The Royal Melbourne Hospital Academic Centre
(RMH Departments: Medicine, Surgery, Psychiatry, Radiology, and Obstetrics and Gynaecology RWH)
Faculty of Medicine, Dentistry & Health Sciences, The University of Melbourne

Master of Science
(Biomedical & Health Sciences)

PROJECTS 2013

Medical Research — Bench to Bedside

Affiliations:
The Royal Melbourne Hospital, The Royal Women’s Hospital, NorthWest Academic Centre (NWAC), National Ageing Research Institute (NARI), The Peter MacCallum Cancer Centre, The Burnet Institute—Centre for Population Health, Melbourne Brain Centre, Florey Neuroscience Institute, Melbourne Neuropsychiatry Centre, Mental Health Research Institute, CSIRO, Northern Clinical Research Centre, The Northern Hospital, Turning Point Alcohol Centre.
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**MASTER OF SCIENCE (BIOMEDICAL AND HEALTH SCIENCES)**

**CONTACTS**

**RMH ACADEMIC CENTRE DEPARTMENT LINKS:**
AGEING

1. Exploring data from COHORT (Cooperative Huntington's observational research trial) - a long-term international observational study in Huntington's disease
   Supervisor: Dr Anita Goh
   Other staff: Professor Nicola Lautenschlager, Emeritus Professor Edmond Chiu, Professor David Ames, Dr Samantha Loi, Stephanie Antonopoulos
   Project Site: Academic Unit for Psychiatry of Old Age, St George’s Hospital, Cotham Rd, Kew
   Contact: Anita Goh T: 9816 0513 E: goha@unimelb.edu.au

   Project Description: This long-term observational study was conducted at North American and Australian Huntington Study Group (HSG) sites. The goal of COHORT was to collect information in order to learn more about HD, potential treatments, and to plan future research studies of experimental drugs aimed at postponing the onset or slowing the progression of HD. This study recruited individuals of any age who have clinically diagnosed features of HD in the setting of a confirmatory family history, adults, 18 years of age and older & older adolescents (15-17 years old) who are at-risk for developing HD and adults, 18 years of age and older that are part of an HD family. At each visit, individuals participating in COHORT underwent a clinical evaluation, including blood draws for genetic testing of the CAG polymorphism and for other genetic changes.

   This project involves mining the updated cut of the COHORT database. This revised cut of the COHORT database contains clinical, family history and genotyping data collected from 2/14/06 to 7/07/11. Data is available for about 3,200 subjects. The dataset includes:
   - 1,512 Individuals with manifest HD
   - Approximately 450 Individuals at-risk for HD who carry an expanded number of CAG repeats
   - Approximately 430 Individuals at-risk for HD who do not carry an expanded number of CAG repeats
   - 691 Individuals who have married into the family and serve as controls

   Data from 7,380 visits are included. Some subjects have as many as 6 visits.

   Opportunities:
   - The data and samples will provide researchers with a valuable resource to address a wide variety of research questions in Huntington’s disease.
   - The project offers students an opportunity to develop research skills in a comprehensive international dataset, as well as develop skills in literature reviewing, data analysis, and epidemiological study skills
   - Internationally renowned study and research team with international recognition.
   - Dataset is already complete and accessible (thesis easily achievable in time frame)
   - Publication of results

2. Electrophysiology and drug response of seizures in alzheimer’s disease
   Supervisors: Professor Patrick Kwan, Dr Chris French
   Project Sites: Department of Medicine (RMH), Melbourne Brain Centre at Parkville
   Contact: Professor Patrick Kwan, E: Patrick.kwan@unimelb.edu.au
   Dr Chris French, E: frenche@unimelb.edu.au

   Project Description: People with Alzheimer’s disease (AD) are 10 times more likely than the general population to develop recurrent seizures. The relationship between the pathological processes of AD and abnormal firing of brain cells that manifest as seizures has been poorly studied. We aim to gain a better understanding of the relationship between AD pathology and seizure susceptibility as well as response to AEDs.

   This project will involve comparing the electrophysiological characteristics of brain slices and brain cells between normal and transgenic mice (Tg2576) that mimic human AD in terms of brain pathologies and behaviour. Responses of seizures generated experimentally in the slices and cells to different classes of AEDs will also be measured.
3. Assessing the burden of caregiving of older people with type 2 diabetes  
Supervisors: Dr Irene Blackberry and Dr Briony Dow  
Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.  
Contact: Dr Irene Blackberry T: 8344 3373 E: i.blackberry@unimelb.edu.au  

Project Description: Type 2 diabetes is highly prevalent among the elderly. Yet little is known about their caregivers, who provide a significant amount of informal care to alleviate diabetes burden, support self-care and assist older people to remain in the community. Research evidence on caregiving has primarily been derived from people with cognitive decline or disability and this may not be readily transferrable to type 2 diabetes, a progressive chronic condition. Given that 80% of type 2 diabetes management in Australia is undertaken in general practice and general practice is the first point of call to access care and services, this gives an ideal opportunity to target and provide support for both caregivers and older people with type 2 diabetes living in the community to achieve better diabetes control. This project will answer key questions about burden and challenges faced by the caregivers and their unmet needs in caring for older people with type 2 diabetes using mixed qualitative and quantitative methods. It will have important implications as disease management and self-care activities are increasingly being placed upon older people with type 2 diabetes and their caregivers.

This project offers student 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. Diabetes management in residential aged care facilities  
Supervisors: Dr Irene Blackberry and Dr Briony Dow  
Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.  
Contact: Dr Irene Blackberry T: 8344 3373 E: i.blackberry@unimelb.edu.au  

Project Description: The number of older people living in a Residential Aged Care Facility (RACF) increases with the ageing population. It is estimated that the proportion of Australians aged 65 year and over will be 22% by 2031, of which nearly 10% will be in RACFs. Management of diabetes among older people is complex due to deterioration of physical function and increased prevalence of co-morbid conditions. In addition, geriatric syndromes such as cognitive impairment, falls, incontinence, low body mass index, dizziness, vision impairment or hearing impairment are present in half of people aged 65 years and over. Evidence around diabetes management for older people living in RACF is currently lacking. This project aims to address this research gap by utilising mixed quantitative and qualitative methods to describe current diabetes management and explore unmet needs among health care professionals. This project offers student an opportunity to undertake medical records audit, become familiar with diabetes medications, biochemical and clinical measures. Semi structured interviews will be conducted with health care professionals providing care in RACF.

5. Lifestyle Factors for healthy Ageing  
Supervisors: A/Professor Cassandra Szooke, Professor David Ames  
Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.  
Women’s Healthy Ageing Project (WHAP),  
Contact: A/Professor Cassandra Szooke T:61 3 8387 2224 F : 61 3 9387 9384  
E: cszoeke@unimelb.edu.au  

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. There is opportunity for publication within one year
2. Rich database with lifestyle data from mid-life and spanning over 20 years
3. This project will suit a candidate with an interest in media or commercialisation in the lifestyle and ageing area

6. Measuring Depressive Symptoms in Early Ageing
   Supervisors: A/Professor Cassandra Szoeke, Professor David Ames
   Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
   Women’s Healthy Ageing Project (WHAP),
   Contact: A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384
   E: cszoeke@unimelb.edu.au.

   Project Description: It is predicted that by 2051, 26.1% of Australians will be older than 65 years and 9.4% will be 80 years or older (Australian Bureau of Statistics, 2001). With prevalence rates of depression in the elderly set to rise in accordance with the population surge identifying preventative measures and means of early detection in this population is especially important. The focus of this project will be to examine factors which affect the rating of depressive symptoms on three different standardised and widely used measures in a cross-section of women entering late-life. The Hospital Anxiety and Depression Scale (HADS), the Centre for Epidemiological Studies – Depression Scale (CES-D) and the Geriatric Depression Scale (GDS) will be administered to the cohort of the Women’s Healthy Ageing Project in 2012/2013. Analysis will be conducted examining the consistence of item rating between measures in order to identify correlations between scales. Psychological and social data will also be obtained from the cohort and will allow for the identification of any factors influencing the rating of measures.

   Major benefits from this study are:
   1. There is opportunity for publication within one year
   2. You will have access to a unique database with two decades of psychological and social data
   3. This study would be particularly suited to an individual wishing to gain experience in the areas of geriatric psychology and/or depression.

7. Early detection and prevention of age associated diseases using imaging
   Supervisor: Professor Patricia Desmond, A/Professor Cassandra Szoeke
   Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
   Women’s Healthy Ageing Project (WHAP),
   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

   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. The study has data over 20 years already collected
   2. There is opportunity for a publication
   3. This project will suit a candidate with an interest in neuroimaging

8. Vitamin D deficiency and mood
   Supervisors: A/Professor Cassandra Szoeke, Professor Lorraine Dennerstein, Professor David Ames
   Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052. Women’s Healthy Ageing Project (WHAP),
   Contact: A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384
   E: cszoeke@unimelb.edu.au

   Project Description: 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 research has only recently started to associate low levels of vitamin D to depression and other mood related disorders. The effects of mild to moderate deficiency are less clear-cut, but symptoms may include muscle pain, weak bones, low energy, fatigue, lowered immunity, and symptoms of depression; moods swings, and sleep irregularities. 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 level in the blood, vitamin D level mood disorders may arise. The purpose of this project is to investigate the consequences of mild to moderate
vitamin D deficiency (blood already collected) on mood including depression, anxiety, and wellbeing (measures already collected) in healthy women from the internationally re-known Women’s Healthy Ageing Project (WHAP).

**Opportunities:-**
1. You will have the opportunity to work with an internationally re-known cohort and research team each with international recognition. (Prof L Dennerstein, Prof D Ames, Dr C Szoeke)
2. The study has data over 20 years already collected
3. There is opportunity for publication within one year
4. This project will suit a candidate with an interest in media or commercialisation.

9. **Can statins protect against cognitive decline associated with dementia?**

   **Supervisors:** A/Professor Cassandra Szoeke, Professor David Ames
   **Project Site:** National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052. Women’s Healthy Ageing Project (WHAP)
   **Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384 E: cszoeke@unimelb.edu.au

   **Project Description:** Cognitive impairment is becoming an increasingly researched field in ageing, particularly with dementia being in the top five leading causes of burden in Australia. Despite these already high and increasing prevalence rates, there is no curative treatment for AD. Therefore the identification of individuals who are at increased risk of AD and the implementation of preventive interventions is necessary until a treatment is found. Cardiovascular risk factors, including cholesterol, are typically thought to be associated with an increased risk of dementia. However the use of statins (cholesterol lowering medication) and its effect on cognitive performance has not been thoroughly investigated, particularly assessing duration of use. This research will help us identify the short term and long term effects of cholesterol-lowering medication on cognition, and whether statins can be used as prevention against dementia.

   **Major benefits from this study are:-**
   1. A unique opportunity to work on an Australian dataset with midlife and late-life data collected (data over 20 years).
   2. There is opportunity for publication within one year
   3. This project will suit a candidate with interest in commercialisation and ageing

10. **Nutrient intake and plasma beta-amyloid**

    **Supervisors:** A/Professor Cassandra Szoeke, Professor David Ames
    **Project Site:** National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052. Women’s Healthy Ageing Project (WHAP)
    **Contact:** A/Professor Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384 E: cszoeke@unimelb.edu.au

    **Project Description:** There is increasing evidence to suggest that diet may play an important role in preventing or delaying the on-set of Alzheimer’s disease (AD). Research has reported that a Mediterranean-type diet is associated with a lower risk of prevalent AD. One important pathological hallmark of AD is beta-amyloid (Aβ) peptide deposition in the brain, resulting in formation of plaques. However little is known about the possible association between nutrient intake and Aβ plasma. In this study, we will examine whether dietary intake of nutrients (data already collected from a food frequency questionnaire) is associated with plasma Aβ levels in a cross-sectional analysis of women aged 65 years and over. Aβ levels will be examined using Positron Emission Tomography (PET) scans (data already collected) in collaboration with imaging experts.

    **Major benefits from this study are:-**
    1. The nutritional data set has already been collected
    2. The project will suit a candidate with interest in dietary factors and health
    3. There is opportunity for publication within one year
    4. This project will suit a candidate with an interest in media or commercialisation and is keen for industry interaction
    5. You will gain invaluable experience and networking opportunities in ground breaking research
ALCOHOL

11. **Population drinking and alcohol-related traffic accidents in Australia: A temporal analysis**
   
   **Supervisors:** Jason (Heng) Jiang, Turning Point Alcohol and Drug Centre; Dr. Michael Livingston, CHS  
   **Project Site:** Possibly Turning Point Alcohol and Drug Centre- to be confirmed  
   **Contact:** Jason (Heng) Jiang, T: 8413 8452 E: jasonj@turningpoint.org.au  
   
   **Project Description:** It is a well-established fact that heavy drinking is associated with an increased risk for traffic accidents. The causality of alcohol in accidents probably varies considerably across different historical period and region, depending on levels of consumption and drinking patterns. This study will utilise aggregate-level data to investigate the associations between per capita alcohol consumption and mortality rates from alcohol-related traffic accidents in Australia. The causal role of beverage-specific alcohol consumption (beer, wine & spirit) in accidents will be explored by using a series of time-series analysis techniques. The impact of major changes in alcohol policy on consumption and traffic accidents mortality could be further investigated. The research outcomes could facilitate Australian government policy makers in budget allocation and alcohol policy formulation.  
   
   **Skill acquisition:** Literature review, secondary data analysis; Univariate statistical methods; Public health approaches to alcohol

12. **Alcohol health promotion using mobile phones**
   
   **Supervisor:** Professor Paul Dietze, Co-Head, Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute  
   **Project Site:** Burnet Institute  
   **Email:** pdietze@burnet.edu.au  
   
   **Project Description:** Binge drinking is a serious and common problem among Australian youth. Novel methods of health promotion are urgently needed to address this problem. This project is a scoping study investigating the potential uses of and acceptability of various health promotion approaches to binge drinking, including mobile phone SMS and smart phone apps.  
   
   The project will involve a mixed methods approach working with young people. The project will begin by scoping and evaluating existing health promotion interventions using smart phones. Studies will include quantitative methods - for example, online surveys and analysis of existing data. Qualitative methods including focus groups and in-depth interviews with young people will also be applied. The project could lead to or include the development of a smart phone app and testing of health promotion messages to be sent via SMS.

13. **Street drinking in Footscray**
   
   **Supervisor:** Professor Paul Dietze, Co-Head, Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute  
   **Project Site:** Burnet Institute  
   **Email:** pdietze@burnet.edu.au  
   
   **Project Description:** Public alcohol consumption is a major issue in many local communities. The Footscray Central Business District has been identified as a site in the City of Maribyrnong with public drinking issues, with pockets of drinkers identified across different parts of the CBD. This study will involve structured observation of the Footscray CBD along with interviews with in-depth interviews with public drinkers about their experiences of drinking and choices of drinking locations.

14. **Why do some people with hepatitis C continue to drink?**
   
   **Supervisor:** Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute  
   **Project Site:** Burnet Institute  
   **Contact:** Hellard@burnet.edu.au  
   
   **Project Description:** 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.
ARTHRITIS AND INFLAMMATION RESEARCH

15. Examining the Quality of Orthopaedic Care in Australia
Supervisors: Dr Megan Bohensky /Professor Danny Liew
Project Site: Melbourne EpiCentre, Royal Melbourne Hospital (Block E, Level 7), Department of Medicine, University of Melbourne
Contact: Dr Megan Bohensky T: 9342 8285 |E: megan.bohensky@unimelb.edu.au; Professor Danny Liew T: 9342 8285 |E: dyliew@unimelb.edu.au

Background and hypothesis: This study is part of a larger study examining various dimensions of healthcare quality in orthopaedic care. This first phase of the study seeks to identify the incidence of adverse outcomes from major and minor orthopaedic surgeries using routinely collected data. The second phase of the study will employ cost-modelling and decision-modelling to understand the cost implications if preventative methods were to be utilised according to different strategies.

Methods: We have data from the department of health on all orthopaedic surgeries (public & private hospitals) performed in Victoria from a previous study (July 2000- June 2009) that we plan to follow-up to identify adverse outcomes (specifically thromboembolism and infections) using data linkage. By linking our data to disease registries and emergency presentation data, we can identify adverse outcomes related to orthopaedic surgeries.

Acquired skills: This project would suit a student that is seeking to learn skills in data analysis, data linkage, regression analysis, database management and cost-effectiveness analysis. Work hours would also be flexible.

BIOLOGY — BONE

16. Bone health in children and young people with epilepsy treated with anti-epileptic drugs (AEDs)
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

Project Description: 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.

17. Hallux valgus: is it by nature or by nurture? A twin study
Supervisor: Prof John Wark, A/Prof Anita Wluka, Prof Hylton Menz
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.

18. Enhancing fracture risk prediction in osteoporosis
Supervisors: Professor John Wark, Ms Sue Kantor and Dr Andrew Briggs
Project Site: Department of Medicine (RMH), University of Melbourne, Parkville Campus
Project Description: Osteoporosis is a common condition where bones are fragile leading to fractures, predominantly of hip, spine, forearm and ribs. Dual energy X-ray 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.

19. Validation of bone density testing in women of south Asian background

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

Project Description: Osteoporosis is a common condition where bones are fragile leading to fractures, predominantly 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 X-ray 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.

20. Assessing the clinical usefulness of peripheral quantitative CT in fracture prediction

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

Project Description: Bone density measurement by dual energy X-ray 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.

21. 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

Project Description: 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.

**22. Does the use of health and community-based services following an osteoporotic fracture vary by socio-economic status?**

Supervisors: Dr Sharon Brennan and A/Prof Kerrie Sanders
Project Site: NWAC Sunshine Hospital, St Albans
Contact: Dr Sharon Brennan T: 5226 7915 E: sbrennan@unimelb.edu.au

**Project Description:** Australia’s healthcare policy aims to provide equal access to healthcare services for all Australians yet this goal is often not met. This project will help identify gaps in access to healthcare post-fracture between adults from a range of socio-economic backgrounds. The data is already collected from participants in the AusICUROS study. The acronym refers to the Australian arm of the International Costs and Utilities Related to Osteoporotic fractures initiated through the International Osteoporosis Foundation. The study is funded through the NHMRC with supplementary funding from Merck Pty Ltd. Over 800 participants with recent fracture and aged at least 50 years old have been recruited from the eight study centres around Australia. Quality of life and healthcare utilisation data has been collected at pre-determined time-points and will be used in this project.

**23. Are annual physical functioning assessments predictive of falls risk in older women?**

Supervisors: Dr David Scott and A/Prof Kerrie Sanders
Project Site: NWAC Sunshine Hospital, St Albans
Contact: A/Prof Kerrie Sanders T: 8395 8114 E: ksanders@unimelb.edu.au

**Project Description:** We have previously conducted a large randomised placebo-controlled trial in older women with the primary outcomes of falls and fractures. Falls were ascertained on a self-reported monthly basis for 3 to 5 years with all details of the falls events recorded. The study is now completed and investigators have been ‘unblinded’. Approximately 50 participants in the placebo group have had annual assessments of balance, gait, and muscle strength in conjunction with data collection on medication use and medical conditions.

This project would investigate an association between risk of falling and the longitudinal results of their annual physical functioning assessments among these women who were randomised to receive placebo. The work is unique in the 5-year duration of follow-up and robust methodology used to ascertain falls. The results will produce sound evidence to support or otherwise the validity of physical function assessments in older women at increased risk of falls and fractures in predicting future risk of falls.

**24. Are there differences in the characteristics of older women who fall at home compared with those who fall outside the home?**

Supervisors: Dr David Scott and A/Prof Kerrie Sanders
Project Site: NWAC Sunshine Hospital, St Albans
Contact: A/Prof Kerrie Sanders T: 8395 8114 E: ksanders@unimelb.edu.au

**Project Description:** Falls are an important health problem with about 30% of people aged 65 years and older having at least one fall each year. We have previously conducted a large randomised placebo-controlled trial in older women with the primary outcomes of falls and fractures. Falls were ascertained on a self-reported monthly basis for 3 to 5 years with all details of the falls events recorded. The study is now completed and investigators have been ‘unblinded’. The circumstances and characteristics of the 2,512 falls that occurred in the 1,125 participants in the placebo group have been recorded.

Through database management skills and basic statistical analysis this project involves developing a typical profile of the older woman who falls in their familiar home environment and investigate differences in ‘falls risk behaviour’ between those that have fallen at home and older women who fall outside the home. The results will provide unique Australian data particularly relating to the longitudinal 5-year duration of falls ascertainment and the level of detail collected surrounding each fall event. The work could form the basis for new strategies to prevent falls in older persons based on whether they are in familiar environments or not.
25. How does dietary calcium intake affect health outcomes?

Supervisors: Prof Peter Ebeling, Prof Dallas English and A/Prof Kerrie Sanders
Project Site: NWAC Sunshine Hospital, St Albans
Contact: Prof Peter Ebeling T: 8395 8115 E: peterre@unimelb.edu.au

Project Description: There is a concern that calcium supplement use is associated with an increased risk of adverse cardiovascular outcomes. Increasing dietary calcium may improve bone health and reduce fractures without increasing the risk of adverse cardiovascular events, including acute myocardial infarction. We have established a database of health outcomes over 20 years from the Health 2020 cohort, a longitudinal study of over 41,000 Victorians. All participants have had dietary calcium intake assessed on two occasions.

Through database management skills and basic statistical analysis this project involves relating diet calcium with health outcomes during the study. The results will provide important data regarding effects of diet calcium on health outcomes in a large established cohort.

26. How does being born with extremely low birth weight or extremely pre-term affect bone mass, body composition and insulin sensitivity?

Supervisors: Prof Peter Ebeling, Prof Glenn McConell and Dr Gunveen Kaur
Project Site: NWAC Sunshine Hospital, St Albans
Contact: Prof Peter Ebeling T: 8395 8115 E: peterre@unimelb.edu.au

Project Description: There is a rapidly increasing prevalence of extremely low birth weight (ELBW; <1000g birth weight) and extremely preterm (EPT; <28 weeks’ gestational age) survivors. Although 55% of <1000g babies have low bone mineralization, the long-term consequences of metabolic bone disease (MBD) of prematurity on later bone health are not well described. In particular, the influence of surviving ELBW/EPT birth on the peak bone mass achieved has not been assessed. Similarly, ELBW/EPT survivors also develop obesity and insulin resistance, that continues into young adulthood, increasing their lifetime risk for type 2 diabetes.

Through database management skills and basic statistical analysis this project involves assessing bone mass, body composition and insulin sensitivity in ELBW/EPT survivors from an established cohort at 8 years of age. The results will provide important data regarding bone mass, body composition and diabetes risk in a large established cohort.

BIOLOGY —WOMEN’S HEALTH

27. The young female health initiative (YFHI)

Supervisors: Professor Suzanne Garland, Professor John Wark, Dr Elisa Young
Project Site: Department of Medicine (RMH), University of Melbourne, Department of Microbiology and Infectious Diseases, RWH, Parkville Campus
Contact: Prof Suzanne Garland: E: Suzanne.Garland@thewomens.org.au
Prof. John Wark: E: jdwark@unimelb.edu.au
Dr Elisa Young: E: elisa.young@mcri.edu.au

Project Description: 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 sociological 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.
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.

28. 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; Dr Elisa Young: elisa.young@mcri.edu.au; A/Prof Sepehr Tabrizi: sepehr.tabrizi@thewomens.org.au;

Project Description: 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.

29. 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: parogers@unimelb.edu.au or Dr Marina Zaitseva: zaitseva@unimelb.edu.au

Project Description: 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.

30. Regulation of Nerve Fibre Growth in Eutopic and Ectopic Endometrium: Links with endometriosis-Associated Pain

Supervisors: Dr Jane Girling and Prof Janet Keast

Project Site: Department of Obstetrics and Gynaecology, Royal Women’s Hospital, Department of Anatomy and Neuroscience, Parkville

Contact: Dr Jane Girling T: 8345 3721 E: jgirling@unimelb.edu.au; Prof Janet Keast T: 9035 9759 E: janet.keast@unimelb.edu.au

Project Description: Endometriosis affects 8-10% of reproductive-aged women. Women living with endometriosis endure chronic pelvic pain, including severe menstrual pain, pain during sexual intercourse and pain during defecation. The personal and healthcare costs of endometriosis are huge. Various types of nerve fibres are present in endometriotic
lesions and are thought to mediate endometriosis-induced pain. There are also distinct patterns of nerve fibres present in the uterus; the distribution of these fibres is abnormal in women with endometriosis.

The overall aim of this research is to elucidate how aberrant uterine innervation leads to endometriosis-induced pain. The overall hypothesis is that endometriosis-associated pain reflects an imbalance of localised neuronal growth factors and chemo-repellents in uterine tissues and endometriotic lesions, resulting in aberrant innervation and nociceptive function.

Projects will be available to examine the expression of proteins that are critical for initiating and directing new nerve growth (neurotrophic and guidance factors), and the features of nociceptor nerves in carefully characterised clinical samples (uterus, endometriotic lesions) collected on the basis of presence/absence of endometriosis and specific pain symptoms. Potential techniques for analysis include laser-capture microscopy and quantitative PCR, multi-label fluorescence immunohistochemistry and confocal microscopy. Projects may also be available to examine the mechanisms responsible for abnormal nerve growth and function in endometriotic lesions using a well validated rodent model of endometriosis. This may include visualising individual nociceptor neurons that have innervated endometrial lesions to investigate how they have developed abnormal function.

**BRAIN INJURY**

31. **Targeting Tau phosphorylation to treat and prevent acquired epilepsy, neurodegeneration and neuropsychiatric disease following a brain injury**

*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.

32. **Post traumatic brain injury and epilepsy onset: Imaging the brain to investigate neural circuits and appropriate therapy interventions**

*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

*Project Description:* 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.
Bench to Bedside - Medical Research

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 neurobehavioural 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.

33. **Repeated brain concussions – understanding mechanisms and proposing new treatments**

**Supervisors:** Dr. Sandy Shultz, Prof. Terence O’Brien, Assoc. Prof. Chris Hovens, Prof. Seong-Seng Tan

**Project Site:** Department of Medicine, The Royal Melbourne Hospital, Melbourne Brain Centre, University of Melbourne

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

**Project description:** Traumatic brain injuries (TBI) are an international health concern and growing socioeconomic problem. To date, no effective pharmaceutical treatment for TBI exists. Concussions, or mild TBI, account for 80% of TBI cases. However, despite the high incidence of concussion, there is a poor understanding of what occurs in the brain following this injury and much debate surrounding the medical management and treatment of concussion. Of particular concern are athletes and soldiers, who are at risk of suffering multiple concussions, as growing evidence indicates that repeated concussions can result in chronic neurological impairments and neurodegenerative disease. As little is known regarding what pathophysiological mechanisms actually contribute to the disease process, there are currently no specific treatment options for concussions and patients are simply instructed to rest until symptoms subside. However, soldiers, athletes, and other high-risk individuals represent a unique population where pre- and/or chronic treatment with neuroprotective compounds is conceivable and should be explored. Considering the limited understanding, high incidence, lack of effective treatment, and increased public concern it is imperative that research is carried out to address the issue of concussion.

Given the limitations associated with studying the pathophysiological mechanisms and novel treatments of TBI in the clinical setting, the use of animal models is beneficial. The lateral fluid percussion injury is the most commonly used and well-validated animal model of TBI, and our lab recently developed a repeated injury schedule that is similar to what might occur in athletes and soldiers. The proposed project will utilize this novel model with the goal of examining the underlying mechanisms and potential treatments of concussion.

**Aim 1** will examine the role of hyperphosphorylated tau in repeated concussion, and its potential treatment with sodium selenate, a potent inhibitor of hyperphosphorylated tau. Our previous work has found sodium selenate to be neuroprotective after severe TBI in rats.

**Aim 2** will examine the role of Neddd4-WW domain-binding protein 5 (Ndfip1), an endogenous neuroprotective protein, in repeated concussion, and the use of a novel cobalt complex treatment to up-regulate Ndfip1. Ndfip1 is up-regulated in surviving neurons post-TBI, and cobalt complexes are capable of increasing Ndfip1 expression in the brain. Therefore, increasing Ndfip1 expression in rats with cobalt complex treatment may reduce neuronal death and improve outcome after repeated concussions.

Both aims will incorporate advanced neuroimaging, behavioural, molecular, and immunohistochemical techniques. Taken together, these projects will provide novel data regarding the underlying mechanisms and potential treatments of concussions, and hold important implications for their management in the clinical setting.
CANCER

34. **Stat3-mediates Resistance to EGFR targeted therapy in Cancer**  
*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  

**Project Description:** 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.

35. **The Molecular Determinates of Brain Tumour Resistance to Temozolomide**  
*Supervisors:* Dr Rodney Luwor and Mr Stanley Stylli  
*Location:* Dept of Surgery, Level 5, Clinical Sciences Building, Royal Melbourne Hospital  
*Contact:* Dr Rodney Luwor T: 9342-7703, E: rluwor@unimelb.edu.au or Mr Stan Stylli T: 9342-7703, E: stanley.stylli@mh.org.au  

**Project Description:** Glioblastoma Multiforme (GBM) is the most devastating and aggressive tumour of the central nervous system accounting for approximately 50% of all primary brain tumours. Surgery, followed by irradiation and concomitant and adjuvant temozolomide is now considered the standard of care for GBM patients. However, despite temozolomide treatment, the overall prognosis remains abysmal for GBM patients with a median survival of only 12-15 months. The presence of pre-existing intrinsic resistance and the ability of GBM tumours to develop or acquire resistance represents a major challenge to successful treatment. Resistance to temozolomide is common; however the exact mechanisms and key molecules that mediate resistance are not clearly elucidated. This honours project seeks to explore potential molecular candidates in mediating resistance to temozolomide, using brain tumour cell lines and human brain tumour tissue archived within our department. Furthermore, this project has the scope to evolve into a PhD project starting in 2014 pending the ability of the incumbent honours student.

**Skills/Techniques acquired:** Cell biology techniques including Cell transfections, western blotting, immunohistochemistry, confocal microscopy, luciferase reporter assays, RT-PCR and potentially animal handling and injecting.

36. **The role of the Eph/Ephrin signaling system in the progression of colon cancer**  
*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  

**Project Description:** 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.

37. **Exploring a Tumour-Suppressor Function for the Transcription Factor, IRF6**  
*Supervisor:* A/Prof Glen Scholz  
*Location:* Bio21 Institute
Contact: A/Prof Glen Scholz; Tel: 8344-3298; E: glenms@unimelb.edu.au

**Project Description:** The coordinated down-regulation of mesenchymal cell proliferation, coupled with the terminal differentiation of mesenchymal cells into different types of epithelial cells, is critical for normal tissue development. Dysregulation of this process has the potential to result in the growth of tumours. The transcription factor, Interferon Regulator Factor 6, plays a critical role in regulating keratinocyte (skin epithelial cells) differentiation. Significantly, mutations in IRF6 have recently been identified in squamous cell tumours; thus, suggesting that IRF6 is a tumour suppressor protein. In this project you will investigate the potential tumour-suppressor mechanisms of IRF6 in the context of oral cancer.

**Techniques:** In this project you will gain expertise in a variety of techniques, including mammalian cell, siRNA-mediated gene silencing, PCR-mediated mutagenesis and cloning, Real-Time PCR, Western blotting, and confocal microscopy.

**Scholarships:** Available to eligible students

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**CANCER – WOMEN’S RESEARCH**

38. **microRNAs as puppeteers of ovarian cancer chemoresistance**
   
   **Supervisor:** Dr Nuzhat Ahmed and Dr Mark Ziemann
   
   **Project Site:** Women’s Cancer Research Centre, Royal Women’s Hospital
   
   **Contact:** Dr Nuzhat Ahmed, Women’s Cancer Research Centre, RWH. Tel: 8345 3734; E: Nuzhat.Ahmed@thewomens.org.au

**Project Description:** Ovarian cancer is the second most common gynaecological cancer diagnosed in Australian women. Approximately 80% of patients diagnosed with ovarian cancer initially respond to chemotherapy. However, most (almost all) return after few months with resistant recurrent disease resulting in mortality within five years. Recent data in our laboratory suggests that a set of small non-coding RNAs commonly known as microRNAs (miRs) associated with cancer stemness may be responsible for chemoresistance (platinum and taxol) in ovarian cancer patients. The aim of this study is to investigate the involvement of these miRs in the development of chemoresistance in ovarian cancer.

**Methods:** Selected miRs identified by next generation sequence will be validated in ovarian cancer cell lines (treated with or without chemotherapy), and also in tumor cells isolated from the ascites of chemonaive and chemoresistant ovarian cancer patients by quantitative real-time polymerase chain reaction. Levels of targeting miRNA will be manipulated in ovarian cancer cell lines by mimics and inhibitors. Functional assays in the manipulated cells such as sensitization of cells to chemotherapy, changes in the metastatic features such as migration/invasion, and activation of signaling pathways will be determined by MTT assay, XCELLigence, Western blot, immunofluorescence, q-PCR, etc.

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**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.

39. **Quantitative and qualitative analysis of atherosclerotic plaque and stents using coronary optical coherence tomography**
   
   **Supervisor:** A/Professor Peter Barlis
   
   **Project Site:** NWAC, Northern Hospital, Epping.
   
   **Contact:** A/Professor Peter Barlis  T: 03 8405 8000  E: pbarlis@unimelb.edu.au

**Project Description:** 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

40. **Do the coronary small vessels respond less well to medication in patients with diabetes or renal failure**

**Supervisors:** Professor Judy Savige and A/Prof Deb Colville  
**Project Site:** NWAC, Northern Hospital, Epping  
**Contact:** Professor Judy Savige, T 8405 8823, jasavige@unimelb.edu.au

**Project description:** Most research into the causes of heart disease has focused on disease in the coronary arteries but the importance of small vessel disease is recognized increasingly. However the coronary small vessels are difficult to study. Nevertheless whenever the small vessels in the heart are affected, small vessels are diseased throughout the body. This includes the vessels in the retina, which are very accessible using a retinal camera and photography. So we propose to examine the retinal small vessels as a model for the coronary arterioles and determine whether renal failure or diabetes means these vessels are diseased and respond less well to medication.

This study involves recruiting patients from the wards with renal failure or diabetes and testing the effect of a tablet that usually dilates small vessels. You will help the patient fill out a questionnaire and also take their blood pressure and retinal photographs, and then review the photographs under the supervision of an ophthalmologist. In addition the retinal photos will be sent to the Centre for Eye Research Australia for the vessel diameters to be measured precisely. The aim of this project is then to determine whether small vessels are less responsive in diabetes and renal failure, and whether medication doses should be increased. The analysis includes univariate and multivariate statistics and backwards linear regression (we will help you with the statistics).

**Techniques to be used and skills acquired:** This project involves a lot of patient contact, going onto the wards and getting to know hospital staff, learning how to take retinal photographs, and how to interpret abnormalities, as well as statistics.

**Feasibility:** We already have Human Research Ethics Committee Approval for this project and many of the medical students who have undertaken similar projects during an AMS yyear have achieved a publication from their work.  
*This project is also listed under Opthalmology*

CLINICAL RESEARCH

41. **Are readmissions to The Northern Hospital related to hospital acquired diagnoses in a previous admission?**

**Supervisors:** Dr Terri Jackson, Dr Anastasia Hutchinson, Prof Peter Brooks  
**Project Site:** Northern Clinical Research Centre (NCRC), The Northern Hospital, Epping  
**Contact:** Dr. Terri Jackson T: 044 872 7240 E: terri.jackson@nh.org.au

**Project Description:** Routine hospital demographic and diagnosis data are used in many health care systems to investigate and improve inpatient care. Diagnosis data in Australia includes 'condition onset' (timing) markers that distinguish comorbidities (diagnoses documented as present on admission) from hospital-acquired diagnoses. A body of research has demonstrated that such markers allow for identification of the range of complications and adverse events that compromise patient outcomes. This project seeks to use information on hospital-acquired diagnoses to quantify the proportion of readmissions to The Northern Hospital that are attributable to conditions that arose during a previous hospitalisation.

**The specific aims of this project are:**
- To estimate the proportion of readmissions associated with a previous hospital-acquired diagnosis and attributable additional days of stay;
• To use multivariate analysis to identify the contributions of demographic characteristics, principal diagnosis, and hospital-acquired diagnoses to the probability of readmission;

• To use the Classification of Hospital Acquired Diagnoses (CHADx) to characterise the major contributors to readmission rates and days of stay at The Northern Hospital.

Skills: The skills expected to be learnt from this project include: secondary analysis of large hospital data sets (including data validation and cleaning), data linkage, descriptive statistics and multivariate logistic regression.

COLORECTAL MEDICINE AND GENETICS

42. Pharmacogenomics in IBD
Supervisors: Professor Finlay Macrae and Prof Les Sheffield
Project Site: Colorectal Medicine and Genetics, The Royal Melbourne Hospital
Contact: Prof Finlay Macrae E: finlay.macrae@mh.org.au
Project description: The Royal Melbourne Hospital, with GenesDX, is pioneering the implementation of a pharmacogenomics clinical support program. In the case of inflammatory bowel disease, this relates to the use of thiopurines. The project will assist in the implementation of the program and its evaluation. It will guage the clinical utility of TPMT genotyping and the clinical decision support tools that will be built into the program, and thiopurine metabolite testing, in the management of inflammatory bowel disease
This project is also listed under Pharmacogenetics and Personalised Medicine.

43. Bioinformatics in colorectal cancer genetics and prevention
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

Project Description: 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 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?

44. The Human Variome Project (HVP) and familial bowel cancer
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

Project Description: 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

45. Biogrid and IBD data basing
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

Project Description: 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
46. **Capsule Colonoscopy as a Screen for Colorectal Cancer**  
* 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  

**Project Description:** 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 test 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.

47. **Dietary prevention of adenomas in familial adenomatous polyposis**  
* 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  

**Project Description:** 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.

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**DERMATOLOGY**

48. **Assessment of the Digital Dermoscopic diagnosis and clinical 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 Email: george.varigos@mh.org.au  

**Project Description:** 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.

49. **Cardiovascular risk and outcomes in PSORIASIS patients**  
* Supervisors: Dr Anna Braue, Dr George Varigos  
* Project Site: Department of Dermatology and Dept Medicine RMH  
* Contact: Dr George Varigos 93424531 Email: dermatsec@mh.org.au  

**Project Description:** Recently it has been shown that severe psoriasis is associated with significant cardiovascular mortality.  

In this project you will be studying the effects of continuous Biologic systemic therapy on the cardiovascular risk of patients with severe plaque-type psoriasis.  

In the RMH Psoriasis Registry we have a total of 120 consecutive patients receiving biologics systemic treatment for their severe plaque-type psoriasis for more than 3 years. The clinical course of cases are monitored over several years, along with comprehensive laboratory monitoring and PASI score of Psoriasis severity. Measuring the Framingham index and several cardiac risk markers together with changes of weight BMI and metabolic tests will be compared with PASI responses and Cardio Vascular Outcomes.

50. **Cardiovascular and Metabolic measures including the using endoPat Assessments of peripheral arterial tone in PSORIASIS patients on beginning on Biologic therapy compared to non biologic treatment over 16 weeks**  
* Supervisors: Dr Anna Braue, Dr George Varigos
Project Site: Department of Dermatology and Dept Medicine RMH
Contact: Dr George Varigos  T: 93424531  E: dermsec@mh.org.au

Project Description: Recently it has been shown that severe psoriasis is associated with significant cardiovascular mortality or morbidity and that the Biologics (anti TNF agents) used may reduce these. In this project you will be comparing the EndoPat Assessments and cardiovascular and metabolic measures in patients with severe plaque-type psoriasis on conventional therapy and those commencing on Biologic systemic therapy, over 16 weeks with comparable PASI measures. The benefits of commencing Biologics compared to time on conventional therapies may be important aspect of this study to improve prescribing policy for patient quality of care and outcomes.

ELECTROPHYSIOLOGY

51. 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

Project Description: 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).

52. 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

Project Description: 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).

53. Investigating inhibitory synaptic function in a mouse model of Autism
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 Neurexin-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.

### 54. How do Anti-Epileptic Drugs Work?

**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/](http://sites.google.com/a/hfbg1.net/crf_lab/)

**Project Description:** 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.

### 55. How do Antipsychotic Drugs Trigger Seizures?

**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/](http://sites.google.com/a/hfbg1.net/crf_lab/)

**Project Description:** 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.

### 56. Multi-Electrode Recording in the Rat Brain

**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/](http://sites.google.com/a/hfbg1.net/crf_lab/)

**Project Description:** 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

57. 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

Project Description: It is unclear how large scale electrical oscillations in the CNS are produced with epileptic seizures. Simple hyper-excitability 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.

58. How do people with epilepsy respond to treatment?
Supervisors: Professor Patrick Kwan, Professor Martin Brodie
Projects sites: Department of Medicine (RMH), University of Melbourne; Epilepsy Unit, Western Infirmary, Glasgow, Scotland
Contact: Professor Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: Seventy million people have epilepsy with 34–76 per 100,000 developing the condition every year. To formulate rational treatment plans, it is important to understand the different clinical courses and patterns of response to antiepileptic drugs, ideally by following outcomes from the point of treatment initiation. Such a study has been conducted at the Epilepsy Unit of the Western Infirmary, Glasgow, Scotland, with findings reported in a series of publications in high impact journals [e.g. New England Journal of Medicine 2000;342:314-9; Neurology 2012;78:1548–54]. The expanding database contains information on the largest studied cohort of newly diagnosed patients followed up for up to 26 years. This project will perform further analysis focusing on response to the initial therapies and their relationship with long-term treatment outcomes and development of pharmacoresistance. The student will spend a period of attachment at the Epilepsy Unit in Glasgow where the database is housed under the direction of Professor Martin Brodie. Basic knowledge and skills in biostatistics is required.

59. Expression of efflux multidrug transporters in temporal lobe as a biomarker for outcome after surgery for pharmacoresistant temporal lobe epilepsy
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: obrienjt@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 pharmacoresistant 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 bloting.

Reference

60. Genetics of epilepsy in Han Chinese
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

Project description: Affecting up to 1% of the population, epilepsy is the most common chronic neurological disorder. Twin and family studies suggest that epilepsy is highly heritable but its genetic architecture in most patients remains unknown. Using a genome-wide association study (GWAS) approach that compared the frequencies of over 400,000 common single nucleotide polymorphisms (SNPs) across the genome between cases and controls, we have identified potential SNPs predisposing to epilepsy in Han Chinese in Hong Kong. These SNPs will be tested in an additional 2000 epilepsy patients recruited in rural China.

This honours project will analyse the clinical and genetics data to determine the validity of the phenotyping, and to identify significant SNPs associated with epilepsy in this largest Han Chinese cohort ever studied. The project is suitable for students with background in statistical genetics and bioinformatics.

61. Evaluation of Dynamin Inhibitors as Novel Therapies for Epilepsy
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: robinson@cmri.com.au
Dr. Nigel Jones T: 9035 6402 E: ncjones@unimelb.edu.au

Project Description: 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.

62. Investigations into the role of neuropeptide Y in a genetic rat model of absence epilepsy
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
**Project Description:** 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.

### 63. Antiepileptic drugs and effects on bone health

**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

**Project Description:** 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.

### 64. Investigation of the role of Y receptors in the seizure suppression effect of valproate in a rat model of genetic generalised epilepsy

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

**Project Description:** 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.

65. Sodium Channels in Epilepsy
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.

66. 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: njones@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 and human patient brain samples, several projects, available as Honours, Masters or PhD projects, are exploring this hypothesis:

Research project 1: Characterisation of DNA methylation changes in epilepsy
Using genome-wide and gene specific approaches, this project will characterise the changes in DNA methylation which occur during the course of epilepsy development, and in chronic disease. For this, we will use tissue from animal models, and also surgically resected brain tissue from epilepsy patients.

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-derived 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: Pharmacological inhibition of epigenetic machinery and the development of disease
This project will use well-established inhibitors of DNA methylation to prevent the aberrant changes in DNA methylation after epileptogenic brain injury. We will then assess the ability of these interventions to block the development of epilepsy.

Research project 4: 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 epigenetic modifiers 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 lentiviral constructs; techniques specific for epigenetic analysis, including bisulfite conversion, pyrosequencing, Methyl-DNA immunoprecipitation, allelic sequencing, and other molecular biology techniques, such as real-time qPCR, Western blotting, gel electrophoresis.

67. Stargazin and AMPA receptor expression at cortical synapses in epileptic rats

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 Description: 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 generalised 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).

68. Dynamin activation in acute epileptic seizures and chronically epileptic rats

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 Description: 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.

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### 69. Investigating the role of a Cav3.2 calcium channel mutation in contributing to the epileptic phenotype using congenic rat strains and a knock in mouse model

**Supervisors:** Dr Kim Powell, Professor 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 genetic generalised epilepsy (GGE), 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 is 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 the mechanisms by which they act to result in epilepsy remains to be determined. In an important, well characterised model of GGE with absence seizures, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), our research group has discovered a homozygous, missense, single nucleotide (G to C) mutation in the Ca(v)3.2 T-type calcium (Ca2+) channel gene (Cacna1h) resulting in an amino acid from arginine to proline (R1584P). The R1584P mutation correlates with the epileptic phenotype in GAERS doubled crossed with Non-Epileptic Control (NEC) rats. Additionally, the R1584P mutation increases the rate of recovery from channel inactivation in a splice variant specific manner, producing a predicted gain-of-function phenotype.

We have a knock-in mouse model of the R1584P Ca(v)3.2 mutation as well as two congenic rat strains; a NEC strain expressing the R1584P mutation and a GAERS strain without the R1584P mutation which we will use as tools to investigate the neurobiological mechanisms by which the R1584P mutation results in is pro-absence effects. These experiments will explore further the specific role played by the R1584P mutation in the absence phenotype of GAERS and the effect of genetic background.

**Project 1:** To examine the expression of spike-wave-discharges (SWD) in two different congenic rat strains, an NEC congenic strain expressing the R1584P mutation and a GAERS congenic rat strain without the R1584P mutation.

**Project 2:** To characterise the epileptic phenotype of a knock-in mouse expressing the R1584P mutation and to investigate the effect of genetic background.

**Skills**

The skills expected to be learnt from this project include: Small animal handling and surgery, EEG recording and analysis.

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### 70. Investigating molecular and physiological determinants of Sudden Unexplained Death in Epilepsy in acquired and genetic animal models of epilepsy

**Supervisors:** Dr Kim Powell, Professor 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:** 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. Furthermore, its functional role becomes more marked in...
the process of pathological cardiac hypertrophy and heart failure. Thus HCN ion channels are an attractive candidate for investigating molecular mechanisms of SUDEP. Our research has identified a cardiac transcriptional channelopathy of HCN2 channels, with associated detrimental cardiac electrophysiological changes, in rat models of both genetic generalised epilepsy (GAERS) and acquired temporal lobe epilepsy (kainic acid (KA) induced post-status epilepticus (SE)). Several projects will be offered to investigate different aspect of SUDEP and cardiac dysfunction in animal models of genetic and acquired epilepsy

**Project 1:** To investigate the molecular and epigenetic mechanisms contributing to the epilepsy-induced HCN2 transcriptional repression.

**Project 2:** To investigate if decreased HCN2 expression translates to a decrease in HCN channel current ($Ih$) in cardiomyocytes in animal models of genetic and acquired epilepsy.

**Project 3:** To investigate if by pharmacologically suppressing seizures we can alleviate the altered cardiac electrophysiological function and HCN2 transcriptional repression

**Skills:** The skills expected to be learnt from this project include: Small animal handling and surgery, Drug testing in animal models of epilepsy, electrophysiology recordings and analysis, biochemical and molecular analysis (real time PCR, western blotting).

71. **Role of the in utero nutritional environment on the development of epilepsy and autism spectrum disorders (ASD)**

   **Supervisor:** Dr Krista Gilby, Professor Terence O’Brien, A/Professor Mary Wlodek
   **Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville
   **Contact:** Krista Gilby T: 9035 6353 E: kgilby@unimelb.edu.au

   We have used selective breeding processes to develop two unique rat strains; one that is inherently seizure-prone (FAST) and another that is seizure-resistant (SLOW). Remarkably, over generations, as FAST rats became more seizure-prone, they naturally began to show ASD-like behavioural patterns. We have also determined that the seizure-prone FAST rats have a natural deficiency in circulating free fatty acids compared to SLOW rats, despite being fed the same diet. Similar fatty acid deficiencies have been documented in children with epilepsy and ASD. Further, our recent data suggests that disparities in metabolic strategies between these strains may have been programmed by differing in utero nutritive environments. This study will compare placental regulation of nutrient transport and growth factor expression in FAST versus SLOW mothers during pregnancy.

72. **Investigating the effects of fetal growth restriction on rates of neurodevelopment**

   **Supervisor:** Dr Krista Gilby, Professor A/Professor Mary Wlodek
   **Project Site:** Department of Physiology
   **Contact:** Mary Wlodek E: m.wlodek@unimelb.edu.au

   Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing disease as adults. Babies that are born small also often exhibit altered rates of neurodevelopment. Using our model of uteroplacental insufficiency we will determine whether neurodevelopmental trajectories are altered in growth restricted rat pups. This study will involve several behavioural assessments in rat pups and molecular comparisons between brain regions of offspring born small and those of normal birth weight.

73. **Investigating the neurological impact of fetal growth restriction**

   **Supervisor:** A/Professor Mary Wlodek
   **Project Site:** Department of Physiology
   **Contact:** Mary Wlodek E: m.wlodek@unimelb.edu.au

   Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing disease as adults. Recently, many neurological disorders that develop in adults, including schizophrenia and some epilepsies, have been mechanistically linked to events occurring during neurodevelopment. The aim of this project is to determine the effects of fetal growth restriction on neurological function and behaviour in adults. This project will involve several behavioural assessments that will compare seizure susceptibility, learning capacity, anxiety, hyperactivity and impulsivity in offspring born small and those of normal birth weight.

74. **Epilepsy and Autism: Exploring environmental factors that predispose individuals towards these comorbid neurodevelopmental disorders**

   **Supervisor:** Dr Sandy Shultz
   **Project Site:** Department of Medicine (RMH), MBC Neurosciences Building, Parkville
   **Contact:** Sandy Shultz E: sandy.shultz@unimelb.edu.au

   Epilepsy and autism spectrum disorder (ASD) are highly comorbid and there is a growing need to examine how environmental factors influence pathogenesis in these conditions. Propionic acid (PPA) and related short chain fatty acids...
have recently been identified as potential risk factors for ASD. Although largely derived from the gut, propionic acid (PPA) and related short chain fatty acids can readily gain access to the brain, where they can induce a diverse range of neuropathological processes capable of altering both brain function and behavior. Using our unique rodent model, in which contrasting traits relevant to epilepsy and ASD are expressed in two rat strains, we will investigate the effects of PPA on seizure sensitivity and ASD-like behavioural profiles. In this way, we will examine suspected links between diet, metabolic and/or gastrointestinal factors in these interrelated disorders.

75. Epilepsy and Autism: Investigating molecular mechanisms that predispose individuals towards these comorbid neurodevelopmental disorders

Supervisor: Dr Krista Gilby, Professor Terence O’Brien, A/Professor Mary Wlodek
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Terence O’Brien E: obrientj@unimelb.edu.au

Symptom expression can be very similar in children diagnosed with various epilepsies and autism spectrum disorder (ASD). Such a degree of clinical overlap suggests a common dysfunction in central nervous system development lead to the onset of these interrelated disorders. We have used selective breeding processes to develop two unique rat strains; one that is inherently seizure-prone (FAST) and another that is seizure-resistant (SLOW). Remarkably, over generations, as FAST rats became more seizure-prone, they naturally began to show ASD-like behavioural patterns. This project will compare neurodevelopmental gene expression in FAST versus SLOW rats in order to identify molecular events that might be responsible for the co-expression of increased seizure sensitivity and ASD-like behavioural pathologies in FAST, but not SLOW, rats.

76. Fatty Acid Modulation of Ion Channels in Neurological Disorders

Supervisor: Dr. Krista Gilby and A/Prof. Steve Petrou
Project Site: Melbourne Brain Center (UoM, FNI)
Contact: Steven Petrou E: spetrou@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.

77. Do balance deficits in patients chronically taking anti-epileptic medications reflect neurodegeneration of the cerebellum?

Supervisor: Professor Terence O’Brien, Professor John Wark, Dr Frances Batchelor 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; Dr Frances Batchelor F.Batchelor@nari.unimelb.edu.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: 25 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.

THE ION CHANNELS AND DISEASE LABORATORY
Our laboratory is located on the first floor in the Melbourne Brain Centre, Kenneth Myer Building, and is fully equipped
with state of the art neurophysiological and imaging capabilities. We are a 20 person multidisciplinary team working on
individual and joint projects in the neurosciences. Our primary interest is in diseases and therapies that involve ion
channels with a particular focus on epilepsy. In epilepsy our work begins with clinical and genetics collaborators who
identify gene mutations. Many of these are in ion channels and we seek to understand how these mutated genes lead to
behavioural seizures. We use a range of methods, appropriate to the scale of investigation and combine, genetic,
molecular, biophysical, computational, neurophysiological and behavioural approaches. In addition, our laboratory
houses the Australian Optogenetics Repository and we are well positioned to exploit this exciting new method. The
projects below give a sample of the work being undertaken and available for suitable candidates.

78. Identification of serum glycoproteins inhibiting innate immunity
Supervisors: Dr Ben Gu, Professor James Wiley, A/Professor Steven Petrou
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Melbourne Brain Centre, Parkville
Contact: Ben Gu T: 03 9035 6317 E gub@unimelb.edu.au; James Wiley E: jwiley@florey.edu.au; Steven Petrou E: spetrou@unimelb.edu.au
Project Description: Innate immunity is the first line defense of host against invaded pathogens. Phagocytosis of non-
opsonized particles (bacteria or viruses not coated by immunoglobulin, complement, etc) is an important part of innate
immunity. Our recent findings show that innate phagocytosis is completely abolished by a group of serum glycoproteins,
i.e. serum inhibits innate immunity. These proteins play an important role in regulation of innate immunity and the most
potent protein remains unknown. Identifying this protein will lead to a new therapies to boost resistance against
infectious diseases.
Techniques involved are chromatography, cell culture, flow cytometry, electrophoresis, western blotting and mass
spectrometry.

79. Raising innate immunity to fight with severe infection
Supervisors: Dr Ben Gu, Dr Rohit Ramchandra, Professor James Wiley, A/Professor Steven Petrou
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Melbourne Brain Centre.
Contact: Ben Gu T: 03 9035 6317 E gub@unimelb.edu.au; Rohit Ramchandra E: rohit.ramchandra@florey.edu.au; James Wiley E: jwiley@florey.edu.au; Steven Petrou E: spetrou@unimelb.edu.au
Project Description: Septic shock contributes to around 8000 deaths annually in Australia. Innate immunity is the first line
of host (patient) defence against invading microorganisms. The most dangerous microorganisms are those resistant to
antibiotics and in such situations, phagocytosis of these microorganisms by immune cells (such as neutrophils and
monocytes) becomes the only line of defence.
We have recently found that copper binding proteins (e.g. ceruloplasmin) in serum are potent inhibitors of phagocytosis
of non-opsonized bacteria. Our preliminary results show that chelation of copper with 1-5 mM tetraethylenepentamine
(TEPA, a drug that binds to copper) can neutralize the inhibitory effect of serum thereby restoring innate resistance
against bacteria. This project aims to boost innate immunity by copper chelation (using TEPA) and show the benefit of
copper chelation a sheep model of septic shock.
Techniques involved are large animal (sheep) handling, flow cytometry and protein separation.

80. Identification of the unique epitope expressed on the surface of early apoptotic neuronal cells
Supervisors: Dr Ben Gu, Professor James Wiley, A/Professor Steven Petrou
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Melbourne Brain Centre, Parkville
Contact: Ben Gu T: 03 9035 6317 E gub@unimelb.edu.au; James Wiley E: jwiley@florey.edu.au; Steven Petrou E: spetrou@unimelb.edu.au
Cell death by apoptosis and clearance of these dying cells are important for our body to avoid autoimmunity or
inflammation in the brain. Apoptotic cells express unique markers which enable them to be recognized and engulfed
by phagocytes. The knowledge of these unique markers is limited at present to certain cell membrane lipids, e.g.
phosphatidylserine. Our recent novel finding suggests that a unique protein epitope is expressed early in apoptosis and
this is recognized by P2X7 receptors on phagocytes. This project will examine how apoptotic cells are recognized and
cleared by phagocytes during normal development and in disease. This result will have relevance to neurological diseases as well as neurodevelopment.

Techniques involved are cell culture, immunoprecipitation, western blotting, flow cytometry, peptide screen, molecular biology and mass spectrometry.

81. Rescue brain cells by stopping phagocytic attack following head injury
Supervisors: Dr Ben Gu, Professor James Wiley, A/Professor Steven Petrou
Project Site: Ion channel & Human Disease, Florey Neuroscience Institute, Melbourne Brain Centre, Parkville
Contact: Ben Gu T: 03 9035 6317 E gub@unimelb.edu.au; James Wiley E: james.wiley@florey.edu.au; Steven Petrou E: spetrou@unimelb.edu.au

Project Description: Recent studies show that inhibition of P2X7 receptors improves recovery from spinal cord injury due to the reduction of inflammatory response. Our recent findings reveal that P2X7 can function in two alternative modes either as a pro-inflammatory receptor or as a scavenger receptor for clearance of apoptotic cells. This project will link the cognitive decline which follows traumatic brain injury with innate phagocytosis of stressed or ischemic neurones by activated microglia expressing large amount of P2X7. P2X7 antagonists given shortly after brain injury have the potential to improve functional recovery by minimizing both the immediate inflammatory response over hours and the slow phase of neuronal loss over days and weeks.

Techniques involved are small animal (mouse) handling, immunohistochemical staining, flow cytometry and Magnetic Resonance Imaging (MRI).

82. The role of P2X7 receptors in multiple sclerosis
Supervisors: Dr Ben Gu, Professor James Wiley, A/Professor Steven Petrou
Project Site: Ion channel & Human Disease, Florey Neuroscience Institute, Melbourne Brain Centre, Parkville
Contact: Ben Gu T: 03 9035 6317 E gub@unimelb.edu.au; James Wiley E: james.wiley@florey.edu.au; Steven Petrou E: spetrou@unimelb.edu.au

Project Description: Microglia and macrophages of the brain are responsible for the prompt clearance of apoptotic (dying) cells by a process of phagocytosis. Our previous work has shown that the P2X7 receptor expressed on the surface of microglia/macrophages binds to apoptotic cells to allow their rapid engulfment. Genetic variants of the P2X7 receptor are common and affect the rate of clearance of apoptotic cells. This project aims to show that P2X7 mediated phagocytosis of apoptotic cells is important to prevent inflammation in several neurological disorders such as multiple sclerosis, age related macular degeneration (AMD) of the eye, and possibly Parkinson’s disease. In this project, we will use both genetic and cell biological approaches to investigate the role of P2X7 in the inflammation of multiple sclerosis and other neurological disorders.

Techniques involved are genetic analysis, molecular biology, flow cytometry, and immunohistochemical staining.

83. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire
Supervisors: Prof Patrick Kwan, Prof James McCluskey
Project Site: Department of Microbiology & Immunology, Department of Medicine (RMH)
Contact: Patrick Kwan E: patrick.kwan@unimelb.edu.au

Project Description: Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen derived peptide antigens selected by different HLA allotypes. Recently, a growing number of immunologically based drug reactions have been found to be strongly associated with specific HLA alleles. In particular, HLA-B*15:02 greatly increased the risk of carbamazepine-induced severe skin reactions in Chinese/South Asians, but little is known about the underlying mechanisms of these associations. Recent research at the Department of Microbiology & Immunology has demonstrated that direct binding of the drug to the HLA molecule led to changes in the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and driving T-cell activation. This project aims to find out whether this mechanism also applies to the case of carbamazepine-HLA-B*15:02 interaction.

This project is also listed under Pharmacogenetics and Personalised Medicine and Innate Immunity and Host Defence

GASTROENTEROLOGY

84. Testing the feasibility of hand held Apps to support clinical decision making in Fiji Islands
Supervisors: Professor Finlay Macrae; Dr Jim Black; Dr Chris Hair
Project Site: Nossal Institute, Alan Gilbert Building.
Contact: Professor Finlay Macrae E: finlay.macrae@mh.org.au,
**IMAGING**

85. **Network Activity in Brain Tissue Recorded with Combined Calcium and Voltage-Sensitive Dye Imaging and Electrophysiology**  
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/](http://sites.google.com/a/hfbg1.net/crf_lab/)

**Project Description:** 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**

86. **Primary tuberculosis infection in immunocompromised travelers**  
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

**Project Description:** 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**

87. **Monitoring the efficacy of a training program in gastroenterology in the Pacific**  
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

**Project Description:** 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 (eg 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**

88. **The dangerousness of drugs: how do classifications under the international drug treaties compare with current knowledge?**
   Supervisor: Robin Room, Turning Point Alcohol and Drug Centre & CHS
   Project Site: Turning Point Alcohol & Drug Centre
   Contact: Robin Room, T: 8413 8430 E: roinr@turningpoint.org.au
   **Project description:** Under international treaties, nations are required to criminalise nonmedical use of cannabis, opiates, and over 250 other psychoactive substances, and to exert varying degrees of control over the substances. There are four schedules in each of two treaties which specify the degree of control required for each drug. Which schedule a drug is on is supposed to depend on its harmfulness as determined by a World Health Organization expert committee, but many of the decisions on this date from 40 or 50 years ago. The research will look at the scheduling of drugs under the treaties, and compare this to the current pharmacological, epidemiological and other literature on the harmfulness of different drugs. This project may lead to opportunities for publication in peer reviewed journals.
   Skill acquisition: Literature review, policy analysis, publication drafting

89. **Mapping public injecting drug use in urban Melbourne**
   Supervisor/s: Paul Dietze, Rebecca Winter, Peter Higgs
   Project Site: Burnet Institute, 85 Commercial Road, Melbourne
   Contact: Paul Dietze E: pault@burnet.edu.au; Peter Higgs E: peterh@burnet.edu.au
   **Project Description:** 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.

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

91. **Risk environments and injecting drug use – the impact of CCTV**
   Supervisor: Dr Mark Stoove, Head, Head of HIV, AIDS and STI Research, Centre for Population Health, Burnet Institute
   Project Site: Burnet Institute
   Contact: stoove@burnet.edu.au
   **Project Description:** 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 people who inject drugs that mediate 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, in the context of the introduction of closed circuit television (CCTV) monitoring systems in key locations. 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 stakeholders.

92. **Barriers to successful reintegration among people with a history of injecting drug use transitioning from prison to the community**
   
   **Supervisor:** Dr Mark Stoove, Head of HIV, AIDS and STI Research, Centre for Population Health, Burnet Institute
   
   **Project Site:** Burnet Institute
   
   **Contact:** stoove@burnet.edu.au
   
   **Project description:** Although release from prison is a challenging and particularly vulnerable period for people with a history of injecting drug use, this transition also offers opportunity for intervention and support. This Honours project will involve a targeted epidemiological examination of health and social outcomes among a cohort of people who inject drugs recently released from prison. Individual and structural barriers and facilitators related to successful reintegration outcomes (e.g., avoidance of problematic drug use and recidivism, stable accommodation, accessing drug dependence treatment, supportive social relationships) will be examined.

93. **Who’s talking about whom? An evaluation of techniques used to match individuals who inject drugs who have named each other in a research study**

   **Supervisor:** Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute
   
   **Project Site:** Burnet Institute
   
   **Contact:** Hellard@burnet.edu.au
   
   **Project Description:** The Networks Study aims to understand how hepatitis C is transmitted between people who inject drugs (PWID) by modelling the structure of the injecting network. We have collected five years of social network data from PWID including first names, nicknames and some other characteristics of the people with whom participants inject drugs. A number of links have been made between named injecting partners and study participants but some may have been missed and multiple participants may have named the same partners who have not been recruited into the study. This project aims to identify more matches using (a) traditional probabilistic matching techniques, (b) a technique that explicitly accounts for whether the participants have other common injecting partners? What is the influence of the additional matches on the structure of the social network? Is the second technique biased because it assumes social clustering and what are the implications of this for social network analysis?

94. **Understanding the social structures of relationships between people who inject drugs: a mixed-methods project**

   **Supervisor:** Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute
   
   **Project Site:** Burnet Institute
   
   **Contact:** Hellard@burnet.edu.au
   
   **Project Description:** We have conducted an empirical study of a drug injecting network and identified a number of social-structural features of that network. Some of these were unexpected: for example, we found that there were many people who reported injecting with two other participants but the two injecting partners did not report injecting with each other (this is surprising because usually there is a high propensity for two people with a friend in common to also be friends). This project would include interviewing networks study participants in more depth about relationships that they have already reported in the past in order to understand some of the structural features. Quantitative methods would be used to identify potential interviewees and describe profiles of people with similar positions in the social network.

95. **A systematic review of the structural features of injecting networks**

   **Supervisor:** Professor Margaret Hellard, Head, Centre for Population Health, Burnet Institute
   
   **Project Site:** Burnet Institute
   
   **Contact:** Hellard@burnet.edu.au
   
   **Project description:** Hepatitis C and other blood-borne viruses are transmitted through sharing needles and other injecting equipment. These risk behaviours are embedded in social relationships but there is little known about the types and structures of social relationships in which these behaviours take place. A number of empirical studies have been conducted of injecting networks. This study would involve systematic searches of scientific literature in order to identify published empirical injecting networks, characterising common structural features of injecting networks (if these exist), and describing how these injecting networks differ from other types of contact networks.

96. **The persistence of risk among people who inject drugs**

   **Supervisor:** Professor Paul Dietze, Co-Head, Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute
   
   **Project Site:** Burnet Institute
   
   **Email:** pdietze@burnet.edu.au
Project Description: The prevalence of risk behaviours such as sharing of injecting equipment among people who inject drugs (PWID) has been well described in the Australian context. However, little is known about transitions in risk behaviours among PWID over time and whether Australian PWID moderate their behaviours in response to their changing circumstances. In this study data from the Melbourne Injecting Drug User Cohort Study (MIX) will be examined to determine the extent to which risk behaviours change over time in the cohort and what impact any changes have on key health outcomes such as blood-borne virus transmission.

INNATE IMMUNITY AND HOST DEFENCE

97. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire
Supervisors: Prof Patrick Kwan, Prof James McCluskey
Project Site: Department of Microbiology & Immunology, Department of Medicine (RMH)
Contact: Patrick Kwan E: patrick.kwan@unimelb.edu.au
Project Description: Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen derived peptide antigens selected by different HLA allotypes. Recently, a growing number of immunologically based drug reactions have been found to be strongly associated with specific HLA alleles. In particular, HLA-B*15:02 greatly increased the risk of carbamazepine-induced severe skin reactions in Chinese/South Asians, but little is known about the underlying mechanisms of these associations. Recent research at the Department of Microbiology & Immunology has demonstrated that direct binding of the drug to the HLA molecule led to changes in the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and driving T-cell activation. This project aims to find out whether this mechanism also applies to the case of carbamazepine-HLA-B*15:02 interaction.

This project is also listed under Epilepsy and Neuropharmacology, and Pharmacogenetics and Personalised Medicine.

98. Regulation of Mucosal Immunity by the Transcription Factor, IRF6
Supervisor: A/Prof Glen Scholz
Location: Bio21 Institute
Contact: A/Prof Glen Scholz; Tel: 8344-3298; E: gelenms@unimelb.edu.au
Project Description: Mucosal epithelial cells express a variety of innate immune receptors (e.g. Toll-like receptors) that allow them to directly participate in the host immune response to pathogen infection. Dysregulation of the immune responses of mucosal epithelial cells is central to a number of diseases, including inflammatory bowel disease, asthma and periodontal disease. Therefore, in this project you will investigate how IRF6, a member of the Interferon Regulatory Factor family, regulates the responses of mucosal epithelial cells to bacterial pathogens.

Techniques: In this project you will gain expertise in a variety of techniques, including mammalian cell and bacterial cell culture, siRNA-mediated gene silencing, Real-Time PCR, ELISA assays, Western blotting, and confocal microscopy.

Scholarships: Available to eligible students.

99. Epigenetic Regulation of the Innate Immune Response to Bacterial Pathogens
Supervisor: A/Prof Glen Scholz
Location: Bio21 Institute
Contact: A/Prof Glen Scholz; Tel: 8344-3298; E: gelenms@unimelb.edu.au
Project Description: Epigenetic mechanisms (e.g. DNA methylation, chromatin remodelling) play important roles in regulating many biological processes. Significantly, epigenetic mechanisms are emerging as being important in regulating immune responses to pathogens. Dysregulation of these mechanisms may therefore be important in immune-driven diseases, such as inflammatory bowel disease, asthma and periodontal disease. In this project you will investigate how epigenetic mechanisms regulate the immune responses of innate immune cells (e.g. mucosal epithelial cells and macrophages) to bacterial pathogens.

Techniques: In this project you will gain expertise in a variety of techniques, including mammalian cell and bacterial cell culture, genomic DNA analysis, Real-Time PCR, siRNA-mediated gene silencing, Western blotting, and confocal microscopy.

Scholarships: Available to eligible students.

100. Bacterial Outer Membrane Vesicles: A Key Weapon in the Arsenal of Bacterial Pathogens?
Supervisor: A/Prof Glen Scholz
Location: Bio21 Institute
Contact: A/Prof Glen Scholz; Tel: 8344-3298; E: gelenms@unimelb.edu.au
Project Description: Suppression and/or evasion of the immune system is critical to the survival of many bacterial pathogens, and hence to their ability to cause disease. Some bacterial pathogens may do this by releasing outer
membrane vesicles (OMVs) containing specific virulence factors which can impair the host immune response. In this project you will investigate the effects of OMVs from the bacterial pathogen, *Porphyromonas gingivalis*, on different innate immune cells (e.g. mucosal epithelial cells and macrophages).

**Techniques:** In this project you will gain expertise in a variety of techniques, including mammalian cell and bacterial cell culture, confocal microscopy, ELISA assays, flow cytometry, Real-Time PCR, Western blotting, and siRNA-mediated gene silencing.

**Scholarships:** Available to eligible students.

101. Using Nanoparticle-Delivered siRNAs to Modulate the Host Immune Response to Pathogens

**Supervisor:** A/Prof Glen Scholz

**Location:** Bio21 Institute

**Contact:** A/Prof Glen Scholz; Tel: 8344-3298; E: glenms@unimelb.edu.au

**Project Description:** Regulation of the host immune response to pathogen infection largely occurs through intracellular signalling pathways that control the production of inflammatory factors (e.g. cytokines). Significantly, the dysregulated production of these factors plays a crucial role in many diseases, including inflammatory bowel disease, septic shock, and periodontal disease. Selective down-regulation of the expression levels of specific proteins in cells (e.g. signalling proteins) can be achieved through the use of short-interfering RNAs (siRNAs). In this project you will validate the therapeutic potential of nanoparticle-delivered siRNAs to modulate the host immune response.

**Techniques:** In this project you will gain expertise in a variety of techniques, including mammalian cell and bacterial cell culture, siRNA-mediated gene silencing, Real-Time PCR, ELISA assays, Western blotting, confocal microscopy, and animal (mouse) models of infection.

**Scholarships:** Available to eligible students.

MALARIA

102. Malaria parasite adhesion to the human placenta

**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

**Project Description:** 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 placetas 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.

103. Next Generation Sequencing to identify sequence elements important for gene expression in malaria parasites

**Supervisors:** Dr Michael Duffy

**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

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. A central component of epigenetic control is the reversible, covalent modification of histones. Recent data suggests that specific histone modifications at enhancers precede and control changes in gene expression. Studies of *P. falciparum* cis regulatory elements are only now emerging and there is a tremendous opportunity to experimentally identify enhancers, which could lead to therapies targeting the *trans* factors that bind these sequence elements. We will use an Illumina platform for genome wide Chromatin immunoprecipitation sequencing (ChiPseq) to identify sequences enriched in two histone modifications that are enriched in the enhancers of other species. Identified sequences will constitute putative enhancers. We will also collect parasite RNA in parallel and perform genome
wide gene expression analysis. These experiments will be performed over a timecourse of the parasite’s 48 hour lifecycle and gene expression data will then be correlated with fluctuations in histone modifications to identify putative enhancers for specific, regulated genes.

**Keywords:** malaria, next gen sequencing, molecular biology

**104. Investigating nuclear pores as sites critical for gene regulation in malaria parasites**

**Supervisors:** Dr Michael Duffy  
**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

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 a putative *P. falciparum* ortholog of a nuclear pore protein that recruits genes and regulates their activity. Antibodies to the tag and to other nuclear pore proteins together with probes to transcribed genes will be used in imaging analysis to study the location 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.

**Keywords:** malaria, molecular biology, advanced microscopy

**105. Gene regulation mechanisms in the transmissible stages of the malaria parasite**

**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 Michael Duffy and Dr Michaela Petter; T: 8344 3264; E: mduffy@unimelb.edu.au, mpetter@unimelb.edu.au

**Project Description:** 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.

**106. Characterizing new surface proteins of the malaria parasite**

**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; E: mpetter@unimelb.edu.au

**Project Description:** 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.

**107. Functional assays for immunity to malaria**

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

**Project Description:** 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.

108. Malaria in pregnancy: risk factors and consequences

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

Project Description: 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.

109. Malara immunity and treatment outcome

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

Project Description: 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.

110. Investigating the effects of GM-CSF and M-CSF derived human macrophages on phagocytosing P. falciparum infected erythrocytes and cytokine production

Supervisors: Dr. Adrian Achuthan and Dr. Louise Ludlow
Project site: Department of Medicine (RMH), University of Melbourne
Contact: Dr. Adrian Achuthan T: 8344-3290 E: aaa@unimelb.edu.au; Dr. Louise Ludlow T: 8344-3264 E: lludlow@unimelb.edu.au

Project Description: An important way in which the body clears malaria infection is through opsonisation of P. falciparum-infected erythrocytes (IE) and phagocytosis by monocytes/macrophages. This process leads to activation of signalling pathway and cytokine production. Current studies utilize human monocytes cultured in vitro in the presence of either granulocyte-macrophage colony stimulating factor (GM-CSF) or M-CSF to produce monocyte-derived macrophages (MDMs). Classical activation of monocytes by GM-CSF yields “M1-like” MDMs with a pro-inflammatory cytokine profile while M-CSF promotes “M2-like” MDMs that produce an anti-inflammatory cytokine repertoire. In this project you will explore the effects of IE phagocytosis by M1-like and M2-like MDMs on cytokine production and trafficking. Furthermore, you will be investigating the expression and function of signalling proteins that govern phagocytosis and cytokine secretion in these two types of MDMs.

Techniques: The project involves a range of molecular and cell biology techniques including culture and purification of P. falciparum-infected erythrocytes, isolation and culture of human monocytes/macrophages, qPCR to assay cytokine mRNA, ELISA to measure cytokine secretion and Western blotting and confocal imaging to determine protein expression and localisation.
MEDICATION SAFETY

111. Clinical audit of sedation assessment and sedative use in intubated and ventilated patients in intensive care (Melbourne Health)
   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.

112. Early pharmacotherapy and a risk of bleeding following transurethral prostatectomy (TURP): is there a link between medications and bleeding
   Supervisors: Dr Snezana Kusljic and Professor Elizabeth Manias
   Project Site: Royal Melbourne Hospital, Melbourne School of Health Sciences
   Contact: Dr Snezana Kusljic T: 8344 9428 E: skusljic@unimelb.edu.au
   Project description: Transurethral prostatectomy (TURP) is the current gold standard surgical intervention for lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) as well as for prostate cancer. It is just as effective while producing lower morbidity and fewer complications than an older surgical procedure known as prostatectomy. However, despite substantial improvement in symptom severity, a TURP is associated with short and long-term complications such as bleeding, retrograde ejaculation and urinary incontinence. Bleeding associated with a TURP can often be significant and lead to increased morbidity and occasionally mortality. Considering that TURP is commonly performed to relieve LUTS associated with age-dependent conditions such as BPH and prostate cancer, it is highly likely that due to the normal ageing process, most patients undergoing a TURP are likely to be on multiple medications. The aim of this retrospective clinical audit is to review patients' medication charts prior to TURP, during TURP and at postoperative days 1, 2 and 3. The audit will determine whether there is a link between early pharmacotherapy and the incidence of bleeding following a TURP and which medications or medication categories appear to be associated with bleeding.

113. Safe and appropriate medication prescribing of older patients in hospital
   Supervisors: Professor Elizabeth Manias and Dr Snezana Kusljic
   Project Site: Royal Melbourne Hospital, Melbourne School of Health Sciences
   Contact: Professor Elizabeth Manias T: 8344 9463 E: emanias@unimelb.edu.au
   Project description: Older people generally have a number of chronic conditions and therefore are prescribed many medications. Administration of many medications, also known as polypharmacy, puts older people at risk of developing adverse events such as falls, gastrointestinal bleeding, and cognitive impairment. In addition, older people are often denied potentially beneficial medications without a valid reason. In this study, the STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert doctors to Right Treatment) screening tool will be applied to a random sample of older people admitted to the Royal Melbourne Hospital. Use of this screening tool will determine what medications have been inappropriately commenced in older people and what medications have been inappropriately stopped or not commenced in older people. Medical histories of older people will be examined retrospectively on admission, at three days following admission and at discharge. Following completion of the study recommendations will be made about the safety and appropriateness of medication prescribing for older people in hospitals.

MULTIPLE SCLEROSIS/NEUROLOGY

114. How do Multiple Sclerosis Risk Genes work?
   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
   Project Description: In the last three years, around 30 risk genotypes for MS have been confirmed. Many of these carry small risks (e.g. 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.

115. How do relapses relate to progression of disability in multiple sclerosis?

Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven

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

Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au

Project Description: The disease course of multiple sclerosis (MS) is highly variable and therefore difficult to predict. Information about individual prognosis is invaluable to both clinicians and patients with MS and if known, has the potential to significantly influence treatment decisions. Based on our current knowledge of MS limited prognostication is possible using predictive markers such as age at disease onset, sex, initial symptoms, extent of recovery from first relapse etc.

This project aims at broadening our knowledge of prognostic markers. It will evaluate the relationship between neurological domains affected during relapses and the long-term accumulation of disability. We hypothesise that repeated impacts to certain neurological systems are more likely to result in accelerated accumulation of permanent disability. This project will utilise a large longitudinal collection of data obtained through the international observational database of MS patients - MSBase.

This project would suit people with interest in statistics and health outcome analysis. During the course of the project, you will become familiar with statistical approaches to longitudinal and predictive analyses. You will explore strategies for predictive modelling and for clinical application of the outcomes of your statistical analyses. You will add to the current knowledge about prognostic markers in MS.

116. Predicting treatment response in multiple sclerosis

Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven

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

Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au

Project Description: The range of treatments available to patients with multiple sclerosis has recently grown and more disease modifying agents are expected to become available soon. These comprise agents with various mechanisms of action, efficacy and potential adverse effects. Since MS is a variable disease whose course is difficult to predict in individual patients, pre-treatment estimation of future response to various agents is crucial for maximising treatment efficacy, and for implementation of individually-tailored treatment regimens in clinical practice. Even though some predictors of treatment response have previously been suggested (e.g. intensity of relapsing activity or severity of MRI changes), a retrospective analysis of treatment response within a large and heterogeneous sample of patients representative of the MS population has been missing.

This project uses the MSBase - a large international, observational database of MS patients - to evaluate routinely available demographic and clinical information as potential predictors of response to several commonly used therapeutic agents. It aims at recognising these predictors in individual patients prior to the treatment initiation, in order to allow clinicians to choose the most appropriate therapeutic regimen.

This project would suit people with interest in statistics and health outcome analysis. The project will enable you to develop your analytical and statistical skills, whilst undertaking research using a large, well powered data collection. You will become familiar with retrospective evaluation of potential predictive markers, validation of the resulting predictors and planning their clinical implementation.

117. Evaluation of novel treatments for multiple sclerosis

Supervisors: Dr Tomas Kalincik, Dr Vilija Jokubaitis and A/Prof Helmut Butzkueven

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

Contact: Tomas Kalincik, E: tomas.kalincik@unimelb.edu.au
Project Description: Randomised controlled trials (RCT) represent the gold standard for obtaining evidence about treatment efficacy and tolerability. However, they are expensive, time consuming and usually limited by tight selection criteria, which may restrict translation of their outcomes to general populations. Therefore, validation of RCT results in large populations managed in routine clinical practice may be required. For the emerging, more potent treatments for multiple sclerosis (MS), such validation constitutes the opportunity to confirm the outcomes of previous RCTs and at the same time to enhance generalisation of these outcomes to the broad population of patients with MS.

This project aims to compare the efficacy and tolerability of a novel agent, Fingolimod, to the more traditional disease modifying agents, interferon beta and glatiramer acetate. It utilises the MSBase - a large international, observational database of MS patients, to construct pseudo-randomised trials. This project aims to validate the outcomes of previous RCTs in a large real world patient sample to determine whether the outcomes of large RCTs apply to a broader MS population.

This project would suit people with interest in statistics and health outcome analysis. During the project, you will improve your statistical skills, learning some of the more complex statistical analytical techniques. You will become familiar with propensity estimation and matching procedures and with the construction of pseudo-randomised trials in observational datasets.

118. The changing treatment landscape in multiple sclerosis

Supervisors: Dr Vilija Jokubaitis, Dr Tomas Kalincik and A/Prof Helmut Butzkueven
Project Site: Department of Medicine, Royal Melbourne Hospital, The University of Melbourne
Contact: Vilija Jokubaitis, E: vilija.jokubaitis@unimelb.edu.au

Project Description: Multiple sclerosis is the most common cause of neurological disability in young adults. Whilst some people with MS have a relatively benign disease with little disability, others experience a rapidly progressive disease course that in rare cases may be terminal. The disease burden of MS is great with approximately 50% of people with MS exiting the workforce prematurely.

Disease-modifying therapies (DMT) for the treatment of MS have been shown to reduce relapse rate and attenuate disability accumulation. However, MS-specific DMT have only been commercially available for the last 15 years with varying access globally. The range of MS-specific DMT has also been limited until recently, however, new agents have recently been approved by the TGA, FDA and EMA with more to come. These DMT have various mechanisms of action, efficacy, tolerability, mode of delivery and adverse event profiles all of which influence treatment decisions.

The aims of this study are to understand the changing landscape of MS treatment, to determine treatment utilisation patterns, treatment persistence, switch patterns and to determine predictors of treatment discontinuation in a global MS population. This will help inform treatment decisions in the real world, and also aid in the understanding of whether the disease burden is likely to be reduced with the introduction of new DMT.

This project will require you to use and develop statistical and analytical skills to answer real world questions utilising a large international, observational database of MS patients – MSBase.

NEPHROLOGY

119. Finding genetic mutations in new types of inherited kidney disease: focal segmental glomerulosclerosis

Supervisors: Professor Judy Savidge and Dr Yanyan Wang
Project Site: NWAC, Northern Hospital, Epping.
Contact: Professor Judy Savidge, T 8405 8823, jasavige@unimelb.edu.au

Project description: To date, more than 120 different inherited kidney diseases due to mutations in 160 different genes have been identified. However there are still many diseases where the genes are not known. We have an Inherited renal disease clinic and are referred many families with unclassified kidney diseases. We have a number where the mutant genes are not known, and in the first instance are looking at some candidate genes. The aim of this project is to help characterize the patients (many have hearing loss and eye abnormalities too) and determine the mutant gene that is responsible for the disease in each family. For example, we have 12 families with inherited focal segmental glomerulosclerosis (FSGS), and also some candidate genes. Patients with focal segmental glomerulosclerosis have proteinuria and invariably develop renal failure, requiring life long dialysis or a renal transplant. The aim of this project is to determine which genes are affected in FSGS and some other inherited renal diseases.

Techniques to be used and skills acquired: This study involves extracting DNA from peripheral blood, designing amplification/PCR primers, amplifying DNA, purifying it, sequencing it, and determining if the DNA change is pathogenic. This work is likely to result in a publication and could easily lead on to a PhD. This project involves working with a kidney specialist (Prof Judy Savidge in her clinic) and with A/Prof Deb Colville an ophthalmologist.

Feasibility: We already have DNA stored from 12 families with FSGS and have Human Research Ethics Committee Approval for this project. This project has plenty of patient contact and also good laboratory experience.
NEUROPSYCHIATRY AND STRESS BIOLOGY

120. Functional disconnections and the pathophysiology of psychosis
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

Project Description: 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 magnitude association between disruptions to gamma oscillations and behavior.

Skills: small animal surgery, EEG measurement, behavioural analysis.

121. Identifying substrates for Selenium Binding Protein 1 and their functional consequence in the human brain
Supervisors: Dr Tammie Money, Professor Brian Dean, A/Professor Elizabeth Scarr 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: 9035 6664

Background: The aim of this project is to identify substrates for selenium binding protein 1 (SELENBP1) in schizophrenia. Previous studies from our laboratory have shown that SELENBP1 gene expression is significantly upregulated in schizophrenia from several studies in both brain and blood (Glatt et al., 2005, Kanazawa et al., 2007). However, it is not clear what is causing this increase. A previous study showed that selenium is bound to SELENBP1 at the Cys57 residue (Raucci et al., 2011), but in vitro studies from our laboratory showed that physiological levels of selenium do not affect the expression of SELENBP1. Therefore, this project will investigate what else binds to SELENBP1 and what the consequence of this interaction is in the human brain.

Aims:
- To identify substrates for SELENBP1 in the human brain
  To achieve this aim co-immunoprecipitation will be used to isolate SELENBP1 and attached complexes from postmortem human brain tissue. Following isolation, the complex will be identified using mass spectrometry
- To determine the involvement of the identified substrates on the expression of SELENBP1 and functional effects on cell health
  This aim will utilise cell culture to determine the effect of the identified substrate on the level of expression of SELENBP1 and the effect on normal cell function. Cells expressing endogenous SELENBP1 will be grown and exposed to differing levels of the identified substrate. RNA will be extracted and levels of SELENBP1 expression will be measured using quantitative PCR, as well as markers of cell health.

Skills: This project will involve training in postmortem brain tissue handling, protein extraction, co-immunoprecipitation, mass spectrometry, cell culture, quantitative PCR and statistical analysis.

122. Temporal lobe epilepsy, the HPA axis and depression
Supervisor: Prof Terence O'Brien, Dr Dennis Velakoulis, Dr Mike Salzberg
Project Site: Department of Psychiatry and Medicine
Contact: Terence O'Brien T: 8344 5490 E: obrrientj@unimelb.edu.au
Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.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.

123. Does stress contribute to epilepsy?
  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: ncjones@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.

124. Mapping the human brain connectome in healthy and psychiatric populations
  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
  Project Description: The human brain is perhaps the most complex network found in nature, comprising $10^{11}$ neurons connected by $10^{13}$ 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.

125. How does Age of Illness Onset affect severity and extent of MRI Brain Structural Abnormalities in Schizophrenia
  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 H 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
126. Stem Cell based modelling of Human Neurological Disorders: Towards Drug Discovery for improved Therapeutics

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

Project Description: 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.

127. Characterisation of physiological stress responses in patients with depression and epilepsy

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

Project Description: 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.

128. Characterising morphological abnormalities of the cerebral cortex in established schizophrenia: A structural MRI study

Supervisors: Dr Cali Bartholomeusz, Dr Sarah Whittle, Prof Christos Pantelis.
Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience facility, Level 2-3 Alan Gilbert Building.
Contact details: Dr Cali Bartholomeusz Ph: 8344 1878, Email: barc@unimelb.edu.au

Project Description: An extensive body of neuroimaging literature suggests that schizophrenia patients invariably display significant reductions in grey matter volume of various brain structures. Grey matter regions most commonly found affected are localised to the temporal and frontal cortices. These regions are particularly important for learning, memory course of the illness, particularly in frontal and temporal lobe regions. We have also demonstrated that 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.
and higher-order cognitive functioning. Thus the implications of grey matter loss are wide-reaching and can impact on
everyday functioning.

A great deal of research is now beginning to focus on characterising abnormalities in more detail by investigating cortical
thickness, surface area and gyrification/folding. Identifying abnormalities in cortical surface characteristics is now possible
with the recently developed automated surface-based approaches. By investigating these specific morphological
parameters we will better understand the potential origins of brain abnormalities in schizophrenia.

The aim of the proposed study is to characterise morphological cortical abnormalities in schizophrenia by investigating
differences in cortical thickness, surface area and degree of gyrification between healthy controls and individuals with
established schizophrenia. The student will be responsible for pre-processing MRI scans that have been previously
collected and are part of the MNC databank. The student will also be involved in writing scripts for running the multiple
automated processing steps using the neuroimaging Freesurfer software program; and data analysis.

129. Amygdala development across adolescence: links to mental illness
Supervisors: Dr Sarah Whittle, Prof Nicholas Allen.
Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience facility,
Level 2-3 Alan Gilbert Building.
Contact details: Dr Sarah Whittle, Ph: 8344 1958, Email: swhittle@unimelb.edu.au
Project Description: Adolescence is a period of transition between childhood and adulthood characterised by significant
physical, cognitive, emotional, and psycho-social change. Adolescence is also a critical period for the onset of a number
of mental health problems, including depression and anxiety disorders. A growing body of research has revealed that the
social, emotional and cognitive changes, as well as the increased onset of mental illness, during adolescence, may in part
stem from underlying individual differences in brain development.

Morphological and functional differences in one subcortical brain region, the amygdala, have been particularly implicated
in emotional functioning, as well as in the aetiology and maintenance of mood and anxiety disorders. However, less is
known about how the development of the amygdala across adolescence is associated with the onset of these disorders. In
fact, while normative changes in cortical grey matter over adolescence have been extensively studied, we do not yet
know what the normative pattern of development of the amygdala looks like.

The proposed project will take advantage of neuroimaging data from a three-wave longitudinal adolescent development study. Magnetic Resonance Imaging (MRI) data, as well as data on emotional functioning and mental illness, has been acquired from a large group of adolescents at ages 12, 16 and 18. The proposed project will involve the investigation of amygdala development across adolescence, as well as the links between amygdala development and adolescent mental health problems. The student will be involved in the processing of MRI data (i.e., estimation of amygdala volumes) and data analysis (using longitudinal data modelling techniques).

130. Development of orbitofrontal gyrification across adolescence
Supervisors: Dr Sarah Whittle, Dr Cali Bartholomeusz.
Project site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience
Facility, Level 2-3, Alan Gilbert Building.
Contact details: Dr Sarah Whittle, Ph: 8344 1958, Email: swhittle@unimelb.edu.au
Description of project: Gyrification is the process by which the brain undergoes changes in surface morphology to create
sulcal and gyral regions. The period of greatest development of brain gyration is during the third trimester of pregnancy, a period of time in which the brain undergoes considerable growth. Little is known about changes in gyration during childhood and adolescence, although considering the changes in grey matter volume and thickness during this time period, it is conceivable that alterations in the brain surface morphology could also occur during this period of development. The formation of gyri and sulci in the brain allows for compact wiring that promotes and enhances efficient neural processing. If cerebral function and form are linked through the organisation of neural connectivity, then alterations in neural connectivity, i.e., synaptic pruning, may also alter the gyral and sulcal patterns of the brain.

The proposed project will investigate the development of gyration of one specific brain region, the orbitofrontal cortex (OFC), during adolescence. Individual differences in OFC gyration have been linked to a number of mental health problems, including depression, anxiety and schizophrenia. Thus, investigating the development of OFC gyration across adolescence may provide insight into the neurodevelopmental risk mechanisms contributing to the development of these mental health problems.

The proposed project will take advantage of neuroimaging data from a longitudinal adolescent development study. Magnetic Resonance Imaging (MRI) data has been acquired from a large group of adolescents at ages 12 and 18. OFC gyration has already been assessed at age 12. The student will be involved in the processing of MRI data (i.e., assessment of OFC gyration) from the age 18 MRI assessments, and data analysis (i.e., investigating change in OFC gyration over time).
131. Investigating antipsychotic drug action on the epidermal growth factor system as a gateway to novel treatment for schizophrenia

Supervisors: Dr Avril Pereira and A/Prof Suresh Sundram
Project Site: Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, The University of Melbourne, Parkville
Contact: Dr Avril Pereira T: 9035 6573 E: avril.pereira@unimelb.edu.au

Project Description: Schizophrenia is a devastating disorder that strikes at young people and persists throughout life. Much of this suffering is borne by a third of those for whom current treatments are ineffective. For these treatment resistant patients the alternative is the atypical antipsychotic drug (APD) clozapine, however, its use is limited by disabling side effects. Why clozapine is uniquely effective is unknown but may reside in interactions with intracellular signalling cascades that govern gene transcription and neuronal function. In this regard, we have demonstrated in vitro and in vivo that clozapine signals to the MAPK-ERK cascade in cortical neurons differently compared to other APDs. This pathway is central to the regulation of neuronal differentiation, maturation and plasticity, processes disrupted in schizophrenia. We have also determined that the mechanism through which clozapine affects ERK is mediated by the epidermal growth factor (EGF) receptor. Our cellular, animal and clinical data support our hypothesis of EGF system hypofunction in a sub-type of patients that respond to clozapine via a novel mechanism that augments EGF signalling. This project will characterise how clozapine recruits the EGF receptor to phosphorylate ERK in cortical neurons and delineate the intracellular path through which this transactivation occurs: activation of mediators such as Src kinases, Ca\(^{2+}\), Pyk or PKC; activation of a matrix metalloproteinase; or through \(\beta\)-arrestin mediated endocytosis.

Skills: The candidate will receive training in derivation and culture of primary frontal cortical neurons and will use SDS-PAGE, immunoblotting, immunocytochemical, siRNA, RNA extraction, PCR or RT-PCR methods on cortical cells and APD treated mouse prefrontal cortex to study key proteins in the targeted pathway. An understanding of our current thinking on how the brain is disturbed in psychotic disorders will be gained.

NEUROVASCULAR

132. 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

Project Description: 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 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.

133. 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,
**Project Description:** 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 thrombolitics, mechanical clot retrieval holds promise as an effective means to reopen blocked arteries. However, the success of 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.

**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

134. Do the coronary small vessels respond less well to medication in patients with diabetes or renal failure  
**Supervisors:** Professor Judy Savige and A/Prof Deb Colville  
**Project Site:** T NWAC, Northern Hospital, Epping  
**Contact:** Professor Judy Savige, T 8405 8823, jasavige@unimelb.edu.au

**Project description:** Most research into the causes of heart disease has focused on disease in the coronary arteries but the importance of small vessel disease is recognized increasingly. However the coronary small vessels are difficult to study. Nevertheless whenever the small vessels in the heart are affected, small vessels are diseased throughout the body. This includes the vessels in the retina, which are very accessible using a retinal camera and photography. So we propose to examine the retinal small vessels as a model for the coronary arterioles and determine whether renal failure or diabetes means these vessels are diseased and respond less well to medication.

This study involves recruiting patients from the wards with renal failure or diabetes and testing the effect of a tablet that usually dilates small vessels. You will help the patient fill out a questionnaire and also take their blood pressure and retinal photographs, and then review the photographs under the supervision of an ophthalmologist. In addition the retinal photos will be sent to the Centre for Eye Research Australia for the vessel diameters to be measured precisely. The aim of this project is then to determine whether small vessels are less responsive in diabetes and renal failure, and whether medication doses should be increased. The analysis includes univariate and multivariate statistics and backwards linear regression (we will help you with the statistics).

**Techniques to be used and skills acquired:** This project involves a lot of patient contact, going onto the wards and getting to know hospital staff, learning how to take retinal photographs, and how to interpret abnormalities, as well as statistics.

**Feasibility:** We already have Human Research Ethics Committee Approval for this project and many of the medical students who have undertaken similar projects during an AMS year have achieved a publication from their work.

**PHARMACOGENETICS AND PERSONALISED MEDICINE**

135. Pharmacogenomics in IBD  
**Supervisors:** Professor Finlay Macrae and Prof Les Sheffield  
**Project Site:** Colorectal Medicine and Genetics, The Royal Melbourne Hospital  
**Contact:** Prof Finlay Macrae E: finlay.macrae@mh.org.au

**Project description:** The Royal Melbourne Hospital, with GenesDX, is pioneering the implementation of a pharmacogenomics clinical support program. In the case of inflammatory bowel disease, this relates to the use of thiopurines. The project will assist in the implementation of the program and its evaluation. It will guage the clinical utility of TPMT genotyping and the clinical decision support tools that will be built into the program, and thiopurine metabolite testing, in the management of inflammatory bowel disease. This project is also listed under Colorectal Medicine.
136. Development of novel rapid genotyping techniques to detect genetic variants predictive of response to drugs for application in personalized medicine

Supervisors: Professor Patrick Kwan, Dr Marian Todaro
Project Site: Department of Medicine (RMH)
Contact: Patrick Kwan, Department of Medicine (RMH) E: patrick.kwan@unimelb.edu.au; Dr Marian Todaro, Department of Neurology E: Marian.Todaro@mh.org.au

Project Description: This study is part of a large project aiming to bring personalised medicine into widespread clinical practice (see project numbers 192 and 193). Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. 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. Testing is expensive and typically takes 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.

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. The protocol developed will be adapted for use in a compact automated device through collaboration with electronic engineers (see project number 192). This project will be suitable for students with background in molecular biology.

137. Lab-on-a-chip nanotechnology testing device for personalized medicine

Supervisors: Professor Stan Skafidas and Professor Patrick Kwan
Project Site: Centre for Neural Engineering, Department of Electrical Engineering
Contact: Professor Stan Skafidas, Department of Electrical Engineering, E: sskaf@unimelb.edu.au

Project Description: A novel rapid genotyping platform has been identified by the study team. 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 platform developed will be engineered into a compact device prototype that can carry out the genotyping steps and product detection using silicon nanowire technology in automated operation. There is very strong potential for technological innovation and eventual application of the device in clinical practice. This project is suitable for students with background in electrical engineering.

138. The health economics of personalized medicine

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

Project Description: 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*15:02 which is strongly associated with rare but life-threatening severe skin reaction to carbamazepine in Chinese/South Asians. Carbamazepine is a first-line medication for the treatment of epilepsy, neuropathic pain and bipolar affective disorder. However, the health economics of a routine testing policy has not been studied.

This project will study the cost-effectiveness of such a policy using 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 findings could have potential impact upon decision-making in healthcare policy. This project is suitable for students with background in biostatistics.

139. Electrophysiological characterization of effects of MDR1 (ABCB1) polymorphisms on efflux transport of antiepileptic drugs

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

Project Description: 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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**140. A decision support system for implementation of pharmacogenomics in epilepsy treatment**

**Supervisors:** Professor Patrick Kwan, Professor Terence O’Brien, A/Professor Les Sheffield

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

**Contact:** Professor Patrick Kwan, Departments of Medicine and Neurology, E: patrick.kwan@unimelb.edu.au

**Project description:** Personalised medicine based on pharmacogenetics knowledge promises to revolutionise healthcare by harnessing individual genetic information to improve drug safety and effectiveness. Yet its uptake has been limited partly owing to the lack of appropriate systems that can support its widespread application in clinical practice. Through partnership with a business enterprise, The Royal Melbourne Hospital is pioneering the implementation of such a system in Australia. One of the projects relates to HLA genotyping prior to the prescription of certain antiepileptic drugs to prevent severe, life-threatening allergic skin reactions. This honours project will assist in the development, implementation and evaluation of the program by collecting and analysing the relevant clinical and test information.

**141. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire**

**Supervisors:** Professor Patrick Kwan, Professor James McCluskey

**Project Site:** Department of Microbiology & Immunology, Department of Medicine (RMH)

**Contact:** Professor Patrick Kwan, Departments of Medicine and Neurology, E: patrick.kwan@unimelb.edu.au

**Project Description:** Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen derived peptide antigens selected by different HLA allotypes. Recently, a growing number of immunologically based drug reactions have been found to be strongly associated with specific HLA alleles. In particular, HLA-B*15:02 greatly increased the risk of carbamazepine-induced severe skin reactions in Chinese/South Asians, but little is known about the underlying mechanisms of these associations. Recent research at the Department of Microbiology & Immunology has demonstrated that direct binding of the drug to the HLA molecule led to changes in the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and driving T-cell activation. This project aims to find out whether this mechanism also applies to the case of carbamazepine-HLA-B*15:02 interaction. This project is also listed under Epilepsy and Neuropharmacology and Innate Immunity and Host Defence

**142. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effect**

**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: obrientj@unimelb.edu.au

**Project Description:** 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 hypersensitivity 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 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.

### 143. Pharmacogenomics: 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

**Project Description:** 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-platelets 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 P 450 family of enzymes (CYP 2C19). A genetic mutation, e.g. CYP 2C19*2, predicts lower levels of the active form clopidogrel leading to failure of platelet inhibition. We hypothesize that patients with genetic mutations of CYP 2C19 (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 pharmacogenenomics project led by Professor Patrick Kwan’s research group. Our research arm focuses on CYP 2C19 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.

### 144. A Pharmacogenomics study of the teratogenicity valproate based on the prospective Australian Register for Anti-epileptic Drugs in Pregnancy

**Supervisors:** Professor Terence O’Brien, Professor Frank Vajda and Dr Slave Petrovski - Epilepsy and Neuropharmacology Group, The Department of Medicine: The Royal Melbourne Hospital.  
**Project Site:** The Department of Medicine (RMH)  
**Contacts:** Terence O’Brien T: 8344 5479 E: obrientj@unimelb.edu.au; Frank Vajda E: vajda@netspace.net.au; Slave Petrovski E: slavep@unimelb.edu.au

**Project Description:** 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:

- 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 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.

**POPULATION HEALTH**

**145.  Key strategies for engaging users of Social Networking Sites for health promotion**

*Supervisor:* Dr Mark Stoove, Head, Head of HIV, AIDS and STI Research, Centre for Population Health, Burnet Institute

*Project Site:* Burnet Institute

*Contact:* stoove@burnet.edu.au

*Project description:* We recently conducted a review of social networking sites (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 and the project will involve novel online recruitment methods.

**146.  Providing testing reports to general practitioners as an intervention to increase Chlamydia screening**

*Supervisor:* Dr Mark Stoove, Head, Head of HIV, AIDS and STI Research, Centre for Population Health, Burnet Institute

*Project Site:* Burnet Institute

*Contact:* stoove@burnet.edu.au

*Project description:* Chlamydia is the most commonly notified infection in Australia. An important component of chlamydia control is screening and testing; the majority of which occurs in general practice. Encouraging GPs to offer more chlamydia tests to young people is vital.

This is a study to look at the effectiveness of providing GPs with individual testing/positivity reports to examine if such reports change testing behaviour. This study would use a pre-post-test design, looking at number of tests requested in 2012 following receipt of a report presenting the number of chlamydia tests requested in 2011, and the number of positive tests. The study will use data from the Australian Collaboration for Chlamydia Enhanced Sentinel Surveillance (ACCESS).

**147.  Chlamydia epidemiology in Australia**

*Supervisor:* Dr Mark Stoove, Head, Head of HIV, AIDS and STI Research, Centre for Population Health, Burnet Institute

*Project Site:* Burnet Institute

*Contact:* stoove@burnet.edu.au

*Project Description:* Sentinel surveillance systems that provide key indicators of testing rates, positivity rates, prevalence and incidence can enhance the capacity of Australia to evaluate interventions in priority populations to control the spread of infection. The ACCESS project is such a surveillance system; it is a comprehensive surveillance system developed to evaluate the impact of national and local strategies designed to control genital chlamydia infection in Australia and to underpin Australia’s strategic response to chlamydia. Data collected through the ACCESS project is available for analysis to measure chlamydia infection and reinfection in young Australians

*This project is also listed under Infectious Diseases*

**148.  Content analysis of the successful health promotion project “Queer as F**K delivery sexual health to gay men on Social Networking Sites**
149. Risk behaviours and HIV among young gay and bisexual men

Project Description: In recent years, the notification of newly acquired HIV has increased among young gay men in Victoria. Studies have found that gay men in Australia are having anal sex much younger than in the past and do not test for HIV as often as older gay men do. This project will investigate reported sexual and testing behaviours of young MSM by consolidating and analysing data from various surveillance data sources, with the aim of better understanding what is contributing to the increased detection of HIV in this group.

Several ongoing projects conducted by the Burnet Institute collect behavioural data from young gay and bisexual men in Melbourne, such as the Big Day Out study, HIV passive surveillance, the Victorian Primary Care Network for Sentinel Surveillance on BBVs and STIs and focus groups conducted as part of a large campaign evaluation study. These data would be analysed and interpreted alongside other available behavioural surveillance data such as those collected annually for the Melbourne Gay Periodic Survey.

150. Structural and environmental impacts on women’s relationships with their children following imprisonment

Project Description: 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.

151. SEXT ME UR (.)(.)

Project Description: There is growing media interest and public concern about the practices of ‘SEXTing’ and posting of explicit images and text to social media sites among young people. This project will use data from the Big Day Out project surveys to determine the frequency of such behaviours. Further investigation of the practices will elucidate who engages in SEXTing, who SEXTs are sent to, and the type of content that is shared. It will determine young people’s opinions and attitudes towards SEXTing and sharing of explicit content, and measures they undertake to maintain control of content and ensure its privacy. These data could be collected from online surveys, in-depth interviews, and thematic analysis of social network pages.

152. Sex, drugs and rock’n’roll: Young people and risk behaviours in a survey at the Big Day Out music festival

Note: This project is only available for mid-year enrolment. Please check the website for mid year enrolments.

Project Description: Sexually transmitted infections (STI) are on the rise among young Victorians. Since 2005, we have surveyed over 9,000 people aged between 16 and 29 years of age at Melbourne’s Big Day Out about sexual risk behaviour and drug use. Questions have covered participant’s sexual histories, condom use, knowledge and perceptions of STIs, and STI testing histories. We ask about alcohol and other drug use, and other risks and behaviours such as diet and exercise,
contact with police, mental health, and smoking. The Big Day Out festival also gives us an excellent opportunity to inform this population group about sexual health and behaviour that may place them at risk of sexually transmitted infections. Showbags containing safer sex and other harm reduction information are distributed to survey participants and other Big Day Out patrons.

In this project the student will manage and organise recruitment of participants at the Big Day Out. They will then use the data collected to investigate patterns of sexual risk behaviours, knowledge, and attitudes. This will involve quantitative analysis of the relationship between variables such as condom use, number of sexual partners, drug and alcohol use, and perceptions of risk. These findings, in the context of current public health measures, will be used to advise on the design of future sexual health promotion campaigns.

**153. Low income as a barrier to opioid substitution therapy**  
*Supervisor:* Dr Peter Higgs, Co-Head, Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute  
*Project site:* Burnet Institute  
*Email:* peterh@burnet.edu.au  
*Project description:* People who inject drugs (PWID) often report low levels of income, with many reporting weekly incomes of less than $250. PWID on opioid substitution therapy (OST) commonly describe an adverse impact from pharmacy dispensing fees for accessing OST. These fees are typically around $5 per dose, or $35 per week – for many a significant proportion of weekly income, especially after necessary expenditures (rent, food, etc.) are deducted.

This project would involve analysis of data from the Suboxone (a national year-long examination of a particular OST formulation, with a number of cross-sectional arms investigating the health domains of PWID and practices of prescribing pharmacists) and MIX studies (a Melbourne-based prospective cohort study running since 2008 with over 700 PWID as participants), examining the dispensing practice/cost for differing pharmacies, and personal in-depth interviews with PWID to further illicit the impact of dispensing costs and the extent that low income is a barrier to substitution therapy.

**PREGNANCY RESEARCH**

**154. Multiple serum markers and mid trimester uterine artery Doppler in the prediction of pre-eclampsia**  
*Supervisor:* Dr Padma Murthi, Dr Fabricio Costa  
*Project Site:* Pregnancy Research Centre, Royal Women’s Hospital  
*Contact:* Padma Murthi E: padma@unimelb.edu.au  
*Project Description:* 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.

**155. 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  
*Project Description:* 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

**156. 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
**Project Description:** 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.

157. **Pregnancy hormones and their receptors in trophoblast function**

**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

**Project Description:** Progesterone (PG) and human chorionic gonadotropin hormone (hCG) are critical for the establishment and for the maintenance of pregnancy. The genomic actions of PG and hCG are mediated by their intracellular receptors. The project will investigate PG and hCG-mediated and signaling pathways that are critical for successful placental cell proliferation, differentiation, and angiogenesis that are important for decidualization. The project will also identify regulators of pregnancy hormone expression in trophoblast cells.

**Techniques:** Cellular and molecular biological techniques including cell culture, functional cell assays (proliferation, differentiation, network formation) real time PCR and RNAi.

158. **Transcriptional regulation of placental angiogenesis in complicated pregnancies**

**Supervisors:** Dr Padma Murthi, Dr Rosemary Keogh  
**Project Site:** Pregnancy Research Centre, Royal Women’s Hospital  
**Contact:** Dr Padma Murthi E: padma@unimelb.edu.au

**Project Description:** In pregnancies complicated by gestational hypertension the feto-placental vasculature is affected by altered expression of several pro-inflammatory cytokines and angiogenic molecules leading to aberrant placental angiogenesis. The molecular mechanisms governing placental angiogenesis are unknown. The project will identify the transcriptional profile of placental endothelial cells and their influence on placental endothelial functions.

**Techniques:** Tissue culture, ligand binding assays, functional cell assays, protein and molecular biology.

159. **Improving the health of newborn babies: investigating the role of heparins in preventing thrombosis within the human placenta**

**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

**Project Description:** 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.

160. **Improving the health of newborn babies: investigating the role of proteoglycans in causing abnormal growth problems in pregnancies from women with diabetes**

**Supervisors:** Dr. Joanne Said and Dr. Amy Chui  
**Project Site:** Pregnancy Research Centre, Royal Women’s Hospital
**Project Description:** 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 glycosaminoglycans 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.
MASTER OF SCIENCE (BIOMEDICAL AND HEALTH SCIENCES)

Biomedical and Health Sciences Course code: MC-SCHIBHS

The Master of Science (Biomedical and Health Sciences) is one of the research training streams of the Master of Science. The research training streams give students the opportunity to undertake a substantive research project in a field of choice as well as a broad range of coursework subjects including a professional tools component, as a pathway to PhD study or to the workforce. The MSci is a two year course that can be taken in place of Honours.

Students must complete 200 points comprising of:

- Major Research Project 125 points
- Discipline Subjects 50 points
- Professional Tool Subjects 25 points

MAJOR RESEARCH PROJECT: 125 points.
A literature review of up to 4,000 words. Due end of 2nd semester Year 1. Assessment hurdle – marked satisfactory/unsatisfactory.
- Two 20 minute oral presentations. Due end of 2nd semester Year 1 and final semester Year 2.
- Major research report of up to 15,000 words. Due end of final semester Year 2.

As this project is a larger body of research work than an Honours research project (75pts) the expectation about the extent of work undertaken is adjusted and more research output is expected to be achieved. More supervisor input is required but this is over the 2 year duration.

DISCIPLINE SUBJECTS: 50 points
4 subjects x 12.5 points each.
- Subject 1: BIOM40001 - Compulsory core subject – Introduction to Biomedical Research (FMDHS co-requisite subject undertaken in semester 1)
- Subject 2: MEDI40004 – Seminars in Translational Medicine (Research Lecture Program & MCQ). A preferred option if undertaking your MSci with the RMH Academic Centre. Undertaken in Semester 1.

Students need to select an additional two subjects - or three if MEDI4004 is not selected. Two discipline subjects may also be selected from undergraduate 3rd year subjects in a relevant area of interest.

PROFESSIONAL TOOL SUBJECTS: 25 points
2 subjects x 12.5 points each.

Available Projects:
For MSci projects available with the Royal Melbourne Hospital Academic Centre please contact the supervisor listed in this handbook.

How to Apply:
Master of Science (BHS) projects will be available through the University of Melbourne online application process. Please visit the Melbourne Graduate School of Science (MGSS) website:
http://graduate.science.unimelb.edu.au/graduate-coursework-how-apply

FOR MORE DETAILS PLEASE VISIT:
- Melbourne Graduate School of Science website link: http://graduate.science.unimelb.edu.au/master-of-science-biomedical-health-sciences
- Master of Science (BHS) Information Guide for Staff and Students:

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- Dr Chris French  E: frenchc@unimelb.edu.au
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- Faculty of Science MSci (BHS) Coordinator: Professor Lea Delbridge  E: lmd@unimelb.edu.au
RMH ACADEMIC CENTRE DEPARTMENT LINKS:

RMH Academic Centre:  http://www.rmh.unimelb.edu.au

Department of Medicine (Royal Melbourne Hospital)  
Hhttp://www.medrmhwh.unimelb.edu.au/

Department of Surgery (Royal Melbourne Hospital)  
Hhttp://www.surgeryrmh.unimelb.edu.au/

Department of Psychiatry (Royal Melbourne Hospital)  
Hhttp://www.psychiatry.unimelb.edu.au/

Department of Radiology (Royal Melbourne Hospital)  
Hhttp://www.melbourne-radiology.org/Staff.html

Obstetrics & Gynaecology (Royal Women’s Hospital)  
Hhttp://www.thewomens.org.au/PregnancyResearchCentre