epigenetics describes the way chromatin/DNA structure can influence gene expression. This field of molecular biology is well-advanced in organism development and in cancer research, but has received little to no attention with respect to neurological conditions such as epilepsy, despite compelling reasons to suggest it is involved. Changes in gene expression are heavily implicated in the disease process of epilepsy (referred to as epileptogenesis) which turns a normal healthy brain into an epileptic brain, and epigenetic mechanisms are strong candidates to mediate such gene expression changes. This program seeks to investigate epigenetic changes associated with epilepsy to determine whether such modifications in chromatin structure contribute to epileptogenesis. Using animal models of epilepsy, several experimental projects are exploring this hypothesis:

Research project 1: Cell specific DNA methylation changes following epileptogenic insult.
Our pilot data demonstrates clear changes in DNA methylation (an epigenetic mark) in the brain after injury, but the relative contribution of varying brain cell types clouds our interpretation of this. This project will use MACS cell sorting technology to separate neurons, astrocytes and microglia and assess changes in DNA methylation at the BDNF promoter after injury, comparing the changes observed across different cell lineages.

Research project 2: Epigenetic signatures in blood as biomarkers of disease.
The potential to predict the onset of disease, and to map disease trajectory would have far-reaching implications for neurological disorders, including epilepsy. This project will attempt this by comparing epigenetic marks after brain injury in inflammatory genes from blood T cells and brain cells. We will also take serial blood samples and examine these same marks over time in their ability to predict the onset and severity of the epilepsy.

Research project 3: Viral-mediated manipulation of epigenetic machinery and the development of disease.
This project will use lenti-viral technology to down-regulate genes which are involved in catalysing DNA methylation. We will inject these viruses into brain, and assess whether changing expression of such genes can interfere with the development and severity of epilepsy.

Skills: Small animal handling; animal models of epilepsy; small animal surgery and EEG recording; experience with lenti-viral constructs; experience using MACS technology; techniques specific for epigenetic analysis, including bisulfite conversion, pyrosequencing, Methyl-DNA immunoprecipitation, and other molecular biology techniques, such as real-time qPCR, Western blotting, gel electrophoresis.

113. Imaging neurogenesis using Magnetic Resonance Spectroscopy

Supervisors: Dr Nigel Jones, Dr Dennis Velakoulis, Professor Gary Egan
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
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Professor Gary Egan  E: gary.egan@florey.edu.au

Background: The realisation that the mammalian brain is capable of producing new neurons (a process termed ‘neurogenesis’) stimulated world-wide interest in many scientific disciplines, both with regards to normal brain
function, and also a range of disease states. We now know that seizures, the hallmark symptom of epilepsy, stimulate a burst of neurogenesis in both animal models and in human patients. Intense speculation now surrounds the involvement of these newly born cells in the disease process of epilepsy. However, the limits of current technology allow us only to visualize these new cells in post-mortem tissue, making clinical translation of this research difficult. Through the use of advanced in vivo imaging (Magnetic Resonance Spectroscopy - MRS), this project aims to develop and characterize a method of visualizing newly born neurons in the functioning epileptic brain. Parallel studies are also being performed in human epilepsy patients.

Research plan: Seizures are induced in rats using a chemoconvulsant called Kainic acid, an insult known to induce neurogenesis in the brain. One week after the seizure, animals undergo a series of MRI and MRS scans at the Howard Florey Institute small animal imaging facility. The animals are then euthanized, and the brains processed for histological assessment of the extent of neurogenesis in seizure animals and controls. The MRI/MRS signals are processed for the presence of a biomarker using established protocols of our collaborators (Manganas et al, Science, 318:980-5, 2007), and correlated with the histological data.

Skills: Small animal handling; drug injections and the induction of status epilepticus; cardiac perfusions; immunohistochemistry; immunofluorescence; confocal microscopy; Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy.

114. Using a new mouse model of severe epilepsy to discover new antiepileptic drugs
Supervisors: Dr Chris Reid & Dr Steve Petrou
Project Site: Florey neuroscience Institutes (Howard Florey Building)
Contact: Dr Chris Reid T: 8344 1954 E: careid@unimelb.edu.au
Dr Steven Petrou T : 8344 1957 E: spetrou@unimelb.edu.au
Dravet syndrome is a severe form of epilepsy that is very difficult to treat and often results in death (http://www.ninds.nih.gov/disorders/dravet_syndrome/dravet_syndrome.htm). Our group has developed a new mouse model of the disease that is based on a human mutation. The mouse has all the major symptoms seen in patients with the disease. Some antiepileptic drugs reduce seizures in patient while others make the disease worse. We want to test these antiepileptic drugs on the mouse to see if they have the same ‘pharmaco-therapeutic’ profile as humans with the disease. This will validate the model potentially making it a powerful tool with which to test new and hopefully more effective antiepileptic treatments for Dravet syndrome.

115. Stopping Epilepsy before it starts
Supervisors: Dr Chris Reid & Dr Steve Petrou
Project Site: Florey neuroscience Institutes (Howard Florey Building)
Contact: Dr Chris Reid T: 8344 1954 E: careid@unimelb.edu.au
Dr Steven Petrou T : 8344 1957 E: spetrou@unimelb.edu.au
Idiopathic generalised epilepsy is a common form of epilepsy with a strong genetic component. Advances in gene discovery suggests that genetic profiling will allow us to predict what chance an individual has of getting epilepsy. In an exciting recent discovery our group has shown that the impact of an epilepsy mutation in early brain development can increase the chance of adults having seizures (Chui et al Annals of Neurology 2008). Therefore, if we can stop the impact of the epilepsy mutation in early development we may be able to stop epilepsy from ever occurring. This project has two parts. First, to administer antiepileptic drugs in the early part of brain development and see if we can reverse the impact of an epilepsy mutation. Second, to record early brain activity in a mouse model of idiopathic generalised epilepsy that is based on a human epilepsy mutation. This will determine what may be going wrong with the brain in the early developmental time window. Together, projects outlined here will help devise new therapeutic strategies that may allow us to stop epilepsy from ever occurring in susceptible patients.

116. Stargazin and AMPA receptor expression at cortical synapses in epileptic rats - also offered as MSc
Supervisors: Dr Kim Powell, Professor Terence O’Brien
Project Site:: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contacts: Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au
Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au.
Project Overview: Absence seizures, one of the most common seizure types in humans with idiopathic generalised epilepsy (IGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Absence seizures most commonly affect children and adolescents who can experience hundreds of seizures per day and if left untreated can lead to disruptions in learning. Despite the important recent identification of
genetic mutations in some rare families with IGEs showing a monogenic inheritance, in the common situation (>95% of sufferers) with complex inheritance patterns the genetic determinants of the absence seizures are still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and how they interact to result in epilepsy remains to be determined. GAERS are a strain of rats which spontaneously develop generalized absence seizures.

AMPA receptors are ionotropic transmembrane receptors for the excitatory neurotransmitter glutamate, which mediates fast synaptic transmission in the central nervous system. Stargazin is the archetypal member of a family of proteins called Transmembrane AMPA Receptor Regulatory Proteins (TARPs), and is critical for the trafficking and anchoring of AMPA receptors to synaptic membranes. Stargazin also influences electrophysiological properties of AMPA receptors including the slowing of deactivation and reducing desensitization rates. This newly identified TARP role for stargazin may have major functional implications on the homeostatic balance of neuronal excitation, and potentially for the pathophysiology of epilepsy. Recent work from our lab has shown increased expression of stargazin at neuronal membranes in the somatosensory cortex of epileptic GAERS animals, a brain region thought to be involved in the generation of absence seizures. These animals also show increased membrane AMPA receptor expression, which may be driven by elevated stargazin levels. Stargazin is known to interact with other synaptic proteins to localise AMPA receptors to the postsynaptic density (PSD), the region of the postsynapse opposite sites of neurotransmitter release.

The specific aims of this project are:
- To biochemically isolate the PSD from the somatosensory cortex of epileptic GAERS and non-epileptic control (NEC) rats
- To compare PSD localization of stargazin, AMPA receptor subunits and other synaptic proteins in GAERS and NECs
- To correlate membrane and synaptic expression of stargazin and AMPA receptors with seizure parameters

Skills: The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), EEG recordings and analysis, and biochemical and molecular analysis (subcellular fractionation, western blotting).

117. Investigating TARP and AMPA receptor protein expression in Genetic Absence Epilepsy Rats from Strasbourg - also offered as MSc

Supervisors: Dr Kim Powell, Prof Terry O’Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au, Prof. Terry O’Brien E: obrientj@unimelb.edu.au

Project Overview: Absence seizures, one of the most common seizure types in humans with idiopathic generalised epilepsy (IGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Absence seizures most commonly affect children and adolescents who can experience hundreds of seizures per day and if left untreated can lead to disruptions in learning. Despite the important recent identification of genetic mutations in some rare families with IGEs showing a monogenic inheritance, in the common situation (>95% of sufferers) with complex inheritance patterns the genetic determinants of the absence seizures are still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and how they interact to result in epilepsy remains to be determined. GAERS are a strain of rats which spontaneously develop generalized absence seizures.

AMPA receptors are ionotropic transmembrane receptors for the excitatory neurotransmitter glutamate, which mediates fast synaptic transmission in the central nervous system. Stargazin is the archetypal member of a family of proteins called Transmembrane AMPA Receptor Regulatory Proteins (TARPs), and is critical for the trafficking and anchoring of AMPA receptors to synaptic membranes. Stargazin also influences electrophysiological properties of AMPA receptors including the slowing of deactivation and reducing desensitization rates. This newly identified TARP role for stargazin may have major functional implications on the homeostatic balance of neuronal excitation, and potentially for the pathophysiology of epilepsy. Recent work from our lab has shown increased expression of stargazin at neuronal membranes in the somatosensory cortex of epileptic GAERS animals, a brain region thought to be involved in the generation of absence seizures. These animals also show increased membrane AMPA receptor expression, which may be driven by elevated stargazin levels.

The specific aims of this project are:
- To measure protein expression (membrane vs. cytosol) of the TARPs (γ2, γ3, γ4 and γ8) in AMPA receptors in young pre-epileptic and adult epileptic GAERS and to correlate with seizure expression
- To determine using immunohistochemistry at the cellular level where the TARP and AMPA receptor protein changes are occurring.
• To determine using protein complex-immunoprecipitations (Co-IP) which TARPS specifically interact with AMPA receptors.

Skills: The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), EEG recordings and analysis, and biochemical and molecular analysis (subcellular fractionation, western blotting, immunohistochemistry, Co-IP).

118. Dynamin activation in acute epileptic seizures and chronically epileptic rats - also offered as MSci

Supervisors: Dr Nigel Jones, Dr Caroline Ng, Professor Terence O’Brien, Prof Phil Robinson (University of Sydney)

Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville

Contacts: Dr Nigel Jones T: 9035 6402 E: ncjones@unimelb.edu.au
Dr Caroline Ng T: 9035 6445; Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au.

Project Overview: The Epilepsy and Neuropharmacology Research group is currently investigating novel anti-epileptic drugs that act to inhibit dynamin. This protein is critical to the rapid recycling of synaptic vesicles required for excessive neurotransmitter release that occurs during epileptic seizures. Dynamin activation is regulated through calcium-dependent dephosphorylation of key serine residues in the protein’s C-terminal region. Using mass spectrometry techniques, it is possible to determine the extent to which dynamin is phosphorylated at these different residues. In this way, the activation of dynamin can be assayed.

A group of compounds have proved effective as dynamin-inhibiting agents in the in vitro models of our collaborators at the Children’s Medical Research Institute (Westmead, NSW) but have failed to reduce seizure severity in our epilepsy models. This project aims to determine whether putative dynamin-inhibiting drugs have any effect on the activation of dynamin in vivo, both in non-seizing but chronically-epileptic rats, and during acute epileptic seizure. This will be carried out by preparing synaptic subcellular fractions from different brain regions from drug-treated and non-drug treated epileptic rats, purifying the dynamin from these fractions and quantifying the level of (de)phosphorylation to determine the level of activation of dynamin.

Specifically, this project will entail
• inducing epilepsy in rats through daily electrical stimulation of the amygdala (the Amygdala-kindling model of acquired epilepsy)
• treating the epileptic animals with drugs that inhibit dynamin in vitro
• preparing synaptosomes from the amygdala, hippocampus and cerebral cortex of drug treated and control epileptic animals; synaptosomes are isolated presynaptic terminals capable of neurotransmitter release in vitro
• purifying dynamin from these synaptosomes using GST-pulldown techniques
• quantifying the phosphorylation of the dynamin purified in this way

Skills: The skills expected to be learnt in this project include small animal handling and neurosurgery (electrode implantations, kindling, drug treatments); biochemical subcellular fractionation (preparation of synaptosomes); protein purification (GST-pulldowns, large format SDS-PAGE protein gels); understanding of trypsin digestion and mass spectrometric analysis of phosphoproteins and phosphopeptides.

119. Investigating Ca3.2 splice variant expression and the therapeutic potential of Ca3.2 Ca2+ channel blocking drugs in suppressing absence seizures in a polygenic rat model of idiopathic generalized epilepsy - also offered as MSci

Supervisors: Dr Kim Powell, Prof Terry O’Brien

Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville

Contact: Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au, Prof. Terry O’Brien E: obrientj@unimelb.edu.au.

Project Overview: Absence seizures, one of the most common seizure types in humans with idiopathic generalised epilepsy (IGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Aside from a few genes discovered in rare families where the epilepsy has a monogenic inheritance, the underlying genetic causes of the common IGEs are still largely unknown, but presumed to be polygenic, with more than one genetic variation contributing to the phenotype. In an important, well characterised model of IGE with absence seizures, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), our group has discovered a single nucleotide missense mutation in the highly conserved III-IV linker region of the Ca3.2 T-type Ca2+ gene (R1584P) which correlates with seizure expression in GAERS double-crossed with NEC rats (F2 generation).

Research Project 1: Ethosuximide, a first line drug to treat patients with absence epilepsy, is commonly believed to act via effects on T-type Ca2+ channels. However side effects such as drowsiness, ataxia and blurred vision are common and
some patients (20%) are refractory to its effects. Importantly there is some controversy as to whether it truly acts to suppress absence seizures specifically via effects on T-type Ca\(^{2+}\) channels. Our collaborators from Neuromed Pharmaceuticals (Vancouver, Canada) have developed novel selective T-type Ca\(^{2+}\)channel antagonists. Two selective Ca\(_{\text{v}3.2}\) channel blockers were highly effective at suppressing seizures in GAERS compared to vehicle treatment (DMSO) and standard doses of the two drug most commonly used to treat absence seizures in clinical practice, ethosuximide and valproate.

Therefore the specific aims of this project are:

- To investigate whether the Ca\(_{\text{v}3.2}\)(R1584P) mutation affects the seizure suppression ability of selective Ca\(_{\text{v}3.2}\) channel blocking drugs in double crossed F2 animals.
- To investigate whether T-type Ca\(^{2+}\) channel antagonists are effective at suppressing seizures when administered intra-cortically or intra-nRT in GAERS and F2 animals, and whether this is influenced by the Ca\(_{\text{v}3.2}\)(R1584P) mutation genotype.

Research Project 2: Our collaborative group have also identified two Ca\(_{\text{v}3.2}\) splice variants in rat thalamus (+exon 25) located only 13 residues downstream from the Ca\(_{\text{v}3.2}\)(R1584P) mutation site and demonstrated that channels containing the +exon 25 splice variant and the Ca\(_{\text{v}3.2}\)(R1584P) mutation are faster to recover from inactivation and have greater charge transference during high-frequency burst firing (as is seen during absence seizures).

The specific aims of this project are:

- To investigate the cellular expression of Ca\(_{\text{v}3.2}\) splice variant expression in thalamocortical brain regions of NEC and GAERS, and the relationship to the Ca\(_{\text{v}3.2}\)(R1584P) mutation genotype using double crossed NEC and GAERS (F2 generation).

Skills: The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations cannula placement, drug administration), EEG recordings and analysis.

120. Investigating molecular and physiological determinants of Sudden Unexplained Death in Epilepsy in acquired and genetic animal models of epilepsy - also offered as MSci

Supervisors: Dr Kim Powell, Dr Elisa Hill, Dr Nigel Jones, Prof Terry O’Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
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Project Overview: Epilepsy is associated with an increased risk of sudden unexplained death (SUDEP), possibly due to cardiac arrhythmias, although the precise mechanism remains unknown. SUDEP is considered the most important direct epilepsy-related mode of death and accounts for up to 30% of all deaths in the epilepsy population, being particularly prevalent amongst young patients with uncontrolled or drug-resistant, frequent and severe generalized tonic-clonic seizures.

Ion channels that coexist in the brain and heart would make ideal candidates for SUDEP because defects in intrinsic membrane excitability could predispose an individual to a dual phenotype of epilepsy and cardiac arrhythmias culminating in sudden death. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play an important role in the generation of pacemaker activity in the brain and heart. T-type Ca\(^{2+}\) channels contribute significantly to cardiac pacemaker activity and excitation–contraction coupling in the normal heart. Furthermore, its functional role becomes more marked in the process of pathological cardiac hypertrophy and heart failure. Thus these ion channels are attractive candidates for investigating molecular mechanisms of SUDEP.

The specific aims of this project are:

- To investigate the epigenetic mechanisms of decreased HCN expression in the heart of genetic and acquired animal models of epilepsy.
- To measure HCN channel current (If) in the hearts of genetic and acquired animal models of epilepsy.
- To measure HCN channel subunit and T-type Ca\(^{2+}\) channel expression in the hearts of genetic and acquired animal models of epilepsy.

Skills: The skills expected to be learnt from this project include: Small animal handling, electrophysiology recordings and analysis, biochemical and molecular analysis (real time PCR, western blotting).

121. Investigation into neurodevelopmental mechanisms predisposing individuals towards comorbid ADHD, autism spectrum disorders (ASD) and epilepsy - also offered as MSci

Supervisor: Dr Krista Gilby
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Aims: (1) To identify patterns of developmental gene expression supporting a seizure-prone versus –resistant phenotype, and (2) to determine whether corrections in developmental gene expression patterns can produce a more normal developmental trajectory in seizure-prone animals.

Background: Recurrent seizures, the defining symptom for epilepsy, are frequently observed in both ADHD and ASD patients. Indeed, increased seizure sensitivity may well be inherent to most, if not all, people suffering from ADHD/ASD. Such clinical overlap is currently believed to signify a ‘spectrum of vulnerability’ arising out of an early common dysfunction in central nervous system development. Accordingly natural breeding processes have been used to develop two rat strains; one that is inherently seizure-prone (FAST) and another that is seizure-resistant (SLOW). Alongside the increased seizure sensitivity in FAST rats, several traits naturally evolved that are highly reminiscent of those observed in ADHD/ASD. This project will investigate neurodevelopmental mechanisms that support development of a seizure-prone (FAST) versus seizure-resistant (SLOW) phenotype.

Research plan: Tissue will be extracted from FAST and SLOW embryos/foetuses at several prenatal time points. High throughput and targeted gene screening strategies will then be used to identify pivotal events, by way of altered gene expression, that ultimately dictate the development of a seizure-prone versus –resistant phenotype. If identified early, undesirable shifts in embryonic gene expression may be prevented and, in turn, encourage a ‘normal’ developmental trajectory in a FAST foetus.

Skills: Small animal handling and molecular biology techniques (RNA extraction, differential display & real time RT-PCR).

122. Comparing myelination patterns during neurodevelopment in a seizure-prone (FAST) versus seizure-resistant (SLOW) phenotype - also offered as MSci

Supervisors: Dr. Krista Gilby, Dr. Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr Krista Gilby T: 9035 6353; E: kgilby@unimelb.edu.au; Dr Nigel Jones E: ncjones@unimelb.edu.au

Aims: (1) to use cutting edge imaging techniques to compare myelination patterning during neurodevelopment in seizure-prone (FAST) versus seizure-resistant (SLOW) rats, and (2) to use molecular strategies to compare the quality of myelin in FAST versus SLOW rats.

Background: A high comorbidity exists between epilepsy, ADHD and Autism Spectrum Disorders. Among the numerous similarities in clinical presentation are the oft described developmental delay, heightened seizure sensitivity and biochemical and physical features suggestive of anomalous fatty acid metabolism. Fatty acid availability is critically important for myelination and proper neurodevelopment. Interestingly, natural breeding processes have been used to develop two rat strains; one that is inherently seizure-prone (FAST) and another that is seizure-resistant (SLOW). Alongside the increased seizure sensitivity in FAST rats, several traits naturally evolved that are highly reminiscent of ADHD/ASD, including a marked developmental delay and evidence of altered lipid handling. This project will compare myelination patterning during the development of a seizure-prone versus – resistant brain.

Research plan: Sophisticated and complimentary MR imaging techniques, diffusion tensor (DTI) and magnetization transfer (MT) imaging, will be used to compare white matter development and integrity in Fast versus SLOW rat pups across critical postnatal time points. White matter will also be extracted at these developmental timepoints in order to compare levels of integral myelination genes/proteins.

Skills: Small animal handling and neurodevelopmental assessment, DTI and MT imaging analysis and molecular biology techniques (westerns, real time RT-PCR).

123. Epigenetic Mechanisms contributing to Interrelated Neurodevelopmental Disorders - also offered as MSci

Supervisors: Dr. Krista Gilby and Dr. Nigel Jones
Project Site: Department of Medicine (RMH), Melbourne Brain Center, Neuroscience Building, Parkville, University of Melbourne
Contact: Dr Krista Gilby T: 9035 6353; E: kgilby@unimelb.edu.au

Aims: To investigate epigenetic mechanisms involved in the (1) generation and (2) maintenance of a seizure-prone, ADHD/ASD-like phenotype.

Background: Recurrent seizures, the defining symptom for epilepsy, are frequently observed in both ADHD and ASD patients. Such clinical overlap is currently believed to signify a ‘spectrum of vulnerability’ arising out of an early common dysfunction in central nervous system development. Accordingly natural breeding processes have been used to develop two rat strains; one that is inherently seizure-prone (FAST) and another that is seizure-resistant (SLOW). Alongside the increased seizure sensitivity in FAST rats, several traits naturally evolved that are highly reminiscent of those observed in
ADHD/ASD. Paramount amongst these traits is a relative long chain fatty acid (LCFA) deficiency that is similar in nature to that observed in the clinical conditions. This project will investigate epigenetic mechanisms involving fatty acid metabolism that support development of a seizure-prone (FAST) versus seizure-resistant (SLOW) phenotype.

**Research plan:** Epigenetic marks (such as DNA methylation) of target genes will be assessed in tissue extracted from FAST and SLOW rats, and from epileptic and non-epileptic rats. We will examine key regulatory genes involved in fatty acid metabolism, such as Elovl-5 & -6, and correlate these outcomes to gene expression and circulating fatty acid levels.

**Skills:** Small animal handling, molecular biology techniques (RNA/DNA extraction, pyrosequencing, real time RT-PCR).

124. **Fatty Acid Modulation of Ion Channels in Neurological Disorders** - *also offered as MSci*

**Supervisor:** Dr. Krista Gilby and A/Prof. Steve Petrou

**Project Site:** Melbourne Brain Center (UoM, FNI)

**Contact:** Dr Kirsta Gilby T: 9035 6353; E: kgilby@unimelb.edu.au

**Aims:** We will 1) investigate fatty acid (FA) modulation of ion channels and 2) determine the effects of acute FA application on epileptiform discharges in a seizure-prone (FAST) versus seizure-resistant (SLOW) rat strain.

**Background:** Rats selectively bred to be seizure-prone (FAST), versus seizure-resistant (SLOW), are relatively deficient in circulating free fatty acids despite maintenance on an identical diet. Similar FA deficiencies have been documented in epilepsy and associated neurodevelopmental disorders including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD). This metabolic discrepancy is likely to have a dramatic effect on central nervous system development and homeostasis within the adult brain. Indeed, ion channel modulation in response to a dynamic metabolic state and resultant circulating free fatty acid levels may influence seizure provocation and variations in symptom expression within each of these disorders.

**Research plan:** We will use state-of-the-art patch clamp and two-electrode voltage clamp techniques to investigate fatty acid modulation of sodium and GABAA channels and then determine the effects of fatty acid application on epileptiform discharges in FAST versus SLOW slice preparations.

**Skills:** Small animal handling and surgery (*Xenopus* frogs and rats), automated electrophysiology, cell culture, behavioral analyses.

125. **Do balance deficits in patients chronically taking anti-epileptic medications reflect neurodegeneration of the cerebellum?** - *also offered as MSci*

**Supervisors:** Professor Terence O’Brien, Professor John Wark, Professor Keith Hill and Professor Patricia Desmond.

**Project Site:** Departments of Medicine and Radiology, The Royal Melbourne Hospital, University of Melbourne

**Contact:** Prof Terence O’Brien: obrientj@unimelb.edu.au; Prof. John Wark: jdwark@unimelb.edu.au; Prof. Keith Hill: keith.hill@nh.org.au; Prof. Patricia Desmond: PatriciaDesmond@mh.org.au.

**Background:** Anti-epileptic medications are taken chronically by many people of all ages, for epilepsy and for a range of other high prevalence medical conditions. The adverse effects of the chronic use of these medications on bone and fracture risk is well recognised, but only recently has the negative impact of these medications on balance performance been documented by our group and others. Using a matched twin-sibling pair design we found that worse performance on several sway measures for AED users with longer duration of AED use. The association between chronic AED use, particularly with phenytoin, and cerebellar atrophy has long been recognized, but this has not previously been correlated with measures of balance function.

**Aims of Project:** To investigate whether the magnitude of cerebellar volume on MRI, compared with a matched twin or sibling control, is associated with the severity of quantitative measures of balance dysfunction.

**Methods:** 35 AED use discordant twin or sibling pairs have had a detailed falls and balance assessment. The T1-weighted volumetric MRI images on these patients will be used to quantitatively measure cerebellar, cerebral and brain stem volumes. The relative cerebellar volume will be compared between the AED user and their matched twin/sibling pair for the study population. The within pair difference in cerebellar volumes will then be correlated with that of the within pair difference for the balance measurements.

**Skills:** MRI image analysis, balance assessment interpretation, clinical pharmacology and statistical analysis of data.
126. Neuroanatomical determinants of susceptibility in a model of genetic epilepsy

Supervisors: Verena C Wimmer, Steven Petrou, Ion Channels and Disease Group, Florey Neuroscience Institutes, The University of Melbourne, Parkville, 3010.

Project Site: Florey Neuroscience Institutes, The University of Melbourne, Parkville.

Contact: Verena Wimmer E: vwimmer@florey.edu.au

Epilepsy affects ~1-2% of the population, making it the most common neurological disorder. 50% of all epilepsies are genetic generalized epilepsies (GGE), and currently more than 100,000 Australians live with this disease. These numbers highlight the dire clinical need for better therapy, diagnosis and prognosis. To achieve these goals we need to develop better knowledge of the underlying pathogenic processes. To date, research has focussed on acute functional effects of genetic mutations rather than anatomical changes in the brain as GGEs have been traditionally been considered ‘idiopathic’ without any visible changes in brain structure. Recent results, however, indicate that subtle, microscopic alterations in brain anatomy and neuronal connectivity underlie some aspects of seizure genesis. This prompts the question whether we can understand genetic epilepsy if we are ignoring structural changes or assuming they are non-existent?

This project will examine two forms of anatomical change associated with GGE: Microdysgenesis, which refers to changes during brain development, and homeostatic plasticity, which is an adaptive response to the seizures themselves. Anatomical alterations will be analysed in a mouse model carrying a human epilepsy mutation using cutting edge imaging and quantification techniques. Results will improve our understanding of pathogenic mechanisms in GGE with implications for therapy and diagnosis.

127. The role of hyperpolarization-activated channel 1 (HCN1) in network excitability

Supervisors: Verena C Wimmer, Steven Petrou, Ion Channels and Disease Group, Florey Neuroscience Institutes, The University of Melbourne, Parkville, 3010.

Project Site: Florey Neuroscience Institutes, The University of Melbourne, Parkville.

Contact: Verena Wimmer E: vwimmer@florey.edu.au

Epilepsy is the most common disorder of the Central Nervous System with ~60 million people affected worldwide. It is not a single disorder but includes aetiologies ranging from purely genetic to acquired conditions such as seizures resulting from head trauma. The common feature of “the epilepsies” is highly synchronized activity of large numbers of neurons. Interestingly, recent research suggests a common functional pathway of both inherited and acquired seizure disorders: several studies have mechanistically linked functional changes in hyperpolarization activated currents (Ih) to inherited and acquired epilepsy. Ih regulates dendritic excitability which is a key determinant of neuronal excitability. On a molecular level, Ih is exclusively mediated by hyperpolarization activated cyclic nucleotide gated channels (HCN-channels).

As observed in animal models and human epileptic brain tissue, the activity of HCN-channels is altered in a multitude of seizure disorders. It is yet unclear whether these changes play a compensatory, neuroprotective role or whether they are causative in epileptogenesis. Hence, the precise action of Ih in the transition from physiological to pathological network activity is not understood. This project aims at answering the following question whether a decrease in Ih itself can lead to epilepsy.

To answer this question HCN expression will be manipulated in different brain regions using stereotaxic in vivo injection of recombinant viruses. Effects on network excitability will be assessed by in vivo recording of neuronal spiking activity using tetrodes. Results will clarify specific contributions of HCN activity to the aetiology of different types of epilepsy and provide an important theoretical framework for developing specific therapeutic intervention strategies.

128. Seizure outcome after surgery for epilepsy - also offered as MSci

Supervisors: Dr Anne McIntosh, Professor Patrick Kwan.

Project Site: Department of Medicine, Comprehensive Epilepsy Programs at Royal Melbourne Hospital and Austin Health.

Contact: Dr Anne McIntosh, E: a.mcintosh@unimelb.edu.au, T: 93424419 or 90357007.

Individuals who have severe epilepsy that is refractory to medication may undergo surgical resection of the seizure focus. Although most patients benefit from surgery, between 20-40% of patients will continue to experience some seizures after surgery. The cause of seizure recurrence is not well understood. Epilepsy outcome research in the Department of Medicine at Royal Melbourne Hospital and Austin Health offers the opportunity to utilise two large well-established surgical cohorts to study post-surgical outcome and contribute to the growing international evidence base in this area.

The proposed project comprises an examination of seizure outcome for patients who have undergone resection of a temporal lobe lesion (non-malignant) or structural abnormality. There are several lesion types commonly associated with epilepsy, each has specific characteristics that may impact on seizure recurrence after surgery. The student will collate histopathology findings, conduct follow-up telephone interviews of patients, and analyse seizure outcome according to
the type of lesion resected. Other factors (extent of resection and characteristics of epilepsy prior to surgery) may also impact on outcome and these will also be assessed.

This information will contribute directly to the assessment, counseling and management of patients undertaking surgery at Austin Health and RMH. The study will result in a publication and will contribute to the international epilepsy surgery literature.

The skills expected to be learnt from this project include: Patient interviews, outcomes assessment, clinical epilepsy, statistics.

**IMAGING**

129. **Molecular Neuroimaging**

   **Supervisors:** Drs. Brad Moffat, Chris Steward and Soren Christensen
   **Project Site:** The Brain Imaging Laboratory, Department of Radiology, Level 2, 1B building, Royal Melbourne Hospital.
   **Contact:** Dr Brad Moffat T: 9342 8340 E: brad.moffat@mh.org.au

There is presently a paradigm shift in the way in which patients with neurological diseases (such as Brain Tumours, Stroke and Epilepsy) are treated. Old methods are being replaced by individualised patient management protocols using spatially, molecularly and genetically targeted therapies. Similarly, there is also currently a paradigm shift occurring in the field of Neuroimaging. Molecular Imaging (MI) Biomarkers are being developed to image biological, molecular and functional targets of interest to neuroscientists and clinicians. With this in mind The Brain Imaging Laboratory is currently developing and validating the following MI biomarkers: Functional Diffusion Mapping, Diffusion Tensor Imaging, Fluoro-ethyl-tyrosine positron emission tomography, Magnetic Resonance Spectroscopy and Perfusion MRI. The following are a subset of possible projects:

   **Project A:** Image fusion of Fluoro-ethyl-tyrosine positron emission tomography and Diffusion MRI in Brain Tumour Patients
   **Project B:** Perfusion imaging of stroke using blood oxygen level dependent and dynamic susceptibility MRI.
   **Project C:** Absolute quantification of glutamate using MR spectroscopy.
   **Project D:** Perfusion MRI of Brain Tumour Patients
   **Project E:** Optimisation of diffusion tensor MRI techniques for clinical assessment of white matter integrity.
   **Project F:** Optimisation of functional MRI paradigms for imaging the visual cortex.

130. **Network Activity in Brain Tissue Recorded with Combined Calcium and Voltage-Sensitive Dye Imaging and Electrophysiology - also offered as MSci**

   **Supervisor:** Dr Chris French
   **Project Collaborators – Prof T O'Brien, Prof D Williams**
   **Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital
   **Contact:** Dr Chris French T: 8344 3276 E: frenche@unimelb.edu.au
   **Website:** http://sites.google.com/a/hfbg1.net/crf_lab/

Understanding the normal function as well as pathophysiological states of neural systems requires sampling information from many points in the network simultaneously. One way to do this is using optical methods that allow the activity of many neurons to be imaged simultaneously. Calcium-sensitive fluorescent dyes can be loaded into neurons, so that the “firing” of neurons can be observed as a change in fluorescence in real time across many neurons. Voltage-sensitive dyes have the advantage of better time resolution, but the signal obtained is much smaller than calcium indicators. This project involves imaging groups of neurons in rat hippocampal brain slice in normal and epileptic states, with concomitant electrophysiological recording to better understand epileptogenesis in this structure. Additionally, the effects of anti-epileptic drugs will be examined at the network level using these techniques. In particular, we will be looking for key parameters that permit the stable network to enter oscillatory modes. Confocal and multi-photon imaging will be used for imaging the neurons loaded with dyes, combined with patch-clamp recording.
**INFECTIOUS DISEASES**

131. **Targeted analysis of Victorian Sentinel Surveillance data for HIV and other STIs** - *also offered as MSci*

Supervisor: Dr Mark Stoove, Head HIV/STI Research Group Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

Contact: A/Professor Margaret Hellard  T: 03 9282 2163  E: hellard@burnet.edu.au

The Burnet Institute manages the Victorian Primary Care Network for Sentinel Surveillance on BBVs and STIs on behalf of the Department of Health. The surveillance system collects demographic and risk behaviour data from patients attending clinical sites that see high caseloads of risk populations for HIV and other STIs, such as gay men and young people. The system then links this information with laboratory test results, allowing for crude estimates of transmission incidence and testing histories. Opportunities exist for targeted epidemiological analyses of these data, including quasi-cohort analyses, to answer key questions related to HIV and other STI risk and prevention. Such questions include, but not limited to, an assessment of appropriate testing frequency for different risk populations, testing histories and an examination of socio-demographic correlates of risk behaviour and HIV and other STI transmission.

132. **Social networking sites for sexual health promotion to at risk populations** - *also offered as MSci*

Supervisor: A/Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute and Dr Mark Stoove, Head HIV/STI Research Group Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

Contact: A/Prof Margaret Hellard. T: 03 9282 2163  Email: Hellard@burnet.edu.au

Dr Mark Stoove  E: stoove@burnet.edu.au

The Burnet Institute has conducted a series of projects using social online networking sites such as Facebook to disseminate sexual health promotion messages to gay men and young heterosexual populations through the establishment of a fictitious group of “friends”. This work has been undertaken in collaboration with the University of Melbourne, the Victorian College of the Arts and the Victorian AIDS Council. In 2010/2011 this work will continue and an opportunity exists to evaluate this project through a mixed-method approach. Narrative analysis of online dialogue, interviews with participants and quantitative analysis of evaluation data will inform recommendations and implications regarding the use of new technologies and online social networking for sexual health promotion, particularly to young people.

133. **Patterns of drug use and health outcomes among adult prisoners in Queensland** - *also offered as MSci*

Supervisor: Dr Stuart Kinner, Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

Contact: Dr Stuart Kinner. T: 03 8506 2368 E: kinner@burnet.edu.au

The majority of prisoners in Australia engage in risky substance use, including injecting drug use. Prisoners are also characterised by poor health outcomes including a high prevalence of infectious and chronic disease, yet the links between substance use and poor health in this population remain poorly understood. Using existing data from a study of more than 1300 adult prisoners in Queensland, the aim of this project will be to explore the links between risky substance use and ill health, and to identify targets for prevention and treatment to improve the health of this profoundly marginalised population.

*Note: this project is also listed under 'Injecting Drug Use'*

134. **Mapping the health needs of adult prisoners.** *Also offered as MSci*

Supervisor: Dr Stuart Kinner, Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

Contact: Dr Stuart Kinner. T: 03 8506 2368 E: kinner@burnet.edu.au

Prisoners as a group are characterised by profound social disadvantage, a high prevalence of infectious and chronic disease, mental illness, intellectual disability and risky drug use. These problems are not evenly distributed throughout the prisoner population, and the burden of disease is thus concentrated among those who are particularly at risk. Using data from a comprehensive assessment of more than 1300 adult prisoners in Queensland, the aim of this project will be to document the prevalence and co-occurrence of morbidity among prisoners as a function of characteristics such as age, gender and Indigenous status. Findings will inform the on-going development of evidence-based, targeted health interventions for prisoners.

135. **Monitoring and improving the health of ex-prisoners: A randomized controlled trial** - *also offered as MSci*

Supervisor: Dr Stuart Kinner, Centre for Population Health, Burnet Institute

Location: Centre for Population Health, Burnet Institute

Contact: Dr Stuart Kinner.  T: 03 8506 2368  E: kinner@burnet.edu.au
The Passports to Advantage project is a world-first: a large, randomised controlled trial of a health intervention for adult ex-prisoners in Queensland, Australia. The project involves 1,500 adult men and women completing a comprehensive health assessment in the weeks prior to their release from custody, and again 1, 3 and 6 months post-release. Half of the sample will receive a tailored support package both prior to and after their release from custody. This project involves analysis of the baseline data, with a particular focus on the links between drug use, mental illness and infectious disease.

136. Assessing the long-term outcome of ICU patients with methicillin resistant *Staphylococcus aureus* infection and colonization using data linkage  
Supervisors: A/Professor Emma McBryde, Dr Caroline Marshall, Victorian Infectious Diseases Service (VIDS), Royal Melbourne Hospital  
Project Site: Department of Medicine & VIDS 9th Floor, RMH  
Contact: A/Professor Emma McBryde T: 9342 8890 E: Emma.McBryde@mh.org.au  
**Description:** Preventing spread of methicillin-resistant *Staphylococcus aureus* (MRSA) within hospitals is an urgent priority. Methicillin resistance in *S. aureus* has been independently associated with increases in length of hospital stay, hospital charges, increased risk of delayed therapy and death.  
We have a large ICU cohort of around 4000 unique consecutive ICU admissions from a previous study (2007-2009) that we hope to follow-up looking for long-term events using data linkage. The department of health is the data custodian of all private and public hospital admissions and emergency department visits in Victoria. By linking our available cohort data with long-term information about hospital admissions after the date of discharge from hospital, we hope to determine long-term consequences of MRSA colonisation or infection. This project is ideal for a student looking for a project that has flexible working conditions and will develop skills in data analysis, including data linkage, regression analysis and database management.  
**Skills learned in this project:** Data linkage, data analysis, software including Excel and Stata, scientific writing.

137. Analysis of the social networks of cases of pandemic influenza in Australia. *Also offered as MSci*  
Supervisor/s: Emma McBryde, Caroline van Gemert  
Project Site: Burnet Institute, 85 Commercial Road, Melbourne  
Contact: Emma McBryde E: Emma.mcBryde@burnet.edu.au  
Shortly after the emergence of pandemic influenza A (H1N1) in Australia, the Centre for Population Health at the Burnet Institute led two studies; 1) to examine intra-household secondary transmission of pH1N1; and 2) describe the social contacts of confirmed student cases of pH1N1 in Victoria. The study collected data in November and December 2009. Analysis and dissemination of the results is ongoing. An opportunity exists to undertake a detailed analysis of behavioural data collected in these studies, with a focus on comparing the levels of social contact reported by young people and adults participating in his study and examine other factors that may influence disease transmission.

Supervisor: A/Prof Damon Eisen, Dr Michael Osthoff, Victorian Infectious Diseases Service (VIDS), Royal Melbourne Hospital  
Project Site: Department of Medicine (RMH) & VIDS 9th Floor, RMH  
Contact: Prof Damon Eisen, T: 9342 7212 E: damon.eisen@mh.org.au  
Hepatitis B virus (HBV) infection remains a major global health concern, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. A vaccine against hepatitis B has been available since 1982 and is considered the mainstay of prevention against later complications of chronic hepatitis B infection. However, vaccination fails to induce protective antibody levels in about 5-10% of healthy children and adults. Recent evidence suggests that several genes of the immune system are linked to variable immune responses to vaccination including members of the complement system. Mannose-binding lectin (MBL), the first component of the lectin pathway of complement, is a circulating innate pattern-recognition protein, which is involved in the clearance of microorganisms and apoptotic cells. The concentration of functional MBL multimers is profoundly influenced by several well-known polymorphisms in the *MBL2* gene, resulting in decreased or absent serum MBL levels in up to 30% of apparently healthy individuals. Recent animal studies have provided evidence that MBL deficiency enhances specific antibody production after vaccination. Hence, the aim of this project will be to characterise human MBL deficiency as a potential predictor of individual variability in the immune response to hepatitis B vaccination. The incidence of MBL deficiency in non-responders after hepatitis B vaccination will be compared with controls that show protective antibody titers against the hepatitis B surface antigen. The goal of this research is to eventually allow exploring and developing specific therapeutic interventions in the future to create MBL deficiency in order to improve vaccination efficacy.  
The skills expected to be learnt from this project include: ELISA, PCR, quantitative and qualitative data analysis, scientific literature review and writing.  
**Note:** This project is also listed under Innate Immunity & Host Defence.
139. **Primary tuberculosis infection in immunocompromised travelers – only available for Master of Science**

**Supervisors:** Dr Sharon Van Doornum, Dr Justin Denholm, Dr Irani Ratnam  
**Project Site:** Royal Melbourne Hospital  
**Contact:** Sharon Van Doornum E: svd@unimelb.edu.au

Patients with autoimmune disease such as rheumatoid arthritis frequently require treatment with immune suppression to control the symptoms of their disease. However immunosuppression is associated with risks too, including increased risk of infection. One particular infection that can cause problems in immunocompromised patients is tuberculosis. Although tuberculosis is uncommon in Australia, Australian patients who travel overseas may be at increased risk of contracting tuberculosis during their travels. Little is known about the incidence and risk factors for primary infection with tuberculosis in immunocompromised patients who travel overseas to high risk countries.

This project is offered as MSci, and will evaluate the incidence of, and risk factors for, primary infection with tuberculosis in immunocompromised patients who travel overseas to high risk places. The project includes study design and travel questionnaire design, ethics committee applications, patient recruitment and informed consent, implementation of questionnaires, organisation of patient testing, database development and entry, statistical analysis and manuscript preparation.

**INFECTIOUS DISEASES AND IMMIGRANT HEALTH**

140. **Comparison of medical conditions seen among returned travellers and immigrants presenting to hospital clinics versus those presenting to community-based general practices**

**Supervisors:** Karin Leder, BA Biggs, Caroline Marshall  
**Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital  
**Contact:** A/Professor Beverly Biggs T: 8344 3256/7 E: babiggs@unimelb.edu.au

Project description: Returned travellers and immigrants frequently have health problems related to crossing international borders. In Australia, individuals presenting to the infectious disease units of two hospital-based clinics (Royal Melbourne Hospital and Austin Hospital) and to community based general practice clinics (Traveller’s Medical and Vaccination Centre [TMVC]) have relevant demographic and diagnostic data captured via a standardised form (known as a GeoSentinel form). This data capture is part of a global surveillance system for imported infection.

The successful honours candidate will have the opportunity to analyse data captured from June 2009 to the present. They will be able to examine differences in demographics, reason for presentation and diagnoses between people presenting for care at hospital versus general practice clinics. The results will provide a unique comparative view of the burden and types of illness seen by doctors working in each of these health care settings.

141. **Audit of Patient’s Knowledge of Hepatitis B**

**Supervisors:** Dr Karin Leder, A/Professor Beverley Biggs, Dr Caroline Marshall  
**Project Site:** Department of Medicine (RMH), Royal Melbourne Hospital  
**Contact:** A/Professor Beverly Biggs T: 8344 3256/7 E: babiggs@unimelb.edu.au

Project description: In the infectious diseases clinics at the Royal Melbourne Hospital, we see many patients originating from Africa and Burma with chronic hepatitis B infection. Anecdotally, we know that patients often do not fully understand or remember what they have been told about the implications of having this chronic infection and its treatment.

In this project, you will perform a literature review about health literacy and hepatitis B infection and you will devise and deliver a questionnaire to patients attending the clinics in order to determine their understanding and recollection of information that has been given to them regarding their condition. This will enable us to devise recommendations for improving health literacy amongst these patients.

142. **Monitoring the efficacy of a training program in gastroenterology in the Pacific – also offered as MSci**

**Supervisors:** Professor Finlay Macrae  
**Project Site:** Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital  
**Contact:** Professor Finlay Macrae T: +61 3 9347 0788 E: finlay.macrae@mh.org.au

Diseases in the GI tract are common in the South Pacific. GI Endoscopy access is limited, and training even less available. In association with the World Gastroenterology Organization, we have recently introduced a training program in gastroenterology to support postgraduate training in gastroenterology at the Fiji School of Medicine, with expertise provided from Australia. The project is designed to monitor the effects of this across the South Pacific, through
documentation of higher levels of service delivery in the region, epidemiology of disease detection (e.g. helicobacter pylori) and skills' acquisition by graduates of the program that can be applied in remote communities in the South Pacific with high GI disease burdens.

The applicant would be required to visit South Pacific regions to assess qualitatively and quantitatively, disease burdens and the provision of services to address these needs, with a view to reports for Faculty, the Gastroenterological Society of Australia, the World Gastroenterology Organization and the Australian Government (AusAid).

**INJECTING DRUG USE**

143. **Drug Trend Monitoring in Regional Victoria - also offered as MSci**
   Supervisor: Paul Dietze, Brendan Quinn
   Project Site: Burnet Institute, 85 Commercial Road, Melbourne,
   Contact: Paul Dietze E: pauld@burnet.edu.au

The aim of this project will be to investigate patterns of injecting drug use and characteristics of drug markets in a site in regional Victoria. The Illicit Drug Reporting System (IDRS), established in Melbourne in 1997 has added considerably to our understanding of patterns of injecting drug use and harm along with the characteristics of illicit drug markets in Melbourne. However, in general the IDRS is limited to a consideration of these drug-related issues in metropolitan Melbourne. Indeed, there is little known about drug consumption in Victoria outside of metropolitan Melbourne other than in relation to tobacco and alcohol. The absence of such data presents a significant impediment to the formation of effective policy responses. The implementation of the IDRS methodology in a regional setting will provide useful information on trends in drug use in non-metropolitan Victoria.

144. **Mapping public injecting drug use in urban Melbourne - also offered as MSci**
   Supervisor/s: Paul Dietze, Rebecca Winter, Peter Higgs
   Project Site: Burnet Institute, 85 Commercial Road, Melbourne
   Contact: Paul Dietze E: pauld@burnet.edu.au; Peter Higgs E: peterh@burnet.edu.au

The risks associated with injecting drug use are determined by interactions between individual injecting behaviours and the 'environment' (e.g. physical, social, legislative) in which injecting occurs. Using a mixed methods approach, this project will undertake ethnographic mapping and quantitative secondary data analysis to document aspects of public injecting drug use in inner urban Melbourne. The ethnographic mapping exercise will involve neighbourhood-level observational research to examine sites of public injecting, levels of public injecting and document associated injecting practices and potential risks. Additional secondary data analysis will be undertaken to examine indicators of the impacts of public injecting, such as fatal and non-fatal overdose and impacts on public amenity.

145. **Community views on the establishment of a supervised injecting facility in Melbourne - also offered as MSci**
   Supervisor/s: Paul Dietze, Rebecca Winter, Mark Stoove
   Project Site: Burnet Institute, 85 Commercial Road, Melbourne
   Contact: Mark Stoove E: stoove@burnet.edu.au; Paul Dietze E: pauld@burnet.edu.au

Supervised injecting facilities have operated internationally and in other Australian jurisdictions for some time and have been integrated into respective injecting drug harm reduction responses. With growing evidence of their effectiveness in preventing adverse outcomes associated with supervised injecting drug use, there has been recent public debate about the need to consider the establishment of supervised injecting facility in Melbourne. This project will involve conducting a survey of members of a local urban community in Melbourne that is affected by public injecting drug use and analysing media coverage of community impact and views. Conducted with residents and traders, the survey will investigate community attitudes towards drug use and drug users, determine levels of support for the establishment of a supervised injecting facility in Melbourne and explore the nature of support or objection to such a proposal. The media analysis will contrast the results of the community survey with representations of community attitudes in local media.

146. **A beautiful cocktail? Investigating the relationship between drug use and body image among young people in Melbourne - also offered as MSci**
   Supervisor/s: Rebecca Jenkinson, Paul Dietze, Brendan Quinn
   Project Site: Burnet Institute, 85 Commercial Road, Melbourne
   Contact: Paul Dietze E: pauld@burnet.edu.au

Body image and drug use are significant health concerns for young people. The Burnet Institute coordinates a range of innovative research projects related to the use of alcohol and other drugs. Recent findings from these studies suggest that some young people engage in risky drug-using behaviours in order to 'look good', including using psychostimulants to help lose or maintain weight and injecting melatonin for developing an artificial tan. The aim of this project will be to
enhance our understanding of the relationship between drug use and body image among young people through a detailed literature review, focus groups with young people who use drugs, and interviews with key stakeholders working in the alcohol/other drug and nutrition/eating disorder sectors.

147. **The experience of violence among injecting drug users** - also offered as MSci  
**Supervisor/s:** Paul Dietze, Mark Stoové, Peter Higgs  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Mark Stoove E: stoove@burnet.edu.au; Paul Dietze E: pauld@burnet.edu.au; Peter Higgs E: peterh@burnet.edu.au

Overseas experience shows that injecting drug users are known to experience violence, as both victims and perpetrators. In this project existing data will be analysed to document the nature and extent of violence amongst a sample of injecting drug users. This analysis will be supplemented by a series of qualitative interviews with participants to better understand the context in which some of the experienced violence has occurred.

148. **The feasibility of paying people who inject drugs a modest financial incentive to remain free of hepatitis C (HCV) infections** - also offered as MSci  
**Supervisor/s:** Margaret Hellard, Mark Stoové  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Mark Stoove E: stoove@burnet.edu.au; Margaret Hellard E: Hellard@burnet.edu.au

The predominant blood borne virus (BBV) transmitted through injecting drug risk practices in Australia is hepatitis C (HCV) and it leads to substantial morbidity and mortality in people who develop chronic infection. There are currently no vaccines for these infections, and whilst treatments are improving, prevention of transmission in people who inject drugs (PWID) remains vitally important. Various education and behavioural interventions have been trialled but to date no-one has provided a financial incentive to PWID to remain HCV free.

This project will explore the feasibility of providing a financial incentive to current PWID who have not been exposed to HCV to remain HCV free. It will also explore what would be considered a reasonable incentive to ensure PWID remain HCV free. A series of focus groups and one on one interviews will be conducted with current PWID, community based organisation representing PWID and relevant government officials.

149. **Why do some people with hepatitis C continue to drink?** - also offered as MSci  
**Supervisor/s:** Peter Higgs, Margaret Hellard  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Peter Higgs E: peterh@burnet.edu.au; Margaret Hellard E: Hellard@burnet.edu.au

Whereas injecting drug use is the most significant risk factor for acquiring hepatitis C (HCV) in the developed world, once infected with HCV, alcohol use is the strongest known modifiable determinant of HCV disease progression. Alcohol consumption has been found to raise the viral load and accelerate hepatic fibrosis in the context of HCV infection, and heavy alcohol consumption is a risk factor for premature death from HCV. Moreover, as well as impacting on liver disease progression, heavy alcohol use may influence the likelihood of successful HCV treatment. The proposed project involves in-depth interviews with up to 25 consenting participants living with HCV from the Melbourne Injecting Cohort Study (MIX). Interviews will address alcohol use and other related exposures and outcomes, including participants’ alcohol consumption prior to and after HCV diagnosis, any medical advice regarding alcohol consumption they may have received, advice from peers with HCV regarding alcohol consumption, perception of alcohol consumption practices amongst peers with HCV, participants’ understanding of the relationship between alcohol-related and injecting drug use-related behaviours, clinical symptoms and other effects of HCV on relationships and self-perception, current self management strategies for living with HCV.

*Note: this project is also listed under Alcohol*

150. **Risk environments and injecting drug use** - also offered as MSci  
**Supervisor/s:** Paul Dietze, Mark Stoové, Margaret Hellard  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Paul Dietze E: pauld@burnet.edu.au; Mark Stoove E: stoove@burnet.edu.au; Margaret Hellard E: Hellard@burnet.edu.au

The risks associated with injecting drug use are determined by complex interactions between individual behaviours, drug using networks, socio-political influences, legislative responses and service provision. These factors combine to create an overall risk environment for injecting drug users that mediates blood borne virus transmission, overdose risk, the frequency of drug use and other injecting drug related outcomes. This project offers an opportunity to examine risk environments for injecting drug use from a public health, epidemiological and/or policy perspective. Depending on the
epistemological approach, this study will involve a combination of document review, media analysis, secondary data analysis, and primary quantitative and qualitative data collection from people who inject drugs and other key stakeholder.

151. The experience of violence among injecting drug users - also offered as MSci
   Supervisor: A/Professor Paul Dietze, Head, Alcohol and Drugs Research Group, Ms Rebecca Jenkinson Centre for Population Health, Burnet Institute
   Project Site: Centre for Population Health, Burnet Institute
   Contact: A/Professor Margaret Hellard. T: 03 9282 2163 E: hellard@burnet.edu.au
Overseas experience shows that injecting drug users are known to experience violence, as both victims and perpetrators. In this project existing data will be analysed to document the nature and extent of violence amongst a sample of injecting drug users. This analysis will be supplemented by a series of qualitative interviews with participants to better understand the context in which some of the experienced violence has occurred.

152. The post prison release trajectories and health outcomes of people with a history of injecting drug use: a prospective cohort study - also offered as MSci
   Supervisor: Dr Mark Stoove, Head HIV/STI Research, Centre for Population Health, Burnet Institute
   Project Site: Burnet Institute
   Contact: A/Professor Margaret Hellard. T: 03 9282 2163 E: Hellard@burnet.edu.au
The post-prison release period is a particularly vulnerable period for ex-prisoners with a history of injecting drug use. Recruitment and prospective data collection from a cohort of post-release prisoners with a history of injecting drug use was undertaken at the Burnet Institute and completed in 2010. Opportunities exist to utilise this database to explore the drug use and health and wellbeing outcomes of this population in the immediate post-prison release period. This data is augmented by qualitative interviews with cohort participants and key informant service providers to examine personal, social and structural factors that facilitate or impede successful drug dependence treatment outcomes in this population. This Honours project could constitute a targeted epidemiological examination of health outcomes in this cohort and/or a mixed-methods study to explore a particular aspect of the post-prison release experiences of this population.

153. Patterns of drug use and health outcomes among adult prisoners in Queensland - also offered as MSci
   Supervisor: Dr Stuart Kinner, Centre for Population Health, Burnet Institute
   Project Site: Centre for Population Health, Burnet Institute
   Contact: Dr Stuart Kinner. T: 03 8506 2368 E: kinner@burnet.edu.au
The majority of prisoners in Australia engage in risky substance use, including injecting drug use. Prisoners are also characterised by poor health outcomes including a high prevalence of infectious and chronic disease, yet the links between substance use and poor health in this population remain poorly understood. Using existing data from a study of more than 1300 adult prisoners in Queensland, the aim of this project will be to explore the links between risky substance use and ill health, and to identify targets for prevention and treatment to improve the health of this profoundly marginalised population.
   Note: this project is also listed under ‘Infectious Diseases & Immigrant Health’

INNATE IMMUNITY AND HOST DEFENCE

154. Regulation of the innate immune response to bacterial pathogens in periodontal disease
   Supervisor: A/Prof Glen Scholz
   Project Site: Department of Medicine (RMH)
   Contact: A/Prof Glen Scholz T: 8344-3298; E: glenms@unimelb.edu.au
Project Description: The epithelial cells of the oral mucosa express innate immune receptors (e.g. Toll-like receptors) that allow them to directly participate in the host immune response to infection by periodontal pathogens. Given that oral epithelial cells are the first host cells to encounter periodontal pathogens, the inflammatory factors they secrete (e.g. cytokines and chemokines) is likely to be important for periodontal immunity. However, dysregulation of the inflammatory response of oral epithelial cells to periodontal pathogens is thought to be critical in the development and severity of periodontal disease. The objective of this project is to identify the inflammatory factors produced by oral epithelial cells in response to different periodontal pathogens and to then characterise the cell signalling pathways that regulate their production.
   Techniques: Expertise in a variety of cell biology (cell culture, ELISA assays), microbiological (culturing of pathogens), molecular biology (Real-Time PCR, siRNA-mediated gene silencing) and cell signalling (Western blotting) techniques will be acquired.
155. Using nanoparticles and siRNA to modulate the host immune response to bacterial pathogens

Supervisor: A/Prof Glen Scholz
Project Site: Department of Medicine (RMH)
Contact: A/Prof Glen Scholz T: 8344-3298; E: glenms@unimelb.edu.au

Project Description: The immune system plays a fundamental role in protecting us from infection by pathogens (e.g. bacteria and viruses). At the molecular level, this largely occurs through the integration of the cell signalling pathways that control the production of inflammatory factors (e.g. cytokines and chemokines) by cells within the innate and adaptive immune systems. However, the dysregulated production of inflammatory factors plays a pivotal role in the development and severity of a wide range of diseases (e.g. chronic periodontal disease, septic shock). The objective of this project is to validate the therapeutic potential of using nanoparticle-delivered short-interfering RNAs (siRNAs) that target specific cell signalling molecules or inflammatory factors to modulate the inflammatory responses of oral epithelial cells to periodontal pathogens using cell culture (in vitro) and animal-model (in vivo) based systems.

Techniques: Expertise in a variety of cell biology (cell culture, ELISA assays), microbiological (culturing of pathogens), molecular biology (Real-Time PCR, siRNA-mediated gene silencing) and cell signalling (Western blotting) and animal model techniques will be acquired.

156. Mannose-binding lectin deficiency and its influence on the immune response to hepatitis B vaccination

Supervisor: A/Prof Damon Eisen, Dr Michael Osthoff, Victorian Infectious Diseases Service (VIDS), Royal Melbourne Hospital
Project Site: Department of Medicine (RMH) & VIDS 9th Floor, RMH
Contact: Prof Damon Eisen, T: 9342 7212 E: damon.eisen@mh.org.au

Hepatitis B virus (HBV) infection remains a major global health concern, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. A vaccine against hepatitis B has been available since 1982 and is considered the mainstay of prevention against later complications of chronic hepatitis B infection. However, vaccination fails to induce protective antibody levels in about 5-10% of healthy children and adults. Recent evidence suggests that several genes of the immune system are linked to variable immune responses to vaccination including members of the complement system. Mannose-binding lectin (MBL), the first component of the lectin pathway of complement, is a circulating innate pattern-recognition protein, which is involved in the clearance of microorganisms and apoptotic cells. The concentration of functional MBL multimers is profoundly influenced by several well-known polymorphisms in the MBL2 gene, resulting in decreased or absent serum MBL levels in up to 30% of apparently healthy individuals. Recent animal studies have provided evidence that MBL deficiency enhances specific antibody production after vaccination. Hence, the aim of this project will be to characterise human MBL deficiency as a potential predictor of individual variability in the immune response to hepatitis B vaccination. The incidence of MBL deficiency in non-responders after hepatitis B vaccination will be compared with controls that show protective antibody titers against the hepatitis B surface antigen.

The goal of this research is to eventually allow exploring and developing specific therapeutic interventions in the future to create MBL deficiency in order to improve vaccination efficacy.

The skills expected to be learnt from this project include: ELISA, PCR, quantitative and qualitative data analysis, scientific literature review and writing.

Note: this project is also listed under Infectious Diseases

157. Mannose-binding lectin deficiency as a risk factor for the development and course of age-related macular degeneration

Supervisor: A/Prof Damon Eisen, Dr Michael Osthoff, Victorian Infectious Diseases Service (VIDS), Royal Melbourne Hospital
Project Site: Department of Medicine (RMH) & VIDS 9th Floor, RMH
Contact: A/Prof Damon Eisen, T: 9342 7212 E: damon.eisen@mh.org.au

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population, especially in the Western World. With the overall ageing of the population its prevalence is expected to increase by 50% in the next 10 years. Dysregulated local complement activation and subsequent chronic inflammation are considered to play an essential role in the pathogenesis of AMD. Additionally, certain pathogens (like Chlamydia pneumoniae or Cytomegalovirus) have been implicated in the pathogenesis of AMD by inducing a chronic inflammatory state. Mannose-binding lectin (MBL), the first component of the lectin pathway of complement, is a circulating innate pattern-recognition protein, which is involved in the clearance of microorganisms and apoptotic cells. The concentration of functional MBL multimers is profoundly influenced by several well-known polymorphisms in the MBL2 gene, resulting in decreased or absent serum MBL levels in up to 30% of apparently healthy individuals.
In terms of the pathogenesis of AMD, MBL deficiency might lead to an impaired clearance of apoptotic debris or certain pathogens (like Cytomegalo-virus) in AMD and consequently to sustained inflammation due to the activation of the classical or alternative pathway of complement.

The aim of this project will be to evaluate the importance of MBL deficiency as a risk factor in the development and course of AMD in a case controlled study of 140 patients with varying degrees of AMD. These patients will be compared with 140 age matched controls, who have been carefully examined by ophthalmological collaborators to ensure that they do not suffer from AMD.

The goal of this research is to eventually allow developing specific therapeutic interventions, e.g. by supplementing MBL. Moreover, identification of MBL deficiency as a susceptibility factor for AMD will lead to a more comprehensive understanding of the pathogenesis of AMD.

The skills expected to be learnt from this project include: ELISA, PCR, quantitative and qualitative data analysis, scientific literature review and writing.

Note: this project is also listed under Ophthalmology

**MALARIA**

158. **Malaria parasite adhesion to the human placenta** - also offered as MSci

**Supervisor:** Dr Philippe Boeuf  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contact:** Dr Philippe Boeuf T: 8344 3263 E: pboeuf@unimelb.edu.au

Pregnant women are more susceptible to malaria infection than their non-pregnant peers. This is thought to be due to the adhesion of malaria parasites to the placenta, triggering pathways leading to low birth weight. A better understanding of the mechanisms of malaria parasite adhesion to the human placenta would allow for the design of intervention strategies, including a vaccine. In this project, you will use placentas from women delivering at the Royal Women's Hospital as a matrix for malaria parasite adhesion. By studying the adhesion of various parasite lines under different experimental conditions, you will gain insights in the characteristics of this adhesion.

This project is based at the Department of Medicine, Royal Melbourne Hospital, in the malaria lab that has a long-term experience of malaria parasite adhesion. The lab is made of 1 lab head, 3 post-docs (including your supervisor), 2 research assistants, 6 PhD students and 2 mid-term honour students as well as visiting scientists from all over the world. Techniques involve (but are not limited to): malaria parasite culture, biochemistry, flow cytometry, confocal microscopy and western blotting.

159. **Characterizing new gene regulation mechanisms of the malaria parasite** - also offered as MSci

**Supervisors:** Dr Michael Duffy and Dr Michaela Petter  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contacts:** Dr Michael Duffy and Dr Michaela Petter; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

**Description of project:** *Plasmodium falciparum* malaria kills 800,000 people a year. Three processes are critical to malaria pathogenesis, i) erythrocyte invasion, ii) immune evasion through the parasite changing its appearance and iii) adhesion of parasite infected erythrocytes to small blood vessels. All three of these processes are regulated by epigenetic control of malaria gene expression. Epigenetic control is a rapidly moving and recent field of study with applications beyond malaria to cell development, neurology and cancer. We are investigating a range of malaria proteins that we predict exert epigenetic control and thus are potential drug targets. The project will involve transfecting parasites to express tagged proteins and using advanced molecular and imaging techniques such as chromatin immunoprecipitation, microarray analysis and fluorescence microscopy combined with classical molecular biology.

160. **The role of DNA methylation in malaria pathogenesis** - also offered as MSci

**Supervisors:** Dr Michael Duffy and Dr Michaela Petter  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contacts:** Dr Michael Duffy and Dr Michaela Petter; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

**Description of project:** *Plasmodium falciparum* malaria employs epigenetic mechanisms to regulate gene expression critical for pathogenic processes. One such mechanism is the methylation of DNA, classically associated with the repression of genes. Little is known about DNA methylation in malaria; this project will investigate when methylation
occurs in the malaria parasite lifecycle, where methylation occurs in the parasite genome and characterize the candidate enzyme responsible for methylation and associated trans factors. The project will involve advanced molecular and imaging techniques and functional enzyme studies.

161. **Nuclear architecture and gene regulation of the malaria parasite** - *also offered as MSci*

**Supervisors:** Dr Michael Duffy and Dr Michaela Petter  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contacts:** Dr Michael Duffy and Dr Michaela Petter; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

**Description of project:** An emerging theme in control of gene expression is the existence of functional compartments within the nucleus. One such compartment is the nuclear periphery which is typically associated with gene repression, however the nuclear pores through which mRNA is exported are an exception that are frequently associated with active transcription and retention of expressed genes. In malaria gene families are retained at the nuclear periphery and their expression is differentially regulated in a process implicating nuclear pores. We will investigate the role of nuclear pores in nuclear organization and the regulation of gene expression in the malaria parasite *Plasmodium falciparum*. This project will involve transfecting parasites to tag nuclear pore components and imaging analysis of the nuclear pores in relation to active genes and chromosomal structures. Factors associated with the nuclear pores will also be identified by co-immunoprecipitation.

162. **Gene regulation mechanisms in the transmissible stages of the malaria parasite** - *also offered as MSci*

**Supervisors:** Dr Michaela Petter and Dr Michael Duffy  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contacts:** Dr Michaela Petter and Dr Michael Duffy; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

**Description of project:** During infection with the malaria parasite *Plasmodium falciparum*, some malaria parasites infecting red blood cells differentiate into sexual stages called gametocytes. Gametocytes are transmitted to the mosquito when it feeds on an infected human. The mechanisms that trigger the differentiation of malaria gametocytes are poorly understood. In many eukaryotes, epigenetic mechanisms are crucial for the regulation of cellular differentiation processes. This project aims to identify epigenetic gene regulation mechanisms which are important during the differentiation of malaria gametocytes. The project will involve cultivating *P. falciparum* gametocytes in vitro and the analysis of the expression of candidate epigenetic regulators by using advanced molecular and imaging techniques such as fluorescence microscopy, Western Blot analysis, and chromatin immunoprecipitation, combined with classical molecular biology.

163. **Characterizing new surface proteins of the malaria parasite** - *also offered as MSci*

**Supervisors:** Dr Michaela Petter  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contacts:** Dr Michaela Petter; T: 8344 3264; Email: mpetter@unimelb.edu.au

**Description of project:** The malaria parasite evades the host immune system by constantly changing its appearance, a process called antigenic variation. This is mediated by large protein families encoded in the parasites genome. Due to their important role in the patho-physiology of the disease, a better understanding of these surface proteins may reveal new targets for interventions. This project aims to characterize members of a particular protein family, called RIFIN. You will generate and analyse transgenic parasite lines expressing RIFIN proteins fused to fluorescent markers and use these tools to characterize the protein family with respect to their expression, cellular localization, membrane topology and function.

Techniques include: Cell culture, PCR and cloning, SDS-PAGE and Western blotting, FACS analysis, Immunofluorescence microscopy.

164. **Investigating the role of malarial pigment haemozoin in macrophage biology** - *also offered as MSci*

**Supervisor:** Dr Louise Ludlow  
**Project Site:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne  
**Contact:** Dr Louise Ludlow T: 8344 3264 E: lludlow@unimelb.edu.au

An important way in which the body clears malaria infection is through opsonisation of malaria infected erythrocytes and phagocytosis by monocytes and macrophages. This process also leads to proinflammatory cytokine production. Among
the parasite-derived immune activating factors that may contribute to this inflammatory response is the haemoglobin degradation product haemozoin. Haemozoin can be isolated from malaria infected cells in a native state in complex with parasite DNA, protein and lipids. In this project, you will assess the biological events that occur following uptake of native haemozoin and compare this response to intact malaria infected erythrocytes. We hypothesise that native haemozoin contributes significantly to the macrophage inflammatory response.

The project involves a range of molecular and cell biology techniques including culture and purification of *P. falciparum* infected erythrocytes, purification of native haemozoin, isolation and culture of monocyte-derived macrophages from human blood, qPCR to assess cytokine mRNA and ELISA to measure proinflammatory cytokine secretion.

165. **Defining the innate immune receptor involved in detection of malaria derived immune activating factors** - *also offered as MSci*

- **Supervisors:** Dr. Louise Ludlow and Prof. Stephen Rogerson
- **Location:** Department of Medicine (RMH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne
- **Contact:** Dr. Louise Ludlow T: 8344-3264 E: lludlow@unimelb.edu.au

Toll-like receptors (TLRs) are expressed by cells of the innate immune system and sense conserved molecules from all classes of microorganisms resulting in excessive release of proinflammatory cytokines associated with pathology. Malaria infected erythrocytes activate macrophage phagocytic receptors (complement, CD36 and Fc) and TLRs. This results in ingestion and induction of kinase and transcription factor activation which orchestrates secretion of proinflammatory cytokines. Previous studies indicate a role for the nucleic acid sensing TLR9 located within the endosomal compartment. In this project you will determine the contribution of TLRs in mediating the macrophage proinflammatory response to malaria infected erythrocytes.

Cell lines lacking TLRs and a commercially available TLR9 antagonist will be used to investigate the role of these receptors. The project involves a range of molecular and cell biology techniques including culture and purification of *P. falciparum* infected erythrocytes, isolation and culture of monocyte-derived macrophages from human blood, RNA and cDNA preparation for qPCR and ELISA to measure proinflammatory cytokine production.

166. **Functional assays for immunity to malaria** - *also offered as MSci*

- **Supervisor:** Professor Stephen Rogerson
- **Project Site:** Department of Medicine, Royal Melbourne Hospital
- **Contact:** Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

Identifying antibody responses that protect against malaria and its complications is an important but elusive goal. This may be in part because total, rather than functional, antibody measures have been widely used. In the context of studies of malaria in pregnancy in Papua New Guinea and Malawi, you will learn novel assays developed in our laboratory to measure functional opsonising antibodies, and will apply this to the study of sample sets from pregnant women, integrating results of your laboratory measurements with extensive clinical data bases available on these women. The aim is to discover which antibody responses help clear malaria infection, and which responses prevent complications of malaria like anaemia and low birth weight.

This project is based at the Department of Medicine, Royal Melbourne Hospital, in the malaria laboratory. We have extensive experience in malaria parasite culture and analysis of immune responses. The lab comprises 4 post-docs, 2 research assistants, 4 PhD students and one Masters student as well as visiting scientists from all over the world.

Techniques will include, but not be limited to, malaria parasite and human monocyte cell culture; flow cytometry, and statistical analysis.

167. **Malaria in pregnancy: risk factors and consequences** - *also offered as MSci*

- **Supervisor:** Professor Stephen Rogerson
- **Project Site:** Department of Medicine, Royal Melbourne Hospital
- **Contact:** Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

Our laboratory is part of the Malaria In Pregnancy Consortium, which seeks to understand how to better treat and prevent this condition. As part of this activity, we have a project to understand some of the risk factors for malaria in pregnancy and its consequences. In this project, you will obtain and analyse data from a number of studies, to examine several clinically important questions: Does fetal gender alter the mother’s susceptibility to malaria? If malaria infection is detected only in the placenta, are these babies more likely to be born with low birth weight than uninfected babies? Are current antimalarial drugs adequate at preventing infection?

This project offers an introduction to statistical analysis of multiple data sets. Some basic knowledge of statistics would be useful for this project.
168. Malara immunity and treatment outcome - also offered as MSci
Supervisor: Professor Stephen Rogerson
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

Our laboratory is part of the Malaria in Pregnancy Consortium, which seeks to understand how best to treat and prevent malaria in pregnant women. A recently completed study in Malawi found that the malaria preventive drug sulphadoxine-pyrimethamine (Fansidar, or SP) is no longer protecting pregnant women from malaria, especially women in first pregnancy. In a previous cohort, we found that antibody levels were associated with treatment outcomes. Using samples from these women, you will measure antibodies in these women and relate the levels of antibodies to the outcomes of malaria treatment in this group.

Techniques will include parasite culture, flow cytometry, ELISAs and data analysis and training in basic medical statistics.

169. How changes in malaria exposure affect immunity - also offered as MSci
Supervisor: Professor Stephen Rogerson
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

We collected samples from pregnant Malawian women over 9 years, during which time malaria prevalence declined by over 70%. Such changes are likely to become more widespread as efforts to eliminate malaria gain momentum. Using these plasma samples, you will measure changes in antibody levels over time, to understand how the declines in transmission might translate into loss of protective antibody immunity. The insights from this study will be important to the malaria elimination efforts.

Techniques will include parasite culture, flow cytometry, ELISAs and data analysis and training in basic medical statistics.

170. The genetic epidemiology of the plasmodium vivax Duffy binding protein in Papua New Guinea - also offered as MSci
Supervisor: Professor John Reeder
Project Site: Malaria Genomic Epidemiology Group, Burnet Institute, 85 Commercial Road, Melbourne
Contact: Professor John Reeder E: jreeder@burnet.edu.au

Malaria infects 250 million people, resulting in 1 million deaths annually. The malaria parasites Plasmodium falciparum and Plasmodium vivax account for approximately 80% of the global malaria burden. Traditionally, infection with P. vivax was thought to be benign and self-limiting, and was not considered a research priority in comparison with the enormous burden of morbidity and mortality presented by P. falciparum. However, recent evidence has demonstrated that infection with P. vivax can also result in severe illness, and even death. It is also presenting a very stubborn obstacle in malaria elimination programmes. Presently, 2.85 billion people globally are at risk of P. vivax malaria infection however, research into P. vivax malaria has been relatively neglected and much remains unknown regarding the biology, pathogenesis and epidemiology of this parasite. Development of a vaccine targeting P. vivax lags far behind efforts to design a vaccine against P. falciparum. Essential for both vaccine development and effective malaria control is a thorough understanding of natural P. vivax population genetic structure and transmission dynamics.

The Duffy binding protein (DBP) is vital for P. vivax to invade human red blood cells, and is thus a leading vaccine candidate. Mapping and investigation of genetic diversity of the DBP amongst distinct global populations is required to establish the potential coverage of such a vaccine, and to help better understand the gene flow of the targets of immune selection in natural populations. This honours project will allow the student to join a larger NH&MRC funded project, rooted directly in improving knowledge to assist in evidence based control of malaria in Papua New Guinea. It will involve laboratory analysis and use of molecular epidemiology and population genetic techniques to investigate DBP diversity amongst P. vivax parasites already collected from distinct populations in PNG. The findings of this project will contribute to knowledge of global DBP diversity, and the suitability of DBP as a P. vivax vaccine candidate.

171. Identifying antigen targets of the acquired immune response during severe malaria - also offered as MSci
Supervisors: Dr Freya Fowkes, Professor James Beeson
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Dr Freya Fowkes T: 8506 2310 E: fowkes@burnet.edu.au

Malaria caused by Plasmodium falciparum is a leading cause of mortality and morbidity globally, particularly among young children. After repeated exposure, individuals develop effective immunity that controls blood-stage parasitaemia, thereby reducing clinical symptoms and life-threatening complications. Antibodies are important mediators of this
acquired immunity. The demonstration that naturally acquired antibodies are associated with protection from malaria is one of the criteria used to objectively prioritize malaria antigens for malaria vaccine development.

We have recently completed a case-control study of severe malaria in children living on the North coast of Papua New Guinea. Blood samples were taken from cases at the time of hospital admission and when the patient had recovered. For controls, samples were taken at the time of enrolment into the study. We would like to determine levels of antibodies to a range of malaria antigens by Enzyme-linked immunosorbent assay (ELISA), flow cytometry and functional antibody assays. The levels of these antibodies will then be related to clinical outcome using statistical analysis including regression techniques.

These findings will help us understand how immunity contributes to protection from severe malarial disease progression. The findings are valuable for advancing vaccine development by providing evidence supporting certain malaria antigens as targets of protective immunity in humans.

172. Investigating the acquisition and maintenance of immunity to malaria in infants and pregnant women - also offered as MSci

Supervisors: Dr Freya Fowkes, Professor James Beeson
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Dr Freya Fowkes T: 8506 2310 E: fowkes@burnet.edu.au

Immunity to infectious diseases during pregnancy remains an intriguing area with immunologic and physiologic changes during pregnancy rendering pregnant women to be more susceptible to, and more severely affected by, infectious diseases. Malaria is one of the most important pathogens in pregnancy and world-wide it is estimated that 50 million women living in malaria endemic areas become pregnant. Despite acquiring substantial pre-existing blood-stage immunity pregnant women typically develop higher parasite densities compared to non-pregnant adults, placental infection and associated complications. Very little is known about antibody acquisition, maintenance and boosting during or after gestation. Furthermore little is known about maternal transfer of antibodies and subsequent maternal antibody decay and infant antibody acquisition in infants born in malaria endemic areas. We have samples from several established longitudinal cohorts of pregnant women and infants that can address questions of antibody acquisition and maintenance through antibody assays and epidemiological analyses. Findings will help us understand how immunity develops and is maintained against infectious diseases.

173. Immunity, drug efficacy and the spread of anti-malarial drug resistance - also offered as MSci

Supervisors: Dr Freya Fowkes, Professor James Beeson
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Dr Freya Fowkes T: 8506 2310 E: fowkes@burnet.edu.au

Malaria caused by *Plasmodium falciparum* remains a major cause of morbidity and mortality globally. It is now extremely alarming that resistance to the first-line treatment for falciparum malaria, artemisinin-based combination therapy (ACT), has recently been reported in Asia. The assessment of antimalarial resistance is severely impeded by the presence of host immunity to malaria in patients living in malaria endemic regions. Naturally acquired blood-stage immunity increases the probability of parasite clearance independently of the drugs used, and regardless of their antimalarial resistance. However, the precise immunological targets and mechanisms which enhance antimalarial drug efficacy are unclear. The overall objective of this project is to identify and quantify immunological biomarkers that determine ACT therapeutic efficacy in a malaria endemic area of Thailand, both in the context of clinical disease and malaria transmission. Laboratory techniques will include ELISA and functional antibody assays. Findings will help assess to what extent immunity in populations can mask the presence of drug resistance and are vital for monitoring the global spread of drug resistance.

174. Is the impact of intermittent preventative treatment of malaria in infants (IPTi) dependent on iron status? - also offered as MSci

Supervisors: Dr Freya Fowkes, Professor James Beeson
Project Site: Burnet Institute, 85 Commercial Road, Melbourne
Contact: Dr Freya Fowkes T: 8506 2310 E: fowkes@burnet.edu.au

One approach to help reduce the burden of malaria caused by *Plasmodium falciparum* is intermittent preventive treatment (IPT), which involves periodic therapeutic doses of antimalarials to reduce the incidence of malaria and prevalence of anemia. IPT in infants (IPTi) has been shown to decrease malaria episodes by 22%–59% and substantially reduce the prevalence of anemia. However it is not known whether this population-level intervention is dependent on iron status and whether it is more effective in those that are iron replete compared to those that are iron deficient.

We have recently completed a randomised controlled trial of 1000 IPT in infants living in Papua New Guinea. The trial included two treatment arms and one placebo arm. Blood samples were taken at the time of IPT/placebo administration. In one of the treatment arms and the placebo arm we would like to measure markers of iron deficiency such as soluble
transferrin receptors and ferritin by Enzyme-linked immunosorbent assay (ELISA). The efficacy of IPTi in reducing malaria and anaemia will then be compared in those who are iron replete versus those who are iron deficient. The results of these studies can influence IPT policy in areas of high iron and nutritional deficiencies.

175. **What is the impact of malaria, anemia and iron deficiency during pregnancy on birth outcomes?** - also offered as MSci

**Supervisors:** Dr Freya Fowkes, Professor James Beeson  
**Project Site:** Burnet Institute, 85 Commercial Road, Melbourne  
**Contact:** Dr Freya Fowkes T: 8506 2310 E: fowkes@burnet.edu.au

World-wide, it is estimated that 50 million women living in malaria endemic areas become pregnant. The predominant consequence of malaria during pregnancy for the mother is maternal anaemia which can lead to maternal mortality. In infants, placental malaria is a leading cause of low birth weight (LBW) in infants resulting in 75,000–200,000 infant deaths each year. In these settings, LBW is more commonly due to fetal growth restriction rather than preterm delivery. However the link between anaemia and iron deficiency and these birth outcomes have yet to be elucidated.

We have completed a longitudinal study of malaria in pregnancy in 400 pregnant women attending antenatal care at Alexishafen Health Centre, Madang, Papua New Guinea. Blood samples were taken at enrolment, delivery and post-partum. In these samples we would like to measure markers of iron deficiency such as soluble transferrin receptors and ferritin by Enzyme-linked immunosorbent assay (ELISA). Malaria and haemoglobin data during pregnancy is already available as is data on birth outcomes and placental pathology. The association of malaria, anaemia and iron deficiency markers during pregnancy with respect to birth outcomes will then be assessed using statistical techniques including regression analysis.

**MEDICATION SAFETY**

176. **Testing of the Self-Administration of Medication (SAM) tool in a rehabilitation setting** - also offered as MSci

**Supervisors:** Professor Elizabeth Manias, Dr Snezana Kusljic  
**Project Site:** Melbourne School of Health Sciences, Royal Park Campus, Royal Melbourne Hospital  
**Contact:** Professor Elizabeth Manias T: 8344 9463 E: emanias@unimelb.edu.au, Dr Snezana Kusljic T: 8344 9428 E: skusljic@unimelb.edu.au

Self-administration of medications is the process whereby patients have the responsibility of taking their medications while in hospital rather than the nurse administering these medications. Self-administration practices can help patients to manage their medication regimens at home because they have practiced these routines before they go home. Unfortunately, determining the patients’ ability to self medicate has largely been an intuitive decision without the use of a tested tool. The self-administration of medication (SAM) tool was developed and validated as a means of helping health professionals to identify which patients would be capable of self-medication in hospital. The proposed work will extend previous research by examining the feasibility of introducing the SAM tool into current practice in a rehabilitation ward, by determining the benefits and barriers relating to its use, and by testing the utility and validity of the tool.

177. **Clinical audit of sedation assessment and sedative use in intubated and ventilated patients in intensive care (Melbourne Health)** - also offered as MSci

**Supervisor:** Professor Elizabeth Manias, Dr Snezana Kusljic  
**Project Site:** Melbourne School of Health Sciences, Walter Boas Building, Royal Melbourne Hospital, Health Information Services  
**Contact:** Professor Elizabeth Manias T: 8344 9463 E: emanias@unimelb.edu.au, Dr Snezana Kusljic T: 8344 9428 E: skusljic@unimelb.edu.au

**Project description:** An inadequate level of sedation in intubated and ventilated patients can lead to anxiety, accidental self extubation and physical harm. Excessive administration of sedation can cause prolonged mechanical ventilation, leading to an increased length of stay and complications relating to reduced motility. A retrospective clinical audit will be undertaken of 100 intubated and ventilated patients in intensive care across a 3-day period from initial intubation to determine the types of medications prescribed for sedation, the methods used for assessing the effectiveness of sedation, the sedation levels actually observed and changes made to medication in relation to changes in sedation levels obtained.
178. Shrinking the prostate – helping men to take their hormone tablets - also offered as MSci

Supervisors: Dr Snezana Kusljic, Professor Elizabeth Manias, Associate Professor Allison Williams
Project Site: Royal Melbourne Hospital, Melbourne School of Health Sciences
Contact: Dr Snezana Kusljic T: 8344 9428 E: skusljic@unimelb.edu.au

Project description: About 50% of men from 50-years-of-age show the first signs of prostate enlargement. An increase in prostate size compresses the bladder, obstructing urine flow. Urinary problems, such as urgency, bladder pain and incomplete emptying of urine, affect men’s quality-of-life and place an enormous burden onto society in terms of economical and emotional suffering. Use of hormone therapy reduces the size of the prostate and relieves urinary symptoms. However, in view of the sensitivity of this health problem, anecdotal evidence of men’s negative attitudes to taking hormone medications and the fact that symptoms take a while to improve once treatment commences, men often do not take their medications as prescribed. The aims of this project are to identify the psychosocial enablers and barriers affecting medication-taking behaviour in men with prostate enlargement and to develop guidelines to assist men with prostate enlargement to take their medications. About 20 men with prostate enlargement who attend the outpatient urology clinic of the Royal Melbourne Hospital will be invited to participate in an audio-taped or video-recorded interview. There will also be opportunities for men to express their concerns about the difficulties and barriers they experience with treatment. Guidelines will be developed for health professionals working with men with prostate enlargement to enhance medication-taking.

MOTOR CONTROL

179. Deep brain stimulation of the pedunculopontine nucleus for gait freezing in Parkinson’s disease

Supervisor: Dr Wesley Thevathasan (Universities of Melbourne and Oxford)
Project site: Melbourne Brain centre @ Royal Melbourne Hospital
Contact: Dr Wesley Thevathasan T: 9342 4412 E: wesley.thevathasan@nds.ox.ac.uk

Background and hypothesis: Deep brain stimulation is a rapidly developing treatment for neurological diseases which involves implantation of electrodes into specific brain regions to allow the targeted delivery of chronic electrical stimulation. Deep brain stimulation can have dramatic therapeutic effects, presumably by improving neuronal firing patterns. A new form of deep brain stimulation targeting a brainstem structure called the pedunculopontine nucleus (PPN) improves gait disturbance in Parkinson’s disease. However, the clinical benefits reported from PPN stimulation have been highly variable. In a successful collaboration between Oxford and Australia, we recently found a possible explanation for this variability– that small differences in stimulation location could substantially alter therapeutic outcomes. Specifically, we found evidence that the PPN in humans is topographically organised – with neuronal recordings only in the caudal (deepest) but not rostral nucleus correlating with locomotion. Thus we hypothesize that stimulation of the caudal PPN might be most beneficial for gait disturbance in Parkinson’s disease. This also concurs with our anecdotal clinical experience.

Methods: To test this hypothesis, we will assess patients with Parkinson’s disease implanted with PPN stimulators – comparing three conditions; off PPN stimulation, rostral PPN stimulation and caudal PPN stimulation. The measured variable will be gait freezing quantified by simple spatiotemporal gait analysis. Previous intraoperative neuronal recordings may help guide determination of caudal versus rostral PPN locations in individual patients. If successful, our results would direct neurosurgeons to target the caudal rather than the rostral PPN to achieve optimal results from stimulation.

Skills: Clinical assessment of patients with Parkinson’s disease, simple spatiotemporal gait analysis (e.g. step length, cadence), manipulation of deep brain stimulation, neuronal time series analysis (if available), statistical analysis (e.g. repeated measures ANOVA), manuscript preparation.

Note: this project is also listed under Parkinson’s Disease/Neurology

180. Analysis of factors involved in “freezing” of gait in Parkinson’s disease - also offered as MSci

Supervisors: A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan
Project site: Dept of Neurology, Royal Melbourne Hospital, City Campus
Contact: Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au. T: 9342 8448

Laboratory overview: the project will be conducted within the Dept of Neurology at Royal Melbourne Hospital.

Project overview: Parkinson’s disease (PD) is an inexorably progressive disorder associated with impaired execution of motor programmes. It is recognized that as the disorder progresses, patients develop difficulty with initiation of gait as
well as episodic freezing when walking in a straight line and particularly when approaching “obstacles” such as doorways. Ocular motor studies have demonstrated an increased error rate in the generation of motor programmes, in patients compared with control subjects, when confronted with a defined motor task in the presence of distracting stimuli. This is marked when the stimuli are in the periphery rather than more centrally located. It has been observed in patients walking in a straight line that gait can be improved by placing an obstacle in front of the patient or by placing a series of lines on the floor which must be stepped over. We hypothesise that this is an effect of focusing attention centrally to the exclusion of peripheral stimuli.

In this study we aim to perform pilot experiments looking at the effect of focusing attention artificially in control and patient subjects, by restricting the visual field, and thus exposure to peripheral stimulation, on gait initiation, walking in a straight line and when approaching apparent obstacles such as a doorway.

**Acquired skills:** Proper clinical evaluation of patients with PD; understanding of the Pathophysiology of deficit generation in PD.

*Note: this project is also listed under Parkinson’s Disease/Neurology*

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**181. Inhibitory motor errors in Parkinson’s disease contributing to deficit - also offered as MSci**

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<td>Project site:</td>
<td>Dept of Neurology, Royal Melbourne Hospital, City Campus</td>
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<tr>
<td>Contact:</td>
<td>Owen White, Dept of Neurology, RMH, Parkville. E: <a href="mailto:owen.white@mh.org.au">owen.white@mh.org.au</a>; Joanne Fielding, Dept of Neurology, RMH. E: <a href="mailto:joanne.fielding@monash.edu">joanne.fielding@monash.edu</a>; Bernard Yan, Dept of Neurology, RMH. E: <a href="mailto:Bernard.yan@mh.org.au">Bernard.yan@mh.org.au</a>. T: 9342 8448</td>
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**Laboratory overview:** The project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.

**Project overview:** Parkinson’s disease (PD) is a progressive degenerative disorder of the basal ganglia (BG) characterized by bradykinesia, rigidity and tremor. Clinically evident cognitive decline parallels the development of motor deficit. Motor deficit can be attributed to abnormalities of cognitive processing of afferent information and its integration with ongoing motor activity, the BG being intimately involved in conflict resolution between willed movement, reflexive movement, inhibition of unwanted movement and attentional processes.

The ocular motor system is the first motor system to develop in humans and is the prototypical motor control system. The limited degrees of freedom of movement and the relative lack of inertia provides a unique opportunity to examine cognitive processes involved in motor control, especially looking at working memory, attentional processes and inhibitory processes. We have previously noted that, during smooth pursuit, patients with PD make an increased number of inhibitory errors in the presence of peripheral, as opposed to more central, distractors presented during the performance of a prescribed task. This may have relevance to the generation of freezing and difficulty initiating movement observed in patients with PD.

This is a pilot study to extend the findings seen during pursuit to the saccadic system. We hypothesise that such failure of inhibition may be part of a generalized systems disorder, intimately involved in the generation of clinical deficits otherwise clinically observed in the somatic motor system. Eye movements will be recorded by standard techniques using video oculography. We will examine the generation of antisaccades (saccades to the equal and opposite position indicated by the presentation of a target after it is extinguished) and memory guided saccades in particular.

**Acquired skills:** Understanding of motor deficit and the clinical examination of patients with PD; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

*Note: this project is also listed under Parkinson’s Disease/Neurology*

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**182. Tendency to freeze in Parkinson’s disease: inhibitory errors contributing to deficit - also offered as MSci**

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<thead>
<tr>
<th>Supervisors:</th>
<th>A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan</th>
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<tr>
<td>Project site:</td>
<td>Dept of Neurology, Royal Melbourne Hospital, City Campus</td>
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<tr>
<td>Contact:</td>
<td>Owen White, Dept of Neurology, RMH, Parkville. E: <a href="mailto:owen.white@mh.org.au">owen.white@mh.org.au</a>; Joanne Fielding, Dept of Neurology, RMH. E: <a href="mailto:joanne.fielding@monash.edu">joanne.fielding@monash.edu</a>; Bernard Yan, Dept of Neurology, RMH. E: <a href="mailto:Bernard.yan@mh.org.au">Bernard.yan@mh.org.au</a>. T: 9342 8448</td>
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**Laboratory overview:** The project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.
**Project overview:** Parkinson’s disease (BG) is a progressive degenerative disorder of the basal ganglia (BG) characterized by bradykinesia, rigidity and tremor. Clinically evident cognitive decline parallels the development of motor deficit. Motor deficit can be attributed to abnormalities of cognitive processing of afferent information and its integration with ongoing motor activity, the BG being intimately involved in conflict resolution between willed movement, reflexive movement, inhibition of unwanted movement and attentional processes. It has been observed that patients with moderate disease may freeze as they approach a doorway, or some other obstacle, and then have difficulty reinitiating gait.

We hypothesise that this may be secondary to impaired inhibition of visual stimuli as they move into the peripheral visual field, resulting in impaired conflict resolution between voluntary motor activity and reflex motor activity.

In this pilot study, patients will undertake prescribed ocular motor tasks while eye movements are recorded using video oculography. Distraction, a “door equivalent”, will be provided by a rectangle of LEDs which will be illuminated at varying positions between the subject and the target screen. We would anticipate that there will be more errors, and possibly difficulties with initiation of saccades, in patients, as the “door equivalent” comes closer to the patient and is further from the target.

**Acquired skills:** Understanding of motor deficit and the clinical examination of patients with PD; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

**Note:** this project is also listed under Parkinson’s Disease/Neurology

183. Ocular motor studies in the assessment of mild cognitive deficit in patients with microvascular cerebral disease  - also offered as MSci

**Supervisors:**  A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan
**Project site:**  Dept of Neurology, Royal Melbourne Hospital, City Campus
**Contact:**  Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au. T: 9342 8448

**Laboratory overview:** the project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.

**Project overview:** The ocular motor system is the first motor system to develop in humans. Generation of movement involves planning, reflex movements, integration of sensory information with ongoing activity and inhibition of unwanted movement. Conservation of neural resources predicts that where possible, established circuitry and neural systems are used by like systems. There is evidence that attentional and inhibitory processes develop with the establishment of ocular motor control and subsequently these networks are utilized by somatic motor systems. The circuitry involved in attentional processes, inhibitory processes and working memory ramify widely throughout the cerebral hemispheres and is well defined. As such, ocular motor recordings, using conventional video occulography, may prove uniquely sensitive to systems abnormalities produced by multi lesion disease such as occurs with microvascular disease in hypertension and diabetes.

In this pilot study we aim to establish the sensitivity of such recordings in a range of patients with microvascular disease, compared with conventional neuropsychological studies, and compare them with age matched control studies.

**Acquired skills:** Understanding of cognitive function testing; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

**Note:** this project is also listed under Cerebrovascular

**MULTIPLE SCLEROSIS/NEUROLOGY**

184. How do Multiple Sclerosis Risk Genes work? - also offered as MSci

**Supervisors:**  A/Prof Helmut Butzkueven and Dr Melissa Gresle
**Project Site:**  Department of Medicine, Royal Melbourne Hospital, Royal Parade, Parkville
**Contact:**  Helmut Butzkueven  E: butz@unimelb.edu.au

In the last three years, around 30 risk genotypes for MS have been confirmed. Many of these carry small risks (eg increasing the risk of getting MS by between 10 and 30%), and many of the risk genotypes are actually fairly common in the non-MS population. One major hypothesis explaining these results is that, in MS patients, the risk genotypes are associated with altered expression of the relevant gene. We are conducting an experiment in which people with early MS
and healthy controls are genotyped for the MS risk genotypes and their immune cells are sorted into different subsets (B-cells, T-cells, NK-cells, and monocytes) and their RNA is extracted.

The major aim of this project will be to determine if risk genes alter expression of gene messenger RNA in MS, if this effect does/does not occur in healthy people carrying the same genotype, and, if positive, determine if expression of the relevant protein of interest is also altered in specific immune cell subtypes from patients carrying the risk genotype. We will then progress to genotype-specific functional assessments in human immune cells (functions such as migration, antigen presentation or cytokine production).

We have already identified several potential candidates and will tailor the specific project to the student’s interest.

During this project, you will become familiar with MACS and FACS cell sorting, RNA extraction, genotyping, and will be introduced to relevant statistical and bioinformatic techniques. The project is likely to involve short periods of travel to Hobart, Tasmania to work with our collaborating bioinformaticians.

Feasibility: The cell collection is well under way so that there will be no delays in relation to data availability or ethics applications.

NEPHROLOGY

185. **Mechanisms of Kidney Fibrosis: The Role of Hypoxia**

*Supervisor: Dr Tim Hewitson*
*Project Site: Department of Nephrology, The Royal Melbourne Hospital*
*Contact: Dr Tim Hewitson  T: 9342 7726  E: tim.hewitson@mh.org.au*

Although renal disease manifests itself in many different forms, scarring of the kidney is the final common pathway. In each case injury triggers activation of matrix producing cells, resulting in the accumulation of excess scar tissue (fibrosis), and loss of organ function.

Cells utilize oxygen to metabolise glucose to generate ATP which fuels most active cellular processes. Following injury, vascular damage often occurs resulting in low oxygen tension (hypoxia) which may be exacerbated by the rapid influx of inflammatory and mesenchymal cells with high metabolic demands for oxygen. The kidney is particularly prone to hypoxia suggesting that it may be a major factor contributing to progressive fibrosis. This question is made even more compelling by the realisation that there has been a steady increase in metabolic diseases such as diabetes and obesity, diseases known to damage renal blood vessels.

This study will use techniques in histology, immunohistochemistry and cell culture to examine the role of hypoxia in renal disease. The relationship between injury, hypoxia, and cell kinetics as well as the chemical signals involved will be studied.

It is hoped that results of this study will lead to a better understanding of the cell biology of progressive renal failure in general.

186. **Gene variation in collagen type IV in people of different races**

*Supervisor: Professor Judy Savige and Dr Yanyan Wang*
*Project Site: The Northern Hospital, 185 Cooper St., Epping*
*Contact: Professor Judy Savige  T: 03 8405 8823  E: judy.savige@nh.org.au*

Sequencing of the collagen IV genes to demonstrate normal variants in different races. The aim of this project is to make it easier for genetic testing laboratories to distinguish between mutations and normal variants and to populate our genetic databases.

**Techniques to be used:** DNA extraction, PCR amplification; HRM screening and sequencing

NEUROPSYCHIATRY AND STRESS BIOLOGY

187. **Functional disconnections and the pathophysiology of psychosis - also offered as MSci**

*Supervisors: Dr Nigel Jones and Prof Terence J O’Brien.*
*Project Site: Department of Medicine*
*Contact: Dr Nigel Jones  T: 9035 6402  E: ncjones@unimelb.edu.au*

Functional disconnections in cortico-thalamo-cortical (CTC) systems, the neuronal circuits of attention, cognition and perception, are thought to underlie dysfunctions of conscious integration such as those seen in schizophrenia. More than 80% of the neurons that make up the CTC systems are glutamatergic. There is considerable evidence to suggest that NMDA-type glutamate receptors are implicated in the pathophysiology of schizophrenia. Non-competitive NMDA
receptor antagonists (PCP, ketamine, MK-801), at subanaesthetic doses, induce cognition impairment, schizophreniform psychosis, hallucinations, and exacerbate both positive and negative symptoms in schizophrenic patients. In rodents, ketamine produces a wide spectrum of abnormal behaviour relevant to schizophrenia. The neuronal mechanisms underlying transient disruption in NMDA receptor function remain to be determined. CTC circuits generate coherent synchronized gamma frequency (30-80 Hz) oscillations during conscious brain operations. Disruption of cognition-related coherences of gamma oscillations between cortical areas is a major functional abnormality in schizophrenic patients.

This project will explore the hypothesis that aberrant cortical gamma frequency activity induced by ketamine mediates alterations in behavioural activity, thereby linking NMDA-mediated dysfunction of neuronal activity to schizophrenic-like behaviour.

**Research plan:** Rats are surgically implanted with recording electrodes and connected to a computer facilitating measurement of the EEG and analysis of the effects of drugs on cortical brain rhythms in the gamma frequency. The resultant changes in cortical rhythms will be concurrently measured with either sensorimotor gating or working memory to establish a temporal and magnitudinal association between disruptions to gamma oscillations and behavior.

**Skills:** small animal surgery, EEG measurement, behavioural analysis.

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**188. Genomic Biomarker Discovery for Major Psychiatric Disorders**

**Supervisors:** Dr. Chad Bousman, Professor Ian Everall

**Project Site:** Department of Psychiatry, Melbourne Brain Centre

**Contact:** Dr. Chad Bousman; T: 03 9035 8844 E: cbousman@unimelb.edu.au

**Description:** The goal of this project is to identify genes and genetic pathways that may serve as biomarkers for major psychiatric disorders (e.g. schizophrenia, bipolar, depression). Identification of biomarkers for major psychiatric disorders has the potential to revolutionize the treatment of these disorders and improve prognosis. This would in turn have a profound effect on global public health by standardizing the process of primary and differential diagnosis, which presently involves considerable time, effort, and uncertainty.

This particular project will involve examination and comparison of gene expression profiles from patients with schizophrenia or bipolar disorder with that of control participants.

**Skills:** The project will involve extensive training and develop essential skills in the following areas: (1) biomarker discovery techniques, (2) use of specialized statistical tools for biomarker discovery, (3) identification of dysregulated genes and genetic pathways, and (4) biological basis of major psychiatric disorders.

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**189. Investigation of the expression and function of selenium binding protein 1 in schizophrenia - also offered as MSci**

**Supervisors:** Doctor Tammie Money, Doctor Gursharan Chana and Professor Ian Everall

**Project Site:** Melbourne Brain Centre, Level 4, Royal Melbourne Hospital City Campus, Parkville

**Contact:** Dr. Tammie Money E: ttmoney@unimelb.edu.au T: 8344 4520

**Background:** Previous studies from our laboratory have identified a potential biomarker of schizophrenia that may aid in diagnosis. Selenium binding protein 1 (SELENBP1) gene expression is significantly upregulated in schizophrenia from studies in both brain and blood of independent cohorts. However, it is not clear whether this increase in expression results in an increase at the protein level and whether an increase in protein expression is related to changes in the synapse in schizophrenia. The aim of this project is to characterise SELENBP1 protein expression in schizophrenia and identify potential mechanisms of an increase in expression. The results of this project will identify potential consequences of an increase in SELENBP1 and its contribution to the pathophysiology of schizophrenia.

**Aims:**

1. To investigate the cellular distribution and protein expression levels of SELENBP1

   Immunohistochemistry will be performed in paraffin-embedded human brain tissue from Brodmann’s areas 8 (the rostral supplementary area) and 22 (the superior temporal gyrus). In addition to confirming the cellular localisation of SELENBP1, we will also assess whether the somal size and cellular density is different between positively stained and negatively stained cells.

2. To identify the mechanisms of increased SELENBP1 expression in schizophrenia

   The expression of SELENBP1 will be increased using cell culture studies with human-derived neuronal cells. Following this, we will quantify the effect of increased SELENBP1 expression on neuronal markers of functioning as well as a neurotrophic marker, which have been shown to be strongly associated with schizophrenia

**Skills:** This project will involve training in histology, immunohistochemistry, stereology, cell culture, quantitative polymerase chain reaction (qPCR) and statistical analysis.
190. Temporal lobe epilepsy, the HPA axis and depression - also offered as MSci  
**Supervisor:** Dr Mike Salzberg, Prof Terence O’Brien  
**Project Site:** Department of Psychiatry and Medicine  
**Contact:** Dr Mike Salzberg T: 0417357205 E: michael.salzberg@svhm.org.au  

**Brief Summary:** The key structures involved in mesial temporal lobe epilepsy – the hippocampus and amygdala – are critical components in the central regulation of the HPA axis. The implications of this have hardly been studied at all. Does the HPA axis function normally when someone has mesial temporal sclerosis (the usual pathology underlying TLE)? What happens to HPA axis function when a temporal lobe is excised to treat intractable TLE (temporal lobectomy)? There are good reasons to think the answers to these questions are very important for several reasons, e.g., glucocorticoids and stress have been shown in animal models of this kind of epilepsy to aggravate the disorder, to speed up its rate of development.  

**Project:** We have a small preliminary study in progress, testing HPA function before and after temporal lobectomy. We’re using the dex/CRH test, doing this about 2 weeks before and at 6 and 12 weeks after surgery. We’re doing the same protocol with surgical control patients, having elective brain surgery for nonepilepsy conditions remote from the temporal lobe.  

We think temporal lobectomy disinhibits the HPA axis, which may help explain the transient mood disturbance that occurs in temporal lobectomy patients in the early months following surgery.  

This study will interest students interested in a topic that involves basic neuroscience and neuroendocrinology but also with a very immediate clinical relevance. It will involve contact with patients – in recruitment, obtaining informed consent, administering questionnaires and helping administer the dex/CRH test (a two hour procedure). It will also involve data analysis and writing-up in the usual way.  

191. Does stress contribute to epilepsy? - also offered as MSci  
**Supervisor:** Dr Nigel Jones and Prof Terence O’Brien  
**Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville  
**Contact:** Dr Nigel Jones T: 9035 6402 E: njones@unimelb.edu.au  

- Chronic stress is strongly linked to the development of psychiatric disturbances, such as depression and anxiety disorders. Interestingly, these disorders are prevalent in a high proportion of people suffering from epilepsy.  
- Recent literature suggests that environmental exposures such as stress may also contribute to the development of epilepsy. This project aims to investigate this hypothesis, with a parallel focus on anxiety and depression-like behaviour.  
- Using rat models, this study will determine whether exposure to repeated stressful situations leads to a vulnerability to limbic epilepsy. It will also study whether psychiatric disturbances are enhanced in subjects who have experienced the stress.  
- The second stage of the project will investigate molecular and plasticity changes which occur after epilepsy to determine whether the stress can influence such parameters as stress receptor expression and neurogenesis.  

**Skills:** Small animal handling and neurosurgery (electrode implantations), neurobehavioural testing and analysis, post-mortem stereology.  

192. EEG assessment of high frequency oscillatory activity in a mouse model of Autism - also offered as MSci  
**Supervisors:** Dr Elisa Hill, Dr Nigel Jones, Professor Terence O’Brien.  
**Project Site:** Department of Medicine, MBC Neurosciences Building, Parkville.  
**Contact:** Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au, Dr Nigel Jones Tel: 9035 6402, email: njones@unimelb.edu.au, Prof Terence O’Brien: obrientj@unimelb.edu.au  

**Aims:** This project will investigate high frequency (gamma) brain rhythms in NL3 mice using:  
- Baseline EEG  
- Following administration of low dose ketamine  
- EEG during memory task  
- EEG during behavioural tasks including locomotor, anxiety tests.  

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder in which the vast majority of patients show altered sensory perception. A small number of patients show extraordinary “savant” abilities in restricted areas. ASD patients demonstrate altered EEG in the gamma (30 - 80 Hz) range, frequencies which have been correlated with sensory processing function. In addition, up to 30% of ASD patients also experience seizures. NL3 mice express a mutation in the Neuronalin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as enhanced spatial learning. This project will assess for alterations in baseline (no task) EEG in addition to
EEG changes during behavioural tasks including locomotor, anxiety tests and learning memory tasks, and following administration of a low dose of the NMDA receptor antagonist ketamine (induces increases in EEG gamma activity and psychotic like behaviour).

**Skills:** Surgery for EEG in adult mice. Analysis for high frequency (gamma) oscillatory activity from EEG recordings using matlab software. Behavioural and animal handling skills.

### 193. Investigating the stress response in a mouse model of autism

**Supervisors:** Dr Elisa Hill, Assoc. Professor Anthony Hannan.

**Project Site:** Howard Florey Institute, University of Melbourne

**Contact:** Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au, Assoc. Prof Anthony Hannan Email: aih@florey.edu.au

**Aims of Project:** This project will investigate behavioural aspects and markers of stress in the NL3 mouse model of autism using:

- Anxiety and stress paradigms
- Cortisol and c-fos levels with labelling for neuronal markers.
- Ultrasonic vocalisation pattern analysis

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder characterised by impairments in social interactions, communication, and repetitive behaviour. NL3 mice express a mutation in the Neuroligin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as impairments in social behaviour.

In addition to altered sociability, these mice demonstrate an aggressive phenotype and one aim of this project is to investigate possible links with an altered stress response using a cortisol assay for stress. To investigate the possibility that specific neuron types are upregulated in the stress response, a c-fos assay will be carried out following stress (isolation housing and aggression test) with double labelling immunocytochemistry for neuronal subtypes (GAD and neu-N). There is also scope to assess mice for altered communication patterns by recording ultrasonic vocalisation patterns.

**Skills:** Behavioural and animal handling skills. Vocalisation pattern data acquisition and analysis. Cortisol assay for stress and c-fos assay for neuronal activity.

### 194. Investigating effects of cannabinoids on sensorimotor gating in a mouse model of autism

**Supervisors:** Dr Dan Malone (Monash Institute of Pharmaceutical Sciences) and Dr Elisa L Hill (Dept of Medicine, University of Melbourne).

**Project Site:** Monash Institute of Pharmaceutical Sciences, Royal Pde, Parkville 3050

**Contact:** Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au

Dr Dan Malone Tel:99039576 Dan.malone@monash.edu

**Aim:** to investigate the effects of pharmacological agents that modulate cannabinoid pathways (CB agonists and antagonists) on sensorimotor gating in a mouse model of autism.

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder in which the vast majority of patients show altered sensory perception. ASD patients demonstrate deficits in sensory motor gating compared to controls. NL3 mice express a mutation in the Neuroligin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as deficits in social behaviour including decreased sociability and increased aggression. While the NL3 mutation is known to be located at the postsynapse, the increase in frequency of inhibitory synaptic events suggests a change in presynaptic release of neurotransmitter. Cannabinoids serve as retrograde inhibitory messengers (ie they travel in the reverse direction across synapses) in the brain to inhibit neuronal function and transmitter release. A disruption in this pathway could result in increased inhibition as reported in the NL3 mice and contribute to the observed behavioural phenotype.

In this project we aim to use the non-invasive PPI test in the NL3 mouse model of autism to assess for alterations in sensorimotor processing. Based on published data demonstrating altered cortical inhibition in these mice, we will also investigate effects of modulating the inhibitory cannabinoid pathway using pharmacological agents.

**Skills:** Behavioural and animal handling skills. Data acquisition and analysis using the Pre Pulse inhibition test for sensorimotor gating. Evaluation of behavioural effects of cannabinoids in NL3 mice and controls.
195. **Amygdala volume and emotion recognition in adolescents at ultra high risk of psychosis: A structural MRI study** - also offered as MSci  
Supervisors: Dr Cali Bartholomeusz, Dr Sarah Whittle, A/Prof G. Paul Amminger.  
Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience facility, Level 2-3 Alan Gilbert Building.  
Contact details: Cali Bartholomeusz Ph: 8344 1878, Email: barc@unimelb.edu.au  
**Description of project:** The study of young individuals at increased risk of psychosis has become a promising approach to unravelling developmental mechanisms involved in the aetiology of psychotic illnesses such as schizophrenia. The ability to recognize others’ emotional states is essential for social cognition to guide social functioning and behaviour. Problems in the perception of emotional material, in particular deficits in the recognition of negative stimuli, have been demonstrated in schizophrenia as well as in clinical high-risk samples.

Emotions are perceived bimodal by the ear and the eye. Research indicates that there are differences in the effectiveness with which the face and the voice convey different emotions. For example, happiness is the easiest facial expression to recognize, but when it comes to expression in the voice, happiness is harder to distinguish from other emotions. The amygdala is an anatomical region of the brain that has been associated with emotion perception, and more specifically, with the recognition of negative emotional expressions. Structural and functional abnormalities of the amygdala and the fusiform gyrus, and impaired facial emotion recognition, have been both reported in schizophrenia and ultra high-risk states. Hence, these abnormalities may underlie the dysfunction in facial and vocal emotion recognition. Consistent with this hypothesis, we have recently shown both, a deficit in the recognition of facial expressions of fear and sadness, and a deficit in the recognition of anger in voices in high-risk individuals and in people with first-episode schizophrenia.

The aim of the proposed study is to investigate the relationship between amygdala volume and emotion recognition in a sample of adolescents at clinical high-risk for schizophrenia. The student will be responsible for tracing the amygdala using MRI scans that have been previously collected, and will also be involved in data analysis.

196. **Orbitofrontal Cortex Sulcogyral Patterns in Adolescents born Premature** - also offered as MSci  
Supervisors: Dr Cali Bartholomeusz, Dr Deanne Thompson and Dr Jeanie Cheong.  
Project Site: Melbourne Neuropsychiatry Centre, Murdoch Children’s Research Institute and the Royal Women’s Hospital.  
Contact details: Cali Bartholomeusz; T: 8344 1878 E: barc@unimelb.edu.au  
This project aims to classify the brain folding patterns of the orbitofrontal cortex (OFC) in adolescents who were born preterm or of extremely low birth weight. Findings from this project may have implications for identification of a possible vulnerability marker for development of certain mental illnesses and/or poor functional outcome in early adult life.

The orbitofrontal cortex (OFC) is a region known to be involved in not only somatosensory and emotion processing but various higher-order cognitive functions. In particular, those associated with reward and punishment, moral judgement, decision-making and social cognition. Dysfunction and morphological abnormalities of the OFC have long been associated with schizophrenia pathology, obsessive compulsive disorder, and more recently with mood disorders. However, researchers have only just begun to characterize the nature of such OFC irregularities and the subsequent implications for various higher-order cognitive functions. In particular begins from the 16th week of gestation, starting with the olfactory sulcus (OS) and gradually extending laterally and anteriorly, with the medial orbital sulcus beginning to appear around week 28, and the lateral orbital sulcus around week 32. Thus, OFC sulci primarily develop during weeks 30–40. Babies born before week 31 have been found to display reduced OFC sulcal depth in comparison to healthy controls. To date no study has investigated variations in the typical OFC ‘H-shaped’ sulcogyrar pattern of individuals born premature.

This project would involve an honours student learning the OFC Pattern Type classification technique and applying this to a large sample of MRI scans that have already been collected. The student would then analyse this data to see whether: 1) Pattern Type distribution is altered in individuals born preterm, and 2) whether certain factors, such as parental socio-economic status and presence of mental illness, are related to OFC Pattern Type.

197. **Mapping the human brain connectome in healthy and psychiatric populations** - also offered as MSci  
Supervisors: Dr Alex Fornito, Dr Andrew Zalesky, Dr Ben Harrison, A/Prof. Murat Yücel, Prof Christos Pantelis  
Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience Facility, Alan Gilbert Building.  
Contact: Dr Alex Fornito T: 8344 1876. E: fornitoa@unimelb.edu.au  
The human brain is perhaps the most complex network found in nature, comprising $10^{11}$ neurons connected by $10^{15}$ axonal fibers. In recent years, non-invasive neuroimaging techniques, particularly magnetic resonance imaging (MRI),
have occupied a central role in attempts to map this connectivity web, termed the brain ‘connectome’, at various spatial and temporal scales. Students working in this project will have the opportunity to use these exciting new techniques to address a variety of important questions concerning the structure and function of the human brain connectome in healthy individuals and people with psychiatric disorders. Current project topics include:

- brain network dysfunction in schizophrenia;
- the effect of chronic cannabis use on brain functional connectivity;
- brain network dysfunction obsessive-compulsive disorder;
- the effect of chronic opiate use on brain functional connectivity;
- genetic influences on human cortico-striatal networks; and
- novel statistical methods for analyzing brain networks.

Students will gain a variety of skills, including developing their understanding of the neurobiological basis of psychiatric illness, the application of statistical models to neuroimaging data, and techniques for analyzing large-scale brain networks.

**198. Meta-analysis of functional brain imaging studies of executive functioning and emotional processing in schizophrenia and mood disorders**

**Supervisors:** Dr Emre Bora, Professor Christos Pantelis

**Project Site:** Melbourne Neuropsychiatry Centre, Alan Gilbert Building, University of Melbourne

**Contact:** Dr Emre Bora  E: ibora@unimelb.edu.au  T: 8345 5611

**Overview:** There is increasing evidence suggesting that dysfunctional neural networks play a role in the emergence of symptoms in schizophrenia and mood disorders, as well as cognitive and emotional difficulties in these patients. Functional MRI is a sophisticated method that can help us investigate and compare neural network abnormalities in schizophrenia and mood disorders (including major depression and bipolar disorder).

**Aims:** To conduct a comparative meta-analytical review of functional brain imaging abnormalities in schizophrenia, bipolar disorder and major depression in comparison to healthy controls. The student will be responsible for literature review, data-extraction, and preparation of the database and will also be involved in data-analysis. The student will develop their understanding of the dysfunctional networks in schizophrenia and mood disorders and will gain a variety of skills for conducting systematic reviews and meta-analyses.

**Methods:** No patient will be recruited as the meta-analysis is based on published reports. Standard and coordinate based statistical methods will be used.

**199. Cognitive impairment and neuroimaging abnormalities in individuals at clinical and genetic high risk for schizophrenia**

**Supervisors:** Dr Emre Bora, Professor Christos Pantelis

**Location:** Melbourne Neuropsychiatry Centre, Alan Gilbert Building, University of Melbourne

**Contact:** Dr Emre Bora  E: ibora@unimelb.edu.au  T: 8345 5611

**Overview:** Schizophrenia has been associated with cognitive dysfunction and both structural and functional brain imaging abnormalities. It has been hypothesized that these abnormalities are related to the aetiology of this severe mental disorder. However, most of these findings have been reported in chronic patients and it has been argued that these abnormalities might be secondary effects following the onset and progression of the illness. It is argued that these neurobiological changes are related to factors like medication, stress and changes in lifestyle rather than representing a marker of susceptibility to schizophrenia. Therefore, it is important to investigate whether similar abnormalities exist before the onset of the illness in individuals who have an increased risk for the development of schizophrenia. Recent studies have examined individuals with a genetic (family history) or clinical (at risk mental states) high risk for psychosis and schizophrenia.

**Aims:** To conduct a meta-analytical review of cognitive and brain imaging abnormalities in genetic-high-risk and clinical-high-risk subjects in comparison to healthy controls. The student will be responsible for undertaking a thorough literature review, data-extraction, preparation of the database, and will also be involved in data-analysis. The student will develop their understanding of cognitive and brain imaging endophenotypes of schizophrenia and related disorders and will gain a variety of skills for conducting systematic reviews and meta-analyses.

**Methods:** No patient will be recruited as the meta-analysis is based on published reports. Standard and coordinate based statistical methods in brain imaging (region-of-interest and whole brain) and cognitive functions will be used.
200. Olfactory sensitivity in psychosis - also offered as MSci
Supervisors: Dr Debra Foley, A/Prof Warrick Brewer, Prof Christos Pantelis
Melbourne Neuropsychiatry Centre, Orygen Research Centre
Project Site: Melbourne Neuropsychiatry Centre, Sunshine Hospital.
176 Furlong Rd, St Albans
Contact: Dr Debra Foley E: dfoley@unimelb.edu.au; Prof Christos Pantelis E cpant@unimelb.edu.au;
Project description: Reduced olfactory sensitivity for some unique odours is found in some people with schizophrenia. The aim of this project is to test sensitivity to two smells based on a synthesis of the genetic literature for schizophrenia and olfaction. Candidate genes for schizophrenia that map to the same chromosome band location as functional odorant receptors will be examined. We aim to test if these smells discriminate patients with chronic schizophrenia from matched controls. The relationship of sensitivity for candidate odours to olfactory identification ability may reveal vulnerability for negative symptoms of schizophrenia.

201. How does Age of Illness Onset affect severity and extent of MRI Brain Structural Abnormalities in Schizophrenia - also offered as MSci
Supervisors: Prof Christos Pantelis, Dr Alex Fornito, Melbourne Neuropsychiatry Centre
Project Site: Melbourne Neuropsychiatry Centre, National Neuroscience Facility (NNF), Alan Gilbert Building, Level 3, 161 Barry Street, Carlton South, Vic 3053
Contact: Prof Christos Pantelis E: cpant@unimelb.edu.au; Dr Alex Fornito T: 8344 1876. E: fornitoa@unimelb.edu.au
Project description: Research at the Melbourne Neuropsychiatry Centre has demonstrated that the onset of schizophrenia is characterised by dynamic brain changes that begin prior to illness onset and progress throughout the course of the illness, particularly in frontal and temporal lobe regions. We have also demonstrated that the onset of schizophrenia is associated with pronounced cognitive changes that parallel clinical symptoms, and that these changes indicate that onset of the disease may 'arrest' normal brain maturational processes. Given that frontal and temporal brain regions continue to develop into the second and third decades of life, when the onset of schizophrenia is most common, we hypothesise that the timing of illness onset is a critical factor in determining the nature and extent of these brain changes. Specifically, we predict that later illness onset will be associated with relatively preserved neuroanatomy and cognition, due to reduced maturational disruption. By addressing this question the proposed applicant will specifically investigate issues related to normal brain maturation, schizophrenia-specific changes, and the interaction between the two. The research will be conducted using magnetic resonance images already acquired as part of the Australian Schizophrenia Research Bank together with computerised techniques to delineate differences in brain structure and cognition.

202. Stem Cell based modelling of Human Neurological Disorders: Towards Drug Discovery for improved Therapeutics - also offered as MSci
Supervisors: Assoc. Prof. Jeremy M Crook, Dr Nao Kobayashi, Prof. Stan Skafidas, Prof. Christos Pantelis, Prof. Ian Everall
Project Site: Centre for Neural Engineering, Melbourne Neuropsychiatry Centre, and Department of Psychiatry, The University of Melbourne
Contact: Prof Jeremy Crook T: 03 9035 3647 E: jcrook@unimelb.edu.au
Stem cells represent useful tools for modelling development and disease. For example, induced pluripotent stem (iPS) cells carrying or modified to carry defective genes can be investigated in vitro to understand latent molecular mechanisms and disease characteristics. Once characterised, cell lines can be employed for drug screening towards developing novel pharmacological therapies.

We have a number of Honours projects available for clinical or science graduates involving human brain derived neural progenitor cells (NPCs) and iPS cells. Disease models of interest include schizophrenia, autism and other disorders of brain development. Successful candidates will have the opportunity to receive training in somatic cell reprogramming for iPS cell derivation, culture and differentiation and will develop experience in methods of RNA interference, and molecular and functional assays for in vitro characterisation. We anticipate studies will result in better understanding disease aetiology, pathology and the development of new medicines for improved therapeutics.

203. Cholinergic muscarinic receptor expression in the orbitofrontal cortex in mood disorders
Supervisors: Dr Andrew Gibbons and Professor Brian Dean
Project Site: The Rebecca L Cooper Laboratories, The Mental Health Research Institute of Victoria
Contact: Dr Andrew Gibbons T: 9389 2990 E: a.gibbons@mhri.edu.au
Project: Mood disorders are amongst the most prevalent psychiatric disorders in society. However, the underlying cause of these disorders remains elusive. Pharmacological evidence has long supported a role for the cholinergic system in
mediating the depressive symptoms seen in major depression and bipolar disorder. However, only recently have molecular studies suggested that abnormal signalling through the cholinergic muscarinic receptors is central to the cholinergic dysfunction in mood disorders. Specifically the muscarinic M2 receptor appears to play a key role. We have recently reported decreased binding of $[^3H]$AFDX-384, a muscarinic M2 / M4 receptor selective antagonist, in the dorsolateral prefrontal cortex of subjects with major depression and subjects with bipolar disorder, suggesting a decrease in M2/M4 receptor expression. We have also reported a decrease in the binding of $[^3H]$4-DAMP, a muscarinic M3 receptor selective antagonist in the frontal pole of people with bipolar disorder.

We are interested in finding out whether muscarinic receptor expression is altered in other brain regions from people with mood disorders. The orbitofrontal cortex is involved in emotional response and is thought to be affected in the pathology of mood disorders. This study will use the muscarinic receptor selective radioligand antagonists $[^3H]AFDX-384$ (M2/M4), $[^3H]$4-DAMP (M3) and $[^3H]$pirenzepine (M1) to examine the expression of muscarinic receptors in the Brodmann Area 11, part of the orbitofrontal cortex, from post-mortem subjects diagnosed with major depression and bipolar disorder and matched control subjects. During this project the student will develop skills in protein biochemistry as well as learn protocols for the appropriate handling of human post-mortem tissue.

### 204. MRI volumetry and shape analysis in frontotemporal dementia and schizophrenia
**Supervisors:** Dr Dennis Velakoulis and Dr Mark Walterfang  
**Project Site:** Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital  
**Contact:** Dr Dennis Velakoulis  
T: 93428750  
E: dennis.velakoulis@mh.org.au

**Background:** It has been well recognised for over a century that some patients with schizophrenia develop a dementia but the nature of this dementia has remained unclear. Recent clinical, neuropathological and genetic studies have identified a previously unrecognised association between chronic schizophrenia and frontotemporal dementia. This project aims to examine whether the volume and shape changes identified in schizophrenia are quantitatively and qualitatively similar to patients with a frontotemporal dementia. In addition to demographic and diagnostic information a subset of the subjects have neuropsychological and bedside screening cognitive testing which can be correlated with brain structural volumes and shape.

**Aims:** To estimate and compare brain structure volume and shape in an existing database of MRI images of patients with chronic schizophrenia and frontotemporal dementia compared to control subjects.

**Methods:** Specific regions of interest to examine would include:
- Frontal and temporal lobes  
- Orbitofrontal / dorsolateral / medial frontal cortex  
- Hippocampus  
- Insula cortex  
- Superior temporal gyrus

Depending on the region of interest the project would require the learning of methods for analysing the region and developing a reliable method for this assessment.

**Outcome:** To assess and compare the nature and pattern of brain changes in chronic schizophrenia and FTD.

### 205. Characterisation of physiological stress responses in patients with depression and epilepsy - also offered as MSci
**Supervisors:** Dr Dennis Velakoulis, Dr Chris Turnbull and Professor Terry O'Brien  
**Project Site:** Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital and Alan Gilbert Building, University of Melbourne  
**Contact:** Dr Dennis Velakoulis  
T: 93428750  
E: dennis.velakoulis@mh.org.au

**Background:** Depression and epilepsy are disabling disorders that are common in the community. Both disorders have been shown to have effects on the human body's physiological response to stress. These effects have been identified in both the autonomic nervous system (responsible for immediate responses to stress) and the hypothalamic-pituitary-adrenal axis (which mediates longer-term stress responses). However, it is not known whether these effects occur through similar mechanisms, partly because previous research has not focused extensively on patients with both disorders. This project will broaden our understanding of stress physiology in these disorders by assessing stress physiology in patients who have been admitted to hospital for assessment of seizures and have one or both disorders.

**Aims:** To compare the effects of depression and epilepsy, particularly temporal lobe epilepsy, human physiological stress responses and to assess whether these effects are additive or have a more complex interaction

**Methods:** The project will measure parameters of the physiological stress response in patients who have been admitted to investigate their epilepsy. Assessment of the autonomic nervous system will use a variety of measures of heart rate...
variability, and the HPA axis will be measured by the level of the hormone cortisol in saliva. Clinical data will be obtained by working with the clinical team caring for the patient and involves direct patient contact.

**Outcome**: To better understand stress physiology in depression (a psychiatric illness) and epilepsy (a neurological disorder) by assessing their interaction.

### NEUROVASCULAR

#### 206. Continuous monitoring of motor recovery post acute stroke rescue: development of a broadband-based portable motion detector (REWIRE system)

**Supervisors**: A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
**Location**: Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
**Contact**: A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital,  
T: +61 3 9349 2477 / F: +61 3 9349 4489, Email: bernard.yan@mh.org.au

**Background**: Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. The clinical manifestation is acute loss of neurological function e.g. paralysis of arms and legs.

One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) in order to unblock the blocked artery. A proportion of patients will experience recanalization (reopening) of blocked arteries with consequent recovery of arm and leg movements (motor recovery).

The monitoring of motor recovery is by clinical observation is critical in the management of stroke patients. Patients who do not exhibit early motor recovery post thrombolysis may benefit from more aggressive treatment. However, the current clinical observation paradigm is time consuming and subjected to inter-observer bias. We aim to validate the clinical utility of a novel portable motion detector (REWIRE system) which allows for continuous monitoring of motor recovery in stroke patients treated with thrombolysis. The findings of the study may inform future decision to mandate continuous motor monitoring of patients post thrombolysis. We envisage that the study findings may lead to investigations of the REWIRE system in other neurological diseases e.g. Epilepsy.

**Research Plan**: Human Ethics Committee approval has been obtained. The first phase of the project has been completed with 10 healthy controls. The second phase of the project aims to study the motor recovery of stroke patients. We hypothesize that the motion detector (REWIRE system) is able to better detect motor recovery compared to standard clinical observations. Inclusion criteria: acute stroke patients admitted to RMH Stroke Care Unit. Methods: study subjects will wear the REWIRE system on each limb for 4 hours. Accelerometry raw data will be continuously transmitted by WIFI to a base station for analysis. Study subjects are also examined by standard clinical examination for comparison.

#### 207. Acute stroke rescue: clot retrieval. Does imaging characteristics predict the histopathology of clot composition?

**Supervisors**: A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
**Location**: Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
**Contact**: A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital,  
T: +61 3 9349 2477 / F: +61 3 9349 4489, Email: bernard.yan@mh.org.au

**Background**: Acute stroke is caused by a blockage of one of the arteries in the brain by clot(s). The clinical consequences result from acute neuronal failure secondary to precipitous decrease in arterial perfusion. Apart from intravenous thrombolytics, mechanical clot retrieval holds promise as an effective means to reopen blocked arteries. However, the success clot retrieval depends partly on clot composition. It is known that clots undergo pathological change from red-cell dominant, then to fibrin dominant and finally to organized fibrin strands. It is thought that clots with organized fibrin are the most resistant to mechanical retrieval. The difficulty is that up till now, there are no reliable methods to judge clot composition prior to mechanical retrieval. In this project, we aim to employ advanced CT angiogram imaging pre-procedure and to correlate the imaging characteristics with histopathological examination of clots. The implication of the findings is that we may be able to more accurately predict the success rate of clot retrieval and to triage patients prior to invasive therapies.

**Research plan**: Human research ethics committee approval has been obtained. Acute stroke patients eligible for acute clot retrieval will be recruited prospectively into the study. Imaging modalities include plain CT, CT angiogram and CT perfusion (this is part of standard stroke treatment protocol). Clot retrieval will be performed by RMH
neurointerventionists. Clot samples will be sent for standard H & E staining and immunohistochemistry for platelet markers. The imaging parameters will be correlated with histopathological examination of clots and the degree of success of clot retrieval and vessel recanalization.

**OPHTHALMOLOGY**

208. **Mannose-binding lectin deficiency as a risk factor for the development and course of age-related macular degeneration**

**Supervisor:** A/Prof Damon Eisen, Dr Michael Osthoff, Victorian Infectious Diseases Service (VIDS), Royal Melbourne Hospital

**Project Site:** Department of Medicine (RMH) & VIDS 9th Floor, RMH

**Contact:** A/Prof Damon Eisen, T: 9342 7212 E: damon.eisen@mh.org.au

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population, especially in the Western World. With the overall ageing of the population its prevalence is expected to increase by 50% in the next 10 years. Dysregulated local complement activation and subsequent chronic inflammation are considered to play an essential role in the pathogenesis of AMD. Additionally, certain pathogens (like Chlamydia pneumoniae or Cytomegalovirus) have been implicated in the pathogenesis of AMD by inducing a chronic inflammatory state. Mannose-binding lectin (MBL), the first component of the lectin pathway of complement, is a circulating innate pattern-recognition protein, which is involved in the clearance of microorganisms and apoptotic cells. The concentration of functional MBL multimers is profoundly influenced by several well-known polymorphisms in the **MBL2** gene, resulting in decreased or absent serum MBL levels in up to 30% of apparently healthy individuals. In terms of the pathogenesis of AMD, MBL deficiency might lead to an impaired clearance of apoptotic debris or certain pathogens (like Cytomegalovirus) in AMD and consequently to sustained inflammation due to the activation of the classical or alternative pathway of complement.

The aim of this project will be to evaluate the importance of MBL deficiency as a risk factor in the development and course of AMD in a case controlled study of 140 patients with varying degrees of AMD. These patients will be compared with 140 age matched controls, who have been carefully examined by ophthalmological collaborators to ensure that they do not suffer from AMD.

The goal of this research is to eventually allow developing specific therapeutic interventions, e.g. by supplementing MBL. Moreover, identification of MBL deficiency as a susceptibility factor for AMD will lead to a more comprehensive understanding of the pathogenesis of AMD.

The skills expected to be learnt from this project include: ELISA, PCR, quantitative and qualitative data analysis, scientific literature review and writing.

*Note: this project is also listed under Innate Immunity & Host Defence*

**MOLECULAR GENETICS @ NORTHERN HEALTH**

**Head of Research Group:** Professor Judy Savige

**Laboratory/Group Location:** The Northern Hospital, 185 Cooper Street, Epping

**What we do:** We use eye photographs to predict heart disease; molecular genetics.

209. **Eye changes to predict heart disease**

**Supervisor:** Professor Judy Savige

**Project Site:** The Northern Hospital, 185 Cooper St., Epping

**Contact:** Professor Judy Savige T: 03 8405 8823 E: judy.savige@nh.org.au

Taking retinal photos of patients in the hospital and correlating vessel changes with risk of heart attacks.

**Techniques to be used:** Retinal photos, grading and simple statistics.

*Note: this project is also listed under Cardiology*
PARKINSON’S DISEASE/NEUROLOGY

210. Deep brain stimulation of the pedunculopontine nucleus for gait freezing in Parkinson’s disease

Supervisor: Dr Wesley Thevathasan (Universities of Melbourne and Oxford)
Project site: Melbourne Brain Centre @ Royal Melbourne Hospital
Contact: Dr Wesley Thevathasan T: 9342 4412 E: wesley.thevathasan@nds.ox.ac.uk

Background and hypothesis: Deep brain stimulation is a rapidly developing treatment for neurological diseases which involves implantation of electrodes into specific brain regions to allow the targeted delivery of chronic electrical stimulation. Deep brain stimulation can have dramatic therapeutic effects, presumably by improving neuronal firing patterns. A new form of deep brain stimulation targeting a brainstem structure called the pedunculopontine nucleus (PPN) improves gait disturbance in Parkinson’s disease. However, the clinical benefits reported from PPN stimulation have been highly variable. In a successful collaboration between Oxford and Australia, we recently found a possible explanation for this variability— that small differences in stimulation location could substantially alter therapeutic outcomes. Specifically, we found evidence that the PPN in humans is topographically organised — with neuronal recordings only in the caudal (deepest) but not rostral nucleus correlating with locomotion. Thus we hypothesize that stimulation of the caudal PPN might be most beneficial for gait disturbance in Parkinson’s disease. This also concurs with our anecdotal clinical experience.

Methods: To test this hypothesis, we will assess patients with Parkinson’s disease implanted with PPN stimulators – comparing three conditions; off PPN stimulation, rostral PPN stimulation and caudal PPN stimulation. The measured variable will be gait freezing quantified by simple spatiotemporal gait analysis. Previous intraoperative neuronal recordings may help guide determination of caudal versus rostral PPN locations in individual patients. If successful, our results would direct neurosurgeons to target the caudal rather than the rostral PPN to achieve optimal results from stimulation.

Skills: Clinical assessment of patients with Parkinson’s disease, simple spatiotemporal gait analysis (e.g. step length, cadence), manipulation of deep brain stimulation, neuronal time series analysis (if available), statistical analysis (e.g. repeated measures ANOVA), manuscript preparation.

Note: this project is also listed under Motor Control

211. Analysis of factors involved in “freezing” of gait in Parkinson’s disease - also offered as MSci

Supervisors: A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan
Project site: Dept of Neurology, Royal Melbourne Hospital , City Campus
Contact: Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au.
T: 9342 8448

Laboratory overview: the project will be conducted within the Dept of Neurology at Royal Melbourne Hospital.

Project overview: Parkinson’s disease (PD) is an inexorably progressive disorder associated with impaired execution of motor programmes. It is recognized that as the disorder progresses, patients develop difficulty with initiation of gait as well as episodic freezing when walking in a straight line and particularly when approaching “obstacles” such as doorways. Ocular motor studies have demonstrated an increased error rate in the generation of motor programmes, in patients compared with control subjects, when confronted with a defined motor task in the presence of distracting stimuli. This is marked when the stimuli are in the periphery rather than more centrally located. It has been observed in patients walking in a straight line that gait can be improved by placing an obstacle in front of the patient or by placing a series of lines on the floor which must be stepped over. We hypothesise that this is an effect of focusing attention centrally to the exclusion of peripheral stimuli. In this study we aim to perform pilot experiments looking at the effect of focusing attention artificially in control and patient subjects, by restricting the visual field, and thus exposure to peripheral stimulation, on gait initiation, walking in a straight line and when approaching apparent obstacles such as a doorway.

Note: this project is also listed under Motor Control

Acquired skills: Proper clinical evaluation of patients with PD; understanding of the Pathophysiology of deficit generation in PD.

212. Inhibitory motor errors in Parkinson’s disease contributing to deficit - also offered as MSci

Supervisors: A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan
Project site: Dept of Neurology, Royal Melbourne Hospital , City Campus
Contact: Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au.
T: 9342 8448

Laboratory overview: the project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.

RMH Academic Centre Honours Projects 2012
Project overview: Parkinson’s disease (BG) is a progressive degenerative disorder of the basal ganglia (BG) characterized by bradykinesia, rigidity and tremor. Clinically evident cognitive decline parallels the development of motor deficit. Motor deficit can be attributed to abnormalities of cognitive processing of afferent information and its integration with ongoing motor activity, the BG being intimately involved in conflict resolution between willed movement, reflexive movement, inhibition of unwanted movement and attentional processes.

The ocular motor system is the first motor system to develop in humans and is the prototypical motor control system. The limited degrees of freedom of movement and the relative lack of inertia provides a unique opportunity to examine cognitive processes involved in motor control, especially looking at working memory, attentional processes and inhibitory processes. We have previously noted that, during smooth pursuit, patients with PD make an increased number of inhibitory errors in the presence of peripheral, as opposed to more central, distractors presented during the performance of a prescribed task. This may have relevance to the generation of freezing and difficulty initiating movement observed in patients with PD.

This is a pilot study to extend the findings seen during pursuit to the saccadic system. We hypothesise that such failure of inhibition may be part of a generalized systems disorder, intimately involved in the generation of clinical deficits otherwise clinically observed in the somatic motor system. Eye movements will be recorded by standard techniques using video oculography. We will examine the generation of antisaccades (saccades to the equal and opposite position indicated by the presentation of a target after it extinguishes) and memory guided saccades in particular.

Acquired skills: Understanding of motor deficit and the clinical examination of patients with PD; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

Note: this project is also listed under Motor Control

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213. **Tendency to freeze in Parkinson’s disease: inhibitory errors contributing to deficit** - also offered as MSci

Supervisors: A/Prof Owen B White, Dr Joanne Fielding, A/Prof Bernard Yan

Project site: Dept of Neurology, Royal Melbourne Hospital, City Campus

Contact: Owen White, Dept of Neurology, RMH, Parkville. E: owen.white@mh.org.au; Joanne Fielding, Dept of Neurology, RMH. E: joanne.fielding@monash.edu; Bernard Yan, Dept of Neurology, RMH. E: Bernard.yan@mh.org.au.

T: 9342 8448

Laboratory overview: the project will be conducted in the Ocular Motor Research Laboratory within the Dept of Neurology at Royal Melbourne Hospital.

Project overview: Parkinson’s disease (BG) is a progressive degenerative disorder of the basal ganglia (BG) characterized by bradykinesia, rigidity and tremor. Clinically evident cognitive decline parallels the development of motor deficit. Motor deficit can be attributed to abnormalities of cognitive processing of afferent information and its integration with ongoing motor activity, the BG being intimately involved in conflict resolution between willed movement, reflexive movement, inhibition of unwanted movement and attentional processes. It has been observed that patients with moderate disease may freeze as they approach a doorway, or some other obstacle, and then have difficulty reinitiating gait.

We hypothesise that this may be secondary to impaired inhibition of visual stimuli as they move into the peripheral visual field, resulting in impaired conflict resolution between voluntary motor activity and reflex motor activity.

In this pilot study, patients will undertake prescribed ocular motor tasks while eye movements are recorded using video oculography. Distraction, a “door equivalent”, will be provided by a rectangle of LEDs which will be illuminated at varying positions between the subject and the target screen. We would anticipate that there will be more errors, and possibly difficulties with initiation of saccades, in patients, as the “door equivalent” comes closer to the patient and is further from the target.

Acquired skills: Understanding of motor deficit and the clinical examination of patients with PD; understanding of the function of the ocular motor system; learning how to direct ocular motor recordings and analyse the data from such studies.

Note: this project is also listed under Motor Control
PHARMACOGENETICS AND PERSONALISED MEDICINE

214. Development of novel rapid genotyping techniques to detect genetic variants predictive of response to drugs for application in personalized medicine - also offered as MSci

Supervisors: Professor Patrick Kwan, Dr Marian Todaro
Project Site: Department of Medicine (RMH)
Contact: Professor Patrick Kwan, Department of Medicine (RMH)
E: patrick.kwan@unimelb.edu.au; Dr Marian Todaro, Department of Neurology E: Marian.Todaro@mh.org.au

Background: Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. Regulators such as the FDA recognise a growing list of genetic variants that should be tested before prescription of medications because of their critical role in predicting drug effectiveness and/or safety. However, conventional genotyping platforms in the clinical setting typically rely on polymerase chain reaction (PCR) or direct sequencing, which require complex sample handling and are performed in laboratories using expensive equipment operated by highly skilled personnel. Their availability is usually restricted to specialised centres. Testing is costly and typically takes one to two days. With the addition of sample transportation and report delivery time, it may take days to weeks for the results to become available to the requesting physician. These logistic barriers cause delay in starting appropriate treatment, and add administration time for extra clinic visits or patient contacts, hampering the adoption of regulatory recommendations into routine practice. To overcome these logistic and economic barriers, we propose an innovative combination of biochemical and engineering technologies that will perform genotyping rapidly using compact ‘smart’ devices at the point of care.

Figure. Detection of HLA-B*1502 allele by rapid genotyping technique in heated blood. Amplified products were identified by colour change after the addition of Sybr Green I to the reaction mixture. The individual was a carrier of the allele if both reactions turned green, and a non-carrier if either one was orange.

Research Plan: This project is part of a large project aiming to bring personalised medicine into widespread clinical practice (see project numbers 209 and 210). A novel rapid genotyping platform has been identified capable of detecting HLA-B*1502 (Figure), a genetic variant strongly associated with severe cutaneous reactions to carbamazepine in Chinese/southeast Asian populations. This project will further optimise and validate this novel technique for the detection of HLA-B*1502 as well as other pharmacogenetic markers, using blood and DNA samples already obtained. The protocol developed will be adapted for use in a compact automated device through collaboration with electronic engineers.

Acquired skills: DNA extraction, gene sequencing, PCR, novel genotyping techniques

215. Lab-on-a-chip nanotechnology testing device for personalized medicine - also offered as MSci

Supervisors: Professor Stan Skafidas and Professor Patrick Kwan
Project Site: Centre for Neural Engineering, Department of Electrical Engineering; and Departments of Medicine and Neurology (RMH)
Contact: Professor Stan Skafidas, Department of Electrical Engineering, E: sskaf@unimelb.edu.au
Professor Patrick Kwan, Department of Medicine, E: patrick.kwan@unimelb.edu.au

Background: Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. Regulators such as the FDA recognise a growing list of genetic variants that should be tested before prescription of medications because of their critical role in predicting drug effectiveness and/or safety. However, conventional genotyping platforms in the clinical setting typically rely on polymerase chain reaction (PCR) or direct sequencing, which require complex sample handling and are performed in laboratories using expensive equipment operated by highly skilled personnel. Their availability is usually restricted to specialised centres. Testing is costly and typically takes one to two days. With the addition of sample transportation and report delivery time, it may take days to weeks for the results to become available to the requesting physician. These logistic barriers cause delay in starting appropriate treatment, and add administration time for extra clinic visits or patient contacts, hampering the adoption of regulatory recommendations into routine practice. To overcome these logistic and economic barriers, we propose an innovative combination of biochemical and engineering technologies that will perform genotyping rapidly using compact ‘smart’ devices at the point of care.
economic barriers, we propose an innovative combination of biochemical and engineering technologies that will perform genotyping rapidly using compact ‘smart’ devices at the point of care.

A novel rapid genotyping platform has been identified capable of detecting HLA-B*1502, a genetic marker strongly associated with severe cutaneous reactions to carbamazepine in Chinese/southeast Asian populations. However, identification of the amplified DNA is subjective and insensitive. To overcome this limitation and to improve sensitivity, we propose the use of silicon nanowire for more rapid and objective detection. The objective are to engineer and fabricate a compact device prototype to carry out the genotyping steps and product detection using silicon nanowire technology in automated operation. This generic platform can be easily adapted for other genetic markers by using appropriate primers and optimising test conditions.

**Research Plan:** This project is part of a large project aiming to bring personalised medicine into widespread clinical practice (see project numbers 208 and 210). The development of the lab-on-a-chip system requires multiple technologies to be integrated on a single chip platform in order to facilitate a small, low cost and reliable real time DNA detection system. The device will have microfluidic handling capability and precise temperature control, coupled with silicon nanowire (siNW) for ultrasensitive electrical detection of the amplified DNA products containing the specific genetic variants. The device will carry out sample preparation, integration of the rapid genotyping protocol, and nanotechnology based detection system, using HLA-B*1502 as an example. Blood and DNA samples of known HLA-B*1502 carrier status are already available to carry out the device development. There is very strong potential for technological innovation and eventual application of the device in clinical practice.

**Acquired skills:** DNA amplification techniques, microfluidic technology, nanowire fabrication, CMOS circuitry

### 216. The health economics of personalized medicine - also offered as MSci

**Supervisors:** Professor Patrick Kwan and Professor Danny Liew  
**Project Site:** Department of Medicine (RMH)  
**Contact:** Professor Patrick Kwan, Departments of Medicine and Neurology,  
E: patrick.kwan@unimelb.edu.au; Professor Danny Liew, Centre for Clinical Epidemiology, Biostatistics and Health Services Research, RMH,  
E: dyliew@unimelb.edu.au

**Background:** Personalised medicine is emerging as the new healthcare paradigm. Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. Regulators such as the FDA recognise a growing list of genetic variants that should be tested before prescription of medications because of their critical role in predicting drug effectiveness and/or safety. A prime example is HLA-B*1502 which is strongly associated with rare but life-threatening severe skin reaction to carbamazepine, a first-line medication for the treatment of epilepsy, neuropathic pain and bipolar affective disorder. However, conventional laboratory-based testing poses logistic and economic barriers to testing in clinical practice. In addition, the cost-effectiveness of routine testing has been poorly studied.

**Research Plan:**  
This project is part of a large project aiming to bring personalised medicine into widespread clinical practice through the development of point-of-care (POC) genotyping device (see project numbers 208 and 209). Cost-effectiveness modelling of the application of the device for POC genetic testing will be compared with conventional testing practice to estimate its market potential. The modelling will be based on real-life data tracking the testing and prescribing behaviour of physicians in a healthcare system in which HLA-B*1502 testing is already mandatory for carbamazepine prescription (Hong Kong). The analysis will take into account currently observed practice associated with the policy of mandatory laboratory-based testing, which is often avoided because of logistic barrier so that an alternative (usually more expensive) drug is prescribed instead.

**Acquired skills:**  
Cost-effectiveness modelling and analysis, biostatistics, decision-making in health policy

### 217. Electrophysiological characterization of effects of MDR1 (ABCB1) polymorphisms on efflux transport of antiepileptic drugs - also offered as MSci

**Supervisors:** Professor Patrick Kwan and Dr Chris French  
**Project site:** Melbourne Brain Centre @ RMH, Parkville  
**Contact Details:** Dr Chris French, E: frenche@unimelb.edu.au;  
Professor Patrick Kwan, E: patrick.kwan@unimelb.edu.au

**Background:** Pharmacoresistance of antiepileptic drugs (AEDs) is a major public health problem and epilepsy resists pharmacotherapy in 30-40% of patients. Polymorphisms of MDR1 or ABCB1, which encodes the multidrug transporter P-glycoprotein (Pgp) at the blood-brain barrier, are associated with drug responsiveness. Drug-resistant epilepsy patients
more frequently have the 2677T/A and 3435T MDR1 alleles compared with drug responsive patients. Using cells transfected with MDR1 variants, we found that Pgp with 2677T allele had higher transport function of pumping AEDs from basolateral to apical side than 2677G allele in cell monolayers, suggesting that polymorphisms of MDR1 influence the transport of AEDs. Pgp is an ATP-transporter, and some AEDs have an electrostatic dipole. To elucidate the molecular mechanisms of the associations between the polymorphisms and pharmacoresistance, this project will use electrophysiological methods to 1) investigate possible functional effects of MDR1 polymorphisms on intrinsic function of Pgp, and 2) to assess effects of these polymorphisms on AED transport. The results will provide a clearer basis for the design of genetic-based personalised treatment of epilepsy with the prospect of significantly enhanced therapeutic effectiveness.

**Research Plan:** LLC-PK1 cells transfected with MDR1 haplotypes of 2677G>T/A and 3435C>T have been established and validated in our laboratory. Western blotting and real-time PCR will be used to measure expression of Pgp (wildtype and mutants) in the stably transfected cell lines. Single channel and whole cell currents will be measured to study the effect of polymorphisms on the Pgp properties, and transport of phenytoin, a Pgp substrate and a widely used AED. Cell uptake assay for rhodamine-123 will be performed to confirm the functional difference of MDR1 variants by flow cytometry.

**Acquired skills:** Single channel and whole cell electrophysiology, flow cytometry, western blotting, real-time PCR, cell culture

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**218. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effect** - also offered as MSci  
**Supervisors:** Dr. Marian Todaro, Dr Slave Petrovski, Prof Terence O'Brien, Prof Patrick Kwan  
**Project Site:** The Comprehensive Epilepsy Program, Department of Neurology, The Royal Melbourne Hospital.  
**Contact:** Dr Marian Todaro T: 9342 7500; E: Marian.Todaro@mh.org.au; Dr Slave Petrovski E: slavep@unimelb.edu.au; Professor Terence O’Brien T: 8344 5479 E: obrienti@unimelb.edu.au

This study aims to investigate the individual responses of patients who developed a rash or drug-induced hepatitis due to an anti-epileptic drug (AED), and link this information to the genetic profile of each patient – in particular that for the human leukocyte antigens (HLA). The results will help to identify genetic markers that could predict when a patient is at risk of having side effects with a particular medication.

Previous experience has shown that individuals vary greatly in their responses to drugs. Although medication is effective and well tolerated in most patients side-effects can necessitate treatment changes. One of the most common, and potential serious, types of side effects to anti-epileptic drugs is hypersensitivity reactions - including generalised skin rashes, Steven Johnson Syndrome (SJS), and drug-induced hepatitis. It has been shown that genetic factors play an important role in determining an individual’s response to medication. Recently, the occurrence of SJS in Asian patients taking carbamazepine has been repeatedly associated with the carriage of a particular HLA antigen, HLA-B*1502. However, this association does not persist in non-Asian populations and HLA associations in other populations, or with other types of AED-induced hypersensitive reactions, have not yet been identified. Understanding why responses vary has the potential to improve the safety and effectiveness of medical treatment for various conditions.

This project will utilize an international unique cohort of more than 400 patients who have been prospectively enrolled and followed following starting treatment with an AED for the first time. The HLA profiles of patients who developed hypersensitivity reactions will be compared with those who took the same drug but did not develop any such reactions. The goal of this research is to eventually allow the choice of medication to be tailored to an individual’s specific genetic profile.

**Skills to be learned:** Human genomics, immunogenetics, bioinformatics, clinical phenotyping, multivariate statistics.

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**219. Pharmacogenetics: do mutations in CYP 2C19 alter the clinical effectiveness of clopidogrel in patients with cerebrovascular disease?**  
**Supervisors:** A/Professor Bernard Yan, A/Professor Peter Mitchell, A/Professor Richard Dowling  
**Location:** Department of Neurology & Department of Radiology, Royal Melbourne Hospital  
**Contact:** A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital, T: +61 3 9349 2477 / F: +61 3 9349 4489, Email: bernard.yan@mh.org.au

**Background:** Stroke is the third leading cause of death in Australia. The prevention of recurrent strokes is an important strategy to improve health and reduce medical costs. Globally, anti-platelet agents (aspirin, clopidogrel, prasugrel etc) are the first-line treatment to prevent further ischaemic events (i.e. strokes). Anti-platelet work by inhibiting platelet aggregation with consequent reduced risk of artery blockages. However, up to 30% of patients are “resistant” to
clopidogrel treatment. Of note, activity of clopidogrel is critically dependent on its conversion from the pro-drug to its active form by a member of the P450 family of enzymes (CYP2C19). A genetic mutation, e.g. CYP2C19*2, predicts lower levels of the active form clopidogrel leading to failure of platelet inhibition. We hypothesize that patients with genetic mutations of CYP2C19 (e.g. CYP2C19*2) will demonstrate clopidogrel failure and increased risk of stroke. The results will have the potential to change clinical practice in the prescription of clopidogrel.

Research Plan: Our project is part of a large pharmacogenomics project led by Professor Patrick Kwan’s research group. Our research arm focuses on CYP2C19 genetic mutation and its clinical consequences. Human ethics committee approval has been obtained to test anti-platelet resistance. Inclusions criteria: patients previously exposed to clopidogrel or with plans to start clopidogrel (e.g. aneurysm coiling, pipeline flow diversion device implantation etc). Methods: all patients will be tested for CYP2C19 genetic status by PCR and a novel DNA amplification technique. The patients will be followed clinically and by neuroimaging to identify recurrent cerebral ischaemic events.

220. A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy - also offered as MSci

Supervisors: Professor Terence O’Brien and Professor Frank Vajda, Epilepsy and Neuropharmacology Group, The Department of Medicine: The Royal Melbourne Hospital, Associate Professor Les Sheffield, The Murdoch Children’s Research Institute

Project Site: The Department of Medicine (RMH)

Contacts: Professor Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au
Professor Frank Vajda E: vajda@netspace.net.au
A/Professor Les Sheffield E: les.sheffield@ghsv.org.au, The Murdoch Childrens Research Institute.

It is long been recognised that women with epilepsy who become pregnant while taking an anti-epileptic drug (AED) have an increased risk of having a foetus or infant with a birth defect (BD). This is particular high for valproate. Despite the increased risk associated with taking AED in pregnancy, most women with epilepsy who become pregnant, or plan to do so in the near future, cannot simply cease the drugs because of the risk to the health and safety of the mother and child of uncontrolled seizures. The development of methods that would allow the prediction that a specific drug would be associated with a higher risk of a birth defect in a particular woman would be of great potential benefit. There is evidence from family and twin studies that genetic factors may play a role in determining predisposing an individual to having a child with an AED associated birth defect. The Australian Register of Anti-epileptic Drugs in Pregnancy has been established in an attempt to obtain more accurate information about the risks of specific AEDs. This is a prospective, voluntary, telephone interview based study that enrols pregnant women with epilepsy, prior to the outcome of the pregnancy being known, and follows the outcomes of their pregnancies. The study has been running since July 1999, and to date has enrolled more than 1600 pregnant women.

This study will attempt to identify genetic markers that predict the risk of valproate-induced birth defects. Participants will be identified through the Australian Registry of Anti-epileptic drugs in pregnancy. Women with epilepsy who were taking an AED in the first trimester, and their partners, will be offered enrollment. Two types of genetic tests will be performed:

- A case-control genetic association studies comparing genetic information from mothers and infants taking a valproate AED during the first trimester with those who were taking the same valproate but did not have a child with a birth defect
- A transmission disequilibrium test (TDT), design will be also be employed. This test looks for significant disequilibrium in the transmission of the allele of interest in the patient with a characteristic of interest. It therefore eliminates any potential sources of bias between the affected patients and non-affected controls, which may occur in case-control association studies. Blood for genetic analysis would be taken from the mother, father and child.

This project is also listed under Biology – Women’s Health

PREGNANCY RESEARCH

221. Multiple serum markers and mid trimester uterine artery Doppler in the prediction of pre-eclampsia - also offered as MSci

Supervisor: Dr Fabricio Costa

Project Site: Pregnancy Research Centre, Royal Women’s Hospital

Contact: Dr Fabricio Costa T: 8345 2262 E: fabricio.costa@thewomens.org.au

No single biomarker already tested has been shown to have sufficient clinical value in the prediction of pre-eclampsia in isolation. Instead, their value seems to be in increasing the predictive value of panels of tests which include other clinical
measurements. The aim of this project is to examine the combination of maternal risk factors, mean arterial blood pressure, and uterine artery Doppler, together with novel biomarkers in the prediction of pre-eclampsia. This project would suit a biomedical graduate with an interest in clinical medicine and there will be opportunity for laboratory work. The techniques involved will include learning how to analyse clinical data and perform laboratory assays on serum for biomarkers.

222. Mesenchymal stem cell and vascular endothelial cell interactions in the placental bed in human pregnancy

Supervisors: Dr Bill Kalionis
Project Site: Pregnancy Research Centre, Royal Women’s Hospital
Contact: Dr Bill Kalionis T: 8345 3748 E: bill.kalionis@thewomens.org.au

A healthy pregnancy is dependent on successful remodelling of the uterine blood vessels at the site of placental formation. This process involves replacement of maternal vascular cells with placental trophoblast cells and results in reduction in vascular resistance and increased maternal blood flow to the growing placenta. The common, serious pregnancy disorders of pre-eclampsia and fetal growth restriction have significant adverse effects on the health and well-being of mothers and their babies. During these disorders uterine blood vessel remodelling and placental perfusion is deficient. The aim of this project is to elucidate the role of mesenchymal stem cell and vascular endothelial cell interactions in the processes of uterine vascular remodelling. It is proposed that a critical role of uterine mesenchymal stem cells is to regulate the changing functions of endothelial cells during early pregnancy. It is further proposed that this important regulatory interaction is disturbed during pregnancy disorders.

Techniques: human cell isolation and culture, whole cell functional assays, PCR-based analysis, immunocytochemical analysis, Western blotting and ELISA

223. Stem cells of Reproductive Tissues: their biology and potential in regenerative medicine

Supervisors: Dr Bill Kalionis
Project Site: Pregnancy Research Centre, Royal Women’s Hospital
Contact: Dr Bill Kalionis T: 8345 3748 E: bill.kalionis@thewomens.org.au

Stem cells are precursor cells with the ability to differentiate into a variety of different cell types. Typically, stem cells are categorized into “embryonic” (which arise from embryos and have the capacity to give rise to all cell types) and “adult” (which are undifferentiated cells found amongst differentiated cells in a tissue or organ and give rise to a more restricted range of cells.). Stem cells are being used in clinical trials for regeneration and repair of bone and other tissues and even for the treatment of cancers. The placenta is a rich source of stem cells with advantages over other sources of cells. Our understanding of the biology of stem cells in the placenta is still at a rudimentary stage. The project will involve gene expression and functional analysis of a gene we believe is important in placental stem cells.

Techniques: stem cell preparation and characterisation by immunocytochemistry and FACS, RNA/DNA extraction methods, real-time PCR, siRNA and gene overexpression analysis and immunohistochemistry. Functional analyses will include proliferation, migration and differentiation assays.

224. How do chemokines affect fetal trophoblast adhesion?

Supervisors: Dr Rosemary Keogh
Project Site: Pregnancy Research Centre, Royal Women’s Hospital
Contact: Dr Rosemary Keogh E: rosemary.keogh@thewomens.org.au

Late in the first trimester of human pregnancy, cells known as trophoblast migrate from the placenta and invade the arteries of the uterine wall. As they invade, the trophoblast interact with the vessels and instigate remodelling of the vessel walls. The end result is that the arteries are transformed from narrow to wide bore vessels thus facilitating blood flow to, and from, the placenta. This is an essential process to enable the fetus to develop and grow normally. In pregnancies where this remodelling is compromised, complications can arise such as pre-eclampsia, leading to poor outcomes for both the mother and baby. This project will investigate how trophoblast cells are able to migrate into maternal vessels by examining their ability to adhere to the blood vessel wall and components of the extracellular matrix using an innovative real-time technology, xCELLigence. In particular, the effect of chemokines, a subgroup of cytokines, on trophoblast adhesion will be studied. The specific objectives will be to determine 1) chemokine adhesion to matrix components, 2) the effect of chemokines on trophoblast adhesion to matrix components and 3) the effect of chemokines on trophoblast adhesion to endothelial cells.

Techniques: tissue culture, western blotting, adhesion assays, immunofluorescence and xCELLigence real-time analysis.
225. **Characterization of novel genes associated with the pregnancy disorder pre-eclampsia**  
Supervisors: Dr Rosemary Keogh, Dr Bill Kalionis, Dr Padma Murthi and Dr Maria Kokkinos  
Project Site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Rosemary Keogh E: rosemary.keogh@thewomens.org.au  

Pre-eclampsia is a common and serious disorder of human pregnancy that is associated with serious health issues for both the mother and baby. It is characterized by the onset of maternal hypertension in the latter half of pregnancy, however, the pathogenesis of pre-eclampsia is not known. In conjunction with our collaborators, we have identified 8 candidate genes that show a very strong association with the development of pre-eclampsia. The aim of this project is to characterize the expression and function of these genes. The specific objectives will be to determine the expression and localization of these genes in maternal and placental tissue. Using this information, the function of these genes will then be investigated using the real-time analysis technology xCELLigence.

**Techniques:** Tissue preparation and culture, real time PCR, RNAi, immunolotting, immunocytochemistry and real-time cell analysis with xCELLigence.

226. **Progesterone receptors in trophoblast function** - *also offered as MSci*  
Supervisors: Dr Padma Murthi, Dr Penny Sheehan and Dr Rosemary Keogh  
Project Site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Padma Murthi E: padma@unimelb.edu.au or Dr Rosemary Keogh E: rosemary.keogh@thewomens.org.au  

Progesterone is critical for the establishment and for the maintenance of pregnancy, as it regulates menstrual bleeding, tissue repair and regeneration, inflammation, angiogenesis, and in late pregnancy, by interfering with arachidonic acid metabolism it contributes to uterine quiescence. The genomic actions of progesterone are mediated by two intracellular receptors, progesterone receptor A (PR-A) and progesterone receptor B (PR-B), which are both members of the nuclear receptor superfamily. The project will investigate PR mediated transcriptional control and signaling pathways that are critical for successful placental cell proliferation, differentiation, and angiogenesis, that are important for decidualization.

**Techniques:** Cellular and molecular biological techniques including cell culture, functional cell assays (proliferation, differentiation, network formation) real time PCR and RNAi.

227. **Transcriptional regulation of insulin signalling on placental angiogenesis in diabetes and obesity.** - *also offered as MSci*  
Supervisors: Dr Padma Murthi, Dr Penny Sheehan  
Project site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Padma Murthi E: padma@unimelb.edu.au  

In a pregnancy complicated by type 2 diabetes, gestational diabetes and obesity, the increased maternal insulin resistance and chronic inflammation causes fetal hyperglycemia and hyperinsulinemia. Increased fetal insulin affects feto-placental vasculature by altering expression of several pro-inflammatory cytokines and angiogenic molecules that lead to aberrant placental angiogenesis. The molecular mechanisms governing insulin signalling on placental angiogenesis is unknown. The project will identify the transcriptional control of insulin mediated changes in placental endothelial functions in diabetes and obesity during pregnancy.

**Techniques:** Tissue culture, ligand binding assays, functional cell based assays, protein and molecular biology.

228. **Improving the health of newborn babies: investigating the role of heparins in preventing thrombosis within the human placenta** - *also offered as MSci*  
Supervisors: Dr. Joanne Said and Dr. Amy Chui  
Project Site: Pregnancy Research Centre, Royal Women’s Hospital  
Contact: Dr Joanne Said E: jsaid@unimelb.edu.au or Dr Amy Chui E: achui@unimelb.edu.au  

Fetal growth restriction (FGR) is a serious pregnancy complication in which the baby fails to grow properly within the womb. It has significant short and long term sequelae with many of these babies being stillborn or requiring premature delivery in order to survive. Those who survive are at increased risk of developing obesity, diabetes and hypertension. The aetiology remains largely idiopathic, although thrombosis within the placental circulation is a frequent finding. Proteoglycans and the glycosaminoglycan (GAG) side chains display important anticoagulant properties and our recent work supports a possible association between reduced expression of these macromolecules and FGR. Heparins are important anticoagulants which may prevent these problems. This study aims to investigate the effects of different types of heparins on proteoglycans and placental tissues. If our hypothesis is confirmed, there will be the potential to develop appropriate therapeutic strategies which may help to prevent the development of thrombosis and thus, the
complications of FGR. Given the serious life-long consequences of this complication, such intervention strategies would be regarded as well worthwhile.

This project is being run by an established pregnancy research group. The methodologies are established within our laboratories at The Royal Women’s Hospital. You will have an exciting opportunity to be a part of this dynamic clinical research team comprising obstetricians, haematologists, placental researchers and biochemists.

**Techniques:** Tissue culture, PCR, western immunoblotting, thrombin generation assays.

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**229. Improving the health of newborn babies: investigating the role of proteoglycans in causing abnormal growth problems in pregnancies from women with diabetes - also offered as MSci**

**Supervisors:** Dr. Joanne Said and Dr. Amy Chui

**Project Site:** Pregnancy Research Centre, Royal Women’s Hospital

**Contact:** Dr Joanne Said E: jsaid@unimelb.edu.au or Dr Amy Chui E: achui@unimelb.edu.au

As more and more younger women are developing Type 2 diabetes, we are seeing an increasing number of pregnancies in women with this condition. Type 2 diabetes has significant effects on the pregnancy and leads to an increased risk of stillbirth, fetal abnormalities and problems with growth of the baby. Proteoglycans are important molecules located within the placenta which have a variety of functions. High glucose levels, such as those seen in diabetes, can alter the structure of the glycosaminoglycan side chains of proteoglycans and hence affect their function. The aim of this study will be to extract proteoglycans and glycosaminnoglycans from placentas obtained from women with diabetes complicating their pregnancies as well as control (uncomplicated pregnancies) and compare differences in the function of the glycosaminoglycans.

This project is being run by an established pregnancy research group. The methodologies are established within our laboratories at The Royal Women’s Hospital. You will have an exciting opportunity to be a part of this dynamic clinical research team comprising obstetricians, haematologists, placental researchers and biochemists.

**Techniques:** Recruitment of patients, sample collection, HPLC, protein electrophoresis, thrombin generation assays.

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**230. How do hormones work: investigating new steroid receptors**

**Supervisors:** Dr. Penelope Sheehan and Dr. Padma Murthi

**Project Site:** Pregnancy Research Centre, Royal Women’s Hospital

**Contact:** Dr Penelope Sheehan E: penny.sheehan@thewomens.org.au

Progesterone is known to be a key hormone in human pregnancy and is particularly thought to play a role in maintaining myometrial quiescence throughout gestation, allowing the fetus to grow. Antiprogestins, such as mifepristone (RU 486), are known to contribute to parturition\(^1\). Yet, in humans, maternal serum progesterone concentrations do not significantly decrease at labour onset\(^2\), suggesting a change at the receptor level. However detailed knowledge of intracellular and molecular mechanisms are unknown. We have identified two new receptors capable of binding progesterone which may help improve our understanding of progesterone action. The pregnane X receptor (PXR) is a nuclear receptor which is able to regulate gene transcription. The endogenous ligand with the highest affinity for the PXR is the progesterone metabolite, 5βDHP. Progesterone receptor membrane components 1 and 2 (PGRMC1, PGRMC2) are also putative progesterone receptors. Detailed study of the pathways affected by these receptors using myometrial explant cultures and gene silencing techniques may provide new therapeutic targets for treatment of preterm birth and also for induction of labour in postdates pregnancy.

This project will build on previous Pregnancy Research Centre findings identifying changes in expression of these two new receptors in association with human labour at term in myometrium. The methodologies are established within our laboratories at The Royal Women’s Hospital.

**Techniques:** Tissue culture, siRNA gene silencing, Real-time RT-PCR, western immunoblotting, microarray.

**Day 11 explant with myometrial cells growing into the culture medium ready for experiment**
2011/12 KEY DATES

Aug-November 2011: Contact potential supervisors to discuss Honours projects (Step 1)
Mid September 2011: On-line Applications OPEN to register for HATS (Honours Applications Tracking System)
18 November 2011: Closing date to submit on line application for Bachelor of Science (Honours) or Bachelor of Biomedicine (Honours) (Step 2)
27 November 2011: Closing date for project preference submission through HATS (Step 3)
3rd wk December 2011: First round of offer letters sent by mail to students
6 January 2012: Closing date for acceptance/rejection by students of First Round offers
9 January 2012: Second round of selection and mailing of offer letters begins
13 February 2012: Honours 2011 Program commences.

ENTRY REQUIREMENTS

To be eligible to enter the Bachelor of Biomedicine (Honours) or the Bachelor of Science (Honours), applicants must satisfy both:

• the Faculty of Medicine, Dentistry and Health Sciences or Faculty of Science entry requirements;
• and the requirements of the department offering the Honours program.

Please note: demonstrated eligibility does not guarantee a place in the Honours program. All successful applicants will also need to be selected for admission by the department. The University of Melbourne handbook contains detailed information about the subjects available and entry requirements for departments offering Honours. The 2011 handbook is available at https://handbook.unimelb.edu.au.

For further details see Faculty of Medicine, Dentistry & Health Sciences website: http://sc.mdhs.unimelb.edu.au/entry-requirements

COURSE WORK

MEDI40003 & MEDI40012 – Research Project (75%) – Semester 1 & 2
The written thesis together with an Oral Presentation constitutes the Research Project for Semester 1 & 2 and contributes 75% to the total mark of the Honours Year.

Structure: Research Project (Thesis)
Assessment: Semester 1: Oral Presentation on project outline. Feedback only - not assessed.
Semester 2: Written research report (thesis) to be submitted. 80%
Formal Thesis Oral presentation. 20%

MEDI40004 – Advanced Coursework (12.5%) – Semester 1
This subject contributes 12.5% to the total mark of the Honours year.

Structure: Semester 1: Attend Seminars in Translational Medicine - thematic topics of approximately 1 hour each - approximately 24 lectures.
Semester 1 & 2: Attend Weekly Research Seminars. Attendance is compulsory but not assessed.
Assessment: Semester 1: Multiple Choice Question examination covering examinable topics from the Seminars in Translational Medicine.

BIOM40001 – Introduction to Biomedical Research (12.5%) – Semester 1
This core subject contributes 12.5% to the total mark of the Honours year.

Structure: Series of 10 x 2 hr tutorials to introduce students to processes and strategies at the core of modern biomedical research.
Assessment: Semester 1: 2 written reports (each not exceeding 3000 words).

For further details on course work please see the RMH Academic Centre Honours Program Course Structure website: http://honoursrmh.unimelb.edu.au/Applications/CourseDetails.html
HOW TO APPLY

Course Codes:
Bachelor of Biomedicine (Honours) – BH-BMED
Bachelor of Science (Honours) – BH-SCI

RMH Academic Centre Enrolling Unit is: Department of Medicine (RMH)

2012 APPLICATION FOR HONOURS IN THE FACULTY OF MEDICINE, DENTISTRY & HEALTH SCIENCES (FMDHS)

If you wish to be considered for Honours in 2011, and you would like to undertake your project and coursework with the Royal Melbourne Hospital Academic Centre, Faculty of Medicine and Dentistry Sciences or affiliated institute with the enrolling unit being Department of Medicine (RMH), you will need to carry out a THREE STEP PROCESS.

STEP 1:
You will need to decide which Department or Institute(s), Supervisor(s) and Project(s) that you wish to apply for. To do this, you must speak to potential supervisors. Please see our Honours project book and Department of Medicine (RMH) website to review our projects available for 2011.

STEP 2:
Mid September 2011: Honours Applications OPENS to register for HATS
Lodge an online application by Friday 18 November 2011. Applications for Honours are lodged to MDHS via one of the following processes:

a) Current Local and International University of Melbourne Students:
   Apply through the Student Portal under the Admin Tab:
   http://portal.unimelb.edu.au
   Your current University of Melbourne student ID should be used for Step 3

b) Non-University of Melbourne Applicants:
   Local applicants click here to apply online:
   http://www.futurestudents.unimelb.edu.au/admissions/applications/graduate-domestic
   International applicants click here to apply online:
   http://www.futurestudents.unimelb.edu.au/admissions/applications/graduate-international

All non-University of Melbourne applicants – please provide an original or certified copy of your complete official academic transcript to the MDHS Student Centre as part of your application -
http://www.sc.mdhs.unimelb.edu.au/contact
MDHS Student Centre is located at Level 1, Brownless Biomedical Library, University of Melbourne. T: 8344 5890:

It is essential that you carry out Step 2 BEFORE you carry out Step 3. Note that the closing date for the Step 2 Application is 18 November 2010.

STEP 3:
Lodge project preferences in Honours Applications and tracking System (HATS) by Sunday 27 November 2011.

It is essential that you have already identified which projects you wish to apply for by speaking to potential supervisors (Step 1) and have applied for Honours (Step 2) BEFORE you carry out Step 3.

To carry out STEP 3 in HATS you will need to:

A. Enter your Application ID into HATS
B. Enter your HATS password
   HATS passwords are issued once a week. Your HATS password will be emailed to you on the Monday following the date you completed Step 2.
C. Click on Preferences then Search Projects
   Use this search to make sure that the project(s) you wish to apply for are present in HATS. If you cannot find the project you are interested in, you should contact the supervisor of these projects, who will be able to take steps to have the project details entered into HATS.
D. Click on Preferences then Lodge/Update Preferences to lodge your project preferences with HATS.
   You can update/change your preferences as many times as you wish. However, you must ensure that your final preference list (in order of 1-10; you must enter at least 1 preference, and you can enter up to 10) is lodged by
Sunday 28 November 2010. This list will be supplied to Departments to allow them to carry out their selection process in early December 2010.

You will receive a round one offer letter for the highest preference project you have been offered by mail before Christmas. You can choose to accept the offer or not. If you choose not to accept, you will be considered for selection by Departments for the second round of selection in mid January.

**Note:** The Department of Medicine (RMH) is the enrolling unit for the RMH Academic Centre Honours Program.

**Example of search result for Honours project:**

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Department</th>
<th>Supervisor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channels in epilepsy</td>
<td>Medicine (RMH)</td>
<td>Chris French, Terence O’Brien</td>
<td>This project is carried out at the Department of Medicine (RMH) through the RMH Academic Centre.</td>
</tr>
</tbody>
</table>

For further details on ‘How to Apply’ please refer to the following websites:

Faculty of Medicine, Dentistry and Health Sciences Honours 2011: [http://sc.mdhs.unimelb.edu.au/why-honours](http://sc.mdhs.unimelb.edu.au/why-honours)

Faculty of Medicine, Dentistry and Health Sciences Application Process: [http://www.mdhs.unimelb.edu.au/future_students/honours/application_process](http://www.mdhs.unimelb.edu.au/future_students/honours/application_process)


(You must submit your preferences in HATS to ensure your application is complete and will be considered).

Department of Medicine Honours: [http://honoursrmh.unimelb.edu.au/](http://honoursrmh.unimelb.edu.au/)

**ROUND 2 APPLICATIONS**

Late applications will be considered from students for ROUND 2. Please check the Department of Medicine (RMH) Honours website for further details in January 2012.

**CONTACT**

Honours Coordinator: Professor Gary Anderson  E: gpa@unimelb.edu.au
Honours Administrator: Mary Ljubanovic  E: mlju@unimelb.edu.au

**RMH/WH ACADEMIC CENTRE DEPARTMENT LINKS:**

Department of Medicine (Royal Melbourne Hospital) [http://www.medrmhwh.unimelb.edu.au/](http://www.medrmhwh.unimelb.edu.au/)

Department of Surgery (Royal Melbourne Hospital) [http://www.surgeryrmh.unimelb.edu.au/](http://www.surgeryrmh.unimelb.edu.au/)

Department of Psychiatry (Royal Melbourne Hospital) [http://www.psychiatry.unimelb.edu.au/](http://www.psychiatry.unimelb.edu.au/)

Department of Radiology (Royal Melbourne Hospital) [http://www.melbourne-radiology.org/Staff.html](http://www.melbourne-radiology.org/Staff.html)

Obstetrics & Gynaecology (Royal Women’s Hospital) [http://www.thewomens.org.au/PregnancyResearchCentre](http://www.thewomens.org.au/PregnancyResearchCentre)