The Royal Melbourne Hospital

Bench to Bedside – Medical Research

THE UNIVERSITY OF MELBOURNE

PROJECTS 2018

THE ROYAL MELBOURNE HOSPITAL

(RMH Departments: Medicine, Radiology, Surgery, Psychiatry, Obstetrics & Gynaecology RWH and affiliated institutes)
Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences,
The University of Melbourne

HONOURS

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

Honours enrolling department – Medicine RMH

Course Codes:
BH-BMED - Bachelor of Biomedicine (Honours)
For students who have successfully completed or are about to complete the Bachelor of Biomedicine at the University of Melbourne.

BH-SCI - Bachelor of Science (Honours)
For all other applicants who have successfully completed or are about to complete a Bachelor of Science or equivalent

MASTER OF BIOMEDICAL SCIENCE

Course Code: MC-BMEDSC

Affiliations: The Royal Women's Hospital, Northern Health, The Peter MacCallum Cancer Centre, The Burnet Institute, Melbourne Brain Centre, Florey Neuroscience Institute, Melbourne Neuropsychiatry Centre, Mental Health Research Institute, Baker IDI Heart & Diabetes Institute.

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Master of Biomedical Science

THE UNIVERSITY OF MELBOURNE AT THE ROYAL MELBOURNE HOSPITAL

Listed below are brief outlines of the projects being offered in 2018.
For further information, contact the supervisors on the numbers and email addresses as listed.

AGEING

1. Inter- and intra-individual pattern of disease – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: The accumulation of age related diseases is one of the most striking phenomenon during the (human) ageing process. Chronological age is the most important risk factor for the development of diseases due to the underlying ageing process, which has been partly unraveled during the last decennia. Little is known about the rate of ageing of different organ systems within individuals, which might eventually result in different pattern of diseases. This knowledge is essential to disentangle disease specific traits from ageing specific traits, which eventually defines the counteracting interventions to overcome multimorbidity at older age.

Prerequisite: epidemiological/statistical skills, capacity to work in a multidisciplinary team, fascination with the ageing process.

2. The intra-individual rate of ageing – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: The ageing process is the underlying cause of most age related diseases in humans. Antagonizing the ageing process prevents the development of age related diseases in model organisms. In humans, the accumulation of DNA damage and senescent cells has been shown to be positively associated with the chronological age as well as biological age, e.g. the rate of aging, of the donors of tissue. Currently, the rate of ageing of different organ / cell systems within individuals is unknown. The aim is to characterize different tissues of the same individual in terms of their senescent load to determine the rate of ageing intra-individually.

Prerequisite: biomedical background and preferable lab skills, basic epidemiological/statistical skills, capacity to work in a multidisciplinary team, passion to unravel the ageing process.

3. Towards a biological geriatric assessment – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: In current geriatric practice, patients are assessed by use of the comprehensive geriatric assessment (CGA) evaluating the functional, mental and social state of the aged patient using predominantly

subjective, not well defined and badly standardized tools. The consequence is that CGAs are not comparable and that the causal mechanisms of the geriatric condition often remain unidentified. The aim is to refine the CGA and define the biological basis of geriatric conditions to eventually introduce a standardized biological geriatric assessment being predictive for relevant outcomes and sensitive and specific for change over time.

Prerequisite: basic lab skills (preferable), basic epidemiological/statistical skills, capacity to work in a multidisciplinary team, passion to unravel the ageing process, enjoy working with patients.

4. The underestimated power of human muscle – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: Muscle is one of the most powerful, but most neglected organs of our human body. Physical inactivity leads to immediate significant decrease in volume and therewith muscle function, whereas recovery of function is hard to accomplish without dedicated intervention. The EMPOWER II study aims to 1. evaluate the course of muscle mass and function during acute hospitalization and geriatric rehabilitation and 2. intervene by use of dedicated strength and nutritional interventions during geriatric rehabilitation to increase muscle mass and function. The EMPOWER II study is based on results of the EMPOWER I study conducted in the acute patient setting (papers in press), indicating the urgent need for individualized interventions to preserve physical function in the aged patient. Three positions are available (one for the observational part and two for the intervention part).

Prerequisite: intention to learn how to conduct epidemiological studies / interventions, epidemiological/statistical skills, intention to write a journal article, good communication skills, capacity to work in a multidisciplinary team.

5. Muscle health and nutritional needs during recovery from acute disease – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: .Sarcopenia, or age-related low muscle mass and/or strength, is central to the development of physical deconditioning. Sarcopenia, often underdiagnosed, is associated with falls, morbidity and mortality. Among geriatric patients in a rehabilitation program, prevalence is estimated at 40%, placing a major burden on the healthcare system. Geriatric rehabilitation care is focused on community-dwelling older persons, who are admitted to short-term rehabilitation programs after hospitalization and accompanied physical deconditioning. Evidence based protocols to regain physical condition in geriatric rehabilitation are currently not available. As such, 80% of patients in geriatric rehabilitation programs have insufficient dietary intake to support muscle metabolism that facilitates recovery from a hospital stay. Additionally, the energy expenditure could be increased due to the acute disease. Therefore, there is a disbalance between energy expenditure and energy intake which could cause unintentional weight loss and thereby loss of muscle mass. An understanding of the nutritional needs, energy expenditure and dietary intake (especially energy and protein intake), are largely unknown in older populations. This information is crucial to develop tailored nutritional and exercise interventions with the aim to prevent loss of- and to gain muscle mass and muscle strength.

Two positions are available:

Aim project 1: Phenotypic characterization of sarcopenia inpatients versus non- sarcopenic inpatients.
Aim project 2: Relationship between energy expenditure and muscle health (muscle mass, muscle strength)
Aim project 3: Relationship between dietary intake and muscle health (muscle mass, muscle strength)

Prerequisite: intention to learn how to conduct epidemiological studies / interventions, epidemiological/statistical skills, intention to write a journal article, good communication skills, capacity to work in a multidisciplinary team.

6. Refining the comprehensive geriatric assessment – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: The comprehensive geriatric assessment (CGA) is currently the most important assessment tool of geriatricians to define the functional, mental and social state of geriatric patients, but not well defined. There is an urgent need to refine the CGA to increase the power to predict detrimental outcome and to increase sensitivity and specificity for changes of geriatric conditions over time. From 2013-2015 all patients of a Dutch academic geriatric outpatient clinic were assessed using a standardized CGA, the unique dataset is now available for data analysis to define: 1. the functional, 2. mental and 3. social domain of the CGA. The defined CGA will then be validated in a dataset of Australian geriatric outpatients. Three positions are available.

Prerequisite: intention to improve epidemiological/statistical skills, intention to write a journal article, good communication skills, capacity to work in a multidisciplinary team

7. The blood pressure drop makes you fall……. – *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: (Initial) orthostatic hypotension ((i)OH) is highly prevalent in older adults, especially in those with one or more chronic diseases. iOH is defined as a blood pressure decrease(BP) of 40 mmHg systolic blood pressure (SBP) and/or 20 mmHg diastolic blood pressure (DBP) within 15 seconds after standing up, whereas OH is classically defined as a drop in BP of at least 20 mmHg of SBP and/or 10 mmHg of DBP at 1 and 3 minutes after standing up. iOH has been shown to be most predictive for balance impairment, increased self-reported impaired standing balance and falls in geriatric outpatients. While OH diagnostics are occasionally performed in clinical practice using a sphygmomanometer, continuously measured blood pressure measurements using beat to beat analyses has not entered routine geriatric care yet. Two student positions are available:

Aim project 1: Define the determinates of iOH and OH and consequences of iOH and OH in geriatric outpatients using an existing database and a validation cohort.

Aim project 2: Analysis of effectiveness of non-pharmacological and pharmacological interventions to counteract iOH and OH in geriatric patients.

Prerequisite: intention to improve epidemiological/statistical skills, intention to write a journal article, good communication skills, capacity to work in a multidisciplinary team, pleasure working with patients.

8. Essence of Senescence *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: Cellular senescence, the process by which cells lose their ability to divide is a well-established mechanism of ageing and age-related diseases. A number of ageing associated senescent biomarkers have been identified (e.g. $p^{16INK4a}$ and β-Gal) however, the association of these biomarkers, age and age-related diseases vary depending on the tissue analysed. A good biomarker needs to be clinically practical and easily attainable as such this project will look at the association between senescent biomarkers, tissue types and age-related diseases in humans.

9. Regeneration Proteostasis and Muscle *also offered as MBiomedSc*

Supervisor: Prof Andrea Maier
Project Site: University of Melbourne, RMH, Department of Medicine and Aged Care
Contact: T: + 61 3 9342 2635, E: andrea.maier@mh.org.au

Project description: Protein homeostasis (proteostasis) is essential for the regeneration and health of skeletal muscle. The gradual inability of cells and organism to maintain proteostasis as they age has been proposed to contribute to older individuals overall loss of fitness and reduced healthspan. This project will look at whether

known markers of proteostasis are associated with the gradual loss of muscle mass and strength as we age in a population of outpatients and inpatients.

10. Lifestyle Factors for Healthy Ageing – *also offered as MBiomedSc*

Supervisor: Dr Helen Brown, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital, UoM, Parkville, Vic 3052.
Contact: Prof Cassandra Szoeke T: 61 3 8344 1835
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.

This project will involve direct hands-on participant evaluation. You will also have the opportunity to work with a rich database with lifestyle data that spans over 20 years. There will be the opportunity for publication.

11. Multimorbidity and ageing women - *also offered as MBiomedSc*

Supervisors: Dr Lucy Busija, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital, UoM, Parkville, Vic 3052.
Contact: Prof Cassandra Szoeke T:61 3 8387 2224 F : 61 3 9387 9384
E: cszoeke@unimelb.edu.au

Project description: Multimorbidity is an under-researched area, despite 80% of elderly Australians having 2 or more chronic illnesses. The optimal measure for multimorbidity has not yet been established. This research project will investigate which of the currently available multimorbidity measures has the best predictive power, working with the Healthy Ageing Program in the Department of Medicine. This is a unique opportunity to work on an Australian dataset with midlife and late life data collected over 25 years.

This project will provide opportunity for publication and suits a candidate with an interest in a number of disease areas.

12. Physical Activities for Health Ageing- *also offered as MBiomedSc*

Supervisors: Dr Steve Simpson Jr, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. A lack of physical activity have been linked to an increased rate of cognitive impairment and cardiovascular diseases. Studies investigating physical activity 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 physical activity on cognitive performance and health.

This project will involve direct hands-on participant evaluation and provide clinical skills experience. You will also have the opportunity to work with a rich database with lifestyle data that spans over 20 years, as well as an opportunity for publication.

13. Diet and Healthy Ageing - *also offered as MBiomedSc*

Supervisors: A/Prof Allison Hodge, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

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 diet 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 diet on cognitive performance and health.

Opportunities: You will have the opportunity to work with a rich database with lifestyle data that spans over 20 years. This project will provide clinical skills experience as it involves direct hands-on participant evaluation, and will suit a student with an interest in nutrition who is interested in publishing findings.

14. Patterns of Violence in Australian Women – A twenty year follow up Study - *also offered as MBiomedSc*

Supervisors: Dr Kelly Hand, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Women are more likely than men to experience various forms of violence. One in four Australian women experience physical or sexual assault from a current or former partner (Australian Bureau of Statistics, 2012), and since the age of 15 years, one in three women has experienced physical violence (Cox, 2015). Women are also over two times more likely than men to experience elder abuse (Boldy et al, 2002). This project will examine the cross-sectional relationship between women's experiences of violence and their health and quality of life outcomes, and the impact that experiences of violence have on women's health and quality of life over time.

The main opportunities in this project are:

- Working with a large dataset spanning over 20 years from an internationally renowned cohort
- Working with an internationally recognised research team
- You will also have the opportunity for publication
- This project would suit a student with an interest in women's health

15. Social and physical activities in ageing women - *also offered as MBiomedSc*

Supervisors: Dr Helen Brown, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Social engagement is important for the maintenance of physical health and cognitive function, with these outcomes found to be particularly evident in women. However the role of social engagement in age-related cognitive function is not well understood. In this project we will examine the relationship between social and physical activities, and physical and cognitive health from a cross-sectional perspective. The relationship between these variables over time will also be examined.

The key benefits of this project are:

1. It will involve direct hands-on participant evaluation and provide clinical skills experience
2. The opportunity to work with a rich database with data that spans over 20 years already collected
3. The opportunity for publication

16. The importance of diet in health - *also offered as MBiomedSc*

Supervisors: Dr Allison Hodge, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: There is growing evidence that suggests certain diets may be beneficial for the maintenance of health in ageing. In this project you will examine the relationships between diet and health in ageing women.

Opportunities: You will have the opportunity to work with an internationally renowned cohort and research team each with international recognition.

The study has already collected data over 20 years and there is opportunity for publication. This project will suit a candidate with an interest in nutrition. There will be interaction with industry partners.

17. Identifying and Understanding Early Signs of Dementia - *also offered as MBiomedSc*

Supervisors: Dr Davor Stanic and A/Prof Mathias Dutschmann
Project Site: Florey Institute of Neuroscience and Mental Health (Howard Florey Laboratories)
Contact: Dr Davor Stanic T: 8344 0182 E: davor.stanic@florey.edu.au

Project description: The enormous efforts devoted towards finding the cause and cure for dementia have so far failed, with clinical trials being unsuccessful in improving or even reducing the rate of cognitive impairment. To counter these failures, greater emphasis has been placed on establishing an early diagnosis; recognising presymptomatic and preclinical phases, and ultimately allowing for the earlier introduction of therapies aimed at preventing or delaying dementia.

Research in our laboratory focuses on identifying thus far unrecognised symptoms of dementia that precede the onset of cognitive deficits. In an animal model of frontotemporal dementia, we have detected swallowing deficits and irregular coordination between swallowing and breathing, which are common complications that accompany dementia, but may also be potential early symptoms.

This project aims to characterise the neural mechanisms underlying this swallowing disorder. The onset and progression of tauopathy, neurofibrillary tangle-related morphology, neurodegeneration, and neurotransmitter loss will be characterised in the brainstem of our model of frontotemporal dementia, with focus on three key areas critically involved in coordinating swallowing and breathing: 1) *Nucleus of the solitary tract (NTS)*, which generates a phasic or rhythmic 'command' to produce sequential swallowing in response to sensory stimuli; 2) *Nucleus ambiguus (NA)*, which contains the laryngeal motoneurons innervating the vocal folds; and 3) *Kölliker-Fuse nucleus (KF)*, which provides tonic drive for the laryngeal adductors and completely seals the trachea during, and between, swallows.

This project will provide the framework for future studies aimed at alleviating swallowing disorders and generating potential therapies that restore function to impaired brainstem circuitry that controls swallowing and breathing.

Techniques include: immunohistochemistry and stereology.

Further Reading:

Bautista TG and Dutschmann M (2014). *J Physiol*, 592(12): 2605-23. doi:10.1113/jphysiol.2014.272468

18. Understanding the Role of Vitamin D in Muscle Adaptation - *also offered as MBiomedSc*

Supervisors: A/Prof Alan Hayes and Prof Gustavo Duque
Project Site: Dept of Medicine – Western Health
Contact: A/Prof Alan Hayes E: hayes.a@unimelb.edu.au

Project description: Vitamin D deficiency is common place and older individuals in particular suffer fatigue and muscle weakness as a result. The resultant low bone mineral density and increased falls risk makes fractures and subsequent disability a major consequence. While supplementation is able to reverse this, there is evidence that increasing levels too quickly increases the risks of falls and fractures, possibly due to direct effects of vitamin D on muscle. Indeed, we have recent data that supports a differential role for vitamin D in regulating muscle strength and recovery from fatigue. Interestingly, our most recent study suggests that vitamin D may sensitise skeletal muscles to the effects of exercise. As such it may be important to include activity and exercise with any vitamin D supplementation regime. We aim to further explore this effect with a multifaceted approach to complement our current human trials.

This study aims to understand the complex interplay of vitamin D with muscle function. We will feed animals diets containing different levels of vitamin D, with and without exercise, to deplete, replete and increase vitamin D levels beyond usual physiological levels. At the same time, key enzymes implicated in the sensitizing effect and the vitamin D hormone-muscle molecular pathways will be knocked down or overexpressed to elucidate potential mechanisms of action. Analysis of muscle will be undertaken at the molecular, mitochondrial, single fibre and whole muscle level to provide a complete picture of the direct effects of vitamin D on skeletal muscle.

This project will include the use of animal exercise models and dietary supplementation, animal surgery, recombinant DNA purification and protein purification, the transfection of muscles in vivo, isolation and analysis of single muscle fibres, ex vivo muscle testing, Western blotting, immunohistochemistry, microscopy and enzyme activity assays.

19. Understanding Patient Capacity to Adhere to Prescribed Treatment Regime Post-Fracture - *also offered as MBiomedSc*

Supervisors: Dr Sharon Brennan-Olsen
Project Site: Dept of Medicine – Western Health
Contact: Dr Sharon Brennan-Olsen E: sbrennan@unimelb.edu.au

Project description: In 2012, 4.74 million Australians aged 50yrs or older (66% of those aged ≥50yrs) had poor bone health (22% osteoporosis, 78% osteopenia). Osteoporosis is characterised by low density and quality of bone, with a subsequent increased risk of fracture; currently one fracture occurs every 3.6 minutes. Data show that socially disadvantaged individuals have a disproportionately greater risk of osteoporosis and fracture compared to their less disadvantaged counterparts. Whilst current efforts are aimed at making 'the first fracture the last fracture', persistence with a prescribed treatment regime is imperative for effective prevention of secondary fracture. However, it is concerning that treatment adherence is only 43-53% for osteoporosis, a figure that is much lower compared to other diseases. Furthermore, persistence with a prescribed treatment appears strongly influenced by a patient's ability to seek, understand and utilize health information; aspects referred to as 'health literacy'. Estimates indicate that up to a quarter of the Australian population has suboptimal health literacy, and this is more commonly observed in individuals who are older, socially disadvantaged, or from culturally and/or linguistically diverse populations. To date, very little is known regarding the effect size of low health literacy on a patients' ability to persist with medication post-fracture.

This project will recruit a new cohort of fracture patients from the Western suburbs of Melbourne: an area that is one of the most socially disadvantaged and culturally diverse within Victoria. Health literacy at the time of fracture will be determined, and the roles played by health literacy and social disadvantage in the ability to adhere with prescribed treatment regime over time will be investigated. By understanding situational and personal determinants of health literacy specific to osteoporotic fracture and treatment adherence, we will be better placed to improve healthcare provision and inform effective patient-practitioner alliances.

ALCOHOL

20. Why do some people with hepatitis C continue to drink? - *also offered as MBiomedSc*

Supervisor: Prof Margaret Hellard, Head, Centre for Population Health, Burnet Institute
Project Site: Burnet Institute
Contact: E: margaret.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.

ANAESTHESIA AND PERIOPERATIVE MEDICINE

21. The evaluation of anaesthetic drugs and techniques on the postoperative quality of recovery – *also offered as MBiomedSc*

Supervisors: Prof Colin Royse
Project Site: The Royal Melbourne and Epworth Hospital campuses
Contact: Prof Colin Royse colin.royse@unimelb.edu.au

Project description: Improving postoperative quality of recovery is a major initiative in anaesthesia and perioperative medicine. Different anaesthetic drugs and different techniques will be evaluated in clinical trails using the Postoperative Quality of Recovery Scale (PostopQRS) as the measurement tool. This tool measures recovery from the patient's perspective in physiological, emotive, nociceptive, functional and cognitive domains. Projects are already established, ethics in place and commenced.

ANATOMY & NEUROSCIENCE

22. Diet induced obesity: is it an addiction? *also offered as MBiomedSc*

Supervisors: Dr Robyn Brown and Prof Andrew Lawrence
Location: Addiction Neuroscience Laboratory @ the Florey
Contact: Robyn Brown E: Robyn.Brown@florey.edu.au E: Andrew.Lawrence@florey.edu.au

Project description: Difficulty in managing food intake, especially highly palatable food, can result in obesity and substantial associated health liabilities. A cardinal feature of the pathological over-eating often underlying obesity is that although the individual can describe the negative consequences of their behaviour, they have great difficulty intervening and changing their behaviour. Thus, difficulty in reducing food intake has qualities of an addictive disorder. The disconnect between stated goals to reduce food consumption and actual behaviour suggests the presence of impairments in how information from the frontal cortex is integrating with basal ganglia circuitry to direct behaviour.

We have found that rats prone to diet-induced obesity display some features of 'addiction-like' behaviour towards palatable food. This provides important preliminary evidence to support our central hypothesis that the pathological over-eating commonly observed in diet-induced obesity shares common features with the compulsive drug-taking observed in drug addiction.

Therefore we aim to:
1: Investigate the presence of addiction-like behaviour in rats prone to diet-induced obesity.
2: Conduct a preclinical trial of the glutamate homeostasis restoring drug N-acetylcysteine to reverse synaptic impairments in obesity prone rats to ameliorate aberrant feeding behaviour.

23. Investigating Alcohol-Related Dementia *also offered as MBiomedSc*

Supervisors: Dr Christina Perry and Prof Andrew Lawrence
Location: Addiction Neuroscience Laboratory @ the Florey
Contact: Christina Perry E: Christina.Perry@florey.edu.au E: Andrew.Lawrence@florey.edu.au

Project description: Alcohol-related dementia (ARD) is one of the leading causes of secondary (preventable) dementia, and younger onset dementia (onset of symptoms prior to 65 years) in Australia. Together with the high rates of alcohol consumption in Australia, this means that ARD is becoming an increasingly urgent public health issue. The only treatment currently available for ARD is alcohol rehabilitation and abstinence. However, emerging evidence from animal models indicates that exercise may act as a protective factor against the neurotoxic effects of alcohol, and is even able to reverse some of the brain injury that occurs following alcohol exposure.
The aim of this project is to use a validated rodent model to:
1) Characterise the cognitive and neuropathological symptoms of ARD.
2) Evaluate the restorative effects of abstinence combined with voluntary exercise on these symptoms.

24. Context-induced relapse to alcohol-seeking after voluntary abstinence ***also offered as MBiomedSc***

Supervisors: Dr Erin Campbell and Prof Andrew Lawrence
Location: Addiction Neuroscience Laboratory @ the Florey
Contact: Erin Campbell E: Erin.Campbell@florey.edu.au E: Andrew.Lawrence@florey.edu.au

Project description: Substance abuse is a major health care problem. Accordingly, there is a real need to increase our fundamental understanding of the processes behind addiction, so that more targeted therapeutic strategies can follow. We have identified a potentially critical neural mechanism by which alcohol associated environments promote alcohol seeking during abstinence. We will further unravel the brain mechanisms of relapse to alcohol seeking, and will identify novel brain areas and circuits that future clinical studies can target in treatment-seeking alcoholics.

A limitation identified in animal models is that abstinence is achieved 'non-voluntarily' (experimenter-imposed). In humans, however, abstinence is typically voluntary (self-imposed), despite drug availability and often out of a desire to avoid the negative consequence associated with excessive alcohol use. A recently developed animal model addresses this limitation. In this model, the laboratory animal abstains voluntarily from alcohol use when alcohol-seeking is associated with a negative consequence. We will combine this novel animal model of relapse with an innovative procedure to manipulate neurons in defined neural circuits to determine which circuitry is critical for context-induced relapse to alcohol seeking.

25. The oxytocin system in sugar and alcohol intake ***also offered as MBiomedSc***

Supervisors: Dr Phil Ryan and Prof Andrew Lawrence
Location: Addiction Neuroscience Laboratory @ the Florey
Contact: Phil Ryan E: philip.ryan@florey.edu.au E: Andrew.Lawrence@florey.edu.au

Project description: Oxytocin is well recognized for its role in labour, lactation and social interaction; however, it is also known to be involved in regulating fluid and salt intake. We have recently discovered a population of neurons that express the receptor for oxytocin and are located in the parabrachial nucleus of the hindbrain, which robustly suppress water and saline (NaCl) intake, but not food intake. We are now interested in investigating whether these neurons may also play a role in suppressing sugar, alcohol and non-caloric saccharin intake, which may suggest a role in addictive-like behaviours.
We will use genetically modified mice that allow us to selectively manipulate this neuronal population by techniques such as optogenetics and DREADDs (designer receptors exclusively activated by designer drugs). We are also interested in directly observing these neurons using calcium imaging techniques, which allow us to visualize activity in the neurons in real-time while the mice are actively drinking. The project will also involve anatomical and electrophysiological studies to map out the neural circuitry of fluid intake.

26. Alcohol and striatal adaptation ***also offered as MBiomedSc***

Supervisors: Dr Nicola Chen and Prof Andrew Lawrence
Location: Addiction Neuroscience Laboratory @ the Florey
Contact: Nicola Chen E: Nicola.chen@florey.edu.au E: Andrew.Lawrence@florey.edu.au

Project description: Alcohol drinking and cigarette smoking are amongst the leading worldwide causes of preventable death and disease. Moreover, alcohol and tobacco are commonly co-abused and animal studies have implicated potential overlapping machanisms of action in the brain. In this regard both alcohol and tobacco impact central cholinergic systems and drugs acting at nicotinic receptors can regulate both drinking and smoking. Importantly, we have recently confirmed the functional relevance of lateral striatal M5 muscarinic receptors in regulating voluntary alcohol intake. These novel findings allow us to hypothesise that plastic adaption of cholinergic signaling occurs following chronic intermittent alcohol in the lateral striatum.
Based on these exciting results, we will:

(i) Perform analogous RNA Seq studies in human alcoholic brain compared to age matched control brain.
(ii) Characterize the molecular and electrophysiological consequences of chronic intermittent alcohol intake on cholinergic transmission in the rat striatum.
(iii) Examine in rats how pharmacological manipulation of nicotinic and muscarinic M5 receptors, alone and in combination, impacts upon alcohol use / relapse.

Overall, this novel and innovative study will lead the field by characterizing the molecular effects of chronic alcohol use in human caudate (medial striatum) vs putamen (lateral striatum); characterizing the

impact of alcohol on striatal cholinergic transmission and a parallel preclinical assessment of a potential novel therapeutic target, namely the muscarinic M5 receptor.

ARTHRITIS AND INFLAMMATION RESEARCH CENTRE

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

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

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

27. The role of a novel macrophage inflammatory mediator in arthritis ***also offered as MBiomedSc***

Supervisors: A/Prof Andrew Cook, Dr Ming-Chin Lee and Prof John Hamilton
Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH) , University of Melbourne
Contact: Dr Andrew Cook T: 8344 3290 E: adcook@unimelb.edu.au

Project Description: Through a microarray screen of inflammatory macrophages we have identified a novel potential therapeutic target for the treatment of arthritis. Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. In this project you will investigate the expression of this potential therapeutic target in patients' tissue samples and in an inflammatory model of arthritis, and determine if targeting this protein would be a beneficial treatment. In this project you will be cutting tissue sections and measuring the expression of this novel protein. You will be inducing a murine model of arthritis and measuring a number of clinical parameters, collecting and processing tissue, and measuring gene/protein expression by histology, real-time PCR, Western blotting and FACS analysis. You will also be using siRNA, and nanoparticles to deliver therapeutic drugs in the arthritis model.

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

28. Molecular signaling pathways controlling gene expression during chronic disease progression ***also offered as MBiomedSc***

Supervisors: Dr. Adrian Achuthan and Prof. John Hamilton
Project Site: Department of Medicine (RMH), University of Melbourne
Contact: Dr. Adrian Achuthan T: 8344 3298 E: aaa@unimelb.edu.au

Project description: Inflammation is now known to be associated with many chronic diseases such as cancer, Alzheimer's disease, obesity/type II diabetes and heart disease. This project aims to understand molecular signalling pathways controlling the expression of genes critical for the progression of such diseases. In this project you will explore in molecular terms how a particular inflammatory cell type (macrophage/dendritic cell) can adapt to provide a pro-inflammatory environment with consequences for persistence or otherwise of these significant diseases. More specifically, you will investigate how transcription factors control the expression of pro-inflammatory and anti-inflammatory cytokines. Elucidation of these molecular pathways may lead to the development of novel therapies.

Techniques: You will acquire a wide-range of skills in cell biology (primary human monocytes/macrophage culture, ELISA assays, confocal microscopy and flow cytometry), and biochemistry and molecular biology (Western blotting, Real-Time PCR and siRNA-mediated gene knock-down).

29. Elucidating molecular signaling pathways controlled by anti-inflammatory steroids ***also offered as MBiomedSc***

Supervisors: Dr. Adrian Achuthan and Prof. John Hamilton
Project Site: Department of Medicine (RMH), University of Melbourne
Contact: Dr. Adrian Achuthan T: 8344 3298 E: aaa@unimelb.edu.au

Project description: Steroids (glucocorticoids) are widely used to treat the chronic inflammation and pain associated with many diseases such as rheumatoid arthritis and osteoarthritis. Unfortunately, there are side effects associated with usage of glucocorticoids in such diseases. In this project you will use genome-wide approaches such as microarray to indentify the genes that are regulated by glucocorticoids. More specifically, you will investigate molecular signalling pathways that lead to activation of transcription factors that lead to differential expression of glucocoritcoid-controlled genes in inflammatory conditions. Enhancing our understanding of molecular signalling pathways that are governed by glucocorticoids may lead to improved clinical therapies with minimal side effects.

Techniques: You will acquire a wide-range of skills in cell biology (primary human monocyte/macrophage culture, ELISA assays, confocal microscopy and flow cytometry), and biochemistry and molecular biology (Western blotting, Real-Time PCR and siRNA-mediated gene knock-down).

BONE AND MINERAL RESEARCH

30. Bone health and its long term predictors post-bone marrow transplantation– ***also offered as MBiomedSc***

Supervisors: Prof John Wark, Prof David Ritchie, Ms Alexandra Gorelik, Dr Catherine Seymour
Project Site: Department of Medicine (RMH)
Contact: Prof John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Project Description: Both allogeneic and autologous bone marrow transplantation (BMT) are associated with a high risk of early bone loss particularly at the femoral neck, followed by gradual improvement in bone mineral density (BMD) over the ensuing years. Approximately 50% of BMT patients may develop osteopenia or osteoporosis post-BMT. The bone loss appears to be multifactorial in aetiology and currently the prediction of long term bone health outcomes is uncertain. In this project, the ability of parameters including patient demographics, recognised risk factors for bone loss and BMD changes at 100 days and 1 year to predict BMD and fracture outcomes at 5 years and later will be examined. This information will help in stratifying BMT patients' long-term fracture risk and in appropriately targeting bone-protective interventions.

31. Monitoring for atypical femoral fracture (AFF) risk– ***also offered as MBiomedSc***

Supervisor: Prof John Wark, Dr Chris Yates, Ms Alexandra Gorelik, Dr Ashwini Kale
Project Site: Department of Medicine (RMH), National Ageing Research Institute, Parkville.
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: Evidence suggests that bisphosphonates and other antiresorptive therapy are associated with atypical fractures involving the femoral shaft. This adverse event may be related to treatment duration. As yet, no evidence-based protocol has been developed to monitor patients for this uncommon but serious adverse effect of therapy for osteoporosis, a very common and often disabling condition. The aim of this project is to evaluate the utility of single-energy X-ray absorptiometry screening for femoral morphological changes predictive of AFF. Patients treated with antiresorptive medications for osteoporosis will be recruited for evaluation in the Bone Densitometry Unit when having clinical bone densitometry. A scoring system will be developed and applied to quantify AFF risk and will be compared with potential clinical predictors of risk.

BIOLOGY —WOMEN'S HEALTH

32. Investigation of genes associated with increased risk of endometriosis – ***also offered as MBiomedSc***

Supervisors: Prof Peter Rogers, Dr Sarah Holdsworth-Carson, Dr Premila Paiva

Project Site: Department of Obstetrics and Gynaecology, Royal Women's Hospital
Contact: Prof Peter Rogers E: parogers@unimelb.edu.au;

Project description: Endometriosis is a disease where endometrial tissue grows outside of the uterus, most commonly on the organs and tissues of the peritoneal cavity. It is a horrible disease that significantly reduces quality of life in up to 10% of women through chronic pelvic pain and infertility. There is no permanent cure and current treatment options are inadequate. There is a desperate need to understand the mechanisms responsible for this disease and for the development of diagnostic tools, prevention strategies and improved treatment options (precision medicine).

Endometriosis is a complex disease with a genetic basis. Recent genome wide association studies have identified several candidate genes linked to the risk of endometriosis. We are now working on a 4-year NHMRC-funded project that aims to examine the function of these genes in uterine tissues with the aim of determining how candidate genes and gene pathways may contribute to endometriosis pathophysiology. Potential projects will be based on information derived from our database and associated tissues from over 600 women that includes comprehensive clinical, quality of life, symptom, molecular and genetic information; our database is currently of the largest of its type in the world. Projects will largely be laboratory based with the potential to interact with expert clinicians and undertake questionnaire based studies.

33. A critical analysis of Sunsmart behaviour in young Australian women - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Dr George Varigos, Dr Asvini K Subasinghe, Prof Suzanne Garland.
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: E: jdwark@unimelb.edu.au

Project description: Recommendations regarding sun-smart behaviour can be complex and confusing. What do young women understand about sun-smart behaviour and how do they perceive their own sun-smart behaviour? Young women's understanding of recommended sun-smart behaviours and their perception of their own sun-smart behaviours will be the focus of this research project. Self-reported data will be compared to objectively measured sun exposure using personal UV dosimeters.

34. Air pollution may impair vitamin D status in young Victorian women - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Ms Alexandra Gorelik
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: E: jdwark@unimelb.edu.au

Project description: Recent European research has identified a potentially worrying relationship between vitamin D status and local measures of air quality. Is there an association between air quality and vitamin D levels in young women living in Victoria? This project will explore a possible association between air quality in postcode of residence and serum vitamin D levels in young women. Validated models of air quality based on monitored levels of air pollution will be applied to study these relationships.

35. Dietary habits and mental health in females aged 16-29 years - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik.
Project Site: Bio21 Institute, Parkville
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: There is a large body of evidence linking a poor intake of nutrients and unhealthy dietary patterns with the development and management of mental health conditions such as depression. Using self-reported and clinical data on mental health and dietary intake data collected from a validated food frequency questionnaire (FFQ), in the Young Female Health Initiative (YFHI) and Safe-D studies, students will have the opportunity to investigate the association between diet and several indices of mental health and other behavioural and lifestyle factors. There is also an opportunity to determine whether there are any temporal changes in dietary and lifestyle behaviours using data collected from two year follow up visits. Findings from this study will be able to provide insights into the relationship between poor diet and mental health in an at-risk population. Additionally, findings may also provide the framework for targeted intervention strategies. This project would suit a student interested in women's and mental health.

36. Metabolic health of females with Type 1 Diabetes aged 16-25 years - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: Though there is strong evidence to show that individuals with Type 1 diabetes are at risk of various metabolic and cardiovascular diseases, there is limited evidence to show these associations in adolescent and young adult females. The Young Female Health Initiative (YFHI) Diabetes Study is a comprehensive female health study conducted on 16-25 year old females with Type 1 Diabetes. Students will have the opportunity to investigate the prevalence of metabolic and cardiovascular risk factors and associated behavioural and lifestyle factors in a young female cohort with type 1 diabetes. Findings from this study will be able to shed light on the health profiles of young females with diabetes and provide evidence for targeted intervention strategies for females in this age group. This project would suit a student interested in endocrinology and cardiovascular health

37. Vitamin D status and mental health outcomes in females aged 16-25 years participating in a randomized controlled trial - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: There is a large body of evidence supporting a relationship between Vitamin D and poor mental health. Students will have the unique opportunity to investigate the association between Vitamin D and several indices of mental health in females recruited into the intervention component of the Safe-D study (Part B). Participants with 25 OHD levels 25 to 75 nmol/L are randomized to one of three groups in 1:1:1 ratio: a mobile phone–based application designed to encourage safe sun exposure, vitamin D supplementation (1000 IU/day), and a control group. Data collection points are at baseline, 4 and 12 months post baseline with the major endpoints being at 4 months. A wide range of information is collected from participants throughout the course of this study including validated and self-reported information relating to mental health status and lifestyle behaviours. Students will have the fantastic opportunity to investigate a number of relationships between Vitamin D status and indices of mental health. There is also an opportunity to determine whether there are any temporal changes in these associations at 4 months and 12 months after baseline. Findings from this study will help provide an insight into the effects of improving vitamin D levels on several health outcomes, particularly mental health.

This project would suit a student interested in mental health.

38. Vitamin D status and multiple health outcomes in females aged 16-25 years participating in a randomized controlled trial - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: Low vitamin D levels are associated with an increased risk of numerous chronic health conditions, including poor musculoskeletal health and osteoporosis. However, few researchers have investigated these relationships in young females. We present a novel opportunity for students to investigate these associations in 16-25 year old females participating in a randomized clinical trial as part of the Safe-D study. Participants with 25 OHD levels 25 to 75 nmol/L were randomized to one of three groups in 1:1:1 ratio: a mobile phone–based application designed to encourage safe sun exposure, vitamin D supplementation (1000 IU/day), and a control group. Data from comprehensive surveys, blood tests, bone densitometry, body composition scans, and Leonardo mechanography tests are available on participants at baseline and at 12 months post baseline. Therefore, students will also have the opportunity to determine a research project according to their own interests from this rich dataset, and investigate associations longitudinally. Findings from this study will help provide an insight into the effects of vitamin D levels on several health outcomes, including musculoskeletal health, mental health, and monitoring for skin changes.

39. Longitudinal analysis of health outcomes in 16-29 year old females - *also offered as MBiomedSc*

Supervisors: Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik, Dr Asvini Subasinghe.
Project Site: Department of Medicine, (RMH) Parkville Campus
Contact: Prof John Wark E: jdwark@unimelb.edu.au

Project description: The Young Female Health Initiative (YFHI) and Safe-D studies are comprehensive female health studies conducted with 16-29 year old females. Data are collected via online surveys and clinical site visits for the YFHI study at baseline and at 2 years post baseline. Survey data are available on the following health domains: general health and lifestyle behaviours, mental health, sexual and reproductive health, bone and joint health, cardiovascular and metabolic health, and dietary behaviours. Clinical data include fasting blood tests, anthropometric measurements, sexual health samples, bone mineral density, and body composition scans obtained through site visits. Students will have the novel opportunity to investigate a research question of interest in a representative sample of young Australian females as well as determining variations in health outcomes longitudinally using data collected from two year follow up visits. This project would suit a student interested in women's health.

BRAIN BIONICS

40. Development of a Brain-Machine Interface Training Paradigm also offered as MBiomedSc

Supervisors: Nicholas Opie, Sam John, Thomas Oxley
Project Site: Department of Medicine, Royal Melbourne Hospital
Contact: Nicholas Opie – 0438 089 306; E: Nicholas.opie@unimelb.edu.au

Project description: Our team has developed an endovascular brain machine interface, a device designed to enable people with paralysis to control external equipment with their minds. Over the next year, we will be developing hardware and to enable neural signals acquired with the Stentrode to control communication tools and vehicles. Through this project, we will also be evaluating and optimising fMRI based training protocols that will be used to teach patients to use their minds to control assistive technology.

BRAIN INJURY

41. Biomarkers of brain concussion in Australian Rules Footballers – also offered as MBiomedSc

Supervisors: Dr. Sandy Shultz, Prof. Terence O'Brien, Prof. Andrew Kaye
Project Site: Department of Medicine RMH, Melbourne Brain Centre, Kenneth Myer Building
Contact: Dr. Sandy Shultz, E: sshultz@unimelb.edu.au

Project description: Brain concussion, a common form of mild traumatic brain injury (TBI), is a serious medical and societal issue. Of particular concern are individuals who are at high risk of suffering multiple concussions – such as athletes playing collision sports – because repeated concussions may contribute to chronic neurological impairments and neurodegenerative disease. There is evidence that the long-term adverse effects of repeated concussion are due to the recurring insults occurring before the brain has recovered from the initial concussion and is still in a period of increased vulnerability. Currently there are no reliable markers that indicate when the brain is no longer in this state of increased vulnerability, but the identification of such biomarkers would allow them to be used to guide medical decisions, so as to reduce the effects of repeated concussion.

There are a number of promising concussion biomarker platforms. Physical, psychological, and cognitive symptoms are common after concussion, and symptom scales and neuropsychological testing are currently used in concussion management. Magnetic resonance imaging (MRI) is a non-invasive tool that may identify changes in the brain after a concussion, and monitor the recovery of these changes. Blood samples can be used to measure markers that may provide information about the pathophysiology, progression, and recovery of concussion.

In this project we will us advanced and multimodal MRI, proteomic, behavioural, cellular and molecular methods, to assess the pathophysiology of concussion, and identify MRI, blood, and behavioural biomarkers

that can detect these changes and estimate recovery. This will be done in Melbourne University Football club athletes (i.e. amateur Australian Rules Football).

42. Myelin repair after traumatic brain injury in early life

Supervisors: Dr. Bridgette Semple
Project Site: Department of Medicine RMH
Contact: Dr. Bridgette Semple, E: bridgette.semple@unimelb.edu.au

Project description: Damage to myelin, the insulating sheath surrounding nerves, is a common consequence of traumatic brain injury. Emerging evidence suggests that white matter connectivity problems may underlie social behaviour deficits in other contexts (e.g. autism spectrum disorders), and that enhancing myelination during this critical period of development may reverse these deficits, suggesting that myelination may be a key neuropathological mechanism underlying poor outcomes after brain injury during early life. Previous findings by our group have found that the neurotrophin, brain-derived neurotrophic factor, enhances myelination by signalling through the TrkB receptor expressed on myelin-producing oligodendrocytes.

Here, we aim to:
(a) examine the consequences of brain injury in early life on postnatal myelin development, and
(b) test whether a specific TrkB agonist can preserve and repair myelin following traumatic brain injury.

Experiments may involve behavioural assays, animal handling, and immunohistochemical analysis to evaluate oligodendrocytes, cell death, myelin integrity and TrkB activation. Our findings will provide new proof-of-concept evidence that myelin integrity is critical to functional and neuropathological outcomes, and pave the way for future therapeutic applications.

43. The role of microparticles in traumatic brain injury

Supervisors: Dr Mastura Monif, Prof Terence O'Brien
Project Site: Department of Medicine RMH
Contact: Dr Mastura Monif, E: mmonif@unimelb.edu.au

Project description: Traumatic brain and spinal cord injury are one of the most common causes of acquired disability generally affecting young individuals. The acute injury can occur due to car accident, blunt trauma or fall. The consequences of traumatic brain injury can be lifelong and it can have major implications for the individuals and families afflicted.

The cellular and molecular processes that occur in the acute and chronic phase of traumatic brain injury are unclear. We know that in response to tissue injury and trauma large amounts of adenosine 5' triphosphate (ATP) is released into the surrounding environment and can affect ATP sensing purinergic receptors. One such receptor is P2X7R, which is found in immune cells of the brain (microglia) as well as in the periphery (monocytes). Previous studies in mice have shown that inhibition of this receptor can enhance recovery in setting of spinal cord injury. When activated by ATP, P2X7R can mediate a number of functions, including the release of various cytokines, chemokines as well as microparticles. Microparticles are small (100-400nm) structures that are shed from the surface of immunological cells and can exert their effect locally as well as systemically. Prior studies have shown that stimulation of P2X7R, leads to release of microparticles from monocytes, microglia as well as macrophages. The contents and exact function of microparticles in setting of brain trauma is unclear and will form the basis of this project.

Patients that have sustained traumatic brain injury in the preceding 12-24 hours are recruited for this study. With ethical consent we will obtain blood from these individuals during the acute phase of the injury and then one month post injury. The blood specimens will be processed in the laboratory to quantify the amount of microparticles as well as identify their cell of origin. In addition we will be analysing the content of the microparticles and comparing to healthy controls.

Techniques that will be employed include: microparticle isolation, monocyte cultures, enzyme linked immunosorbent assays, microRNA analysis as well as confocal and fluorescence microscopy. The interconnection between the central (brain) versus peripheral immune system in the acute phase of trauma is

unclear. The findings from this project would help us understand the role of microparticles in setting of traumatic brain injury to help in devising future treatment strategies.

CANCER

44. Psychosocial and behavioural outcomes of women at high pedigree based risk of breast and/or ovarian cancer.

Supervisors: Dr Lesley Stafford, Prof Bruce Mann, Prof Geoff Lindemann
Project Site: Centre for Women's Mental Health, Royal Women's Hospital
Contact: Dr Lesley Stafford. E: Lesley.Stafford@thewomens.org.au T: 61 03 8345 3909

Project description: Data has been collected from 372 women (193 affected by cancer and 178 unaffected by cancer) at high pedigree based risk for breast and/or ovarian cancer who have either had genetic testing for a deleterious gene mutation (BRCA 1 or BRCA 2) with an uninformative result, or who cannot be personally tested for a range of reasons.

It is not well understood how these women perceive their risk of cancer, manage their disease risk or adjust psychologically in the context of a lack of established risk management guidelines.

The cross-sectional data collected relate to risk management practices for breast/ovarian cancer including screening, surgery and lifestyle modification; and psychological morbidity in the form of depression, anxiety, cancer-specific distress and worry. Other psychological data collected include levels of neuroticism and cognitive representations of illness.

45. Inflammatory biomarkers of allogenic haematopoietic cell transplantation outcome

Supervisors: Dr Rachel Koldej, Dr Lynette Chee
Project Site: Victorian Comprehensive Cancer Centre
Contact: Dr Rachel Koldej. E: rachel.koldej@mh.org.au

Project description: The Royal Melbourne Hospital is one of the largest providers of allogeneic haematopoietic cell transplantation (alloHCT) in Australia. AlloHCT is a complex but potentially curative procedure for patients with haematologic malignancies or bone marrow failure syndromes. The fundamental principle of alloHCT is that a donor's haematopoietic stem cells (or graft), when infused into the recipient, will develop into a new set of immunologically active cells that recognise tumour cells as foreign and contain or destroy them. Studies have demonstrated that inflammation associated with alloHCT can contribute to adverse outcomes such as relapse, graft versus host disease and non-relapse mortality. We therefore are undertaking studies to examine the inflammatory process in pre-transplant samples and identify biomarkers that predict for patient outcome post-transplant. We have HREC approved access to over 300 pre-transplant samples with associated clinical outcome measures to use in this project. The biomarkers to be examined in this project include circulating microRNAs, cytokine levels and serum ferritin. Our initial studies in serum microRNAs have identified a number of microRNAs that are prognostic for outcome. These microRNAs require validation in a larger patient cohort. Our studies in ferritin have shown that serum ferritin, albumin and haemoglobin levels pre-allogeneic stem cell transplantation are predictive biomarkers of survival, relapse and non-relapse mortality post-transplant (Chee et al, Bone Marrow Transplantation, 2017). These biomarkers remain significant after accounting for disease risk index and add to its prognostic power. We now wish to analyse the levels of inflammatory markers (e.g. IL-6, CRP) to determine if the increased ferritin is a result of iron overload or an inflammatory state.

46. Glioma stem cells: biology and molecular targets

Supervisor: Dr Andrew Morokoff
Co-Supervisors: A/Prof Kate Drummond, Prof Andrew Kaye.
Location: Department of Surgery, Royal Melbourne Hospital

Contact: Dr Andrew Morokoff (morokoff@unimelb.edu.au) T: 9035 8586

Project Description: Giomas are common malignant brain tumours with an extremely poor survival because of their highly invasive nature and high recurrence rate. Recently a subpopulation of cells with stem-cell like properties has been identified in gliomas and these cells are thought to be related to recurrence and treatment resistance. Furthermore, certain molecular pathways that lead to invasion, apoptosis and drug resistance effects may be 'switched on' specifically in glioma stem cells. This project involves establishing stem cell cultures directly from surgical brain tumour samples and isolating cancer stem cells in neurspher cultures in vitro. These cell lines will be assessed for alterations of molecular signalling pathways including be new techniques such as next-generation whole genome and transciptome sequencing. These celll lines and mouse xenograft models utilising bioluminescence will be used to test novel compounds targeting these pathways.

47. Twist as a Regulator of EMT in Gastric Cancer and its role in invasion

Supervisors: Prof Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre
Contact: Prof Alex Boussioutas T: +61 03 8559 7031 E: alex.boussioutas@petermac.org or;
Dr Rita Busuttil T: +61 03 8559 5488 E: Rita.Busuttil@petermac.org

Project Description: Gastric cancer (GC) is often diagnosed at advanced stages, giving patients a 5-year survival of less than 20%. Advanced stage GC is directly correlated with increased local invasion of the cancer through the gastric wall and, at more advanced stages into adjacent structures.

Epithelial Mesenchymal Transition (EMT) is one mechanism which has been proposed as a modulator of invasion in GC as well as other cancer types. This project seeks to expand on previous work in our laboratory exploring the role of TWIST, a master regulator of EMT, in gastric cancer. We have previously shown that TWIST is more highly expressed at the invasive front of the tumor compared to its core indicating that EMT is occurring in this area. It is conceivable that reducing TWIST expression could be used as a means to decrease the invasive capacity of a cancer.

This project will aim to further explore the role of TWIST in the invasion of GC and its potential utility as a therapeutic target. A broad range of techniques including bioinformatics, cell culture, shRNA lentivirus mediated gene knockdown, and molecular biology will be applied.

We are looking for motivated students (both Honours and PhD students) to strengthen our group.

48. Functional charterization of candidate genes involved in the progression of gastric cancer

Supervisors: Prof Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre
Contact: Prof Alex Boussioutas T: +61 03 8559 7031 E: alex.boussioiutas@petrmac.org
Dr Rita Busuttil T: +61 03 8559 5448 E: Rita.Busuttil@petermac.org

Project Description: Gastric cancer (GC) is the fourth most common cancer globally. It has defined premalignant stages and progresses through Intestinal Metaplasia (IM) in the majority of cases. GC is diagnosed at advanced stage resulting in poor prognosis. Part of this is due to no means to identify and screen persons at risk of GC. Relatively little is known about the key genetic events leading to IM. Our laboratory is currently in the process of completing the first comprehensive analysis of IM in the world and we have identified a number of candidate genes which are likely to be involved in the progression of IM to GC. These could be potentially be used to reliably predict the progression to GC in humans enabling clinical stratification of individuals into high-risk groups. This project would involve functional validation of these candidates using cell culture and organoid

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

49. Role of the Tumour Microenvironment in Gastric Cancer

Supervisors: Prof Alex Boussioutas. Co-supervisor: Dr Rita Busuttil
Project Site: Peter MacCallum Cancer Centre
Contact: Prof Alex Boussioutas T: +61 03 8559 7031 E: alex.boussioutas@petermac.org
Dr Rita Busuttil T: +61 03 8559 5488 E: Rita.Busuttil@petermac.org

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

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

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

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

50. Elucidating the role of mesenchymal stem cells in promoting metastasis of ovarian cancer cells – also offered as MBiomedSc

Supervisors: Dr Bill Kalionis (Pregnancy Research Centre, RWH), Dr Nuzhat Ahmed (The Fiona Elsey Cancer Research Institute, Ballarat).
Project Site: Work will be conducted at the laboratories of the Royal Women's Hospital
Contact: Dr Bill Kalionis, Pregnancy Research Centre, RWH. T: 8345 3748
E: bill.kalionis@thewomens.org.au

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

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

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

Outcomes/Benefits: This proposal will compare the inherent traits and chemotherapy response of ovarian cancer cells in the presence and absence of MSC. MSC will be isolated from the ascites of ovarian cancer patients as well as from the placenta of women undergoing caesarean section. Differences in the biological phenotype of ovarian cancer cells in the presence and absence of MSC will be assessed by methods such as Western blot, quantitative PCR, immunofluorescence, flow cytometry, MTT and ^{3}H-thymidine uptake assays. The identification of these changes/molecules may lead to the development of novel therapeutic targets either independently or by inhibiting the effects of MSC on ovarian cancer cells.
Human ethics application (HEC#09/09) has been approved by the Royal Women's Hospital Human Ethics Committee.

51. Molecular mechanism of cancer metastasis, targeted therapy and immunotherapy – also offered as MBiomedSc

Supervisors: Dr. Hong-Jian Zhu

Project Site: Cancer Signalling Laboratory, Department of Surgery (5th Floor, Clinical Sciences Building, The Royal Melbourne Hospital)
Contact Dr Hong-Jian Zhu T: 8344 3025 E : hongjian@unimelb.edu.au

Project description: The Cancer Signalling Research laboratory focuses on discovering the molecular signalling pathways regulating cancer cell development, from initiation and growth to dissemination, circulation and metastatic seeding.

Targeted therapy is one of the most outstanding successes in cancer treatments today and it is continuing as a major strategic direction for large pharmaceutical companies around the word. It's typified by the development of "silver/magic bullets" such as Imatinib, also known as Gleevec and STI571, for treatment of chronic myeloid leukemia (CML); Vemurafenib (PLX4032) for late-stage melanoma and Crizotinib (Xalkori) for non-small cell lung carcinoma (NSCLC). Fundamental to all these successes are the discoveries of Bcr-abl, B-Raf(V600A), and Eml4-Alk as the true molecular causes of these cancers respectively.

In contrast, there have been many not so successful "miss-targeted bullets" for example the underwhelming results of 20+ phase I, II, III clinical trials targeting TGF-β signalling for treatment of various types of cancers. While it is clear that TGF-β signalling is a major molecular driver for cancer progression, particularly invasion and metastasis, it is in the context of signalling pathway of ligand-receptor-Smad-targeted gene activation. What we have now discovered is that the bioactive microvesicle exosomes are the key regulator of TGF-β signalling, bypassing the traditional ligand-receptor as the signalling initiators. More strikingly, the conventional ligand targeting therapies have little effect on the exosomal TGF-β, directly and clearly explaining the reasons for not so successful outcomes of clinical trials.

The lab currently is geared towards establishing a new paradigm whereby exosomes are the initiater and amplifier of TGF-β signalling that in turn is the true molecular cause of cancer invasion and metastasis. The research projects cover from basic understanding of how at molecular level exosomes delivers tumourigenic TGF-β signalling, particularly in the context of tumour microenvironment to new therapeutic strategies and therapies for treatment of various types of human cancers, i.e. breast, brain, colon and skin cancers.

In addition, we are also developing a new generation of anti-TGF-β therapy with much improved delivery together with cancer vaccination targeting TGF-β signalling's role in immuno-supression. The focuses of latter are on melanoma and breast cancers.

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

Project A: Discovering TGF-□ signalingdriven tumourigenesis in receptor-defective (*TGFBR2*) colorectal cancers with microsatellite instability (MSI) by exosomes

Project B: Targeting TGF-□ exosomes as a novel driver of cancer metastasis and mediator of cancer microenvironment interaction

Project C: Developing novel class of protein therapy targeting TGF-□ signaling in cancer invasion and metastasis

Project D: Cancer vaccine targeting immunosuppressive TGF-□

Techniques to be used: Cell culture, reporter assays (gene expression), adenoviral work, molecular biology, Western and Northern blotting (protein and mRNA respectively), real-time PCR, immunofluorescence and immunohistochemistry, siRNA (gene silencing), animal tumour model and live imaging.

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

52. Integrated Genomics of metastatic, lethal Prostate Cancer - also offered as MBiomedSc
Supervisors: Prof Chris Hovens and Dr Niall Corcoran

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

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

The aim of the project is to delve deeper into our analyses of the genomics of prostate cancers from patients who have either died or who have metastatic disease. We have identified a number of candidate regions and changes that may be key to driving prostate cancer metastasis and subsequent lethality. Projects will focus on validating these findings in independent cohorts of patients and starting to examine experimentally the biology behind the observed changes and how they impact on tumor behaviour. Research students will work within a team of experienced scientists and have access to scientific expertise and equipment through our department, associated institutions and existing collaborations with leading urologists. Our commitment to academic excellence and links with the Australasian Prostate Cancer Conference, one of the largest urology meetings in the region, ensure additional exposure to publication and presentation opportunities for the motivated researcher.

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

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

53. Double Jeopardy – dead prostate cancer cells can't recur – also offered as MBiomedSc

Supervisors: Prof Chris Hovens, Dr Niall Corcoran
Project Site: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building
Contact: Prof Chris Hovens E: chovens@unimelb.edu.au

Background/Rationale: The critical role of androgen (testosterone) signalling in Prostate cancer (CaP) is unequivocally supported by the fact that this cancer can be effectively treated by surgical castration or drugs that disrupt androgen action or production. While androgen deprivation therapy (ADT) provides significant respite from prostate cancer progression, treatment resistant tumors recur with high frequency and are generally associated with poor outcome. We hypothesise that cells are initially rendered "dormant" by ADT and in this state they accumulate mutations that allow them to escape from growth suspension to recommence proliferation. Our recent results, and some published studies, indicate that this dormant state might render cells more sensitive to killing by other agents. If this is true then ADT in combination with a complementary drug has the potential to substantially improve patient treatment and outcome by killing prostate cancer cells rather than just rendering them dormant.

Project Description: We have established cell lines that contain a newly developed marker for programmed cell death (apoptosis) that turns fluorescent red when the cell death program is initiated. We will use this line to screen a library of drugs for their ability to induce cell death in combination with ADT. Our studies with patient derived samples has also provided some clues about what pathways would be best to target. We will prioritise these pathways. In addition to cell based studies we are using an ex vivo system that allows us to culture patient tissue samples, treat them with drugs and examine response.

Skills/Techniques: Advanced cell biology techniques, high throughput semi-automated drug screening, high throughput microscopy and analysis (Operetta system), ex vivo tissue culture, immunohistochemistry, qRTPCR, western blotting.

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

Requirements for students: Dedicated, passionate and committed.

54. STAT3-mediates Resistance to EGFR targeted therapy in Cancer

Supervisors: Dr Rodney Luwor
Project Site: Dept of Surgery, Royal Melbourne Hospital

Contact: T: 8344 3027, 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. Our Honours/Masters program offers students a choice of projects within our STAT3 signalling research. This project seeks to evaluating novel regulators of STAT3 and determining whether these regulators have a role in driving STAT3-mediated resistance to anti-EGFR therapy. We will also assess the potential of delivering novel inhibitors to STAT3 to inhibit cancer growth and resistance to anti-EGFR agents. Furthermore, this project has the scope to evolve into a PhD project starting in 2019/20 pending the ability of the incumbent student.

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

55. The Molecular Determinants of Brain Tumour Progression and Resistance to Therapy

Supervisors: Dr Rodney Luwor, and Dr Theo Mantamadiotis
Project Site: Dept of Surgery, Level 5, Clinical Sciences Building, Royal Melbourne Hospital (also Dept of Dept of Pathology, University of Melbourne)
Contact: Dr Rodney Luwor; T: 8344 3027, E: rluwor@unimelb.edu.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, the overall prognosis remains abysmal for GBM patients with a median survival of only 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.

Our Honours/Masters program offers students a choice of projects within two major themes based on our GBM-orientated research. Firstly, projects will be designed to explore novel molecular mediators of GBM proliferation, migration and invasion and potentially evaluate treatment strategies to overcome GBM progression. Alternatively, students will perform projects that seek to explore potential molecular candidates in mediating resistance to current therapy. Both these project directions will ultilise a large set of brain tumour cell lines and human brain tumour tissue and serum archived within our department. Furthermore, this project has the scope to evolve into a PhD project starting in 2019/20 pending the ability of the incumbent student.

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

56. Defining the Epidermal Growth Factor Receptor Signaling Network in Brain Tumour Stem Cells

Supervisors: Rodney Luwor and Dr. Theo Mantamadiotis
Location: Dept of Surgery RMH and Dept of Pathology
Contact: Dr Rodney Luwor E: rluwor@unimelb.edu.au
Dr. Theo Mantamadiotis: theom@unimelb.edu.au;

Project description: Aberrant cell signalling underlies the loss of growth control, enhanced survival, inappropriate migration and drug resistance in tumour cells. In malignant brain tumours such as Glioblastoma Multiforme (GBM), a number of key components of signaling pathways are known to be inappropriately activated due to mutations. The epidermal growth factor receptor (EGFR) is mutated in about 30% of GBM patients. The downstream effects of the EGFRvIII mutation in brain tumour cells leads to a spectrum of cell

signaling events which promote the transcription of many genes which orchestrate pro-tumorigenic cell characteristics. A key transcription factor which lies downstream of the EGFR pathway is CREB, which has recently been shown to have a role in regulating cell human brain tumour cell growth. In this project, the activation of CREB, in a variety of human tumour cell lines, including cancer stem cells which express wild-type EGFR and EGFRvIII, will be examined using cell and molecular techniques. The CREB-dependent transcriptome will also be investigated to understand whether there is a distinct set of EGFRvIII CREB-dependent target genes compared to wild-type EGFR.

57. Regulation of invadopodium function and involvement in cancer cell invasion ***also offered as MBiomedSc***

Supervisors: Dr Stanley Stylli
Project Site: Dept of Surgery, Level 5, Clinical Sciences Building, The Royal Melbourne Hospital
Contact: Dr Stanley Stylli; T: 9035 5236, E: sstylli@unimelb.edu.au

Project description: The cause of death for up to 90% of cancer patients is the metastatic spread of cancer cells from the primary tumour and the subsequent development of a secondary tumour or tumours at a distant site. Many patients normally present with symptoms relating to the localized primary disease which can be managed with a number of therapies including surgery, radiation and chemotherapy. But numerous patients return post-therapy with a developed metastatic lesion at a secondary site. The dissemination of metastatic cells involving the migration and infiltration of these invasive cells is commonly thought to require two events. This includes increased cellular motility, accompanied with the proteolytic processing of the extracellular matrix (ECM) and subsequent penetration through the surrounding tissues.

A property shared by several types of tumour cells with high invasive or metastatic potential is an ability to form structures known as invadopodia. They are dynamic actin-rich protrusions which adhere to and proteolytically degrade ECM substrates via the activities of secreted extracellular proteases. Functional (matrix-degrading) invadopodia have been observed in tumour cell lines and primary tumour cells derived from ex vivo tumour specimens from a number of cancers, primarily head and neck squamous cell carcinoma and breast cancer specimens. This suggests that there is a possible role for invadopodia in tumour cell invasion of many cancers.

Invadopodia formation and function are dependent on multiple proteins and signaling pathways. Therefore understanding how invadopodia are regulated and controlled within a tumour cell is essential and strategies aimed at disrupting invadopodia could form the basis of novel anti-invasive therapies for treating cancer patients in the future. This honours project will involve studies that explore the role of a number of invadopodia proteins in cancer cells, how they contribute to their invasive/metastatic phenotype and ultimately influence response to treatment protocols.

Skills/Techniques acquired: Cell Biology techniques including cell culture and cell transfections (overexpression and siRNA gene silencing), western blotting, zymography, immunofluorescence and immunohistochemistry, confocal microscopy, migration/invasion assays, reporter assays.

58. Biomarkers of Human Papillomavirus-related cancers ***also offered as MBiomedSc***

Supervisors: Dr Alyssa Cornall, Prof Suzanne Garland
Project Site: Women's Centre for Infectious Diseases (RWH), Bio21 Institute
Contact: Dr Alyssa Cornall: alyssa.cornall@mcri.edu.au

Project description: Human papillomavirus (HPV) is the most common sexually transmitted infection, and is also the causative infectious agent of cervical cancers, a proportion of other female anogenital cancers, and the majority of anal cancers in both men and women. HPV-associated cancers disproportionately affect disadvantaged and/or marginalised populations such as Australian Indigenous and Torres Strait Islander peoples (ATSI), women in low- and middle-income countries (LMIC), immunocompromised and/or HIV-positive people, and gay and bisexual men (GBM). Prevention of cervical cancers has been very successful in higher-income countries such as Australia using intensive, technically-demanding screening programs, however these types of screening programs are unfeasible in many low-resource settings, and are more technically difficult for other HPV-related cancers such as anal cancer. The identification and development of simple to implement, sensitive and specific biomarkers for cancer risk in HPV-positive individuals has the potential to significantly decrease the burden of these cancers. Cancer development is preceded by certain molecular changes; these include epigenetic modifications such as methylation of viral gene promoters, and changes to the expression of viral and cellular gene products.

This project will involve the characterization of molecular patterns in clinical samples from people with and without HPV-related disease – including cancer - with a view to determining the potential of each marker to contribute to effective screening for people at risk of HPV-related cancer.

This project will involve laboratory work in the Molecular Microbiology Department of the Royal Women's Hospital, including nucleic acid purification, polymerase chain reaction (PCR) including real-time PCR, digital droplet PCR, reverse transcriptase PCR to detect messenger RNA (mRNA) transcripts, epigenetic studies including detection and quantification of methylation, and others. Data entry, database design and data manipulation including the possibility of some basic programming, and statistical analysis in the Stata statistics package, will be important for this project. Other tasks may involve co-ordination of sample collection, receipt and processing. For longer projects (i.e. PhD, Masters), additional tasks may include assay design and development, and application and/or reporting for ethics approvals.

The RWH Molecular Microbiology Department is affiliated with the University of Melbourne, the Royal Women's Hospital, the Royal Children's Hospital and Murdoch Childrens Research Institute. We collaborate with numerous other institutions in Australia and internationally including primary health care, research institutions, and private industry including private pathology and biotechnology/pharmaceutical companies, with numerous opportunities for multi-disciplinary engagement.

59. Human Papillomavirus (HPV) prevalence in Australia following a national vaccination program

Supervisors: Dr Dorothy Machalek, Dr Alyssa Cornall, Prof Suzanne Garland
Project Site: Department of Microbiology and Infectious Diseases, RWH, Parkville Campus
Contact: Dr Dorothy Machalek: Dorothy.machalek@mcri.edu.au;
Dr Alyssa Cornall: alyssa.cornall@mcri.edu.au

Project description: Human Papillomavirus (HPV) is the main cause of cervical cancer in women, and anogenital cancer in men (anal and penile cancer). The HPV vaccine, which helps to protect against these cancers, was introduced in Australia in 2007 for girls with a two-year catch up for females up to the age of 26 years through the National Human Papillomavirus Vaccination Program. In 2013, the vaccination program was extended to include 12-13 year old boys, with an initial catch-up period for those aged 14-15 years. Vaccination of children aged 12–13 years through schools is ongoing as part of the program. By the end of 2017, all women and men up to the age of 36 and 20 years respectively, will have been offered free vaccination in Australia.

The program uses the quadrivalent vaccine which provides protection against HPV genotypes 6, 11, 16, and 18. HPV16 and 18 are responsible for 70% of cervical cancers. HPV6 and 11 cause 90% of genital warts.

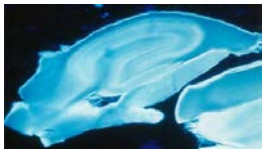
Following the introduction of the vaccination program, surveillance of HPV genotypes in the population is required to monitor the impact of the vaccination program in a real-world setting. This project will involve genotype testing and analysis of clinical samples collected as part of an ongoing National HPV Monitoring Program (called IMPACT), with linkage of data to the National HPV Vaccination Register to confirm HPV vaccination history. Self-collected genital samples from women aged 18 to 35 years attending IMPACT sentinel clinics will be tested for the presence of HPV DNA.

The aims of the project are: 1) to assess the prevalence of type-specific HPV genotypes (both vaccine and non-vaccine types) in prospectively collected IMPACT specimens; 2) to characterise type-specific HPV genotypes by register-confirmed vaccination status; and 3) to identify factors associated with HPV detection.

The project will involve sample logging and processing, DNA extraction, quality control testing, PCR, HPV genotyping, data management and simple epidemiological data analyses.

60. In vitro brain tumour model – studying epileptic seizure development and sensitivity to anti-cancer therapy.

Supervisors: Dr Chris French, Dr Andrew Morokoff, Dr Rodney Luwor
Prof Terence O'Brien
Project Site: Department of Surgery, Department of Medicine RMH,
Melbourne Brain Centre



Contact: Dr Chris French - frenchc@unimelb.edu.au

Project description: Malignant brain tumours are notoriously difficult to treat and are often complicated by severe epileptic seizures. Research into therapies has been hampered by a limited range of model systems to explore pathogenesis and treatment of these tumours. We have developed an *in vitro* model of aggressive brain tumours using a rat brain culture technique. This uses several well-characterised human tumour cell lines as well as tumour "stem-cells" available in our laboratories. These are seeded into a section of brain maintained in tissue culture. The project has two aims – to examine the effects of conventional and novel treatments on the tumours as well as the development of epileptic seizure activity in the system. Seizure development will be assayed by electrophysiological recordings.

This novel technique in this project has the potential to provide important insights into the pathophysiology and treatment of brain tumours and tumour-related epilepsy.

61. Priorities and needs of women living with advanced cancer - *also offered as MBiomedSc*

Supervisors: Dr Jennifer Marino and Dr Michelle Peate
Project Site: Royal Women's Hospital
Contact: E: jennifer.marino@unimelb.edu.au

Project description: Although the survival of patients with cancer has improved greatly over the past 30 years, between 2008 and 2012, a third of all patients with cancer survived less than five years. Generally, cancer research tends to focus on curative therapy, but many patients die of their cancer. These patients, not only have to cope with facing an incurable condition, but are often 'forgotten' or become 'invisible' in the context of this focus on survivorship outcomes. Many people who live with advanced cancer report a feeling of being seen negatively by society, and that they suffer from psychological, physical or financial problems for which they receive little support. Despite this, we know very little about the needs and priorities of people living with advanced cancer. This information is essential to inform clinical decision-making to maximise the quality of the life these patients have left – for some this is only a short time yet others will live with their cancer for many years. To aim of this project is to gather qualitative and quantitative data from advanced cancer patients, their families, and their providers to identify their needs, with the eventual goal of establishing clinical tools, including patient-reported outcome measures and useful tools that can improve the end-of-life experience of these patients and their families.

Benefits to student: This is a multi-collaborative project, so student will gain experience working in a multidisciplinary team. They will also have the opportunity to learn develop qualitative and/or quantitative research skills, gain an understanding of ethical procedures, be trained in high quality data management, collection and analysis processes.

Requirements for students: Looking for a dedicated, passionate, sensitive and committed student with a good academic record and strong writing and communication skills.

62. How to control Natural Killer cells to improve stem cell transplant outcomes

Supervisors: Dr Joanne Davis and Prof David Ritchie
Project Site: Royal Melbourne Hospital
Contact: E: davis.j@unimelb.edu.au

Project description: The Royal Melbourne Hospital (RMH) is the largest provider of allogeneic haematopoietic stem cell transplantation (alloSCT) in Australia. AlloSCT is a complex but potentially curative procedure for patients with haematologic malignancies or bone marrow failure syndromes. The fundamental principle of alloSCT is that a donor's haematopoietic stem cells (or graft), when infused into the recipient, will develop into a new set of immunologically active cells that recognise tumour cells as foreign and contain or destroy them. We must find means to lower conditioning toxicity, promote donor engraftment and limit graft-versus host disease in order to improve alloSCT outcomes.

The ACRF Translational Research Laboratory (located at the Victorian Comprehensive Cancer Centre) has AEEC-approved projects to investigate the role of natural killer (NK) cells in regulating donor cell engraftment after alloSCT. Our innovative approach, which promotes engraftment whilst lessening the risks of alloSCT, utilises drug therapies that are already available clinically. This project will utilise novel mouse models of alloSCT to investigate pharmacological inhibition of NK cells in combination with reduced conditioning, to improve long-term engraftment and anti-cancer responses. Techniques used in this project include immunoprofiling of

mouse alloSCT and acute myeloid leukaemia models using multi-parameter flow cytometry, cytokine bead array, histology, and bioluminescence imaging. This project is based in the ACRF Translational Research Laboratory, with co-supervision and collaboration from the Walter and Eliza Hall Institute.

CANCER – FERTILITY PRESERVATION

63. Fertility issues in children and adolescents with cancer

Supervisors: Dr Yasmin Jayasinghe, Dr Lisa Orme, Dr Leanne Super
Project site: The Royal Children's Hospital and The Royal Women's Hospital, Melbourne
Contact: E: yasmin.jayasinghe@unimelb.edu.au

Project description: Fertility loss is one of the side effects of cancer treatment. Advances in reproductive technologies may one day offer children and adolescents with cancer, the possibility of future fertility through ovarian or oocyte tissue retrieval and storage prior to commencement of cancer therapy. However such treatments are regarded as investigational in children due to immaturity of gonadal tissue, and also pose unique clinical and ethical dilemmas with respect to informed consent and beneficience for the young person. It is now recommended that where cancer treatment poses a fertility risk, fertility preservation should be discussed with all patients, and with parents or guardians. Long-term survivors report dissatisfaction with the quality of such discussions, or have no memory of them. Over 95% of paediatric oncologists surveyed in Australia and New Zealand believe that centre-specific clinical protocols are necessary to establish standards of care. However such guidelines rarely exist. Furthermore there is little information on recovery of gonadal function post chemotherapy in children and adolescents, to further guide discussions regarding fertility options after chemotherapy.

Several sub-studies are available which may assist with the development of Fertility Preservation guidelines and improve patient outcomes at the Royal Children's Hospital Melbourne, which include:

1. An audit of fertility preservation consultations for patients seen at The Royal Children's Hospital between 2002 and 2014. This project is ethics approved. Specifically the audit will report the proportion of subjects who underwent such discussions, the procedures offered, barriers to uptake of the procedures, and complications. .
2. Evaluation of a 'Fertility Preservation Toolkit'. This is a recently introduced resource for health providers, patients and families which aims to improve knowledge and awareness of fertility preservation options for patients and families by providing information in a standardized manner.
3. Mining the haematology oncology database at the Royal Children's Hospital to examine recovery of gonadal function according to cancer treatment in the young.

Benefits to student: A multi-collaborative project encompassing basic research and clinical interaction. Publication.
Requirements for students: Dedicated, passionate, sensitive and committed. Has done well academically.

64. Fertility after cancer predictor (FoRECAsT) study – also offered as MBiomedSc

Supervisors: Dr Michelle Peate, A/Prof Shanton Chang, Prof Martha Hickey
Project Site: Royal Women's Hospital, Parkville
Contact: Dr Michelle Peate, mpeate@unimelb.edu.au

Project description: Breast cancer is the most frequently diagnosed cancer in reproductive aged women and many women are diagnosed before they have started or completed their families. Fortunately, survival from early breast cancer is almost at 90%. These women then need to deal with the consequences of treatment, such as potential infertility. Research has shown that fertility is a priority amongst these women and concerns about how cancer treatment impacts fertility may influence cancer treatment decisions. Thus, being able to provide women with information about how their fertility will be affected by treatment is important. This can help them to make decision around fertility preservation prior to starting adjuvant treatment. Whilst there is general information about the potential effects of cancer treatments on fertility, there is no mechanism for obtaining personalised information about likely fertility outcomes. Current "calculators" consider cancer type and treatment, but do not consider this in the context of a woman's fertility prior to cancer treatment. The aim of this study is to develop an online fertility predictor targeted at young women with breast cancer. This 'calculator' will take into consideration both intrinsic individual fertility-related characteristics, and the likely

impact of cancer treatment to produce a risk of infertility. This tool will be available to women in order to inform decision making around breast cancer treatments.

There are a number of projects available:

a) Exploring needs and potential barriers for the FoRECAsT tool amongst younger women with breast cancer.
b) Exploring needs and potential barriers for the FoRECAsT tool amongst medical oncologists.
c) Determine usability of the FoRECAsT tool using a series of iterated wireframes.
d) Evaluate the acceptability and usability of the functional FoRECAsT tool.

Benefits to student: This is a multi-collaborative project, so student will gain experience working in a multidisciplinary team. They will also have the opportunity to learn develop qualitative and/or quantitative research skills, data collection and analysis and a goal will be to author a peer-reviewed publication.

Requirements for students: Looking for a dedicated, passionate, sensitive and committed student with a good academic record and strong writing and communication skills.

CARDIOLOGY

65. Cardiac benefits by delayed reperfusion after acute myocardial infarction in mice

Supervisors: A/Prof Xiao-Jun Du, Dr Xiao-Ming Gao
Project Site: Experimental Cardiology Laboratory, Baker IDI Heart and Diabetes Institute, AMREP (Prahran)
Contact: A/Prof XJ Du. T: 85321267; E: xiao-jun.du@bakeridi.edu.au

Project Description: Acute myocardial infarction (AMI) occurs following occlusion of a coronary artery. It is important to re-open the blocked artery to re-establish blood supply to the ischemic myocardium (reperfusion) to save ischemic myocardium from necrosis, i.e. infarct size limitation. Clinically, post-ischemia reperfusion can be achieved most commonly by catheter-based percutaneous primary coronary intervention (PCI) or by thrombolytic drugs. It is usually believed that significant delay (i.e. over 12 hours after onset of ischemic symptoms) in reperfusion does not provide clinical benefits, rather, reperfusion per se may exacerbate further injury to the ischemic heart muscle.

AMI in mice can be induced surgically by coronary artery occlusion. Like human patients, mice with AMI develop cardiac wall rupture, a malignant complication due to post-infarct myocardial inflammation and damage to the extracellular matrix (ECM) architecture of the infarct myocardium. In our recent study on mice, reperfusion was done following 1, 2 or 4 hours after coronary artery occlusion. We observed that the onset of cardiac rupture was completely prevented not only by early, but also by delayed reperfusion (Gao XM, et al: 2012. Due to significantly high metabolic rate in mice, reperfusion following a 4-hour period of ischemia in mice is equivalent to a major delay of reperfusion to humans). This finding clearly indicates benefits achieved by delayed reperfusion. This project is designed to explore the mechanism responsible for such cardiac protection by delayed reperfusion focusing on the extent of inflammation and ECM damage.

The specific aims of this project are:

- To compare delayed reperfusion versus non-reperfusion on the extent of inflammation in the infarct myocardium;
- To determine the extent of ECM damage by biochemical and histological means, between hearts without and with delayed reperfusion;
- To measure the degree of post-infarct ventricular remodelling by non-invasive echocardiography.

Skills: The project will enable the student to gain skills in: understanding the principal of reproducing heart disease models in mice, quantitative histology, biochemical assays, echocardiography in mice, data analysis using a variety of statistical methods.

References

Gao XM, White DA, Liu Y, Dart AM, Du XJ. Post-infarct cardiac rupture: Recent research progress on the

pathogenesis and therapeutic interventions. *Pharmacol Ther* 2012;134(2):156-179.

66. Natural History of Coronary Plaque Evolution Through Optical Coherence Tomography– *ONLY offered as MBiomedSc*

Supervisor/s: A/Prof. Peter Barlis, Dr. Vikas Thondapu; Prof Andrew Ooi, Dr. Eric Poon
Project Site: Department of Mechanical Engineering, Parkville
Contact: Dr Vikas Thondapu E: vthondapu@gmail.com

Project description: Despite groundbreaking advances in cardiology over the past several decades, cardiovascular disease remains the most common cause of death worldwide. The unfortunate reality is that many coronary plaques remain asymptomatic until acute rupture and vessel occlusion, forming a clear impetus for the earlier identification and treatment of high-risk lesions. Intracoronary optical coherence tomography (OCT), a light-based analog of intravascular ultrasound, provides a tenfold improvement in resolution, allowing *in vivo* imaging of coronary plaques with near-histologic clarity.

This project aims to evaluate the natural history of coronary plaque over 6 months through analysis of angiographic and OCT-derived plaque features. Students will also have the opportunity to engage in state-of-the-art computational fluid dynamic modeling to better understand the role of local micro-hemodynamics in plaque evolution. This work will improve our fundamental understanding of plaque evolution, better define the role of intravascular imaging in the identification of high-risk plaques, and has a potentially high impact in the prospective diagnosis and treatment of coronary artery disease.

Baseline and follow-up angiography and OCT imaging has already been completed in a series of 60 patients. Students will be trained in quantitative coronary angiography and OCT plaque analysis. Those interested in computational modeling will be guided in 3D coronary artery reconstruction and computational fluid dynamic methods.

67. Evaluation of Coronary Stent Apposition and Intimal Healing Through Opitcla lCoherence Tomography – *ONLY offered as MBiomedSc*

Supervisor/s: A/Prof. Peter Barlis, Dr. Vikas Thondapu; Prof Andrew Ooi, Dr. Eric Poon
Project Site: Department of Mechanical Engineering, Parkville
Contact: Dr Vikas Thondapu E: vthondapu@gmail.com

Project description: Stent placement is the standard of care in the treatment of occlusive coronary artery disease. The vast majority of patients show improvement and remain asymptomatic after stent placement, however a small but significant subset of patients are prone to adverse long-term complications such as in-stent restenosis and stent thrombosis. The causes of these potentially catastrophic late outcomes remain unclear, but early evidence points to features such as incomplete stent strut apposition and persistently uncovered stent struts. Optical coherence tomography, a high-resolution intravascular imaging technique, offers unprecedented *in vivo* visualization of individual stent struts and tissue coverage patterns, and is thus an ideal tool to evaluate potential risk factors for late adverse stent complications.

This project aims to compare the stent apposition and late tissue healing characteristics of two commonly used second-generation drug-eluting stents. Students will also have the opportunity to explore the effect of stent malapposition on local micro-haemodynamics through state-of-the-art computational fluid dynamic modeling. Given that over 4 million stents are placed annually around the world, this high-impact project has potentially great clinical significance.

Baseline and follow-up angiography and OCT imaging has already been completed in a series of 60 patients. Students will be trained in quantitative coronary angiography and OCT stent analysis. Those interested in computational modeling will be guided in 3D coronary artery reconstruction and computational fluid dynamic methods.

CARDIOVASCULAR

68. Lipoproteins and Cardiovascular Risk from Mid-to-Late-Life in Women - *also offered as MBiomedSc*

Supervisors: Dr Stephen Campbell, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Cardiovascular disease (CVD) remains as the number 1 cause of death worldwide and in Australia. Though elderly women have higher rates of cardiovascular disease compared to men, there is a lack of awareness and research of CVD amongst women. Whilst cholesterol is targeted lipid medication, we now know that statins do not have the benefit in women that was seen in men (Virani, 2013). In this study we explore the broader lipid profile and other lipid measurements and their relation to cardiovascular risk as measured by a risk score (non-lipid based Framingham 10-year CVD risk score). This study seeks to evaluate the relationship between all lipoproteins and cardiovascular risk as characterised by a risk score, in an Australian cohort of older women across 20 years.

This project will provide the opportunity to work with a rich database with data that spans over 20 years, as well as having participant contact and clinical skills experience. This project would suit a candidate who is interested in cardiovascular disease. There is also opportunity for publication.

69. The effect of anxiety on cardiovascular risk in healthy ageing women - *also offered as MBiomedSc*

Supervisors: Dr Alicia Goodwill, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Mental health is a key predictor of overall health and wellbeing. Anxiety is widely considered to be positively correlated to cardiovascular risk, and is thought to be responsible for exacerbating existing cardiovascular conditions. However the precise mechanism of this pathophysiology has not yet been discovered. This project will consider whether the presence of anxiety symptoms is related to increased Cardiovascular Risk in a cohort of healthy ageing women from the Women's Healthy Ageing Project (WHAP).

The main opportunities for this project are:

1. An opportunity for publication
2. Hands-on involvement in participant evaluation
3. Work with a large database with over 20 years of lifestyle data
4. This project would be suited to someone with an interest in cardiovascular health

CLINICAL RESEARCH – SLEEP AND THE URINARY TRACT

70. Non-respiratory effects of CPAP in persons with sleep disordered breathing

Supervisor: Dr Jeremy Goldin and Dr Wendy Bower
Project Site: Dept of Respiratory and Sleep Medicine, City Campus Royal Melbourne Hospital
Contact: Dr Wendy Bower T: 61 3 83872194 E: wendy.bower@mh.org.au

Project Description: Sleep Disordered Breathing (SDB) with recurrent upper airway obstructions induces acute and chronic haemodynamic effects. During the obstructive phase negative intrathoracic pressures increase myocardial oxygen consumption and change ventricular load. Arterial blood pressure rises at the end of the apnoea episode with parallel repetitive bradycardia and tachycardia episodes occurring during sleep. Over time patients can develop systemic hypertension, inflammation and atherosclerosis. The beneficial impact of positive pressure ventilation on respiratory patterns in people with sleep apnoea is well known. Recently, however, it has been observed that comorbidities in these patients also improve after CPAP. To date there has been a lack of baseline data quantifying symptoms such as hypertension, postural hypotension, sleep dysfunction, mood disorders, nocturia, urinary urgency and urge incontinence episodes. The aim of this project is to capture baseline variables likely to be reflective of brainstem function and to measure change over the duration of CPAP therapy. This is a nested study that will include all aspects of the research process, culminating in a national level presentation and peer-reviewed publication.

71. Evaluating and improving hospital care of patients with Nocturia: A translational research project addressing the relationship between Nocturia and In-Hospital falls

Supervisor: Dr Frances Batchelor and Dr Wendy Bower
Project Site: National Ageing Research Centre
Contact: Dr Wendy Bower T: 61 3 83872194 E: wendy.bower@mh.org.au

Project Description: In the past, falls, nocturia and poor sleep have all been considered a normal part of ageing. Both older people and health professionals have dismissed or trivialised concerns in these areas. However recent research in each area individually and in studies where two of them are combined, have acknowledged none are a normal part of ageing and evidence exists showing an association and relationship between them.

Nocturia, the need to wake at night to void, is more complex than just lower urinary dysfunction. It has been found to be an independent predictor for early death , even when adjusted for age, gender, diabetes, smoking, coronary disease, renal disease, and stroke. Up to 30% of people aged 65 years and older, fall in any given year. Falls occur for a variety of reasons and can result in injury, fear of falling, physical and functional decline, reduced physical activity, the need for institutionalisation, or in severe cases, death. Poor sleep can impact not only on nights but have daytime consequences e.g. daytime sleepiness. The impact of each i.e. night time voiding, falling over and not sleeping well are closely related.

The components of this project will include:

- Identification of pre-existing nocturia and a history of falls in a sample of ward patients
  - Aged care; General Medicine and Rehabilitation
- Identification of new onset nocturia in patients from specified wards
  - record any falls or near misses whilst an inpatient
- Documentation audit to establish practice in identifying nocturia and recording occurrence in individual patients on specified RMH wards
- Analysis of existing data from a falls intervention study in 1 RMH ward to establish
  - the time to first night void in fallers, evidence of nocturnal polyuria, medical history red flags, balance and mobility parameters
- Development of change model to translate findings into improved care

This project will establish the relationship between falling whilst an inpatient and the presence of nocturia. The ultimate aim is to collect pilot data to enable grant seeking for a larger multi-site project to reduce night time falling in patients with nocturia.

CLINICAL RESEARCH

72. HHT – clinical evaluation of renal involvement and epistaxis

Supervisors: Prof Ingrid Winship
Project Site: Genetic Medicine, Royal Melbourne Hospital
Contact: Prof Ingrid Winship. Ph: 93428530 email: Ingrid.winship@mh.org.au

Project description: Hereditary haemorrhagic telangiectasia (HHT) is a genetic disorder where arteriovenous malformations (AVMs) in organs occur in the lungs, intestine, liver, spine and brain. Most of HHT is caused by heterozygous mutations in the endoglin gene (*ENG*) or activin-like kinase receptor 1 (*ALK1*). Following the successful audit of the HHT clinic at RMH, the team plan two further studies, which will form the basis of a BSc Hons project.

1. Is the kidney vasculature involved in HHT?
2. How effective is a VEGF inhibitor in the prevention of nosebleeds in HHT?

The role of the student is to:

- Evaluate the existing HHT registry
- Prepare HREC submission for studies
- Select participants for the two studies
- Review the MRI scans, and consider the results in consultation with radiologists and nephrologists in the collaborative group
- Work with the RMH business development team in creating the monitoring app
- Liaise with clinical team for observational study
- Liaise with genetic counsellors for parallel quality of life studies
- Prepare manuscripts for publication

CLINICAL RESEARCH – SURGICAL

73. The utility of colonoscopy in women of child bearing age

Supervisors: Ms Karen L Barclay
Project Site: Melbourne Medical School, Epping Hospital
Contact: E: karen.barclay@nh.org.au or kbarclay@unimelb.edu.au;

Project description: To establish the outcomes of colonoscopies performed for women of child-bearing age and attempt to assess the utility of haematinics and occult-blood testing in prioritization.

Colonoscopy is a scarce resource and has potential risks. Women of child-bearing age are more likely to have abnormal haematinic indices which may result in referral for colonoscopy. In our clinical setting, the outcomes of colonoscopy performed for this indication are unknown, as is the utility of laboratory measures.

The student would review colonoscopies performed at the Northern hospital in women of child-bearing age and match the results with clinical and laboratory measures. The information would be used to provide evidence for or against tests and colonoscopy in this group.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

74. Opportunities to diagnose Colorectal Cancer – are we missing them?

Supervisors: Ms Karen L Barclay
Project Site: Melbourne Medical School, Epping Hospital
Contact: E: karen.barclay@nh.org.au or kbarclay@unimelb.edu.au;

Project description: To establish the proportion of people treated for CRC at TNH for whom an opportunity for earlier diagnosis may have been present

The researcher would conduct a retrospective clinical record review of patients managed for Colorectal Cancer and establish which patients have been present within the institution within the last few years in order to see if earlier diagnosis may be possible by the introduction of a generalised screening process. Patients with Colorectal Cancer would be identified from the colorectal database and clinical records and databases used to identify hospital attendances. The information would be recorded and analysed to assess the proportion of patients for whom a generalised screening process may allow earlier diagnosis of CRC.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

75. A scoring system for the assessment of process in rectal cancer management

Supervisors: Ms Karen Barclay
Project Site: Melbourne Medical School, Epping Hospital
Contact: Ms Karen Barclay karen.barclay@nh.org.au

Project description: Standards of care are critical in any type of oncologic surgery. In the management of rectal cancer, key processes in the pathway of care have been shown to lead to improved outcome. Although audit processes are in place in most centres of repute, it is difficult to demonstrate due process simply and quickly.

The current study looks at an original scoring system for assessing key areas of practice. The aim is to show the scoring system is easy, reproducible and a simple way of showing practice standard is adequate or highlighting areas for improvement.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

76. The presentation of colorectal cancer in the era of screening

Supervisors: Ms Karen Barclay
Project Site: Melbourne Medical School, Epping Hospital
Contact: Ms Karen Barclay karen.barclay@nh.org.au

Project description: Since the introduction of the National Bowel Cancer Screening Programme in 2006, little information is available about the effect on presentation of Colorectal Cancer (CRC). With an increase in awareness of screening and numbers of people offered screening over time, it could be expected that more people would be presenting with screen-detected rather than symptomatic tumours. This project looks at the presentation of CRC over time to see whether this has occurred or not.

Potential students are requested to forward a CV, Academic transcript and statement of interest.

COLORECTAL MEDICINE AND GENETICS

77. Serrated Polyposis Syndrome - *also offered as MBiomedSc*

Supervisors: Prof Finlay Macrae
Project Site: The Royal Melbourne Hospital
Contact: E: finlay.macrae@mh.org.au

Project description: Serrated polyposis syndrome is the last polyposis syndrome without a known genetic predisposition identified. Working with Dr Dan Buchanan in the Dept of Pathology, this project will be the clinical arm of phenotype data collection from the records of the Familial Cancer Clinic which will form the basis for the selection of cases for next gen whole genome sequencing in Dan's lab in the Dept of Pathology

78. Prospective studies on penetrance for cancer in Lynch Syndrome – *also offered as MBiomedSc*

Supervisors: Prof Finlay Macrae
Project Site: The Royal Melbourne Hospital
Contact: E: finlay.macrae@mh.org.au

Project description: Well- designed studies on prospectively collected data for studying penetrance, survival and treatment effects of cancers occurring in Lynch Syndrome are scarce. This project will collaborate with European investigators on a common design template to provide important data to guide clinical practice. Two consortia are already formed with whom the candidate will collaborate: the International Mismatch Repair Consortium (leads Robert Hale, Stanford, Mark Jenkins and Finlay Macrae (Melbourne) and Gabriela Moeslein (Dusseldorf, Germany); and the Majorca Group (lead Pal Moller, Norway

79. CAPP3: a randomized controlled trial of aspirin dosage in Lynch Syndrome – *also offered as MBiomedSc*

Supervisors: Prof Finlay Macrae
Project Site: The Royal Melbourne Hospital
Contact: E: finlay.macrae@mh.org.au

Project description: CAPP2 proved aspirin reduces the incidence of LS associated cancers by over 50%. CAPP3 is a dose finding RCT testing 100mg vs 300mg vs 600mg. This si an international study lead from Newcastle UK, with Australian leadership from RMH. Students will learn about multi centre, multi national RCTs, be immersed in aspirin science and cancer genetics, and participate in the clinical aspects of management of Lynch Syndrome.

80. Locus Specific Databases in Hamartomatous polyposis syndromes:

Supervisors: Prof Finlay Macrae
Project Site: Department of Colorectal Medicine & Genetics, Royal Melbourne Hospital
Contact: Prof Finlay Macrae E: Finlay.macrae@mh.org.au

Project description: Hamartomatous polyposis syndromes include : Peutz Jeghers Syndrome (gene locus STK11), Juvenile Polyposis (gene loci SMAD4 & BMPR1A, Cowden's Syndrome (gene locus PTEN). Diagnostic laboratories around the world identify in the gene loci, sometimes clearly pathogenic, other times uncertain. International centralisation of gene variant information with clinical and familial information is one of the best ways to progress the interpretation of variants of uncertain significance. The Human Variome Project, at the University of Melbourne, aims to document variation in all genes across all countries in the world. The Hamartomatous Polyposis Syndrome project will relate to the HVP. The International Society for Gastrointestinal Hereditary Tumours (InSiGHT) hosts LSDB's for genes responsible for inherited gastrointestinal cancers. The InSiGHT mismatch repair gene database is curated at the HVP and Department of Colorectal Medicine and Genetics at The Royal Melbourne Hospital. The Hamartomatous Polyposis LSDB Project will develop similar database, ascertaining variant and clinical data across the published literature, contacting the InSiGHT membership for unpublished information and assembling the data on a LOVD platform. The project will involve extensive international collaboration, understanding genetic variation and variants of uncertain significance, bioinformatics and clinical management of these syndromes.

81. C-reactive protein (CRP) and Crohn's disease – CRP as a potential phenotypic marker for disease

Supervisors: Dr Suresh Sivanesan, Prof. Finlay Macrae
Project site: Royal Melbourne Hospital, Parkville
Contact: Dr Suresh Sivanesan T: 03- 8417 9900 or 03- 9342 7584 E: suresh.sivanesan@mh.org.au

Project description: Crohn's disease is a chronic inflammatory condition which can affect any part of the gastro-intestinal tract to cause significant symptoms and morbidity. The condition can affect and segment of the gastrointestinal tract including the perianal region. It can develop into more complex disease resulting in abscesses, luminal strictures, fistulas and perforation. Clinicians have sought to classify Crohn's disease in terms of the disease distribution or complications that it has caused. The currently used classifications are helpful but they do not assist in reliably predicting appropriate treatment or outcomes.

CRP is a serum inflammatory protein that is commonly elevated in conditions such as rheumatoid arthritis, infection and Crohn's disease. It is produced by hepatocytes and is upregulated by cytokines IL-6, IL1β and TNFα. It has been described that not all patients with Crohn's disease exhibit a rise in CRP. We hypothesize that if there are a subgroup of patients with active Crohn's disease and a express a normal serum CRP.

We intend to study our cohort of patients with active Crohn's disease to determine their levels of CRP, disease phenotype and assess their response to treatment. In particular if the hypothesis is true, we would hope to extend this work in the future to include cytokine and genotypic profiling of these patients.

This work could open the door toward a better understanding of Crohn's disease using widely available tools such as CRP. In future identifying subgroups of patients with Crohn's disease based on cytokine and genetic profiling will enable a more tailored approach to patient care.

ELECTROPHYSIOLOGY

82. How do Anti-Epileptic Drugs Work? - *also offered as MBiomedSc*

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/

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.

83. How do Antipsychotic Drugs Trigger Seizures? - *also offered as MBiomedSc*

Supervisor: Dr Chris French Prof Terence O'Brien, Prof David Williams
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au

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.

84. Multi-Electrode Recording in the Rat Brain - *also offered as MBiomedSc*

Supervisor: Dr Chris French Prof Terence 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

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 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.

85. Electrophysiology of Human Brain Tissue - *also offered as MBiomedSc*

Supervisor: Dr Chris French
Project Site: Department of Medicine (RMH), Royal Melbourne Hospital
Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au

Project Description: Almost all experimental data on neural function is based on animal research; while there are many similarities with human tissue, it is becoming clearer that neurons in the human CNS are considerably more complex structurally and functionally. This unique project involves taking samples of human brain cortex obtained during operations to characterise ionic currents, electrical excitability and drug responsiveness of human neurons

ENDOCRINOLOGY

86. Hormone Therapy and Cardiovascular Disease in Postmenopausal Women *also offered as MBiomedSc*

Supervisors: Dr Alicia Goodwill, Prof Cassandra Szoeke
Project Sites: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke, E: cszoeke@unimelb.edu.au; T: 8344 1835

Project description: Cardiovascular disease is currently the leading cause of death in Australia, and around the world. Post-menopausal women are particularly at risk of developing cardiovascular disease, thought to be due to the change of circulating sex hormone levels such as estradiol. However results are conflicting with latest evidence indicating the time of exposure is most relevant, with the use of hormone therapy also thought to modify risk. This study aims to test the association of the use of hormone therapy with

cardiovascular disease risk over 20 years from pre-–menopause to post-menopause, to determine whether hormone therapy use plays a significant part in cardiovascular health.

You will also have the opportunity to work with a large database from an internationally recognised cohort that spans over 20 years. This project will provide opportunity for publication and to work directly with participants. Candidates who are interested in endocrinology, as well as industry relationships, would be suited to this project.

EPILEPSY AND NEUROPHARMACOLOGY

87. Neuropharmacological strategies for disease modification and prevention of the development of epilepsy – also offered as MBiomedSc

Supervisors: Dr Pablo Casillas-Espinosa, Dr Kim Powell, Prof Terence O'Brien, Dr. Sandy Shultz, A/Prof Nigel Jones.
Project Site: The Department of Medicine, The Royal Melbourne Hospital, and The Melbourne Brain Centre, Parkville.
Contact: Pablo Casillas-Espinosa E:pablo.casillas@unimelb.edu.au; Kim Powell E:kpowell@unimelb.edu.au

Project description: Current therapies for epilepsy are symptomatic, only suppressing the symptoms (seizures), but do not impact the development or progression of disease. Many groups around the world, including ours, are testing novel therapies to impact epileptogenesis, intervening very early in epilepsy development to limit the severity of disease, with some preclinical success. But most patients present at the clinic already experiencing seizures, so a more practical strategy would be to attempt to modify epilepsy disease progression.

For this project, we will investigate whether our novel treatments can reverse epilepsy severity in a rat model of acquired epilepsy in cases of established epilepsy. We then evaluate if the animals are having less seizures, behavioural comorbidities and neuroimaging changes after the completion of treatment. If the results are positive, they would have major clinical implications in patients with already established acquired epilepsy. Moreover, the experimental drugs that we will be tested have a favorable safety profile in early phase clinical trials facilitating the translation of the results of this preclinical study into a clinical trial.

Skills: The skills expected to be learnt from this projects include: Small animal handling and neurosurgery (electrode implantations), animal models of temporal lobe epilepsy, behavioral neuroscience, magnetic resonance imagining interpretation and analysis.

Projects available

1. *Anti-epileptogenic effects of novel T-type calcium channel blocker.*
2. *Behavioural changes and Imaging the during the epileptogenic process*

88. Biomarkers of epileptogenesis and epilepsy disease progression – also offered as MBiomedSc

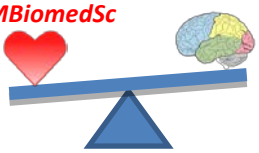
Supervisors: Dr Pablo Casillas-Espinosa, Dr Kim Powell, Dr. Sandy Shultz, A/ Prof Nigel Jones. Prof Terence O'Brien
Project Site: The Department of Medicine, The Royal Melbourne Hospital, and The Melbourne Brain Centre, Parkville.
Contact: Pablo Casillas-Espinosa E:pablo.casillas@unimelb.edu.au; Kim Powell E:kpowell@unimelb.edu.au

Project description: A biomarker is an objectively measured characteristic of a normal or pathologic biological process. The development of novel interventions to treat, cure, and prevent epilepsy would benefit greatly from the identification and validation of such biomarkers. In addition, identification of biomarkers may facilitate the development of novel interventions to prevent epilepsy; to prevent the occurrence of epileptic seizures, reverse progression of epilepsy, and potentially even cure epilepsy after it is established. This project will investigate blood- and brain-derived biomarkers of epileptogenesis (the development of epilepsy) and of disease progression of epilepsy using small animal models.

Skills: The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), models of acquired epilepsy, blood and cerebrospinal fluid (CSF) collection, EEG recordings and analysis, and biochemical and molecular analysis (subcellular fractionation, western blotting), magnetic resonance imagining interpretation and analysis.

Project: **Serum, cerebrospinal fluid and neuroimaging biomarkers of epilepsy**

89. Keeping the Brain and the Heart in Sync – HERG channels in the CNS - ***also offered as MBiomedSc***



Supervisors: Dr Chris French,
Project Site: Melbourne Brain Centre
Contact: Chris French frenchc@unimelb.edu.au

Project description: (H)ERG ("human ether a go-go") ion channels are important in for pacing the heart. Genetic disorders of this channel or drug inhibition lead to serious cardiac arrhythmias. It is known that (H)ERG channels are also in the mammalian CNS, but there is almost no data on their effects on neural function. Recent studies in this lab have disclosed evidence of electrical activity of these channels in rat hippocampus, and that they are exquisitely sensitive to antipsychotic drugs. Additionally, computer simulations show activity of this channel may modulate brain rhythms known to be important in epilepsy and schizophrenia. The project will involve further characterization of these channels in single neurons, as well as looking at how brain rhythms and epileptic activity in brain slices are affected by these channels, especially their modulation by antipsychotic drugs. Additionally, we will have the unique opportunity of studying these channels in human brain tissue obtained from neurosurgical procedures.

90. 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.

91. Sodium Channels in Epilepsy - ***also offered as MBiomedSc***

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.

92. Long-term Prognosis of Antiepilpetic Drug Therapy in People with Newly Diagnosed and Treated Epilepsy- ***also offered as MBiomedSc***

Supervisors: Prof. Patrick Kwan, Dr Ben Chen
Projects site: Department of Medicine (RMH), University of Melbourne
Contact: Prof Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: Antiepileptic drug is the mainstay of treatment modality for epilepsy. People with epilepsy often require lifelong antiepileptic drug treatment. Previous Glasgow study in 2000 demonstrated a-third of the epilepsy patient did not response well to antiepileptic drug therapy. Despite the introduction of more than a dozen new antiepileptic drugs in the past two decades, there remain no robust data to suggest improvement in treatment outcomes in the recent expanded Glasgow study. To valid the prognosis and antiepileptic drug response patterns observed in the Glasgow studies. We will assess treatment outcomes of 796 newly treated epilepsy patients who were seen at a First Seizure Clinic between 1 May 1999 and 31 May 2016 and were prospectively followed for up to 16 years in Australia. We will extract seizure, diagnostic and treatment information from baseline and follow-up clinical documents and construct a digital database. The prognosis and response patterns in the Australia cohort will be compared with the findings in the Glasgow study

93. Treatment Gap in People with Newly Diagnosed Epilepsy in Australia- ***also offered as MBiomedSc***

Supervisors: Prof. Patrick Kwan, Dr Ben Chen
Projects site: Department of Medicine (RMH), University of Melbourne
Contact: Prof Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: Epilepsy is one of the most common serious chronic neurological disorders and is estimated to affect approximately 68 million people worldwide. Antiepileptic drugs are the mainstay of treatment and suppress seizure occurrence. Epilepsy treatment gap is a recognised public health issue in resource-poor countries where up to 80% of people with epilepsy do not receive appropriate treatment. However, recent preliminary study of 1,235 people with newly onset of unprovoked seizure(s) who were seen at a First Seizure Clinic between 1 May 1999 and 31 May 2016 and were prospectively followed for up to 16 years in Australia demonstrated nearly a quarter of the people newly diagnosed with epilepsy did not commence treatment. The causes of epilepsy treatment gap in resource-rich countries have not been well studied. We will review the clinical documents of these 1,235 individuals and extract additional information of neurologists' and patients' perspectives on commencing antiepileptic drug treatment. We will assess potential factors contributed to the treatment gap in the cohort.

94. Does epilepsy cause a secondary cardiac channelopathy?

Supervisors: Dr. Kim Powell, Prof Terence O'Brien, Dr. Marian Todaro
Project Site: The Department of Medicine, The Royal Melbourne Hospital and Melbourne Brain Centre, Parkville
Contact: Dr KimPowell E: kpowell@unimelb.edu.au; Prof Terence O'Brien E: obrientj@unimelb.edu.au

Project description: People with epilepsy are at a higher risk of death than the general population. People with epilepsy may die suddenly without an obvious pathologic cause for death. Such deaths are termed Sudden Unexpected Death in EPilepsy (SUDEP), and this is the major clinical problem facing epilepsy patients, accounting for 17-38% of all epilepsy related deaths. Basic research investigating the causal mechanisms underlying SUDEP is lacking. Alterations in function or expression of ion channels expressed in both cerebral and cardiac tissue represent strong candidate mechanisms for SUDEP - defects in membrane excitability could predispose an individual to a dual phenotype of epilepsy and cardiac arrhythmia. In both a genetic and an acquired animal model of epilepsy we have identified altered cardiac electrophysiological function with an associated down-regulation of the cardiac pacemaker HCN2 channel. Based on this data We have hypothesised that the development of epilepsy itself can results in secondary changes in cardiac ion channel expression and function that could contribute to an increased risk of cardiac arrhythmias and therefore SUDEP.

Aims: To investigate whether patients with chronic epilepsy have alterations in cardiac electrophysiology and ion channel expression compared to matched non-epileptic control subjects.

Methods: This will be investigated by examining cardiac tissue from patients with chronic epilepsy collected during open heart surgery at the Royal Melbourne Hospital and Melbourne Private. This tissue collected will be atrial muscle, which is routinely excised, and discarded as part of the routine cannulation of patients that are being placed on cardiopulmonary bypass for cardiac surgery. These patients would be identified by using a screening questionnaire given to all patients during the pre-admission clinic assessment. Identified patients will then be given a more detailed interview collecting data about their epilepsy syndrome, aetiology, duration, seizure frequency, and medication history. Control subjects will be patients without a history of epilepsy matched to the epilepsy patients for age, sex, cardiac disease status in a ratio of 1:3 (i.e. three controls for each patient with epilepsy). The mRNA and protein levels for the ion channels, HCN2 and 4 channels, which are expressed both in the hearth and the brain will be measured, and compared between the epilepsy and control patients. The patients' ECG recordings will also be compared for significant electrophysiological difference. Any significant molecular or electrophysiological changes identified will be correlated with the epilepsy syndrome (i.e. genetic vs. acquired), the duration of epilepsy and the seizure frequency. Parrellel studies are being undertaken in animal models of chronic epilepsy to enable the mechanisms causing the epilepsy-associated cardiac changes to be better elucidated.

Outcome: This study has the potential to identify the mechanism responsible for epilepsy-associated cardiac dysfunction and thereby provide an opportunity to target interventions that can prevent the cardiac dysfunction, and mitigate the risk of SUDEP.

95. Identifying Predictors of Death in Patients with Epileptic and Psychogenic Seizures ***also offered as MBiomedSc***

Supervisors: Prof Terence O'Brien, Dr. Anne McIntosh
Project Site: The Department of Medicine, The Royal Melbourne Hospital and Melbourne Brain Centre, Parkville
Contact: Prof Terence O'Brien E: obrientj@unimelb.edu.au

Project Aims: To link databases of the Comprehensive Epilepsy Program of Melbourne Epilepsy Centres with the National Death and National Coroners Database to determine who has died and the cause of death, and to identify risk factors. Project Descr Patients with epilepsy have at least 4 fold increased risk of death, with one of the most common cases being sudden unexp death in epilepsy (SUDEP) which is up to 40 times more common than age and sex matched people without epilepsy. Iden patients at risk of premature death is one of the major challenges for the field, so that interventions can been applied to redu incidence of this tragic consequence of this common condition. This internationally unique study will link the databases con detailed clinical and psychosocial data from patients seen in the Comprehensive Epilepsy Program of the Royal Melbourne, The The Austin and St. Vincent's over 2 decades with the National Death Index and National Coroners Database to determine w died, the cause of death and identify risk factors.

96. Sodium Selenate as a Disease Modifying Treatment for Probable Behavioural Variant Front-temporal Dementia ***also o as MBiomedSc***

Supervisors: Prof Terence O'Brien, Prof Dennis Velakoulis
Project Site: The Department of Medicine, The Royal Melbourne Hospital and Melbourne Brain Centre, Parkville
Contact: Prof Terence O'Brien E: obrientj@unimelb.edu.au

Project description: Frontotemporal dementia (FTD) is generally due to abnormalities either in a protein called tau (45%) or a p called TDP-43 (45%). In both types of FTD the protein aggregates into 'clumps' that block brain cell function. There are curren treatments for either type of FTD. Our group has successfully run several research trials using a drug called sodium selenat prevents the aggregation of tau in brain cells. We have shown that sodium selenate is safe in humans and that it has meas benefits in Alzheimers disease (a different type of dementia to FTD). This study is an early phase study in which participants wi receive sodium selenate and are followed over 12 months. During this period standardised measurements of safety, cognitio neuroimaging (MRI, PET) will be undertaken.

97. The contribution of P2X7R and microglial activation in the neurological deficits of temporal lobe epilepsy ***also offered as MBiomedSc***

Supervisors: Dr. Mastura Monif, Prof Terence O'Brien
Project Site: The Department of Medicine, The Royal Melbourne Hospital
Contact: Dr Mastura Monif E: mmonif@unimelb.edu.au; Prof Terence O'Brien

E: obrientj@unimelb.edu.au

Project description: Epilepsy is a neurological condition characterized by recurrent unprovoked seizures that affects approximately 1% of the global population. In temporal lobe epilepsy (TLE) the seizures originate from the medial or lateral temporal lobe. TLE is frequently associated with hippocampal sclerosis (HS) with significant neurodegeneration, as well as activation of microglia in various regions of the hippocampus. HS is observed in approximately 70% of surgical specimens from patients undergoing surgery for drug-resistant seizures. Previous studies in animals have shown that a specific receptor, P2X7R, is over-expressed in acute and chronic phases of TLE in glial cells of the hippocampus, suggesting an involvement of this receptor in disease pathogenesis. Similarly in the region of HS there is enhanced activation of microglial cell. For the first series of studies we will be characterizing the presence of P2X7R and activated microglia in temporal lobectomy specimens from epilepsy patients undergoing surgery. Temporal lobectomy samples with HS will be compared to non-HS. Presurgical MRI data will be used to confirm HS. Some of the questions that we will be addressing are: Is P2X7R expression increased in HS versus non-HS TLE? Techniques: immunohistochemistry confirmed by mRNA levels (real time PCR). Does the level of P2X7R expression in the hippocampus correlate with the degree of neuronal loss? Is microglial activation increased in HS versus non-HS TLE? Techniques: immunohistochemistry on primary human cultures or organotypic brain slices. Does the level of microglial activation in the hippocampus (from temporal lobectomy patients) correlate with the degree of neuronal loss? Understanding the role of P2X7R and microglial activation in temporal lobe epilepsy would assist in the development of more targeted therapies to combat this devastating and debilitating condition.

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

Supervisors: Dr Kim Powell, Dr Pablo Casillas-Espinosa and Prof Terence O'Brien
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: Dr. Kim Powell T: 9035 6394 E: kpowell@unimelb.edu.au;

Project Description: 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 and T-type calcium 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 and T-type calcium channels are attractive candidates for investigating molecular mechanisms of SUDEP. Our research has identified a cardiac transcriptional channelopathy of HCN2 and Cav3.1 and Cav3.2 T-type calcium 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 mechanisms contributing to the cardiac dysfunction in genetic and acquired animal models of epilepsy.

Project 2: To investigate if decreased HCN2 expression translates to a decrease in HCN channel current (If) 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 and T-type calcium channel 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).

99. Is telomere length associated with cardiac dysfunction in chronic epilepsy?- *also offered as MBiomedSc*

Supervisors: Dr Kim Powell, Dr Anne McIntosh and Prof Terence 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 Terence O'Brien E: obrientj@unimelb.edu.au

Project Description: People with epilepsy are at a higher risk of death than the general population. People with epilepsy may die suddenly without an obvious pathologic cause for death. Such deaths are termed Sudden Unexpected Death in EPilepsy (SUDEP), and this is the major clinical problem facing epilepsy patients, accounting for 17-38% of all epilepsy related deaths. Cardiac dysfunction, including arrhythmias, is common in patients with epilepsy, particularly in those with long duration of epilepsy. Short telomeres are associated with increased risk of cardiovascular disease. Telomeres are repetitive non-coding sequences of DNA located at the end eukaryotic chromosomes. They play an important role in protecting the DNA from degradation and damage during DNA replication. Each time a cell divides telomeres shorten by 30-150 base pairs. Telomeres must remain above a certain length to prevent the triggering of apoptosis in eukaryotic cells. In an animal model of acquired epilepsy we have shown that chronically epileptic rats exhibit cardiac dysfunction (diastolic dysfunction) with associated cardiac fibrosis which is positively correlated with seizure frequency.

In this study we will investigate cardiac telomere length, tissue activity of telomerase and the expression of key telomere modulating proteins (telomerase reverse transcriptase (Tert), telomerase RNA component (Terc) and microRNA 34a (miR-34a)).

100. Stargazin and AMPA receptor expression at cortical synapses in epileptic rats - *also offered as MBiomedSc*

Supervisors: Dr Kim Powell, Dr Pablo Casillas-Espinosa and Prof 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

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 generalized absence seizures.

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

101. Serotonin in epilepsy ***also offered as MBiomedSc***

Supervisorr: A/Prof. Nigel Jones
Project Site: Department of Medicine RMH, MBC Neurosciences Building Parkville
Contact: A/Prof Nigel Jones E: ncjones@unimelb.edu.au

Project description: Any type of brain injury can result in epilepsy, a chronic neurological condition associated with seizures or 'fits'. The pathological processes occurring in the brain which drive the development of epilepsy following brain injury are not clear, but certain drugs acting at serotonin receptors, including SSRI antidepressants, accelerate these processes. Using animal models, this project will investigate serotonin signalling in epilepsy, and attempt to understand why SSRIs accelerate the development of disease following injury. We will utilise a variety of techniques, including assessment of serotonin levels, molecular consequences of serotonin activity, immunocytochemical identification of serotonin receptors, and pharmacological manipulation of the serotonin system, all in the context of epilepsy.

Skills: Small animal handling; animal models of epilepsy; small animal surgery and EEG recording; pharmacology; microdialysis; fast-scan cyclic voltammetry; molecular biology techniques, such as real-time qPCR, Western blotting; histology, including immunocytochemistry.

102. Neurogenesis in epilepsy – protective or disruptive ***also offered as MBiomedSc***

Supervisorr: Dr Idrish Ali, Dr Chris French, Prof Terence O'Brien
Project Site: Department of Medicine RMH, MBC Neurosciences Building Parkville
Contact: Dr Idrish Ali E: Idrish.ali@unimelb.edu.au

Project description: New neurons are generated continuously in the hippocampus throughout the lifetime of mammalian brain. They may contribute to cognitive functions, but have also been linked to pathophysiology of neurological disorders such as epilepsy and depression. In animal models of temporal lobe epilepsy, one of the most common forms of epilepsy, an acute transient increase in neural proliferation is evident. Depending on the precipitating injury that precedes epilepsy development, these neurons may migrate abnormally to the hilar region of the dentate gyrus and further contribute to the pathophysiology of epilepsy. Whereas, neurons that integrate within the hippocampal granule cell layer (GCL) may have protective effects as they are reported to receive reduced excitatory and enhanced inhibitory afferent inputs when compared to the new neurons from control animals. However, the exact role of seizure-induced neurogenesis in disease pathology is constantly debated. Furthermore, approaches to ablate neurogenesis before and after an epileptogenic insult has provided mixed outcomes with regards to epilepsy development. In the current study we aim to investigate the physiological role of these newly formed neurons in epileptic pathological environment at various cross-sectional time-points during epilepsy development. Furthermore, we aim to investigate if structural/functional integration of new-born neurons is affected by the environment in which they are born (before or after epileptogenic insult) and the phase of epileptogenesis when their activity is measured. Adult new-born neurons will be labeled with retroviral-vector carrying a GCaMP6 gene before and immediately after the induction of status epilepticus in two different rat cohorts to enable calcium fluorophore imaging from those cells.

103. Plasma biomarkers for epileptogenesis and epileptic seizures ***also offered as MBiomedSc***

Supervisorr: Dr Idrish Ali, Prof Terence O'Brien, A/Prof Nigel Jones
Project Site: Department of Medicine RMH, MBC Neurosciences Building Parkville
Contact: Dr Idrish Ali E: Idrish.ali@unimelb.edu.au

Project description: Epilepsy is a devastating neurological disorder that affects around 50 million people

worldwide. Patients with acquired epilepsy, one of the most common forms of epilepsies, often suffer from comorbid neuropsychiatric and cognitive disorders. Around 1/3rd of the cases are not effectively controlled by current epilepsy therapy, which is only symptomatic and do not inhibit the progression of disorder.

These patients acquire epilepsy as a consequence of a brain insult (e.g. head trauma, encephalitis, glioma, stroke or status epilepticus (SE)) following a period of months to years. This period of epileptogenesis (disease development) clearly represents an important therapeutic window for preventative treatment and therefore, a large body of preclinical epilepsy research has invested heavily on developing preventive disease-modifying therapy for epilepsy. However, the reliable identification of patients at high risk is an unmet urgent clinical need, to be able to effectively target these preventive therapies. Studies in animal model have characterised in details various pathological events during the epileptogenesis process including neuroinflammation, neurodegeneration as well as modulation of neuronal circuitry via axonal/ dendritic modifications.

The aim of this project is to identify those neuropathological changes in blood with the goal of developing them as a biomarker for epileptogenesis and chronic seizures. We have collected blood samples from different cross sectional time points covering the period of epileptogenesis as well as during the established epilepsy phase in a rat model of temporal lobe epilepsy following kainic acid induced SE. The histological evaluations covering the neuroinflammation and neurodegeneration during the epileptogenesis as well as the seizure burden using video/EEG monitoring during the chronic period has already been investigated.

This project will involve evaluating the time course of mRNA expression in blood or protein expression levels in plasma for neuroinflammatory (mainly the M1 and M2 markers)/neurodegeneration/axonal damage markers in blood samples and compare them to control animals. In addition, we will relate them to acute pathological findings during epileptogenesis phase as well as to the seizure burden/severity during chronic epilepsy.

Expected outcome:
1. We will be able to identify the time course for the development of blood levels of mRNA/protein markers for brain pathology.
2. Identify if the blood markers during the chronic epilepsy phase are predictive of seizure burden
3. Identify appropriate time points to target for future blood and brain imaging studies for evaluating predictive biomarker of epilepsy.
4. Potentially identify the timepoints to direct preventive therapies against epileptogenesis- including neuroinflammation modulating therapies altering the M/M2 balance within the brain glia.

104. M2 Polarization of microglia as a new approach targeting temporal lobe epilepsy ***also offered as MBiomedSc (New)***

Supervisor: Dr Idrish Ali, Prof Terence O'Brien, A/Prof Nigel Jones
Project Site: Department of Medicine RMH, MBC Neurosciences Building Parkville
Contact: Dr Idrish Ali E: idrish.ali@unimelb.edu.au

Project description: Brain inflammatory is a characteristic of epileptic disorders and may promote its development and progression by affecting brain cell death, structural connectivity and excitability. The inflammatory response involves an acute classical immune activation (M1) that releases pro-inflammatory mediators promoting disease progression. It may also involve M2 activation that mediates anti-inflammatory mechanisms promoting repair. Here, we aim to compare in an animal model of epilepsy, the seizure related outcomes between strategies to induce an M2 immune activation using genetic approaches or an overall inhibition of inflammatory response. We hypothesize that modulating the neuroinflammatory responses will be protective against development of epilepsy

105. Microglial activation and neurological disease ***also offered as MBiomedSc***

Supervisor: Dr Mastura Monif, Prof Terence O'Brien
Project Site: Department of Medicine RMH
Contact: Dr Mastura Monif E: mmonif@unimelb.edu.au

Project description: Microglia are immunocompetent cells of the central nervous system. In a healthy brain microglia exhibit a quiescent morphology but are capable of sampling their microenvironment for pathogens or other bio-active factors. In response of injury or in the setting of neurological disease (such as multiple

sclerosis, autoimmune encephalitis, autoimmune epilepsy, and brain trauma) microglia becomes activated capable of releasing a variety of cytokines and chemokines. The transition of quiescent to activated microglia is largely unknown. Uncontrolled or 'over-activation' of microglia can lead to neuroinflammation and neurodegeneration.

This project will look at the various factors that contribute to microglial activation, with a particular focus on a purinergic microglial receptor, P2X7R. The project is a translational project involving bed-to-bench clinical and scientific approach, where patients with a number of neurological conditions (multiple sclerosis, autoimmune encephalitis, traumatic brain injury) will be recruited for this study. In the laboratory we will focus on microglial activation, chemokine and cytokine profile analysis, study of exocytosis of various cytokines and chemokines as well as understanding the interaction of microglia with surrounding neurons and astrocytes. By examining microglial activation and proliferation and the implication of that for neuroinflammation, we hope to find a number of therapies that combat neurological diseases such as multiple sclerosis, autoimmune encephalitis autoimmune epilepsy and the neurodegeneration associated with traumatic brain injury.

106. Barriers to early epilepsy diagnosis and the impact of diagnostic delay ***also offered as MBiomedSc***

Supervisor: Dr Anne McIntosh, Dr Piero Perruca
Project Site: Department of Medicine RMH, MBC Neurosciences Building Parkville
Contact: Dr Anne McIntosh E: a.mcintosh@unimelb.edu.au

Project description: New onset epileptic seizures are relatively common in the population. Early expert diagnosis and management of new onset epilepsy has a critical impact on outcomes. Despite this, our data demonstrate a substantial proportion of patients experience diagnostic delay, which may be of several years duration and associated with multiple undiagnosed seizures. Together with one of our previous honors students, we have recently published a paper in an international journal examining some underlying risk factors for diagnostic delay in epilepsy (https://www.ncbi.nlm.nih.gov/pubmed/26332423). We plan to extend this small study, utilizing existing data obtained from a large cohort of patients with a new diagnosis of epilepsy.

The student will identify appropriate data categories of interest, clean and code the data and conduct some statistical analyses. The project supervisors will provide appropriate guidance re these processes. The results of this study will potentially provide a basis for educational programs enabling earlier epilepsy diagnosis, as well as contributing to epidemiological research.

The skills expected to be learnt from this project include: clinical epilepsy, data management, basic statistical analyses. As part of background education related to this project the student will be encouraged to observe epilepsy clinical meetings, clinics, and other research meetings of relevance

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.

107. Elucidating the pharmacology and mechanism of action of phrixotoxin on voltage-gated sodium channels – also offered as MBiomedSc

Supervisors: Dr Geza Berecki and Prof Steven Petrou

Project Site: Epilepsy and Ion Channels Group, The Florey Institute of Neuroscience and Mental Health, Kenneth Myer Bldg
Contact: Dr Geza Berecki E : geza.berecki@florey.edu.au

Project description: Voltage-gated Nav1.2 sodium channel mutations are associated with a number of neurological disorders such as epileptic encephalopathies. Clinically used drugs and experimental compounds can target Nav1.2 channels and modulate neuronal excitability. Among these, phrixotoxin-3 (PTx3) from the venom of the tarantula Grammostola rosea blocks the inward Nav1.2 channel current (INa) by altering Nav1.2 channel gating. Remarkably, PTx3 is one of the most potent and selective peptide modulators of Nav1.2 channels, with a half-maximum inhibitory concentration of 0.6 nM and ~100 fold selectivity for Nav1.2 over other neuronal voltage-gated Nav channels. Therefore PTx3 could emerge as a valuable research tool capable of selectively targeting Nav1.2 channels.

The goal of this project is to elucidate the effect of PTx3 on neuronal human Nav1.1, Nav1.2, and Nav1.6 channels stably expressed in mammalian cell lines using the conventional voltage-clamp (VC) technique, and to study the effect of PTx3 on neuronal firing using the novel dynamic-clamp (DC) technique. The biophysical properties of these Nav channels, including current-voltage characteristics, voltage-dependence of (in)activation, and recovery from inactivation will be determined in the absence and presence of PTx3. In DC configuration, Nav1.2, Nav1.2, or Nav1.6 currents will be implemented as external current input to a realistic cortical pyramidal neuron model cell. This model cell incorporates all major neuronal channel currents; however its Nav channel current is replaced with external Nav1.2, Nav1.2, or Nav1.6 current. The model cell's membrane potential is continuously computed in real time and used to clamp the membrane voltage of the mammalian cell expressing the Nav channel under investigation. This unique DC recording configuration provides a dynamic voltage environment capable of mimicking the physiology of the cell and provides a direct readout PTx3 modulation on neuronal model cell excitability.

108. *Wetware* in a loop: voltage-clamp and dynamic-clamp studies of SCN2A sodium channel mutations underlying childhood epilepsy – also offered as MBiomedSc

Supervisors: Dr Geza Berecki and Prof Steven Petrou
Project Site: Epilepsy and Ion Channels Group, The Florey Institute of Neuroscience and Mental Health, Kenneth Myer Bldg
Contact: Dr Geza Berecki E : geza.berecki@florey.edu.au

Project description: Epileptic encephalopathies (EE) are a group of devastating disorders with poor prognosis and complex etiology presenting in childhood. De novo mutations in the SCN2A gene encoding for the voltage-gated sodium (Nav) channel, type II α subunit (Nav1.2), represent a major cause of EE. Prior to understanding and treatment of a particular EE, the contribution of Nav1.2 channel mutations to individual neuronal excitability need to be determined.

In this project the candidate will use both conventional voltage-clamp (VC) and novel dynamic clamp (DC) techniques to investigate the pathogenicity of selected SCN2A mutations affecting Nav1.2 channel function. Transiently expressed human Nav1.2 channels carrying K905N and D1598G mutations (associated with severe EE), R937C and R1902C mutations (associated with autism and milder epileptic syndromes), and wild-type (wt) Nav1.2 channels (control) will be studied in transfected mammalian cells. Sodium currents through wt or mutant Nav1.2 channels will be recorded in VC mode and applied as external current input to a realistic cortical pyramidal neuron model cell in real time. This model cell incorporates all major neuronal channel currents; however its Nav channel current is replaced with external wild-type or mutant Nav1.2 current. The model cell's membrane potential is continuously computed in real time and it is used as a voltage clamp command for the HEK cell expressing wt or mutant Nav1.2 channels. This unique DC recording configuration provides a dynamic voltage environment capable of mimicking the physiology of the cell and provides a direct readout of the impacts of Nav1.2 dysfunction on neuronal excitability. This is a significant advance over conventional electrophysiological and computational modelling approaches that are the only option currently available, and DC should improve the throughput of mutation analysis and quality of predictions.

109. Multielectrode array analysis of neuronal networks derived from an epilepsy mouse-model – also offered as MBiomedSc

Supervisors: Dr. Snezana Maljevic, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg

Contact: Snezana Maljevic, Steve Petrou E-mail: snezana.maljevic@florey.edu.au, steven.petrou@florey.edu.au

Project description: A recurrent mutation, Arg320His, in the KCNC1 gene, encoding voltage-gated potassium channel Kv3.1, has been recently identified as one of the main causes of progressive myoclonus epilepsy (PME), a rare, inherited disorder manifesting with myoclonus, tonic-clonic seizures, and ataxia. *In vitro* analysis in *Xenopus laevis* oocytes revealed that the mutation causes a loss of channel function (Muona et al., Nat Genet 2015).

To provide in-depth analysis of disease mechanisms, we generated knock-in mouse model carrying Arg320His mutation. The project aims at examining properties of neuronal networks derived from this mouse model using multielectrode array (MEA) analysis. To this end, primary neuronal cultures will be plated on MEA dishes and their activity analysed at different time points. We will also examine the effects of elevated temperature on the network activity, as clinical data suggest improvement of symptoms in patients with fever. This platform will be further used to test the efficiency of different drugs, including specific Kv3.1 channel openers, by assessing their impact on the signatures of network activity altered by the mutation.

Apart from cell culture methods and MEA analysis, the project will include Ca imaging of neuronal network activity, as well as immunostaining to assess the localization of mutant channels in neurons. We expect that the obtained results will lead to the clinical translation and precision medicine approaches in the treatment of the affected individuals.

110. Evaluating the impact of dietary C10 and C8 fatty acids on spontaneous seizures and behavior in mouse models of epilepsy – also offered as MBiomedSc

Supervisors: Nikola Jancovski-PhD and Prof Steve Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Building
Contact: Nikola Jancovski: nikola.jancovski@florey.edu.au/jancovski.n@unimelb.edu.au

Project description: Increasing evidence suggests that medium-chain triglyceride (MCT) diet is one of the most effective therapeutic approaches in patients with drug-resistant epilepsy. Octanoic acid (C8) and decanoic acid (C10) are major constituents in the diet and research has shown increased quantities of these compounds in plasma of children with intractable epilepsy treated with the diet. The antiepileptic properties of MCT diet might be attributed to C10 and C8, and recent studies reported acute anticonvulsant effects of C10 and C8 in several seizure tests in mice. Although it is suggested that C10 acid exerts direct inhibition of excitatory neurotransmission and therefore decreases seizure activity, the exact mechanisms of action remain elusive. Further studies with C10 and C8 acids using animal models are needed to evaluate the role of these acids in seizures control. It is very important to complete pre-clinical work in rodent models of epilepsy before these diets are used in clinical trials.

In this project the student will have the possibility of using a range of experimental techniques, from behavioural studies using different mouse models of epilepsy to recording electrical activity of the brain. The results might lead to developing of new therapeutic approaches for patients with drug-resistant epilepsy.

111. "Glass brain" imaging in health and disease – also offered as MBiomedSc

Supervisors: Dr Tim Karle, Dr Kay Richards, Prof Steve Petrou,
Project Site: Florey Institute
Contact: Prof Steven Petrou E: spetrou@unimelb.edu.au;

Project description: Histochemical optically clearing of whole tissue samples and the development of new microscopes that can image deep within the tissue have created unprecedented insight into the wiring of neural networks. Changes in the wiring of cortical neurons, in particular, have been implicated in a number of disorders such as epilepsy, schizophrenia, autism and depression. In this project the candidate will clear whole brains; allowing imaging of neurons, which have been labelled with fluorescent tags. Multi-photon excitation and custom laser light-sheet based microscopy will allow acquisition and reconstruction of exquisite 3D images in key regions of the mouse cortex. The workflow will include chemical clearing, optical microscopy and software deconvolution of the big data sets which will be generated. By comparing normal and epilepsy models this work will begin to unravel the changes that occur prior to and after the occurrence of seizures. This will shed important light on the scale on which structural changes occur in epilepsy and will guide future experimental and clinical work.

112. Multiphoton imaging of induced pluripotent-stem cell derived brainoids – also offered as MBiomedSc

Supervisors: Dr. Tim Karle, Dr. Snezana Maljevic, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Dr Tim Karle, Dr Snezana Maljevic E: tkarle@florey.edu.au, snezana.maljevic@florey.edu.au

Project description: Development of induced pluripotent stem cell (iPSC) approaches has enabled studies of epilepsy mechanisms in patient –based models. This can be achieved by generating 3-D iPSC-derived neuronal cultures, so called brainoids, which present self-organised neuronal assemblies. Video rate imaging of neuronal activity in these millimetre sized assemblies is made possible using short intense pulses of infrared light to image inside the living tissue. Scanning the light rapidly through the tissue causes fluorescence of genetically tagged populations of neurons, expressing Calcium sensitive fluorescent indicators. This allows multiphoton optical mapping of electrical activity in the neural networks. This project combines stem cell biology with novel imaging techniques to aid the understanding of genetic epilepsy mechanisms.

113. Functional characterization of epilepsy – causing mutations – also offered as MBiomedSc

Supervisors: Dr. Snezana Maljevic, Prof. Steven Petrou
Project Site: Ion Channels and Human Diseases Group, The Florey Institute of Neuroscience and Mental Health
Contact: E: snezana.maljevic@florey.edu.au,

Project description: Increasing number of genetic variants affecting ion channel genes and associated with different forms of epilepsy has been identified in the recent years. One of the important steps in understanding if and how these variants contribute to the disease phenotype is their functional characterization using different in vitro and in vivo approaches. The initial screen of detected variants is often performed in *Xenopus laevis* oocytes or HEK cells and involves site-directed mutagenesis, RNA production and injection, cell culture methods and two-microelectrode or patch clamp technique. In addition, biochemical methods and immunocytochemistry are applied to examine the expression and localization of affected channels. A position is currently available for examining several novel mutations detected in Kv7 voltage-gated potassium channel genes. We aim to examine the common disease mechanisms and select variants for further in depth analysis using mouse and stem cell models.

114. Problematic pumps: the mechanistic basis of Na K-ATPase **mutations – also offered as MBiomedSc**

Supervisors: Ian C Forster, Dr Melody Li, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health
Contact: E: ian.forster@florey.edu.au

Project description: Mutations in the ubiquitous Na-K-ATPase (sodium potassium pump) have been implicated in several neurological disorders such as rapid-onset parkinsonism and alternating hemiplegia. Understanding the molecular basis for these clinical disorders is key to developing appropriate treatments as well as gaining deeper insights into the physiological role and molecular mechanism of the wild-type protein. We will use real-time biophysical assays, combining conventional electrophysiology and fluorometry, to elucidate the mechanistic dysfunction. Interested applicants will gain first-hand experience with molecular biology, electrophysiology, fluorometry and computational biology. Some basic knowledge of molecular biology techniques and basic laboratory practices would be desired.

115. Structure function studies on phosphate transporters – also offered as MBiomedSc

Supervisors: Ian C Forster, Dr Melody Li, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health
Contact: E: ian.forster@florey.edu.au

Project description: Sodium-coupled phosphate transporters provide the main means by which dietary phosphate is absorbed in the gut and reabsorbed in the kidney, to achieve phosphate homeostasis. Understanding the molecular basis of the transport mechanism at the molecular level is essential for developing clinically effective drugs to target phosphate transporters in clinically prevalent conditions such as end-stage kidney disease. We will use biophysical assays, combining conventional electrophysiology and fluorometry, to study the transport dynamics in real time and elucidate potential drug interaction sites.

Interested applicants will gain first-hand experience with molecular biology, electrophysiology, fluorometry and computational biology. Some basic knowledge of molecular biology techniques and standard laboratory practices would be desired.

116. Zinc and seizures *also offered as MBiomedSc*

Supervisors: A/Prof Chris Reid, Prof Steve Petrou, Dr Paul Adlard -
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Chris Reid E : careid@unimelb.edu.au

Project description: Zn^{2+} is an essential element having a multitude of biological functions throughout the body. Our research has demonstrated that low brain Zn^{2+} can increase seizure susceptibility (Hildebrand et al 2015 Sci Rep). This highlights Zn^{2+} supplementation as a potentially good therapeutic strategy for seizure conditions. Before clinical trials can begin we need to complete important pre-clinical work in rodent models of epilepsy. We also need to better understand the mechanisms through which Zn^{2+} modulates neuronal excitability. In this project the student will learn a range of experimental techniques aimed at understanding the role Zn^{2+} plays in changing neuronal excitability. This will include using established rodent models to test diet and drug manipulations of brain Zn^{2+} levels on seizure susceptibility and electrophysiological investigations looking at how neuron excitability is changed by Zn^{2+}. The results have particularly relevance for developing countries, where epilepsy rates are high and nutritional supplementation is a potential practical therapy

117. Novel antiepileptic drug targets based on HCN channel antagonists - *also offered as MBiomedSc*

Supervisors: A/Prof Chris Reid, Prof Steve Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Chris Reid E : careid@unimelb.edu.au

Project description: About 30% of epilepsy patients are not controlled on currently available antiepileptic drugs. Our laboratory has discovered a novel anti-epileptic drug target. HCN channels are an ion channel in the brain that regulates rhythmic behaviour which is a hallmark of a seizure. In collaboration with Italian scientists we have demonstrated that a compound that blocks a certain subtype of this channel reduces seizures. Based on this the NIH Anticonvulsant Screening Program in USA will test this compound on a range of seizure models. In this project we want to begin to understand how blockers of this channel reduce seizures. We have assembled a range of state-of-the-art tools to answer this question. This includes a viral-based knock-down strategy, a conditional knock-out mouse model and pharmacological tools. In this project the student will have the possibility of using a range of experimental techniques; from behaviour to recording single neuron activity. These channels are also thought to be important to the generation of pain and drugs based on this target may be useful in this condition as well.

118. How does pH change brain excitability? - *also offered as MBiomedSc*

Supervisors: A/Prof Christopher A. Reid, Dr Nikola Jancovski, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Chris Reid E: Christopher.reid@florey.edu; careid@unimelb.edu.au

Project Description: Brain pH levels have long been known to modify seizure susceptibility. Breathing too quickly results in brain alkalosis and can trigger seizures. In contrast, acidic shifts in brain pH induced by respiration of increased CO_2 concentrations can reduce seizure susceptibility. In fact, a gas found in emergency departments called carbogen (5% CO_2 – 95% O_2), is a rapid and effective anti-seizure therapy that could be used clinically. Our laboratory is working on how pH causes change in neuronal excitability. We have already discovered that pH impacts excitatory and inhibitory neurons differently. This project will investigate the impact of pH in a mouse model that is missing an acid sensitive channel. It will involve testing the behaviour of the mouse and looking at neuron and network excitability. By understanding these mechanisms we will be better able to develop more targeted therapeutic strategies for stopping seizures.

119. High resolution connectivity mapping to examine epileptogenic tuber structure in Tuber Sclerosis Complex - *also offered as MBiomedSc*

Supervisors: Dr Kay Richards, Prof Steven Petrou

Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Kay Richards E: kay.richards@florey.edu

Project Description: Tuber Sclerosis Complex (TSC) is a genetic disease where pathogenesis includes development of multiple benign cortical tubers in the developing brain and throughout the whole body. The focus of this study is to examine the epileptogenic tuber in the context of the whole brain connectivity; the working hypothesis is cortical tuber connectivity forms the basis of seizure generation. The project will involve analysis of anatomical and diffusion weighted MRI data from several TSC patients before and after removal of epileptogenic tubers. In addition, utilizing high-resolution MRI data of the resected tissue obtained using a 16T MRI system; detailed analysis of tuber circuitry will also be explored. In addition, there is scope to further analyze details about cellular architecture of the tuber, including neuronal sub-types, their population density and morphology obtained using immunohistochemistry methods. Overall, the project is an important step in determining the mechanism of seizure genesis from tuber focus to whole brain dysfunction and will guide future therapeutic strategies including surgical approach

120. Morphometric analysis of a Dravet Syndrome mouse model - *also offered as MBiomedSc*
Supervisors: Dr Kay Richards, Dr David Raffelt, Prof Alan Connelly, Prof Steven Petrou
Project Site: Florey Institute of Neuroscience & Mental Health, Division of Epilepsy, Kenneth Myer Bldg
Contact: Kay Richards E: kay.richards@florey.edu

Project Description: Dravet Syndrome is a devastating neurological disease with early onset at approximately 6 months of age. In Dravet Syndrome patients, seizures predominate and are difficult to treat; patients also have severe learning disabilities and a reduced lifespan. This project will examine disease mechanisms using a genetic epilepsy mouse model that has the Scn1a gene mutation, which has been found in over 85% of Dravet Syndrome patients. The purpose of the current project is to provide evidence of the structural mechansism/s causing seizures and possible therapeutic strategies by examining whole brain anatomy and connectivity by utilising high resolution diffusion MRI and glass brain imaging. In addition, microcircuitry will be explored using immunohistochemistry and electron microscopy techniques.

GASTROENTEROLOGY

121. Barrett's Oesophagus – *also offered as MBiomedSc*
Supervisors: Prof Finlay Macrae and Dr Andrew Metz
Project Site: The Royal Melbourne Hospital
Contact: E: Finlay.macrae@mh.org.au

Project description: Barrett's oesophagus is a premalignant condition which is challenging to manage. Detection of dysplasia is difficult but new advanced imaging modalities are assisting, and new treatments such as radio frequency ablation are allowing the condition to be treated without surgical resection. This project will evaluate new imaging and treatment modalities. It will involve close engagement with the Barrett's clinical service.

GENOMICS

122. GAERS versus NEC: Genetics of epileptic and non-epileptic rat strains– *also offered as MBiomedSc*
Supervisor: Dr Pablo Casillas Espinosa, Prof Terence O'Brien, Dr Slave Petrovski Dr Piero Perucca
Project Site: Department of Medicine RMH
Contact: Dr Pablo Casillas Espinosa E: pablo.casillas@unimelb.edu.au

Project description: Whole genome sequence data is available for the GAERS epilepsy rat and its sibling strain the NEC non-epileptic rat. Moreover, whole-genome sequencing is available for four F2 pups born from breeding GAERS and NEC strains. This project will explore the whole genomes of these strains to identify

potential genetic aberration markers of epilepsy. This project will require interest in genetics, bioinformatics and big data.

123. Neurocognitive complaints and epilepsy prognosis – *also offered as MBiomedSc*

Supervisor: Prof Terence O'Brien, Dr Slave Petrovski
Project Site: Department of Medicine RMH
Contact: Prof Terence O'Brien' E: obrientj@unimelb.edu.au

Project description: It has been previously reported that patient's with pre-treatment neuropsychiatric symptomatology are less likely to respond efficaciously to anti-epileptic drug (AED) therapy. Given what we already know about the potential for neurocognitive side-effects induced by AEDs, this study extends the original observation to investigate whether patient-reported neurocognitive adverse drug reactions (ADRs) within the first three months of therapy along with pre-treatment neuropsychiatric symptomatology could together provide a more sensitive and specific prediction of pharmacoresponse in this population of newly-treated patients.

124. Predictors and mechanisms of cutaneous adverse drug reactions: a multi-omic approach - *also offered as MBiomedSc*

Supervisors: Prof. Patrick Kwan, Dr Alison Anderson
Projects site: Department of Medicine (RMH), University of Melbourne
Contact: Prof Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: Mainstream anti-epileptic drugs (AEDs) that are used to treat epilepsy and some other conditions are associated with a range of cutaneous side effects. Genetic analyses that compare the genomes of those who develop an adverse reaction with those that are tolerant to AEDs has identified specific genetic markers that increase susceptibility in some but not all individuals. It is increasingly understood that multiple genomic and /or environmental factors contribute to drug sensitivity. A better understanding of the underlying molecular mechanisms will enhance capacity for personalised treatment and the design of safer drugs. This project represents a unique opportunity to investigate the underlying molecular mechanisms by integrating genomic analysis with transcriptomics (gene expression) approaches. The transcriptome, derived from T-cells, will be used to identify genes that are differentially expressed or that change their pattern of co-expression in cells from drug-exposed cases as compared to those from drug-tolerant controls. The student will be part of a multidisciplinary team with expertise in neurology, cell biology and bioinformatics and gain an understanding of the rapidly evolving field of pharmacogenomics.

GLOBAL HEALTH

125. Global gastroenterology – *also offered as MBiomedSc*

Supervisors: Prof Finlay Macrae; A/Prof Jioji Malani
Project Site: The Royal Melbourne Hospital and Fiji National University
Contact: E: finlay.macrae@mh.org.au

Project description: In 2016, the Australian and New Zealand Gastroenterology International Training Association is supporting an honours student from Melbourne University to document the buden of pancreatico-biliary disease in Fiji Islands, with a view to justifying training in biliary endoscopy and later, introduction of a biliary enbdoscopy service in Fiji (ERCP). Opportunities to study biliary disease in other South Pacific countries are emerging and there is a need to document the work of ANZGITA in capacity building in gastroenterology in Fiji and elsewhere in the Pacific. This project will attract Honours students interested in Global Health

IMAGING

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

Supervisor: Dr Chris French Prof Terence O'Brien, Prof David 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/

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-senstive 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 elctrophysiological 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.

127. Early detection of age associated diseases using imaging - *ONLY offered as* MBiomedSc

Supervisor: Prof Patricia Desmond, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital,
Contact: Prof Cassandra Szoeke T: 61 3 8344 1835
E: cszoeke@unimelb.edu.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:-

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

128. Non-Invasive Imaging of High-Flow Arteriovenous Intracranial Shunts *also offered as* MBiomedSc

Supervisor: Prof Roland Bammer, Prof Patricia Desmond
Project Site: Dept of Medicine, Royal Melbourne Hospital
Contact: Prof Roland Bammer E: rbammer@unimelb.edu.au

Project description: Intracranial arteriovenous lesions– i.e. dural arteriovenous fistulas (DAVFs) and arteriovenous malformations (AVMs) - are important, treatable causes of long-term neurological disability and potentially of death. These lesions are characterized by a direct passage (shunting) of blood from arteries to veins. The goal of this NIH-funded trial is to use non-invasive imaging methods to detect shunting lesions. In addition to diagnosis, a key aspect of the study will be the characterization of different drainage patterns necessary for treatment planning, risk stratification and prognostication.

This research project will provide students with a rich learning exposure to nascent neuroimaging methods, normal and abnormal intracranial vasculature and in-depth access to high-end data analysis in a brand-new research facility at the Royal Melbourne Hospital. Active participation in publication in top-tier peer-reviewed journals is expected.

129. Phantom Development for Longitudinal Multi-Centre Clinical Trials *also offered as* MBiomedSc

Supervisor: Prof Roland Bammer, Prof Patricia Desmond
Project Site: Dept of Medicine, Royal Melbourne Hospital
Contact: Prof Roland Bammer E: rbammer@unimelb.edu.au

Project description: Longitudinal imaging-based trials are associated with immense costs and huge effort for the personnel involved. Often studies continue over several years and are fraught with bias due to inevitable hardware and software upgrades and system failures. To avoid systematic bias due to changes in the imaging pipeline as well as inter-vendor and intra-vendor differences of imaging devices across trial sites, sophisticated quality assurance pipelines are usually put in place. A central piece of a good quality assurance for a trial is a reproducible quality phantom. Sadly, existing quality phantoms do not consider new contrast mechanisms that are currently used in some of these trials. The purpose of this project is to develop a new quality phantom for MR imaging which addresses the shortcomings of other commercial phantoms.

Aside from an in-depth exposure to the inner workings of imaging-based (multicenter) clinical trials and their challenges, this research project will provide students with a rich learning experience in 3D printing and MR imaging. Students will be working in a brand-new research facility at the Royal Melbourne Hospital together with clinicians, scientists and engineers. Active participation in publication in top-tier peer-reviewed journals is expected. Opportunities for commercialization and spin-offs are possible.

130. An Economics Study of Specialized Radiology Practices ***also offered as*** **MBiomedSc**

Supervisor: Prof Roland Bammer, Prof Patricia Desmond
Project Site: Dept of Medicine, Royal Melbourne Hospital
Contact: Prof Roland Bammer E: rbammer@unimelb.edu.au

Project description: The purpose of this research project is to investigate the benefits of economies of scale in specialized radiology practices. Students will be collecting independent data and integrating them into a multi-factor model to study their impact on key performance indicators and economic outcome factors of specialized radiology practices in U.S. and Australia vis-a-vis general radiology practices as functions of patient flow, case mix/complexity and reimbursement model.

Students will be working in a brand-new research facility at the Royal Melbourne Hospital together with clinicians, scientists and MBAs/economists. Part of the research work may involve also travel within Australia and to the U.S. (e.g. Stanford University, UCSF), thus the student must be allowed to travel (i.e. no restrictions to obtain a short-term visa). Active participation in publication in top-tier peer-reviewed journals and preparation of business case publications is expected.

INFECTIOUS DISEASES AND IMMIGRANT HEALTH

131. Monitoring the efficacy of a training program in gastroenterology in the Pacific - ***also offered as MBiomedSc***

Supervisors: Prof Finlay Macrae
Project Site: Department of Colorectal Medicine and Genetics, Royal Melbourne Hospital
Contact: Prof 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 quantitavely, 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

132. Exploring the similiarities and differences of hepatitis C treatment and opiate substitution treatment therapy in people who inject drugs to inform increasing access HCV treatment in this population

Supervisors: Prof Margaret Hellard, Dr Peter Higgs
Project Site: Burnet Institute
Contact: E: peterh@burnet.edu.au E: margaret.hellard@burnet.edu.au

Project description: Pharmacotherapy, when used with regard to substance dependence refers to the replacement of a person's drug of choice with a legally prescribed and dispensed substitute. Known as opioid substation therapy (OST) in Victoria over 14,000 people are currently being dosed daily with methadone or suboxone for their heroin dependency.

Currently few PWID receive treatment but the advent of new direct-acting antiviral (DAA) treatment provides opportunity for increased uptake of therapy which will have the duel benefit of curing the PWIDs HCV and also potentially reducing HCV transmission (through treatment as prevention (TasP)) leading to HCV elimination in Australia.

Working with participants from the Treatment and Prevention (TAP) Study, a world first study of community based treatment for PWID and HCV elimination, this honours project will explore the PWIDs attitudes and understandings of the new DAA HCV treatment, the best mechanism to provide DAAs to the – separate to or with OST. The overall aim is to identify mechanism to increase PWIDs access to DAAs and compliance with DAA treatment so as to inform HCV elimination in Australia and globally.

The study will use qualitative methods including in-depth semi-structured interviews to achieve the research aims. An interview guide will be developed to map broad areas of investigation and to lead the semi-structured interview process, which will be inductive to allow for the generation of new ideas and knowledge that may otherwise remain uncovered.

133. The outcomes of transitioning between prison and community for people with a history of injecting drug use

Supervisors: Prof Paul Dietze, A Prof Mark Stoove
Project Site: Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute
Contact: Paul Dietze E: paul.dietze@burnet.edu.au

Project description: Injecting drug use contributes disproportionately to the health and social burden of illicit drug use in Australia. Sustained patterns of problematic injecting drug use are influenced by a complex interaction of social, health, structural, and policy factors, including the ongoing criminalisation of drug use and the routine incarceration of people for drug-related crime.

People who inject drugs (PWID) are vastly over-represented in the prison and broader criminal justice system. Transition out of prison represents a particularly vulnerable period for PWID that is characterised by challenges associated with social reintegration, housing, employment, accessing health and other support services, and relationships with significant others. Return to dependent patterns of drug use following prison release is also common, resulting in very high rates or mortality, morbidity, recidivism and re-incarceration in this population.

Burnet Institute is undertaking Australia's first prison-to-community prospective cohort study of people with injecting drug histories. This study provides an opportunity for analysis pre- and post-release data collected from 500 participants in the weeks preceding prison release and in the first three months following their release. A range of post-release outcomes are available for investigation, including but not restricted to patterns of drug use, engagement and retention in treatment and health care, overdose, housing stability and blood borne virus risk. Univariate descriptive and prospective analyses examining the pre- and post-release predictors of outcomes will be undertaken to help inform policy and practice in the Justice and Health arenas.

134. The persistence of risk among people who inject drugs - *also offered as MBiomedSc*

Supervisor: Prof Paul Dietze
Project Site: Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute
Email: Paul Dietze E: paul.dietze@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

135. Train your monocytes with treats: understanding how glycosaminolyscans can modulate monocyte biology - *also offered as MBiomedSc*

Supervisors: Dr. Louise Randall (Medicine RMH, Doherty Inst), A/Prof Anthony Jaworowski (Burnet Inst)
Project Site: Doherty Institute and Burnet Institute
Contact: Dr Louise Randall E: louise.randall@unimelb.edu.au

Project description: Glycobiology is an exciting and rapidly expanding field of science. Glycosaminoglycans consist of repeating chains of disaccharide (2 sugar) units and are generally attached to a protein core, thereby forming a proteoglycan. These molecules have important structural roles but new functions, including roles in cell signaling and the immune system, have now been described. Monocytes are key cells of the immune system with diverse roles, which include responding to infection and aiding in repair. Data generated in our laboratories suggest that specific glycosaminoglycans can modulate the response of monocytes to pathogen products, including the malaria-causing parasite *Plasmodium falciparum*. This new project aims to examine the mechanisms involved in this glycosaminoglycan-dependent education of monocytes by focusing on signaling pathways within the cells. The techniques available for this project include cell culture of primary cells and cell model systems, flow cytometry, ELISA, protein analyses and realtime RT-PCR.

136. Immune Cell Signalling Regulation During Inflammation - *also offered as MBiomedSc*

Supervisors: Dr Rodney Luwor and Dr Paul Licciardi
Location: Dept of Surgery RMH and Murdoch Children's Research Institute
Contact: Dr Rodney Luwor; T: 8344 3027, E: rluwor@unimelb.edu.au

Project Description: Infections with *Streptococcus pneumoniae* (pneumococcus) are a major cause of morbidity and mortality in children <5 years of age globally with ~1.5 million deaths per year due to invasive pneumococcal diseases (IPD) such as pneumonia, meningitis and sepsis. There has been recent interest in understanding the host response to pneumococcal infection, particularly on innate immunity and inflammation. Following infection, recognition of *S. pneumoniae* (and their bacterial components) occurs by pattern recognition receptors such as Toll-like receptors (TLRs-2,4) on monocytes and neutrophils as well as on airway epithelial cells. Activation of TLRs lead to inflammation characterised by cytokine and chemokine secretion (e.g. TNF-α, IL-1β, IL-6, IL-8) which further recruit innate immune cells mainly under the control of NFκB. In addition, large multi-protein complexes known as inflammasomes regulate caspase-1-mediated IL-1β and IL-18 release and are critical in this response. Recent studies have shown that the NLRP3/NALP3 inflammasome is integral in the host inflammatory response to pneumococcal infection but can also contribute to the associated pathology. Therefore, novel anti-inflammatory therapies that target the inflammasome would be effective in limiting the pathological consequences of pneumococcal infections. Dietary short-chain fatty acids (SCFAs) such as butyrate are widely recognised to possess potent anti-inflammatory effects. SCFAs are also produced probiotic bacteria, and represent a possible mechanism by which they exert their reported beneficial effects on inflammation, immune modulation and pathogen colonisation. This study aims to assess the biological role of butyrate on NFkB- and inflammasome-driven responses using a bacterial infection model recently developed in the laboratory.

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

INNATE PHAGOCYTOSIS & NEURODEGENERATION

137. Leukocyte surface and functional biomarkers for prognosis of age-related macular degeneration

Supervisors: Dr. Ben J. Gu, Prof. Robyn Guymer, Prof. Erica Fletcher, Prof. James S. Wiley
Project Site: Florey Institute, Kenneth-Myer Building
Contact: E: ben.gu@florey.edu.au Ph: 03 9035 6317

Project description: Age-related macular degeneration (AMD) is a multifactorial disease and is a leading cause of irreversible vision loss in Australia. AMD at its early stage is characterized by accumulation of debris (lipid rich drusen) in retina, which is believed due to reduced clearance capacity. While AMD can be easily diagnosed with high resolution retina imaging, early prognosis biomarkers are needed to identify people with high risk for preventive treatment. Our previous study has shown that genetic variants leading to defective phagocytosis are risk factors for AMD. In this study, we will measure the phagocytosis ability of monocytes and monocyte subsets from AMD patients as well as age-matched healthy controls, using a real-time tri-colour flow cytometry method developed by our group. Meanwhile, the monocyte surface expression of scavenger receptors, e.g. P2X7, TREM-2, SCARA1 and CD36, will be examined. Cell surface biomarkers will be examined on peripheral blood leukocytes from patients and healthy controls. The sensitivity and specificity of promising parameters will be analysed and validated in a follow-up study. This study will not only identify a useful pattern for early prognosis of AMD, but also provide insights on the pathogenesis and development of this disease.

138. Identification of serum glycoproteins inhibiting innate immunity - *also offered as MBiomedSc*

Supervisors: Dr Ben Gu, Prof James Wiley
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building, Parkville
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au James Wiley E: james.wiley@florey.edu.au

Project description: Innate immunity is the first line defense of host against invading 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.

139. How does the brain remove the excess number of neurons during development and ageing - *also offered as MBiomedSc*

Supervisors: Dr Ben Gu, Prof James Wiley
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building, Parkville
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au James Wiley E: james.wiley@florey.edu.au

Project description: Many more neurons are produced during development than are present in the adult brain. Also many neurons are lost during aging, however the process of innate phagocytosis, which removes unwanted and superfluous neurons is poorly defined. The unwanted neurones enter apoptosis but subsequent clearance of these dying cells is 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. Recent novel finding from our laboratory 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 both in health and in disease. This result will have relevance to many neurological diseases as well as early neurodevelopment.

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

140. Identify the transcriptional regulatory factors of the P2X7 receptor - *also offered as MBiomedSc*

Supervisors: Dr Ben Gu, Prof James Wiley
Project Site: Ion channel & Human Disease, Florey Neuroscience Institutes, Level 1, Kenneth-Myer Building
Contact: Ben Gu T: 03 9035 6317 E: ben.gu@florey.edu.au
James Wiley E: james.wiley@florey.edu.au

Project description: P2X7 is an ATP-gated purinergic receptor and plays a broad role in infection, inflammation, autoimmunity, neurodegeneration and oncogenesis. Several isoforms of P2X7 have been identified to be associated with cancer or other diseases. High expression of non-functional P2X7 has also been found in a broad range of tumour tissues. However, the transcriptional regulatory factors leading to these isoforms and non-functional P2X7 are unclear. This project will identify the transcriptional factors in the P2X7 promoter region, and how these transcriptional factors regulate production of P2X7 isoforms and non-functional P2X7. The results will provide insights on how cancer cells avoid removal by innate immunity.

Techniques involved include molecular biology, including primer extension, transfection, fluorescent super electrophoresis mobility shift assay and chromotin-immunoprecipitation, as well as cell culture, flow cytometry.

141. Do circulating microvesicles from patients with multiple sclerosis (MS) disrupt the blood-brain barrier (BBB)? - *also offered as MBiomedSc*

Supervisors: Dr. Ben J. Gu, Prof. James S. Wiley
Project Site: Florey Institute, Kenneth-Myer Building
Contact: Dr Ben Gu E: ben.gu@florey.edu.au Ph: 03 9035 6317

Project description: Breakdown of the blood brain barrier (BBB) precedes clinical symptoms of new lesions of MS and it is possible that high numbers of microvesicles in multiple sclerosis (MS) plasma are related to episodes of disruption of the BBB. The integrity of BBB will be studied using an *in vitro* model examining lymphocyte transmigration across confluent monolayers of cultured endothelial cells. Human umbilical vein endothelial cells (HUVECs) are grown to confluent monolayers in tissue culture plates and peripheral blood lymphocytes added to each well and incubated for 2-4 h. The HUVEC layer is washed 5 times with saline media, then fixed and examined by phase-contrast microscopy. Cells beneath the monolayer appear phase dark while adherent cells above appear phase light. The number of adherent and migrated cells are counted to give an index of efficiency of migration. To assess if microvesicles impair the integrity of the endothelial monolayer, the migration assay will be performed both in the absence and presence of plasma containing known concentrations of platelet derived microvesicles. Meanwhile, the lysosomal β-hesosaminidase activity will be measured in platelet poor plasma from 20 MS patients and 20 controls using a standard colourimetric assay. The microvesicle counts, β-hesosaminidase activity and the impact on lymphocytes transendothelial migration will be analysed in correlation. Results could provide evidence for a mechanism by which peripheral blood leukocytes infiltrate to brain in MS.

Techniques involved include cell culture, ultra-centrifugation, flow cytometry, fluorescent microscopy and biochemistry.

MALARIA

142. Hiding out in the Placenta. Investigating how glycosaminoglycans can modulate the immune system during malaria and pregnancy – *also offered as MBiomedSc*

Supervisors: Dr Louise Randall and Prof Stephen Rogerson
Project Site: Department of Medicine, University of Melbourne. The laboratory is located at the Peter Doherty Institute for Infection and Immunity
Contact: Dr Louise Randall E: louise.randall@unimelb.edu.au T: 8344 2181

Project description: Malaria during pregnancy can impact both the mother and the developing fetus, resulting in increased morbidity and mortality. Placental malaria is characterised by the accumulation of *P. falciparum*-infected red blood cells in the placenta. Parasite-derived proteins on the infected red blood cell membrane bind to chondroitin sulfate A, a glycosaminoglycan associated with the syncytiotrophoblasts and the intervillous spaces of the placenta. Studies performed in our laboratory suggest that this glycosaminoglycan can modulate the immune system response to the malaria parasite. This new project aims to examine this

modulation more closely and to understand the interaction between the parasite, the placenta and the mother's immune system.

Techniques involved: enzyme-linked immunosorbent assay (ELISA), cell culture, measurement of cytokines, real-time PCR.

143. Altruism in nature: an investigation of transmission-blocking immunity against malaria – *also offered as MBiomedSc*

Supervisors: A/Prof Siddhartha Mahanty and Prof Stephen Rogerson
Project Site: Department of Medicine, University of Melbourne. The laboratory is located at the Peter Doherty Institute for Infection and Immunity
Contact: A/Prof Siddhartha Mahanty E: smahanty@unimelb.edu.au

Project description: The malaria parasite Plasmodium falciparum (Pf) has a complex lifecycle with asexual and sexual stages in two hosts, humans and mosquitoes. Transmission of malaria parasites from humans to the mosquito vector is a complicated phenomenon that successfully overcomes immune defences in both hosts. Immune responses directed towards to sexual (transmittable) stages in humans of are capable of inhibiting parasite growth in mosquitoes, thus interrupting transmission of malaria without benefiting the host, a concept referred to as altruistic immunity. Antibodies directed against sexual stages of Pf are thought to directly mediate growth inhibition of sexual stages. The extent of antibody-mediated immunity against Pf gametocytes, the sexual stage in humans, and the functional properties of antibodies that underlie growth inhibition are not well understood. The goal of this project is to identify malaria-infected individuals who have antibodies to gametocytes and gametocyte-derived antigens of Pf and to determine the functional properties of anti-gametocyte antibodies that confer transmission-blocking properties.

Hypothesis: Pf-infected individuals have antibodies against gametocyte stages of the parasite and that functional properties of these antibodies determine their ability to block transmission Study design: Sera from malaria-infected individuals from Pf endemic regions will be screened for antibodies against gametocytes and gametocyte-derived antigens. Antibodies from highly reactive sera will be characterized for biochemical and functional properties (receptor binding, opsonisation and parasiticidal activity). The functional characteristics will be correlated with transmission blocking activity to identify the most closely correlated properties. Methodology used: ELISA, flow cytometry, immunofluorescence, statistical methods for quantitative analysis of data

Envisaged role of trainee: Development of ELISA assays to screen infected sera for antibodies to gametocytes and gametocyte antigens; functional characterization of reactive antibodies. Significance: A better understanding of the mechanisms of transmission blocking immunity will facilitate the development of vaccines aimed blocking transmission – an "altruistic" vaccine

144. Developing highly sensitive non-invasive point-of-care immunosensor for malaria elimination – *also offered as MBiomedSc*

Supervisors: Prof Patrick Kwan, Prof Stephen Rogerson, Prof Stan Skafidas
Projects site: Doherty Institute, Department of Medicine (RMH), Centre for Neural Engineering University of Melbourne
Contact: Prof Stephen Rogerson, E: sroger@unimelb.edu.au;
Prof Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: Detection of very low-density malaria infection is essential for malaria elimination, but current diagnostics are insensitive and/or costly. We are developing a low-cost, point-of-care diagnostic device based on our novel electrical immunosensor platform with ultra-sensitive detection capacity. The platform will be applicable to blood (for detection of very low density infection) and saliva (for non-invasive testing) to fulfil diagnostic gaps required for malaria elimination.

145. Investigating the effects of GM-CSF and M-CSF derived human macrophages on phagocytosing *P. falciparum* infected erythrocytes and cytokine production - *also offered as MBiomedSc*

Supervisors: Dr. Adrian Achuthan and Prof Stephen Rogerson
Project site: Department of Medicine (RMH), University of Melbourne
Contact: Dr. Adrian Achuthan T: 8344-3298 E: aaa@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 assess cytokine mRNA, ELISA to measure cytokine secretion and Western blotting and confocal imaging to determine protein expression and localisation.

146. A role for Adipose Tissue in Malaria? - *also offered as MBiomedSc*

Supervisors: Dr Elizabeth Aitken & Prof Stephen Rogerson
Project Site: Department of Medicine (RMH), Peter Doherty Institute
Contact: Dr Elizabeth Aitken T: 03 8344 1972 E: Elizabeth.aitken@unimelb.edu.au and Prof Stephen Rogerson T: 03 8344 3259 E: sroger@unimelb.edu.au

Project description: The pathology associated with malaria is partly caused by a strong inflammatory immune response to the Plasmodium parasite. Adipose (fat) tissue has recently been shown not to be an inert energy store, but a tissue which actively regulates the immune response. Interestingly, we know that the parasite likes to sequester in the adipose tissue but we don`t know much else. With increasing obesity worldwide, this could be important for development of severe malaria. In this project you will study adipose tissue from people and mice infected with Plasmodium parasites. You will discover where in the adipose tissue the parasites are, if (and which) immune cells are also there and if there are any other changes in adipose tissue associated with infection. Techniques will include: Immunohistochemistry, light microscopy, image analysis software.

147. Investigating the acquisition and maintenance of immunity to malaria in infants and pregnant women *also offered as MBiomedSc*

Supervisor: A/Prof Freya Fowkes, Prof James Beeson
Project Site: Burnet Institute
Contact: E: Fowkes@burnet.edu.au

Project Description: Immunity to infectious diseases during pregnancy remains an intriguing area with immunologic and physiologic changes during pregnancy rendering pregnant women to be more susceptible to, and more severely affected by, infectious diseases. Malaria is one of the most important pathogens in pregnancy and world-wide it is estimated that 50 million women living in malaria endemic areas become pregnant. Despite acquiring substantial pre-existing blood-stage immunity pregnant women typically develop higher parasite densities compared to non-pregnant adults, placental infection and associated complications. Very little is known about antibody acquisition, maintenance and boosting during or after gestation. Furthermore little is known about maternal transfer of antibodies and subsequent maternal antibody decay and infant antibody acquisition in infants born in malaria endemic areas.

We have samples from several established longitudinal cohorts of pregnant women and infants that can address questions of antibody acquisition and maintenance through antibody assays and epidemiological analyses. Findings will help us understand how immunity develops and is maintained against infectious diseases.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

148. Understanding the targets and mechanisms of human immunity to malaria *also offered as MBiomedSc*

Supervisor: Prof James Beeson, Dr Jack Richards
Project site: Burnet Institute

Contact: E: beeson@burnet.edu.au E: jack.richards@burnet.edu.au

Project Description: This project will focus on identifying the key antigens that are targets of protective immunity against malaria and understanding the mechanisms mediating immunity, which includes antibodies and cell-mediated responses. This knowledge is crucial for the development of effective vaccines against malaria. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect children from malaria, or protect pregnant women and their developing babies from the devastating consequences of malaria in pregnancy. The studies would particularly focus on understanding antibody acquisition, maintenance and boosting and how antibodies neutralize and clear malaria parasites in the blood, and examine interactions with monocytes/macrophages and dendritic cells, and understanding the nature and specificity of antibody responses.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

149. Vaccines against malaria *also offered as MBiomedSc*

Supervisor: Prof James Beeson, Dr Jack Richards
Project site: Burnet Institute
Contact: E: beeson@burnet.edu.au jack.richards@burnet.edu.au

Project Description: The aim of this project is to evaluate candidate antigens as potential malaria vaccines, understand what combinations of antigens could be use to generate the most effective immune responses, and understand the protective activity of vaccine-induced immune responses. These studies will focus on several leading candidate antigens and other promising antigens. They will use novel approaches in molecular biology, cell biology and immunology to address these aims. In addition, the project could include working on optimising vaccine approaches to induce potent protective immune responses (e.g. improving antigen presentation). The project could focus on vaccines for P. falciparum and P. vivax, which are the two main causes of human malaria.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

150. Identifying targets and mechanisms of the acquired immunity to severe malaria in children *also offered as MBiomedSc*

Supervisors: Prof James Beeson, Prof Stephen Rogerson
Project Site: Burnet Institute
Contact: Prof James Beeson E: beeson@burnet.edu.au E: sroger@unimelb.edu.au

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

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

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

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

151. Healthy Mothers, Healthy Babies: Maternal nutrition and inflammation and their impact on pregnancy outcomes (New) *also offered as MBiomedSc*

Supervisors: Prof James Beeson, Dr Philippe Boeuf
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au Philippe.boeuf@burnet.edu.au

Project description: The level of mortality and disease among newborns and children in Papua New Guinea is very high. Every year, 5,000 newborns die and almost half of those who survive have poor growth and development (known as stunting). Low birthweight is a major cause of both newborn death and poor growth and development of young children and is largely due to poor fetal growth. The single strongest determinant of fetal growth is nutrient supply to the fetus and largely depends maternal nutritional stutus and on the nutrient transport capacity of the placenta. Poor maternal nutrition and infectious causes of maternal inflammation (such as malaria) restrict the nutrient transport capacity of the placenta, contributing to poor fetal growth.

This project is part of our flagship Heathy Mothers, Healthy Babies program ongoing in Papua New Guinea in which we are following 700 pregnant women and their infants until 12 months after delivery. This project will use a combination of established assays (e.g. ELISA kits) and new powerful metabolomics/proteomic approaches to identify nutritional and inflammatory markers predictive of poor pregnancy outcomes, especially low birthweight. Currently, the major causes of low birthweight in PNG are poorly understood. Identifying signatures of maternal malnutrition and inflammation could allow the identification of women at risk of delivering low birthweight babies to direct the limited health care resources to these at-risk pregnancies, as well as understanding the key causes of poor pregnancy outcomes

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

152. Healthy Mothers, Healthy Babies in Papua New Guinea – The impact of Nutrition, Malaria and STIs on pregnant women and infants ***also offered as MBiomedSc***

Supervisors: Prof James Beeson, A/Prof Freya Fowkes
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au

Project description: In many resource-poor regions globally, pregnant women experience high rates of malaria, under-nutrition and sexually transmitted infections (STIs) which can lead to maternal morbidity and mortality and in infants, low birth weight (LBW) resulting in a significant number of infant deaths each year. In these settings, LBW is due to fetal growth restriction and preterm delivery. However the link between nutrition, malaria and STIs and these birth outcomes have yet to be elucidated.

At the Burnet Institute, we have initiated a unique research program in rural PNG, called Health Mothers Health Babies, in partnership with the PNG Institute of Medical Research, East New Britain Provincial Goverment, University of PNG, the National Department of Health, and others. We have undertaken a longitudinal study of 700 pregnant women attending antenatal care, and followed them through to delivery. Among these women we will measure markers of nutrition and evaluate micronutrient deficiencies, determine malaria and STIs. The association of nutrition, malaria, and STIs during pregnancy with respect to birth outcomes will then be assessed using epidemiological techniques. The objective of this project is to determine the major preventable causes of poor maternal health and LBW to enable the development of future interventions to improve health and pregnancy outcomes.

This project is offered as a laboratory or epidemiological project, or a combination of the two depending on student interests.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

153. Development of novel point-of-care diagnostics tests and surveillance tools ***also offered as MBiomedSc***

Supervisors: Prof James Beeson, Dr Philippe Boeuf, A/Prof David Anderson
Project Site: Burnet Institute
Contact: beeson@burnet.edu.au Philippe.Boeuf@burnet.edu.au anderson@burnet.edu.au

Project description: There is an urgent need for diagnostic and surveillance tests that could be used in resource-poor settings. These include vaccine antibody testing (malaria, measles, HBV, pneumonia and others) to assess vaccine coverage in populations, and sero-surveillance tools for monitoring and tracking major

infectious diseases. The limited resources and health care infrastructure in many disease-endemic countries means that tools for evaluating the vaccine status of patients, vaccine coverage in populations and for disease surveillance need to be simple to perform without a requirement for laboratory facilities or advanced equipment. The tests need to be being semi-quantitative, have a long shelf-life, stable for periods at ambient temperature, and easy to perform and interpret to ensure their suitability to the specific conditions to resource-poor settings. This project will work towards the development of novel semi-quantitative point-of-care rapid tests and investigate different approaches to improve sensitivity and quantitation. This will build on Burnet's extensive expertise in diagnostic test development and strong links to communities that experience a high burden of disease and have an urgent need for new point-of-care tests. The development of new low cost point-of-care tests for major diseases would facilitate major advances in disease control in resource-limited settings.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

154. Developing new assays to identify mechanisms of human immunity to malaria *also offered as MBiomedSc*

Supervisor: Dr Philippe Boeuf, Prof James Beeson
Project site: Burnet Institute
Contact: E: philippe.boeuf@burnet.edu.au; james.beeson@burnet.edu.au

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

This project will focus on developing new assays to identify the antibody-dependent mechanisms that mediate protective immunity against malaria. This knowledge is crucial for the development of effective vaccines against malaria. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect individuals from malaria; especially how antibodies interact with immune cells to neutralize and clear malaria parasites in the blood.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

155. Developing new antimalarial drugs that block protein trafficking and host cell modification in malaria parasites – *also offered as MBiomedSc*

Supervisors: Dr Paul Gilson, Dr Ben Dickerman
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: paul.gilson@burnet.edu.au

Project description: Malaria is a devastating parasitic disease that infects hundreds of millions of people each year, tragically killing about half a million, mainly children. Antimalarial drugs are the main weapons used to combat infection but alarmingly parasites are starting to become resistant to the latest frontline drugs. For this reason new drug targets need to be identified and new medicines developed.

Thankfully thousands of potent parasite killing compounds have been discovered, but their targets in the parasite are unknow. One potential suite of targets is the protein trafficking pathways used by parasites to shuttle proteins around not only their own cells but also those of the human host cells (RBC) they infect. These so-called exported proteins modify the RBCs so the parasite can evade host immunity and rapidly reproduce.

We have discovered several drugs that not only block parasite protein trafficking, but also prevent the parasite from taking up nutrients via the RBC. These drugs cause parasite death and the aim of this project is to help evaluate the biological targets of these drugs and how to make the drugs more potent and specific for potential clinical applications.

Techniques and methods will include Parasite cell culture, drug assays, fluorescence microsopy, functional assays, molecular biology skills (eg, PCR and cloning), parasite transfection.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

156. To Examine genetic variants of Nfkb1 as a biomarker of poor maternal health – *also offered as MBiomedSc*

Supervisors: Dr Raffi Gugasyan, Dr Philippe Boeuf, A/Prof Freya Fowkes
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: raffi.gugasyan@burnet.edu.au

Project description: Healthy Mothers, Healthy Babies (HMHB) aims to define the major causes of poor maternal, newborn, and child health. Poor pregnancy outcomes, including anaemia, low birth weight, premature delivery and stillbirths are quite common. To identify feasible, acceptable and effective interventions it will be important to recognise those at highest risk.

The transcription factor Nuclear Factor-kappaB1 (NF-kB1) is an essential protein that regulates key physiological processes such as ageing, growth and immune competence. Insufficient production of NF-kB1 may lead to severe complications that become most prevalent during the fertile years of a woman's life. Moreover, recent evidence suggests that genetic variants of NFKB1 alter protein levels that can affect idiopathic recurrent miscarriages.

This project will involve the genetic screening of NFKB1 variants to establish whether such variants correlate with the increased risk of poor pregnancy outcomes. The student will learn conventional PCR technology to screen for genetic variants of NFKB1 in 700 women from rural PNG. CRISPR/Cas9 will be used to examine these variants in cell lines and establish how they alter protein levels. We will determine whether variants of NFKB1 are a suitable biomarker for poor health and pregnancy outcomes, including miscarriages, which may facilitate early intervention and appropriate treatment regimens.

157. The Impact of malaria control measures on the acquisition of immunity to malaria – *also offered as MBiomedSc*

Supervisors: Prof James Beeson, A/Prof Freya Fowkes, Dr Philippe Boeuf
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: james.beeson@burnet.edu.au, E: Freya.fowkes@burnet.edu.au,
E: Philippe.boeuf@burnet.edu.au

Project description: Malaria caused by Plasmodium falciparum remains a major cause of morbidity and mortality globally. It has decreased substantially over the past decade due to increased control measures and access to efficacious treatments. People living in these areas are less exposed to malaria over time due to declining transmission.
Naturally-acquired blood-stage immunity develops to malaria after repeated exposure that controls bloodstage parasitaemia, thereby reducing clinical symptoms and life-threatening complications. Antibodies are important mediators of this acquired immunity, however it is unclear how declining malaria transmission impacts on the acquisition of malarial immunity.
The overall objective of this project is to quantify the impact of declining transmission on the acquisition of malarial immunity in a malaria endemic area of Thailand, both in the context of clinical disease and malaria transmission.
Laboratory techniques will include ELISA and functional antibody assays and/or epidemiological analyses. Findings will help us understand how immunity develops and is maintained against infectious diseases in populations with declining transmission.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

158. Novel serological and molecular tools for malaria surveillance and intervention – *also offered as MBiomedSc*

Supervisors: Dr Leanne Robinson, Dr Jack Richards, Prof James Beeson, A/Prof David Anderson
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne

Contact: leanne.robinson@burnet.edu.au jack.richards@burnet.edu.u: james.beeson@burnet.edu.au david.anderson@burnet.edu.au

Project description: As malaria transmission continues to decline, even the most sensitive methods for determining prevalence via detection of the parasite become inefficient for risk stratification and informing programmatic interventions. In addition, the need to identify individuals at risk of Plasmodium vivax relapse from hypnozoites increases. Validated markers of recent exposure to Plasmodium spp. may be able to play an important role, particularly rapidly advancing technologies for quantitative point-of-care testing. By applying novel validated serological markers of exposure and novel validated molecular markers capable of detecting ultra-low density Plasmodium infections to well characterised existing sample sets from epidemiological surveys and surveillance programs conducted in Papua New Guinea (PNG), this project will identify the best marker for identifying and effectively targeting these infections efficiently and within programmatically realistic timeframes.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

159. Epidemiology of malaria transmission in Papua New Guinea – *also offered as MBiomedSc*

Supervisors: Dr Leanne Robinson, A/Prof Freya Fowkes
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: leanne.robinson@burnet.edu.au Freya.fowkes@burnet.edu.au

Project description: The scale-up of malaria control interventions in Papua New Guinea has resulted in a significant overall reduction in the nationwide prevalence and incidence of malaria. However, this effect has not been uniform across the country and considerable heterogeneity in transmission exists in different areas, despite a standardised approach to the implementation of the control measures. Minimal data currently exists on the determinants of heterogeneity and residual malaria transmission in PNG and which human, vector and/or parasite behaviour/characteristics are the most important obstacles to elimination.

This project will involve analysing data on the prevalence and distribution of malaria infection and together with vector and human behavioral data, generate spatial risk maps and investigate the use of clinical foci to identify asymptomatic reservoirs of infection. Understanding the extent of local heterogeneity in malaria transmission and the driving factors is critical to be able to identify and implement targeted control strategies to ensure the ongoing success of malaria control in PNG and make progress towards elimination.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

160. Immunity to malaria in children and pregnant women – *also offered as MBiomedSc*

Supervisors: A/Prof Freya Fowkes
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: Freya.fowkes@burnet.edu.au

Project description: Malaria caused by the parasite Plasmodium falciparum is a leading cause of mortality and morbidity globally, particularly among young children and pregnant women. After repeated exposure, individuals develop effective immunity that controls blood-stage parasitaemia, thereby reducing clinical symptoms and life-threatening complications.

Antibodies are important mediators of this acquired immunity. Very little is known about antibody acquisition, maintenance and boosting of antibody responses with respect to exposure to parasites during childhood and pregnancy. Furthermore little is known about maternal transfer of antibodies and subsequent maternal antibody decay and infant antibody acquisition in infants born in malaria endemic areas. We have access to samples from several established longitudinal cohorts of pregnant women and children living in malaria endemic areas that can address questions of antibody acquisition and maintenance through antibody assays and epidemiological analyses.

Findings will help us understand how immunity develops and is maintained against infectious diseases.

For all queries please contact Arzum, arzum.cubuk@burnet.edu.au

161. Understanding malaria transmission and immunity to inform malaria elimination – *also offered as MBiomedSc*

Supervisors: Prof James Beeson
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: james.beeson@burnet.edu.au

Project description: Malaria transmission in populations involves interactions between infection rates and prevalence that drive transmission, and the presence of malaria immunity that has the potential to reduce transmission. Malaria immunity can act to reduce infection rates and levels of malaria parasitemia, and specific components of immunity can also function to directly block transmission of malaria; this is known as transmission-blocking immunity. Currently, very little is known about the interactions between malaria infection rates and patterns and malaria immunity in populations, and how these interact. However, this knowledge is essential for achieving malaria elimination in many regions of the world, and is a key research priority. Malaria control programs face the challenge that as malaria transmission declines, malaria immunity also declines, which places the population at higher risk of malaria transmission and rebound epidemics. This project will investigate the impact of malaria immunity on malaria infection rates and transmission of malaria in populations.

The student will analyse various parameters to define the patterns of infection and immunity, with a particular focus on defining the interaction between immunity and malaria transmission. The specific activities and focus of the project will be modified to best suit the interests and training background of the student. Skills acquired may include established high-throughput immunoassays, assays that quantify the functional activity of immune responses (E.g. flow cytometry, Fc-receptor mediated immunity, complement activation, western blots, ELISA, neutralisation assays), epidemiology, and data analysis. Depending on the student's interest, this could be expanded to include modelling of the interaction between infection and immunity, and how this may impact on malaria elimination and control.

The findings of this project will be highly relevant to informing malaria elimination efforts and understanding the value of incorporating vaccines into elimination strategies.

For all queries, please contact Arzum, arzum.cubuk@burnet.edu.au

162. Antibody engineering to study responses mediating protective immunity to malaria and other infectious diseases – *also offered as MBiomedSc*

Supervisors: Dr Jack Richards, Prof James Beeson
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: jack.richards@burnet.edu.au E: james.beeson@burnet.edu.au

Project description: Antibodies are key effector molecules responsible for mediating protection against many other infectious diseases.

This project will involve engineering novel recombinant antibodies against malaria parasite proteins and those of other infectious diseases organisms. These will then be used in a range of in vitro immunological assays to determine their precise functional mechanisms and efficacy in protective immunity.

For all queries, please contact Arzum, arzum.cubuk@burnet.edu.au

163. Understanding the acquisition and maintenance of antibodies against malaria– *also offered as MBiomedSc*

Supervisors: Dr Jack Richards, Dr Leanne Robinson, Prof James Beeson
Project Site: Burnet Institute, 85 Commercial Rd, Melbourne
Contact: E: jack.richards@burnet.edu.au E: Leanne.robinson@burnet.edu.au E: james.beeson@burnet.edu.au

Project description: Antibody responses to malaria, or other infectious diseases, are dynamic and fluctuate over time. Traditionally, most studies of immunity only measure antibody levels at a single time point, and fail to capture the dynamic nature of these responses and changes over time that may alter people's susceptibility to infection and disease.

This study will measure antibody responses to a range of malaria antigens at regular time points in children living in malaria-endemic countries.

Statistical analysis and modelling approaches will be used to examine the relationship between these responses and subsequent protection from symptomatic malaria in these children. These findings will be especially important in identifying threshold antibody concentrations that are required for protection against malaria, and in developing new serological surveillance tools to determine the prevalence of malaria infection within study populations.

For all queries, please contact Arzum, arzum.cubuk@burnet.edu.au

164. How do malaria parasites control expression of their genes?

Supervisors: Michael Duffy, Paul Gilson, James Beeson
Project Site: Burnet Institute
Contact: Michael Duffy mduffy@unimelb.edu.au; Paul Gilson paul.gilson@burnet.edu.au; James Beeson beeson@burnet.edu.au

Project description: *Plasmodium falciparum* causes severe malaria and kills approximately 400,000 people a year. Understanding how the malaria parasite regulates gene expression could provide new therapeutic targets. *P. falciparum* employs unique mechanisms of transcriptional control and the low complexity and 90% AT content of *P. falciparum* intergenic sequence has hindered identification of the *cis* DNA sequences that constitute regulatory sequences such as promoters and enhancers. The ENCODE project has described a comprehensive library of human histone modifications that mark chromatin at enhancer and promoter sequences. We have identified the location of these marks genome wide and correlated their presence with gene expression to identify possible promoter and enhancer pairs in *P. falciparum.* This project will now involve cloning these regulatory sequences into reporter plasmids and determining whether they truly regulate gene expression in *P. falciparum.* This project builds on a substantial body of work in our laboratory and has the potential to make a significant contribution to understanding basic parasite biology. This project will involve molecular biological techniques and malaria parasite cell biology and will be conducted at the University of Melbourne Parkville and at the Burnet Institute Prahran.

MEDICATION SAFETY

165. Appropriate and Inappropriate Medication Prescribing in Oldest Old People Admitted to Hospital – *also offered as MBiomedSc*

Supervisors: Prof Elizabeth Manias, Prof Andrea Maier, Mrs Alex Gorelik
Project Site: Royal Melbourne Hospital, Parkville Campus; Melbourne School of Health Sciences, The University of Melbourne
Contact: Prof Elizabeth Manias T: 0450 308 060 E: emanias@unimelb.edu.au

Project description: Oldest old people, who are defined as those aged 85 years and older, are often prescribed many medications to treat several conditions, which has important implications for medication safety. Individuals aged 85 years and older are the fastest growing population group of many developed countries, such as Australia. They are at enormous risk of developing adverse events such as falls, gastrointestinal bleeding, and cognitive impairment. In addition, oldest old people may be denied potentially beneficial medications without a valid reason. In this study, the STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria will be applied to a random sample of oldest old people admitted to hospital. Use of these validated screening tools will determine what medications have been inappropriately commenced in oldest old people and what medications have been inappropriately stopped or not commenced in these people. The adverse events experienced by oldest old people will also be examined to determine whether the medications they are prescribed may be associated with these adverse events. Medical histories of oldest old 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 oldest old people.

The student will gain experience in literature searching, writing a literature review, examining diverse data sources from medical records, analysing data using statistical calculations, constructing a research thesis, and writing for publication.

166. Medicines optimization in home nursing for older people at high risk of adverse events

Supervisors: Dr Snezana Kusljic, Dr Cikie Lee, Dr Rohan Elliot, Dr July Lowthian
Project Site: Royal District Nursing Service, (RDNS), Melbourne School of Health Sciences
Contact: Dr Snezana Kusljic T: 8344 9428 E: skuslic@unimelb.edu.au

Project description: Medication errors and adverse medication events (AMEs) are common in older people referred to a large, non-profit Melbourne-based community nursing service. We piloted a new model that integrated a formal role for clinical pharmacist working within community nursing service (RDNS). This model was shown to improve medicines safety and reduce risk of AMEs for community nursing clients and has created a positive outcome that influenced changes in medication practice.

The aim of this study is to examine the use of medications (and health service utilisation) in RDNS clients to ascertain whether the study intervention (RDNS Pharmacist model) has made any impacts on changing medication use and/or health service utilisation. This will involve extracting RDNS clients' medication data via a manual audit process, for both the intervention group and the matched control group. The auditing process will involve: a) retrieving clients' medication data from multiple sources; b) retrospective review of clients' medication data; c) manual transcription of clients' medication data into a database (in de-identified form) to facilitate data analysis; and d) classification of clients' medication data and findings based on previously published criteria.

MOTOR NEURON DISEASE

167. Development of bifunctional peptide-oligonucleotide conjugates as a novel RNA based therapy for C9orf72 amyotrophic lateral sclerosis

Supervisors: Dr Fazel Shabanpoor, Dr Bradley Turner
Project Site: Florey Institute of Neuroscience and Mental Health
Contact: Dr Fazel Shabanpoor T: 9035 7273 E: fazel.shabanpoor@unimelb.edu.au

Project description: Amyotrophic lateral sclerosis (ALS) is an incurable disease of motor neuron degeneration in the brain and spinal cord, leading to paralysis of voluntary muscles and death by respiratory failure within a median of 3 years from onset(*1*). The expansion of a GGGGCC (G4C2) hexanucleotide repeat in the first intron/promoter of C9orf72 gene has been reported to be the most common genetic cause of familial and sporadic ALS and frontotemporal dementia (FTD)(*2, 3*). A gain-of-function as a results of sequestration of RNA-binding protein by toxic RNA resulting from the expanded G4C2 repeat has also been proposed (*4*). Another causal mechanism is the repeat-associated non-ATG (RAN) translation of the intronic G4C2 repeat expansion in both sense and antisense direction which can generate up to five different dipeptide repeats proteins that can form toxic aggregates (*4*) (Figure. 1A).

The **aim** of this project is to use oligonucleotide-based therapeutic approach to selectively degrade C9orf72 sense and antisense RNAs with repeat expansion (Fig. 1B) The sense and antisense oligonucleotides will be conjugated to a single cell-penetrating peptide for their simultaneous intracellular delivery. Using this novel therapeutic strategy, the level of repeat-expanded C9orf72 RNA transcripts will be reduced. This approach will mitigate the main pathological hallmark of ALS, repeat-expanded RNA and aggregated protein toxicities.

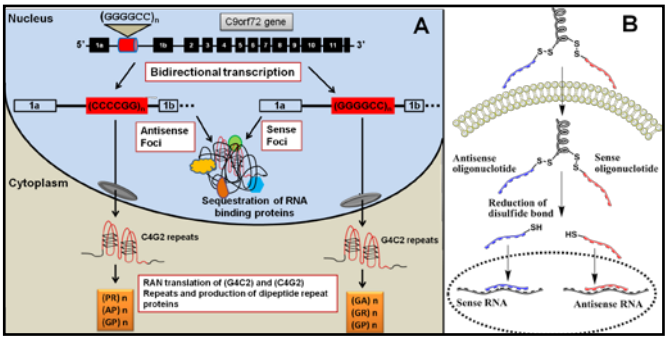


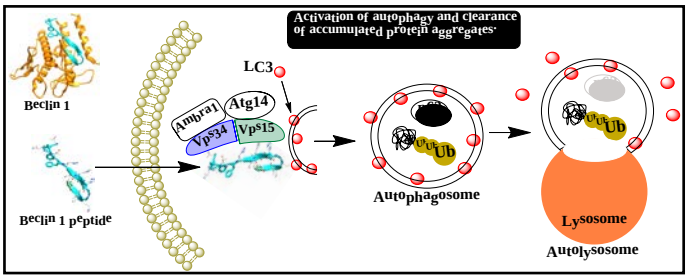
Figure.1: (A) Schematic illustration of bidirectional transcription of chromosome 9 open reading frame (*C9orf72*) gene. Formation of sense and antisense foci and RAN translation of the G4C2 and C4G2 repeats. **(B)** Delivery of sense and antisense oligonucleotides conjugated to a single cell-penetrating peptide for simultaneous knockdown of sense and antisense C9orf72 RNAs with repeat expansion.

Skill acquisition: A broad range of skills will be acquired. Students will be trained in synthesis of peptides, conjugation of peptides to oligonuclotides, HPLC purification, mass spectrometry characterization. Cell culture, RNA extraction, RT-qPCR, protein purification and western-blotting and immunohistochemistry.

168. Development of autophay-inducing peptides as therapy for neurodegenerative diseases

Supervisors: Dr Fazel Shabanpoor, Dr Bradley Turner
Project Site: Florey Institute of Neuroscience and Mental Health
Contact: Dr Fazel Shabanpoor T: 9035 7273 E: fazel.shabanpoor@unimelb.edu.au

Project description: The altered protein degradation and accumulation of misfolded, aggregate-prone proteins is one of the main hallmark of neurodegenerative diseases. Autophagy is an intracellular process which plays a major role in clearance of misfolded/aggregate-prone protein. Motor neurons are in particular very vulnerable to the accumulation of misfolded proteins. Due to their inherent low autophagy capacity, motor neurons can clear their aggregated protein and undergo degeneration (*1*).



Recent identification of an autophagy-inducing peptide (Fig. 1) has provided a platform for development of autophagy-inducing peptide drugs with potential therapeutic application for neurodegenerative diseases (*2*). However, these newly discovered peptides have low efficacy and also poor cell-permeability. They are not capable of crossing cell membrane to reach their target in the cytosol (Fig. 1). Therefore, the **aim** of this project is to **(i)** develop analogues of beclin 1 peptide with higher autophagy-inducing efficacy and **(ii)** to enhance their cell uptake by conjugating them to cell-penetrating peptide.

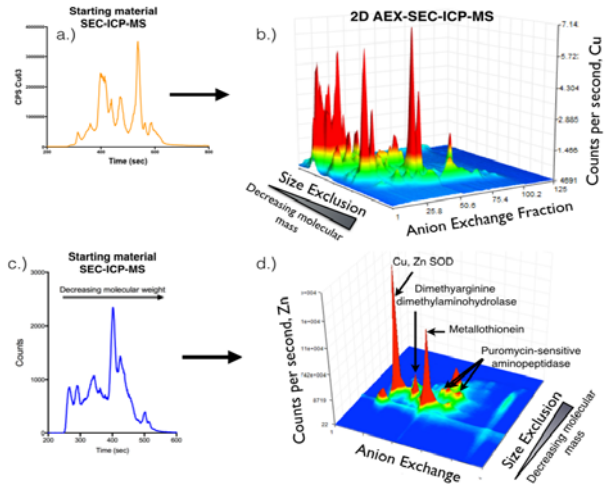
Figure.1: Cellular uptake of Beclin 1 peptide, activation of autophagy and clearance of aggregated proteins.

Skill acquisition: A broad range of skills will be acquired. Students will be trained on synthesis peptides, HPLC purification, mass spectrometry characterization. Cell culture, protein purification, western-blotting, immunofluorescent and immunohostochemistry.

169. Bioanalytical tools to investigate the role of metalloproteins in Alzheimer's disease and amyotrophic lateral sclerosis

Supervisors: Dr. Blaine Roberts
Project Site: Florey Inst. Neuroscience-Melbourne Brain Centre
Contact: Dr. Blaine Roberts blaine.roberts@florey.edu.au

Project description: Trace elements are an essential requirement for life. Transition elements, including copper (Cu), iron (Fe) and zinc (Zn), are used to catalyse a wonderful array of reactions throughout all kingdoms of nature. It is then no surprise that the most complex organ to have evolved, the brain, is a rich source of transition metal chemistry.



However, we still lack the detailed understanding of how transition elements and the biomolecules that rely on them are involved in the function of the brain. Alzheimer's disease and amyotrophic lateral sclerosis both have a rich history indicating a critical role of trace elements Cu, Fe, and Zn in their pathophysiology. My lab has implemented bioanalytical tools that

allow us to investigate the role metalloproteins have in neurodegeneration. This has project will investigate the role of metalloproteins in the neurodegenerative process.

170. Neurodegeneration – Stimulating autophagy to improve intracellular proteostatis in MND

Supervisors: Dr Bradley Turner
Project Site: Florey Institute, Kenneth Myer Building
Contact: Bradley Turner E: Bradley.turner@florey.edu.au T: 9035 6521

Project description: Motor neuron disease (MND) is a neurodegenerative and protein misfolding disorder linked to defects in proteostasis pathways, or protein homeostasis, within affected motor neurons. MND is associated with cytoplasmic accumulation and aggregation of key proteins (SOD1, TDP-43 and FUS) which are implicated in motor neuron death. Strategies that improve proteostasis and clear these misfolded proteins in motor neurons are therefore an attractive candidate therapeutic approach for MND. Our group is interested in autophagy, the main catabolic pathway in neurons that eliminates misfolded proteins, aggregates and damaged organelles by targeting these substrates to lysosomes for digestion.

This project will investigate the therapeutic effect and action of stimulating autophagy in genetic cell culture and mouse models of MND. The effects of newly identified autophagy enhancing drugs will be evaluated on clinical progression, neuropathology and misfolded and aggregated protein load in mouse models of MND. This project will employ transgenic mice, behavioural studies, advanced microscopy, immunohistological and biochemical techniques

171. Neurodegeneration – Development of survival motor neuron gene therapy for spinal muscular atrophy

Supervisors: Dr Bradley Turner
Project Site: Florey Institute, Kenneth Myer Building
Contact: Bradley Turner E: Bradley.turner@florey.edu.au T: 9035 6521

Project description: Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder and the leading genetic cause of infant death. SMA results from inactivation of the survival motor neuron 1 (*SMN1)* gene and retention of the *SMN2* gene, leading to ubiquitous SMN protein deficiency and selective spinal motor neuron loss and muscle weakness. SMN is an essential factor for motor neurons regulating gene splicing and axonal functions important for motor neuron development. SMN gene replacement or upregulation using viral vectors or antisense oligonucleotides show promise in mouse models of SMA.

This project involves testing a novel non-viral SMN gene therapy approach for SMA using immunogenes. Immunogenes consist of motor neuron targeting antibodies complexed with gene expression plasmids. The therapeutic effects of SMN immunogenes will be evaluated on clinical progression, neuropathology, and SMN splicing and axonal functions in a mouse model of SMA. This project will employ knockout mice, behavioural studies, confocal microscopy, immunohistochemical and biochemical techniques

NEUROLOGY/DEMENTIA/ALZHEIMER'S DISEASE

172. Nutrient intake and mental health - *also offered as MBiomedSc*

Supervisors: A/Prof Allison Hodge, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital, UoM, Parkville, Vic 3052.
Contact: Prof 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.

A major benefits of this project is that the nutritional data set has already been collected. The project will suit a candidate with interest in dietary factors and health, as well as media or commercialisation and industry interaction. This project also provides opportunity for publication.

173. Lifestyle Factors and Cognitive Health - *also offered as MBiomedSc*

Supervisors: Dr Helen Brown, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. For example smoking and alcohol consumption 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 factors on cognitive performance and health.

The main opportunities for this project are:

- An opportunity for publication
- Hands-on involvement in participant evaluation
- Work with a large database with over 20 years of lifestyle data
- This project would suit a candidate with an interest in neuropsychology

174. Early detection of cognitive decline and disease - *also offered as MBiomedSc*

Supervisors: Dr Stephen Campbell, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke, E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: The early detection of those likely to develop dementia is essential. Subjective memory complaints have been associated with low mood and subjective cognitive decline. However better selection of those with subjective memory complaints to distinguish the worried well from those with disease is required. Some imaging studies have shown that increased amyloid in those subjective memory complaints despite no objective memory change. In this study we will examine 15 years of cognitive decline with subjective memory complaints and frailty measures, adjusting for mood to examine markers at 45 that predict late life cognitive decline.

Major benefits from this study are:-

- There is opportunity for publication
- You will work with a well-known longitudinal database with over 20 years of data already collected

175. Anxiety and neurodegeneration in preclinical Alzheimer's Disease - *also offered as MBiomedSc*

Supervisors: Dr Stephen Campbell, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke, E: cszoeke@unimelb.edu.au T: 8344 1835

Project description: Anxiety has been shown to have a negative impact on cognitive function, with a strong link between a decline in cognitive performance in later life and increased anxiety levels. Research has demonstrated that increased anxiety was a significant predictor of cognitive decline. However the causal nature of the relationship between anxiety and cognitive decline has not yet been established, with some suggestions that anxiety and depression are instead a reaction to the onset of cognitive decline, although it's likely a bidirectional relationship. In this project, you will examine the relationship between anxiety and neurodegeneration in preclinical Alzheimer's disease in women in later-life.

The project will provide a unique opportunity to work on an Australian dataset with midlife and late-life data collected (data over 20 years), and will suit a candidate with interest in cognition and ageing. There is also opportunity for publication.

176. What causes a neuron to die? Investigating the essential role of selenium nutrition in neurodegenerative disease including Alzheimer's

Supervisors: Dr. Blaine R. Roberts
Project Site: Florey Inst. Neuroscience, Melbourne Brain Centre
Contact: Dr. Blaine R. Roberts blaine.roberts@florey.edu.au

Project description: Selenium is an essential trace element required for normal development. Curiously, out of the entire human genome of ~22,000 genes we only have 25 genes that encode for selenium containing proteins. This indicates an evolutionarily conserved function for selenium proteins. We have recently connected a newly discovered pathway for cell death known as ferroptosis to a key antioxidant selenium enzyme. The enzyme is known as glutathione peroxidase 4 (GPX4) and is a master regulator of ferroptoisis. Ferroptosis was discovered as a new form of cell death in cancer cells. Oxidative stress and selenium nutrition are intimately linked to the incidence and progression of cancer. The brain has a unique requirement for selenium and the levels of selenium in brain tissue are implicated in the pathogenesis of Alzheimer's disease.

This project involves the use of modern cutting edge 'omics' technology (e.g. Proteomics and Metallomics) to investigate the role of selenium containing proteins in human Alzheimer's disease tissue.

177. Acquired epilepsy in Alzheimer's disease *also offered as MBiomedSc*

Supervisors: Prof Patrick Kwan, A/Prof Nigel Jones, Dr Jianziong Chan
Project Site: Department of Medicine (RMH), University of Melbourne
Contact: Prof Patrick Kwan patrick.kwan@unimelb.edu.au

Project description: Alzheimer's disease (AD) patients are 10 times more likely to develop epilepsy compared with age-matched controls. The treatment of recurrent seizures with conventional antiepileptic drugs may exacerbate cognitive decline. There are currently no treatments that prevent epilepsy in AD patients and the pathological basis for the increased risk of epilepsy is largely unknown Understanding the pathomechanisms of epileptogenesis in AD is crucial in identifying effective therapeutic strategies. This will help to prevent the development of epilepsy in this high risk and vulnerable population. This project aims to directly address the mechanisms of epileptogenesis in AD through the study of animal models of AD and acquired epilepsy. The aims will be achieved by subjecting transgenic AD models reflecting the pathological hallmarks to acquired epileptogenesis and treating them novel compounds. The phenotypic changes will be correlated with the molecular and cellular changes in these pathways.

NEUROLOGY/MULTIPLE SCLEROSIS

178. Validation of computerized tools for the assessment of tremor severity in Multiple Sclerosis - *also offered as MBiomedSc*

Supervisors: Dr Anneke van der Walt, Dr Thushara Perera
Project Site: Department of Medicine, Royal Melbourne Hospital and Bionics institute
Contact: Dr Anneke van der Walt, E: anneke.vanderwalt@mh.org.au

Project description: Tremor in MS (MST) is difficult to treat and the development of new interventions is limited by the absence of universal measuring systems. At present, therapeutic outcomes are measured by a variety of clinical rating scales that are subjective and lack sufficient sensitivity. With increasing use of interventional treatments such as Botulinum toxin injections or Deep Brain Stimulation for MST, it has become critical to develop precise measurement instruments.

This project aims to compare two computerized techniques used to measure MS tremor severity. The first is a 3D motion tracker, called TREMBAL, developed by the Bionics institute. The second is a simple joystick-based computer game. The aim of the project is to demonstrate that the simple joystick computer game is equivalent to the 3D motion tracker analysis.

During the project, you will be able to analyse data from MS patients with and without tremor, using both methods. This project requires MATLAB and statistical skills.

179. Defining predictors of clinical and axonal outcomes after optic neuritis in patients in high risk of developing multiple sclerosis - *also offered as MBiomedSc*

Supervisors: Dr Anneke van der Walt, A/Prof Tomas Kalincik
Project Site: Department of Medicine, Royal Melbourne Hospital and Bionics institute
Contact: Dr Anneke van der Walt, E: Anneke.vanderwalt@mh.org.au

Project description: Optic neuritis is a common first manifestation of multiple sclerosis. Although the outcome after optic neuritis is generally good, even minimal residual visual impairment can result in decreased quality of life. In addition, the optic nerve often suffers permanent axonal damage and measurement of this nerve injury could be useful in developing and testing new treatments aimed at neuroprotection in MS. Both functional and structural changes in the optic nerve after optic neuritis can now be measured by sensitive technologies such as optical coherence tomography (OCT), multi-focal visual evoked potentials and advanced MRI techniques.

This project aims to develop a predictive model of clinical and axonal recovery using a hierarchical clustering (decision tree) analysis to determine which factors are the most predictive of outcomes 6 and 12 months after optic neuritis. The data has been collected in a cohort of 44 patients who was studied comprehensively for 12 months after a first episode of optic neuritis.

This project will suit students with interest in statistics and health outcomes research. During the project, you will improve your statistical skills, learning some of the more complex statistical techniques. Knowledge of elementary statistics is a requisite. You will contribute to the evidence-based clinical management of multiple sclerosis.

180. Precision Therapy for Multiple Sclerosis - *also offered as MBiomedSc*

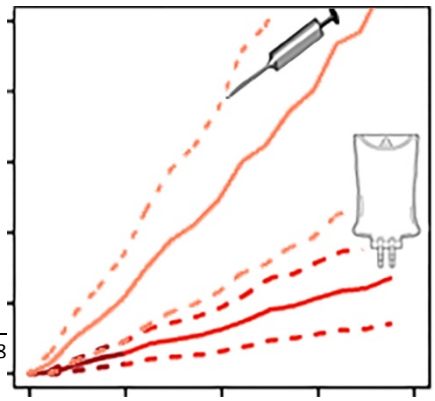
Supervisors: A/Prof Tomas Kalincik
Project Site: CORe, Department of Medicine, Royal Melbourne Hospital
Contact: Tomas Kalincik; E: tomas.kalincik@unimelb.edu.au

Project description: Multiple sclerosis (MS) is the second most common cause of disability in young adults. At the present time, no neuroregenerative or remyelinating therapies are available for clinical use and so the core of multiple sclerosis management lies in preventing episodic inflammation and relapse-related disability accrual.

Prevention of disability in patients with multiple sclerosis has been suboptimal. The most effective of the available immunotherapies mitigate the short-term risk of disability progression by 30-42%. This imperfect result is mainly attributed to the large inter-individual variability in the clinical MS phenotype and the treatment response. From the patients' perspective, the time while exposed to MS disease modifying therapies with a suboptimal individual effect translates into ongoing loss of capacity.

We have recently shown that demographic, clinical and paraclinical information helps predict individual response to disease modifying therapies at the time of their commencement (Kalincik et al., Brain in press). We have designed a prototype of predictive algorithm to help inform selection of therapies for individual patients in clinical practice. The algorithm currently being implemented at 115 MS centres in 33 countries as part of the MSBase collaboration.

This project will further our understanding of individual response to MS therapies. It aims at implementing biological predictors of MS outcomes at the Royal Melbourne Hostpial, including neurofilament light chain, chitinase 3-like 1, volumetric MRI and others. The project will implement these prognostic markers in the recently published prototype of the prognostic models. Finally, it will validate the prognostic value of the enhanced model in independent MS cohorts.



This project will suit students with interest in statistics and health outcomes research. During the project, you will improve your statistical skills, learning some of the more complex statistical

techniques. Knowledge of elementary statistics is a requisite. You will contribute to the evidence-based clinical management of MS.

181. Effectiveness of Immunotherapy in Neuromyelitis Optica - *also offered as MBiomedSc*

Supervisors: A/Prof Tomas Kalincik, Prof Helmut Butzkueven
Project Site: CORe, Department of Medicine, Royal Melbourne Hospital
Contact: Tomas Kalincik; E: tomas.kalincik@unimelb.edu.au

Project description: Neuromyelitis optica (NMO, Devic disease) is a chronic autoimmune disease of the central nervous system. It is characterized by severe relapses involving optic pathways or spinal cord with poor recovery, which often lead to rapid accumulation of neurological disability in young adults. Its pathogensis is centered around antibody- and complement-mediated autoimmune response to aquaporin 4; hence, its therapeutic options differ to those available for multiple sclerosis. The most efficient therapeutic strategies for NMO are yet to be determined.

This project will use the large international cohort of more than 500 patients with NMO from the global MSBase registry to compare different therapies commonly used in NMO and to identify best treatment strategies to control NMO activity.

This project will suit students with interest in statistics and health outcomes research. During the project, you will improve your statistical skills, learning some of the more complex statistical techniques. Knowledge of elementary statistics is a requisite. You will contribute to the evidence-based clinical management of NMO.

182. Monocytes in Multiple Sclerosis- *also offered as MBiomedSc*

Supervisors: Dr Mastura Manif; Prof Terence O'Brien; Prof Helmut Butzkueven
Project Site: Department of Medicine / Royal Melbourne Hospital
Contact: Mastura Monif; E: mmanif@unimelb.edu.au

Project description: Although multiple sclerosis (MS) is considered to be a disease of the central nervous system, there is a vast array of recent data implicating the contribution of the peripheral immune system in disease pathogenesis. In particular, the innate immune system, consisting of monocytes and dendritic cells which form the first line of defence against pathogens are thought to be important in disease initiation. This project will examine the similarities and differences between the peripheral immune system in patients with MS versus healthy controls. The focus will be on monocytes and we will be looking at the various cytokines and chemokine profiles that are generated in the disease state versus control. We will also be looking at the effect of MS disease modifying therapy on monocyte function. Also at the time of disease relapse we will be characterizing various immune signatures and we will aim to decipher how prednisolone (which is a commonly prescribed medication for MS relapse) exerts its effects on the peripheral monocytes. This project will improve our understanding of MS pathogenesis. By characterising monocytes function in MS we hope to develop targeted and effective therapies that combat disease initiation and relapse.

183. Environmental determinants of disability accumulation in Multiple Sclerosis- *also offered as MBiomedSc*

Supervisors: Dr Vilija Jokubaitis; Prof Helmut Butzkueven
Project Site: Department of Medicine / Royal Melbourne Hospital
Contact: Dr Vilija Jokubaitis; E: Vilija.jokubaitis@unimelb.edu.au

Project description: Multiple sclerosis, an autoimmune, neurodegenerative condition, is the most common cause of non-traumatic neurological disability in young adults. There is mounting evidence that, like disease risk, disease outcomes in MS likely involve the interplay between genetic factors and environment. In particular, it has been noted that cigarette smoking is associated with worse MS outcomes in the Swedish population. Here we seek to identify environmental factors that modulate the accrual of disability in MS including smoking behaviour, alcohol consumption, exercise, and vitamin D supplementation.

This project will utilise clinical outcomes data and environmental data derived from the international MSBase Registry to identify environmental determinants of disease outcome.

Outcomes and impact: The identification of environmental factors associated with disease progression risk will

create evidence for appropriate counselling of patients with regards to behavioural changes that can be made to improve their MS outcomes.

Research Environment: The proposed project will be undertaken using the MSBase Registry, an international, prospective, observational MS cohort study. It currently contains over 50,000 longitudinal patient records, with over 230,000-patient years of follow-up.

184. Impact of pregnancy on long-term outcomes in women with multiple sclerosis – assessment of mechanism- ***also offered as MBiomedSc***

Supervisors: Dr Vilija Jokubaitis; Prof Helmut Butzkueven
Project Site: Department of Medicine / Royal Melbourne Hospital
Contact: Dr Vilija Jokubaitis; E: Vilija.jokubaitis@unimelb.edu.au

Project description: Data suggests that pregnancy in women with MS may exert long-term health benefits. Comparisons of women with and without pregnancy (but otherwise equivalent disease at a baseline time point) has shown less accumulation of disability in those who have had pregnancies. Further it has been shown that the risk of developing MS diminishes with increasing parity. The mechanism by which pregnancy protects against MS, and the accumulation of disability has not been established. This project will investigate the biological mechanism by which pregnancy exerts protection against the accumulation of disability.

This is a lab-based project and will involve both genomic and cell-based analyses. This project will also utilise clinical outcomes data and environmental data derived from the international MSBase Registry. Outcomes and impact Determination of the mechanism by which pregnancy impacts on long-term outcomes in women with multiple sclerosis will inform our knowledge of the biology underlying MS, and guide new avenues for therapeutic intervention research. Research Environment

The proposed project will be undertaken in collaboration with other Victorian, NSW, SA and International sites who collaborate with the MSBase Registry, an international, prospective, observational MS cohort study. It currently contains over 50,000 longitudinal patient records, with over 230,000-patient years of follow-up.

185. Determining predictors of post-partum relapse in women with MS- ***also offered as MBiomedSc***

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

Synopsis: Relapse-onset MS is characterised by periods of neurological symptom exacerbation (relapses), and periods of neurological stability (remission). It has been demonstrated that relapse rates diminish during pregnancy in women with relapse-onset MS, being lowest in the third trimester, but then tend rebound post-partum. However, not all women experience post-partum relapses. The determinants of post-partum relapse timing and severity remain poorly understood.

This project will build statistical models utilising data derived from the international MSBase Registry to identify demographic, clinical, therapeutic, paraclinical and environmental determinants of post-partum relapse in women with MS. Findings may inform future relapse biomarker research.

Outcomes and impact: Identification and characterisation of the determinants of post-partum relapse will allow for better stratification of patients at risk of post-partum relapse and will better inform the clinical management of these patients.

Research Environment: The proposed project will be undertaken using the MSBase Registry, an international, prospective, observational MS cohort study. It currently contains over 50,000 longitudinal patient records, with over 230,000-patient years of follow-up.

186. Are women with MS at an increased risk of cervical dysplasia and/or cancer?- ***also offered as MBiomedSc***

Supervisors: Dr Anneke van der Walt; Dr Vilija Jokubaitis
Project Site: Department of Medicine / Royal Melbourne Hospital

Contact: Dr Anneke van der Walt; E: anneke.vanderwalt@unimelb.edu.au

Project description: Disease modifying treatments in MS are used in the majority of patients with relapsing forms of multiple sclerosis. Many of the available treatments are relatively new and the longterm side-effects of these drugs are not known. The risk of cervical dysplasia and cervical cancer due to HPV is increased in immuno-deficient women through a variety of mechanisms. This study aims to collect MS disease specific factors, exposure to disease modifying treatments and risk factors for cervical dysplasia (smoking, vaccination status, sexual partners). Data will be matched with pap smear results stored at the Victorian Cervical Cytology Registry.

The project is suited to a motivated student interested in a clinical project.

NEPHROLOGY

187. Finding genetic mutations in new types of inherited kidney disease – *ONLY offered as MBiomedSc*

Supervisors: Prof Judy Savige and Dr Yanyan Wang
Project Site: Department of Medicine RMH.
Contact: Prof Judy Savige, T 8344 3260, j.savige@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 protoeinuria 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 Savige 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

188. World-wide data sharing to detect neurobiological alterations in MDD: the worldwide ENIGMA Major Depressive Disorder consortium – *also offered as MBiomedSc*

Supervisors: Dr. Lianne Schmaal
Project Site: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne
Contact: D r. Lianne Schmaal, **T**: 0393422886 **E**: lianne.schmaal@unimelb.edu.au

Project description: Major depressive disorder (MDD) is a highly debilitating disorder that has an enormous detrimental impact on patient's life and a high social and economic burden. Many studies have identified structural and functional brain alterations in MDD. However, to date, volumetric and functional brain differences have not always been consistent, which may in part be explained by small sample sizes and differences in methodological and clinical characteristics between studies. To address the limited statistical power of prior studies, the MDD working group within the "Enhancing NeuroImaging Genetics

through Meta-Analysis", or ENIGMA, was initiated a few years ago, see http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/

Figure 1: World map of institutes participating in the ENIGMA MDD working group

The overall aim of the ENIGMA MDD consortium is to establish the neurobiological correlates underlying variation in disease profile and disease course. Currently, 31 research sites from around the world are participating in ENIGMA MDD and share neuroimaging data from >8,000 healthy controls and >2,500 MDD patients.

The student will support ongoing ENIGMA MDD work, which includes development and execution of data processing, quality assurance and statistical analyses protocols for neuroimaging (structural MRI, resting state fMRI and DTI), organising and harmonising databases, communicating with members of the consortium across the world, writing scientific papers on the above topics, and incorporating the research into a PhD thesis. Candidates with an interest in psychology, biological psychiatry and imaging neuroscience are encouraged to apply. Having prior experience with neuroimaging analyses and having strong statistical and computer programming skills is desirable. Further detail about this project is available upon request.

189. Identifying novel subtypes of youth depression and anxoiety using machine learning methods – *also offered as MBiomedSc*

Supervisors: Dr. Lianne Schmaal and Dr. Chris Davey, Dr Ben Harrison
Project Site: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne
Contact: Dr. Lianne Schmaal, **T**: 0393422886 **E**: lianne.schmaal@unimelb.edu.au

Project description: Anxiety and depression, together referred to as internalising disorders, are leading causes of disability in young Australians. Efforts to intervene at an early stage of internalising disorders are critical, but are currently hampered by low diagnostic validity and poor specificity of symptom-based classifications of young people with emerging mental disorders. This can in part be explained by the fact that current symptom-based classifications assume that psychiatric disorders are discrete and dissociable entities, and are agnostic about underlying biological mechanisms. There is a clear need for developing an alternative diagnostic framework that can guide clinicians in the treatment of young people in early stages of mental illness and that can identify young people at-risk for a progressive course of internalising symptoms. This project aims to identify novel subtypes of youth depression and anxiety by integrating neurobiological information with clinical and behavioural data using machine learning techniques.

Figure: Identifying novel subtypes of youth depression and anxiety based on neurobiological and clinical characteristics

This project (or potentially PhD project) will use functional magnetic resonance imaging (fMRI) and data on symptom dimensions. The student will be involved in acquisition of new neuroimaging and clinical data, processing of neuroimaging data and using advanced statistical methods to identify novel phenotypes of youth depression and anxiety. Candidates with an interest in psychology, biological psychiatry and imaging neuroscience are encouraged to apply. Having prior experience with neuroimaging analyses and having strong statistical and computer programming skills is desirable. Further detail about this project is available upon request.

190. Neurobiology of Suicide Thoughts and Behaviours in Youth with Mental Disorders – *also offered as MBiomedSc*

Supervisors: Dr. Lianne Schmaal
Project Site: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne
Contact: Dr. Lianne Schmaal, **T**: 0393422886 **E**: lianne.schmaal@unimelb.edu.au

Project description: Globally, suicide is the second most common cause of death for adolescents and young adults. More adolescents die by suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia, influenza, and chronic lung disease**.** Suicidal thoughts and behaviours (STBs) typically emerge during adolescence, and the incidence of suicide rises sharply from childhood to adolescence (i.e. from 1.2 to 19.2 per 100.000). About 16% of teens think about suicide, and approximately 8% report making an attempt in the past year. To improve preventative intervention treatment for STBs, it is critical to identify neurobiological mechanisms and psychosocial risk factors that confer increased risk. The project aims to elucidate transdiagnostic neurobiological and social mechanisms and trajectories underlying STBs in adolescence, a critical period of development when STBs emerge.

The student will be part of a multidisciplinary international research consortium with extensive expertise in adolescent mental health and STBs, i.e. the Help Overcome and Prevent the Emergence of Suicide (HOPES) consortium. The student will analyse large-scale international datasets from more than 14 countries world-wide and report the results in a scientific paper. The student will help organise and harmonise databases, communicate with members of the consortium across the world. Candidates with an interest in psychology, biological psychiatry, (youth) mental health and imaging neuroscience are encouraged to apply. Having prior experience with neuroimaging analyses and having strong statistical and computer programming skills is desirable. Further detail about this project is available upon request.

191. Neuroimaging in schizophrenia-spectrum disorders – *also offered as MBiomedSc*

Supervisors: Dr.Vanessa Cropley, Dr Tamsyn Van Rheenen, Dr Andrew Zalesky
Project Site: Melbourne Neuropsychiatry Centre , University of Melbourne
Contact: Dr. Vanessa Cropley, **T**: (03)8344 1876 **E**: vcropley@unimelb.edu.au

Project description: The Melbourne Neuropsychiatry Centre (MNC) is a joint centre of Melbourne Health (North Western Mental Health) and The University of Melbourne (Department of Psychiatry). Research at MNC focuses on improving our understanding of the neurobiological processes involved in disorders of the brain and mind.

Our group has established a data resource of structural and functional Magnetic Resonance Image (MRI) scans from neuropsychiatric populations including individuals with schizophrenia, bipolar disorder and non-psychiatric controls. The Psychosis and Developmental Neuropsychiatry Stream of MNC has on offer several projects investigating the neurobiological and behavioural underpinnings of psychotic disorders. These projects will be developed by the student and may utilise brain imaging scans, clinical, cognitive and genetic data previously collected from on-going studies. Example projects include:

- Examining interactions between inflammation, stress and childhood adversity on brain structure and behaviour
- Investigating the impact of neurological soft signs on cortical gyrification, cognition and age of illness onset in schizophrenia
- Characterising brain structural, cognitive and clinical change over 12-months in patients with first-episode psychosis and established schizophrenia and investigating the moderators of such change
- Understanding brain structural influences on component processes involved in verbal declarative memory in bipolar disorder.
- Characterising cognitive intra-individual variability and its links to underlying brain structure in bipolar disorder.
- Investigating structural covariance of the fronto-limbic circuit in bipolar disorder and understanding its relationship to illness duration.

The student will be responsible for the development of the proposal and generation of study hypotheses, data pre-processing and cleaning and statistical analysis of brain imaging scans and associated clinical, cognitive and/or genetic data. The student will be trained in the application of imaging analysis in neuropsychiatry.

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192. Understanding the neural circuitry underpinning emotional information processing in bipolar disorder – *also offered as MBiomedSc*

Supervisors: Dr Tamsyn Van Rheenen, Dr.Vanessa Cropley, Prof Christos Pentelis
Project Site: Melbourne Neuropsychiatry Centre and Dept of Psychiatry, University of Melbourne
Contact: Dr Tamsyn Van Rheenen, **E**: tamsyn.van@unimelb.edu.au

Project description: Bipolar disorder (BD) is a debilitating mental illness of which the underlying mechanisms are still unclear. A better characterization of the neurobiological alterations underpinning bipolar disorder pathophysiology is a crucial next step in developing effective risk identification techniques and treatments that will have an impact on its expression. Currently, abnormal emotion regulation is thought to be a core perpetuator of the disorder's emotional symptoms, but little has been done to examine the early brain mechanisms that are catalyzing this. This PhD project will overcome this by investigating brain connectivity in neural circuits involved in early face and emotion processing in bipolar disorder, and examining the relevance of this connectivity to recognized aberrations in emotion regulation. Key objectives of the PhD are to gain a better understanding of top-down and bottom-up integration of emotional information, and to ascertain the impact that structural brain disturbances have for the coordination of brain function during such information processing. The project is fully funded and data is available from advanced imaging methodologies (fMRI, sMRI, DTI, Magnetoencephalography), which will be used to statistically model the spatiotemporal dynamics of face and emotion processing circuits. The combination of these technologies offers a promising means by which to examine the structural and functional architecture as well as the time course of brain function in bipolar disorder.

Candidates with an interest in psychology, biological psychiatry and imaging neuroscience are encouraged to apply. Further detail about this project is available upon request.

193. A brain based model of anxiety sensitivity in panic disorder – *also offered as MBiomedSc*

Supervisors: A/Prof Ben Harrison, A/Prof Chris Davey
Project Site: Melbourne Neuropsychiatry Centre, Dept of Psychiatry, University of Melbourne
Contact: A/Prof Ben Harrison, **E**: habj@unimelb.edu.au

Project description:

People with panic disorder are characterised by high levels of anxiety sensitivity (AS) – the specific the fear of

bodily anxiety sensations. It is a widely recognized as a core feature of the disorder that contributes to its development, maintenance and treatment. The central aim of this project is to characterise the neural basis of high AS in people with panic disorder and to determine whether it is predictive of longer-term outcomes assessed via naturalistic follow up. Specifically, we will recruit a group of young untreated individuals with panic disorder and assess them with an experimental protocol that combines functional magnetic resonance imaging (fMRI), psychophysiological monitoring and advanced neural systems analysis. We will demonstrate that panic disorder is characterised by a selective functional alteration in the neural appraisal of bodily anxiety sensations and that this alteration will predict poorer clinical outcome over a 12-month period. The significance of this work will be to characterise a core neurobiological feature of panic disorder. Given the existing link between AS and treatment outcomes in this population, our results may inform the discovery of a novel brain systems target with direct relevance to treatment optimisation.

194. Testing a dynamic neural model of impaired medial prefrontal cortex function in youth depression – *also offered as MBiomedSc*

Supervisors: A/Prof Ben Harrison, A/Prof Chris Davey
Project Site: Melbourne Neuropsychiatry Centre, Dept of Psychiatry, University of Melbourne
Contact: A/Prof Ben Harrison, **E**: habj@unimelb.edu.au

Project description: The medial prefrontal cortex is often centrally implicated in the pathophysiology of depression, although it remains unclear how disturbances in its functional interaction with other higher cortical brain regions may distinguish depressed from non-depressed individuals. The aim of this project will be to clarify the role of the medial prefrontal cortex in depression by developing a computational neural model of dynamic functional interactions based on the analysis of resting-state brain functional magnetic resonance imaging (fMRI) data. This data has been recently collected and involves large samples of young people with moderate-to-severe depressive illness (N=120), and demographically matched healthy control participants (N=120). Associations with neural model parameters and the clinical characteristics of the depressed participants will be examined in detail.

195. Human brain systems supporting the flexible control of fear – *also offered as MBiomedSc*

Supervisors: A/Prof Ben Harrison, A/Prof Chris Davey
Project Site: Melbourne Neuropsychiatry Centre, Dept of Psychiatry, University of Melbourne
Contact: A/Prof Ben Harrison, **E**: habj@unimelb.edu.au

Project description: The flexible control of fear in humans is supported by large-scale brain systems that mediate the learned discrimination of threat and safety signals. Within these systems, functionally opposing roles have been identified for subregions of the medial frontal cortex consistent with the selective processing of positive versus negative affective stimuli. The current project will test key predictions regarding the neural dynamics of these brain systems and subregions in relation to their functional interactions. It will examine how these relationships

i) shape individual differences in the affective processing of threat and safety signals, and
ii) are influenced by state and trait measures of anxiety risk.

A large non-clinical sample of participants (18 to 45 years of age) has been recruited and assessed with functional magnetic resonance imaging (fMRI) and an experimental task designed to evoke fear and safety learning. Functional neural network interactions will be examined via dynamic causal modeling. This study will lay the foundations for an advanced neural systems account of adaptive fear processing in the human brain and will have direct implications for the neuroscientific study of clinical anxiety disorders, including their treatment.

196. Mapping the Human Schizophrenia Connectome – *also offered as MBiomedSc*

Supervisors: Dr Andrew Zalesky (Melbourne Neuropsychiatry Centre), Dr Alex Fornito (Monash Biomedical Imaging), Dr Luca Cocchi (Queensland Brain Institute), Prof Christos Pantelis (Melbourne Neuropsychiatry Centre)
Project Site: Melbourne Neuropsychiatry Centre
Contact: Dr Andrew Zalesky: azalesky@unimelb.edu.au

Project description: This project aims to comprehensively map the entire human connectome in schizophrenia. The student will complete one of the largest clinical connectome mapping studies undertaken in the world by analysing high-quality brain imaging data in more than 330 individuals with schizophrenia

provided by the *Australian Schizophrenia Research Bank* (ASRB). The ASRB is the largest brain research project ever undertaken in Australia. This project will apply advanced fibre tracking algorithms to the diffusion-MRI brain imaging data acquired in each patient, with the goal of comprehensively mapping all disrupted connections comprising the entire schizophrenia connectome. VLSCI computational resources may be utilised for this purpose.

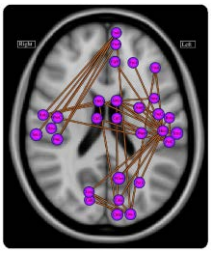

Figure: *Disruptions to functional brain connectivity in schizophrenia.*

197. Human Connectome Bioinformatics – *also offered as MBiomedSc*

Supervisors: Dr Andrew Zalesky, Prof Christos Pantelis
Project Site: Melbourne Neuropsychiatry Centre
Contact: Dr Andrew Zalesky: azalesky@unimelb.edu.au

Project description: The connectome refers to a comprehensive network description of the brain's internal wiring. Advances in magnetic resonance imaging (MRI) have enabled reliable mapping of the large-scale connectome in the living human brain. Comparing the human connectome between healthy and diseased brains has identified disease-specific anomalies in brain circuitry that may provide novel therapeutic targets and potential biomarkers to assess risk and predict patient outcomes. This project aims to develop and apply tools that capitalise on these advances.

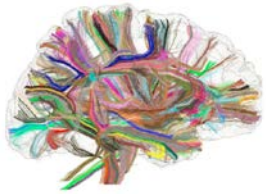

Figure: The human connectome mapped using diffusion-MRI and tractography

198. Effects of oxytocin genetic variants on brain and behavior in schizophrenia – *also offered as MBiomedSc*

Supervisors: Dr Cali Bartholomeusz (Orygen); Dr Chad Bousman (Melbourne Neuropsychiatry Centre); Prof Cyndi Shannon-Weickert (Neuroscience Research Australia); Prof Christos Pantelis (Melbourne Neuropsychiatry Centre)
Project site: Orygen, The National Centre of Excellence in Youth Mental Health and Centre for Youth Mental Health, 35 Poplar Road, Parkville; and Melbourne Neuropsychiatry Centre, The Alan Gilbert Building, 161 Barry Street, Carlton South.
Contact: Dr Cali Bartholomeusz Email: barc@unimelb.edu.au

Project Description: Oxytocin (OXT), a neurohypophysial hormone and neurotransmitter, is widely recognized as having an important role in human social cognition and prosocial behavior. These domains, which contribute to general social functioning, are significantly impaired in schizophrenia. Variation in OXT single nucleotide polymorphisms (SNPs) and OXT receptor (OXTR) SNPs have been linked to risk for schizophrenia. In addition, several of these SNPs have been associated with the severity of psychopathology, as well as social cognitive impairment in schizophrenia. A number of neuroimaging studies support a link between structural differences in social brain areas and OXTR variants in the healthy population, however no study has yet examined the relationship that these variants have to brain volumes in schizophrenia.

Aims: To examine the relationships between genetic load for previously identified OXT/OXTR SNPs and cognition, symptoms, and social functioning, in Australians with schizophrenia and healthy control participants. We will also investigate whether these relationships are linked to and potentially mediated by, brain volumes, particularly of the amygdala, nucleus accumbens and medial prefrontal/anterior cingulate cortices.

Method: Pre-existing data from the Australian Schizophrenia Research Bank will be utilised for the current study. Correlation statistics, and mediation analyses where appropriate, will be conducted to explore the associations between genetic variants and outcome measures and brain volumes. ANOVAs will also be conducted to explore differences between patients and healthy controls.

Outcome: This project will increase our understanding of how variants in key OXT and OXTR SNPs are related to risk for schizophrenia, symptomatology, cognition and general social functioning in an Australian sample

199. MRI volumetry and shape analysis in frontotemporal dementia and schizophrenia

Supervisors: Dr Dennis Velakoulis and Dr Mark Walterfang
Project Site: Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital

Contact: Dr Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.org.au

Project Description: It has been well recognised for over a century that some patients with schizophrenia develop a dementia but the nature of this dementia has remained unclear. Recent clinical, neuropathological and genetic studies have identified a previously unrecognised association between chronic schizophrenia and frontotemporal dementia. This project aims to examine whether the volume and shape changes identified in schizophrenia are quantitatively and qualitatively similar to patients with a frontotemporal dementia. In addition to demographic and diagnostic information a subset of the subjects have neuropsychological and bedside screening cognitive testing which can be correlated with brain structural volumes and shape.

Aims: To estimate and compare brain structure volume and shape in an existing database of MRI images of patients with chronic schizophrenia and frontotemporal dementia compared to control subjects.

Methods: Specific regions of interest to examine would include:

- Frontal and temporal lobes
- Orbitofrontal / dorsolateral / medial frontal cortex
- hippocampus
- Insula cortex
- Superior temporal gyrus

Depending on the region of interest the project would require the learning of methods for analysing the region and developing a reliable method for this assessment.

Outcome: To assess and compare the nature and pattern of brain changes in chronic schizophrenia and FTD.

200. Characterisation of physiological stress responses in patients with depression and epilepsy - *also offered as MBiomedSc*

Supervisors: Dr Dennis Velakoulis, Dr Chris Turnbull and Prof Terence 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.

201. Functional disconnections and the pathophysiology of psychosis - *also offered as MBiomedSc*

Supervisors: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville
Contact: A/Prof 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 dysfunction 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. Available as Honours, Masters or PhD projects

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

202. Antidepressants in epilepsy *also offered as MBiomedSc*

Supervisor: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: A/Prof Nigel Jones E: ncjones@unimelb.edu.au

Project description: Patients with epilepsy also frequently suffer from psychiatric disorders such as depression. As a consequence, many patients receive antidepressants to mitigate these mood disorders. While these are generally effective, the influence of antidepressants on the severity of the epilepsy in patients, and on the risk of developing epilepsy, has been little studied. Our provocative recent data suggest that antidepressants actually promote the development of epilepsy, which could have major implications for how these drugs are prescribed to patients. Using a range of animal models, including post-traumatic epilepsy, this project seeks to characterise and understand the influence of antidepressants such as Prozac on epilepsy development.

Skills: Small animal handling; animal models of epilepsy; models of traumatic brain injury; small animal surgery and EEG recording; MRI, animal behaviour and cognition, molecular biology techniques, such as real-time qPCR, Western blotting; histology, including immunocytochemistry

203. Temporal lobe epilepsy, the HPA axis and depression - *also offered as MBiomedSc*

Supervisor: Prof Terence O'Brien, Dr Dennis Velakoulis,
Project Site: Department of Psychiatry and Medicine Royal Melbourne Hospital
Contact: Terence O'Brien T: 8344 5490 E: obrientj@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.

204. Does stress contribute to epilepsy? - *also offered as MBiomedSc*

Supervisor: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: A/Prof Nigel Jones T: 9035 6402 E : ncjones@unimelb.edu.au

Project description: 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.

205. Does stress cause seizures? - *also offered as MBiomedSc*

Supervisor: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: A/Prof Nigel Jones T: 9035 6402 E : ncjones@unimelb.edu.au

Project description: Many patients with epilepsy report that the most commonly experience seizures when they are stressed. However, assessment of a patient's stress level is very subjective, and difficult to control for. This project will use animal models of epilepsy to establish A) whether acute stress does indeed increase the probability of seizures from occurring, and B) determine the physiological mechanisms of how this occurs.

***Skills*:** Small animal handling and neurosurgery (electrode implantations), experience with models of stress and epilepsy, assessment of stress hormones

206. Role of specific interneuron types in cognitive behaviour - *also offered as MBiomedSc*

Supervisor: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: A/Prof Nigel Jones T: 9035 6402 E : ncjones@unimelb.edu.au

Project Description: How does the brain synchronise neural activity to facilitate cognitive processes to occur? This project combines transgenic and DREADD technologies with advanced cognitive testing in mice to assess the requirement of specific interneuron subtypes, including those expressing Parvalbumin, Cholecystokinin, and Somatostatin, to coordinate neuronal cell firing required for complex behaviours such as working memory and attention. Combined with high-resolution electrophysiological recordings, these studies will characterise the role of these cell types in cognitive processing.

Skills: small animal surgery, cognitive behavioural analysis, viral delivery, DREADD technology, immunocytochemistry, in vivo electrophysiology, transgenic technology.

207. NMDA receptor antagonists and cognitive disfunction - *also offered as MBiomedSc*

Supervisor: A/Prof Nigel Jones
Project Site: Department of Medicine (RMH), MBC Neurosciences Building, Parkville.
Contact: A/Prof Nigel Jones T: 9035 6402 E : ncjones@unimelb.edu.au

Project Description: NMDA receptors are ion channels involved in neural communication. Deficits in the signalling through NMDA receptors is associated with learning and memory impairments, although the specific mechanisms underlying this consequence is not clear. Here, we attempt to isolate the specific cell types which, when suffering from NMDA receptor hypofunction, lead to higher-order cognitive dysfunction, such as

impairments in working memory. We will combine transgenic mouse technologies to remove NMDA receptors from specific cell types, and observe the resultant effects on cognitive behaviour.
Skills: small animal surgery, cognitive behavioural analysis, viral delivery, immunocytochemistry, in vivo electrophysiology, transgenic technology.

208. High Frequency Brain Wave Patterns in a Rodent Model of Schizophrenia

Supervisors: Dr Chris French, A/ProfAnthony Hannan, A/Prof Nigel Jones, Prof Terence O'Brien
Project Site: Department of Medicine RMH, MBC Neurosciences Building, Parkville
Contact: Chris French frenchc@unimelb.edu.au

Project description: High frequency ("gamma") brain wave activity has been associated with higher cognitive activity in humans and animals, and has shown to be abnormal in psychosis and schizophrenia. Phospholipase C-β1 (PLCβ1) is an enzyme that is altered in human schizophrenia and a PLCβ1 knockout mouse displays deficits (locomotor hyperactivity, sensorimotor gating and cognitive impairment) homologous to those seen in schizophrenia. Remarkably, some of these deficits can be improved with antipsychotic drugs that are efficacious in humans.
The aim of these experiments is to characterize the gamma-frequency brain wave patterns of normal and PLCβ1 knockout mice, and to investigate whether the behavioural effects of antipsychotic drugs can be correlated with brain wave patterns.

These experiments are likely to lead to a better understanding of the functional abnormalities that lead to schizophrenia in humans and to suggest new and better forms of treatment.

209. Estrogen, antipsychotics and schizophrenia – *also offered as MBiomedSc*

Supervisors: Dr Andrea Gogos and Dr Snezana Kusljic
Project Site: Hormones in Psychiatry Laboratory, The Florey Institute of Neuroscience and Mental Health
Contact: Dr Andrea Gogos E: andrea.gogos@florey.edu.au and
Dr Snezana Kusljic E: skusljic@unimelb.edu.au

Project description: A role for sex hormones in the development of schizophrenia has been hypothesized to explain the observed sex difference in the age-of-onset, with women presenting symptoms on average 3-4 years later than in men. Interestingly, clinical trials have shown that adjunctive estrogen treatment in women with schizophrenia can accelerate the beneficial effect of the antipsychotic treatment. Our laboratory aims to study the role of estradiol, progesterone and testosterone in modulating symptoms of schizophrenia and depression. We currently use both in vivo and in vitro rodent models, as well as post-mortem CNS tissue. This project aims to investigate the expression of estrogen receptors in the brain using one of the approaches commonly-used in our laboratory: radioligand receptor binding, western blot, or in situ hybridization.

DEVELOPMENTAL PSYCHOBIOLOGY @ THE FLOREY

210. Early life stress and memory development

Supervisors: Dr Heather Madsen Co-supervisor: Dr Jee Hyun Kim
Project Site: Florey Institute, Parkville
Contact: heather.madsen@florey.edu.au

Project description: Early life experiences play a pivotal role in shaping personality and psychosocial functioning into adulthood. For example, early life adversity in humans is associated with increased risk of developing mental illnesses such as depression and anxiety. Given the importance of these first few years of life, it is interesting that most adults fail to recall autobiographical events from their early childhood years. Infantile amnesia is the term used to describe this phenomenon of accelerated forgetting during infancy, and it is not unique to humans. In fact, infantile amnesia has been observed in every altricial species examined; that is, animals that undergo extensive post-gestational development.

Many investigations into infantile amnesia have used Pavlovian fear conditioning in rats as a model of learning and memory. While adult rats exhibit excellent memory retention following just a single conditioning episode, infant rats rapidly forget fear associations over short intervals. Recently it has been shown that exposure to

early life stress improves retention of learned fear in infant rats. The aim of this project is to investigate the neurobiological changes that underlie this early transition to adult-like memory.

211. Regulation of emotional memory across development

Supervisors: Dr Despina Ganella, Co-supervisor: Dr Jee Hyun Kim
Project Site: Florey Institute, Parkville
Contact: despina.ganella@florey.edu.au

Project description: Most anxiety disorders emerge during childhood, and individuals with childhood onset express more severe symptoms than do individuals who have adult onset. In fact, there is growing recognition that mental disorders may actually be developmental brain disorders and, as such, treatment strategies should focus on the young population. Currently, the effective treatments for anxiety disorders are cognitive-behavioural therapies that rely on inhibition of emotional memory. This project will examine inhibition of emotional memory throughout development using Pavlovian fear conditioning as a model of anxiety disorders in rats.

212. Latent inhibition in adolescent rats

Supervisors: Dr Jee Hyun Kim
Project Site: Florey Institute, Parkville
Contact: E: jee.kim@florey.edu.au

Project description: Ever wondered why individual differences exist in developing an anxiety disorder following a similar traumatic experience (e.g., a car accident)? It turns out that having previous related experiences before the traumatic event can play a huge part. For example, a veteran driver with many years of safe driving experience will be less likely to develop an anxiety disorder following a car accident, compared to a novice driver who has not had much prior safe driving. This protection from forming fear memories due to previous safe experiences is called 'latent inhibition', and this process shares similar mechanisms to 'extinction' that refers to safe experiences following the traumatic event. In the present project, we'd like to investigate latent inhibition in adolescent vs adult rats, as we know that extinction is different across the two ages. Examining latent inhibition in adolescence may help us to understand why adolescence is a particularly vulnerable age to experience anxiety disorders.

NEUROVASCULAR

213. Imaging predictors of neurological recovery post acute stroke intervention

Supervisors: A/Prof. Bernard Yan, Prof. Peter Mitchell, A/Prof. Rick Dowling
Project Site: Royal Melbourne Hospital
Contact: Bernard.Yan@mh.org.au

Project Description: Stroke is the second leading cause for death and the leading cause for disability worldwide. It accounts for significant financial burden up to $5 billion on health care costs associated with stroke in Australia in 2012 alone. Rapid treatment with thrombolysis (s clot busting medication), within 4.5 hours of ictal onset, increases the chance of blood flow restoration to the ischemic area and decreases the risk of disability and dependence. This benefit diminishes and approaches parity at approximately 6 hours from stroke onset. CT scan is a widely used imaging modality for the initial evaluation of stroke. The Alberta Stroke Program Early CT Score (ASPECTS) tool was developed to provide a standard CT scan with a reproducible grading system. It is a semi-quantitative method of defining infarct extent in the middle cerebral artery (MCA) territory.[11] However, very few studies have examined the impact of time on outcome as adjudicated by ASPECTS. The aim of this retrospective analysis study on an existing prospective database is to assess the impact of time on ASPECTS score and its correlation to functional outcome at 3 months after an acute ischemic stroke. We hypothesize that, in patients with acute ischaemic stroke treated with IV tPA, the predictive capacity of ASPECTS score of clinical outcome increases with time from stroke onset.

214. Monocytes, platelets and P2X7R: unravelling the immunological cascade in setting of acute stroke

Supervisors: Dr Mastura Monif, A/Prof Bruce Campbell, Prof Peter Mitchell, Prof Terence O'Brien
Project Site: Royal Melbourne Hospital
Contact: E: mmonif@unimelb.edu.au

Project Description: Ischemic stroke is a major cause of morbidity and mortality in the developed as well as developing countries. Immune and inflammatory responses are critical factors in the pathophysiology of acute ischemic damage as well as the chronic sequelae. Ischemic stroke is characterized by obliteration of blood flow to a region of the brain as the result of a blood clot. The occluding clot / thrombus is generally fibrin and platelet rich in nature. Vessel occlusion and the associated hypoxia inevitably leads to neuronal damage, with associated activation of glial cells, called microglia. Microglia are the immunomodulatory cells of the central nervous system. Once activated microglia are known to release a myriad of bio-active substances (cytokines and chemokines) locally and into the systemic circulation. These bio-active substances can have short-lived as well long-lasting focal and systemic effects. Also in the ischemic region of the brain, there is infiltration of peripheral macrophages, monocytes and neutrophils. This bidirectional communication between the injured brain and the peripheral immune system can control the progression of stroke pathology as well as tissue repair.

Previously we have shown that an ATP sensing receptor, P2X7R is crucial in driving microglial activation in mice. Others have shown that the same receptor is important in release of microparticles from platelets, which can have implications in setting of stroke. Microparticles are small (200-800nm) structures that contain thrombogenic substances as well as cytokines and chemokines.

For this project, we hypothesize that at the time of acute stroke there is increased platelet microparticle release into the circulation and this release is mediated by P2X7R. Also we postulate that monocytes in the periphery at the time of acute stroke have an 'activated' phenotype capable of releasing various cytokines / chemokines which can alter the clinical course of the stroke patient. With ethical approval and consent, patients who are having an acute ischemic stroke are recruited into this study. If clinically indicated some patients would undergo clot retrieval (as part of their hospital stroke treatment) where the blood clot that is occluding their artery is retrieved with a catheter. For this project we will be analysing the cellular composition of the blood clot. In particular we will be focusing on the presence of monocytes/macrophages and expression and function of P2X7R in these cells. In addition we will characterize platelet microparticles at the time of acute stroke versus one month post stroke. We will also gather clinical and radiological data about each patient to correlate with the laboratory findings. Our research would shed light on the cross talk between the peripheral and central immune system at the time of acute stroke. Better understanding of this would help us to devise targeted therapies that can deal with platelet aggregation, monocyte/microglial activation and hopefully preserve neuronal function in the acute and chronic setting.

215. Acute stroke rescue: clot retrieval. Does imaging characteristics predict the histopathology of clot composition? - *also offered as MBiomedSc*

Supervisors: A/Prof Bernard Yan, Prof Peter Mitchell, A/Prof Richard Dowling
Location: Department of Neurology &Department of Radiology, Royal Melbourne Hospital
Contact: A/Prof 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 by clot(s). The clinical consequences result from acute neuronal failure secondary to precipitous decrease in arterial perfusion. Apart from intravenous thrombolytics, mechanical clot retrieval holds promise as an effective means to reopen blocked arteries. However, the success clot retrieval depends partly on clot composition. It is known that clots undergo pathological change from red-cell dominant, then to fibrin dominant and finally to organized fibrin strands. It is thought that clots with organized fibrin are the most resistant to mechanical retrieval. The difficulty is that up till now, there are no reliable methods to judge clot composition prior to mechanical retrieval. In this project, we aim to employ advanced CT angiogram imaging pre-procedure and to correlate the imaging characteristics with histopathological examination of clots. The implication of the findings is that we may be able to more accurately predict the success rate of clot retrieval and to triage patients prior to invasive therapies.

Research plan: Human research ethics committee approval has been obtained. Acute stroke patients eligible for acute clot retrieval will be recruited prospectively into the study. Imaging modalities include plain CT, CT angiogram and CT perfusion (this is part of standard stroke treatment protocol). Clot retrieval will be performed by RMH neurointerventionists. Clot samples will be sent for standard H & E staining and immunohistochemisty 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.

216. Intensive continuous monitoring of motor function in acute stroke: development of a broadband-based wearable motion detector (STROKE WATCH 3) - *also offered as MBiomedSc*

Supervisors: A/Prof Bernard Yan, Prof Stephen Davis
Project Site: Department of Neurology, Melbourne Brain Centre at Royal Melbourne Hospital
Contact: A/Prof Bernard Yan, Neurointerventionist, Neurovascular Research Group.
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 revascularization (either by mechanically retrieving the clot or by intravenous agents) 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) but about 30% will deteriorate. The monitoring of motor recovery is by clinical observation is critical in the management of stroke patients. Patients who exhibit deterioration may benefit from urgent 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 (STROKE WATCH 3) which allows for continuous monitoring of motor recovery in acute stroke patients. 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 STROKE WATCH 3 system in other neurological diseases e.g. Epilepsy. BENCH TO BEDSIDE - MEDICAL RESEARCH University of Melbourne at Royal Melbourne Hospital Honours/MBiomedSc Projects 2017 64 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 function of stroke patients. We hypothesize that the motion detector (STROKE WATCH 3) is able to better detect motor function fluctuations compared to standard clinical observations. Inclusion criteria: acute stroke patients admitted to RMH Stroke Care Unit. Methods: study subjects will wear the STROKE WATCH system on each limb for 24 hours. Accelerometry raw data will be continuously transmitted

OPHTHALMOLOGY

217. Which genes are affected in structural renal disease and renal complement diseases? – *also offered as MBiomedSc*

Supervisors: Prof Savige and A/Prof Deb Colville
Project Site: Department of Medicine, Royal Melbourne Hospital
Contact: Prof Savige on 8344 3260 or j.savige@unimelb.edu.au

Project description: The genes for many forms of inherited renal disease are still unknown. We have several families with inherited disease in whom we will try to identify the abnormal genes. This involves carefully characterizing clinical features, collecting DNA, undertaking exomic sequencing, and checking for mutations in candidate genes. Any possible mutation will then be confirmed in other affected family members by DNA sequencing.

Techniques to be used and skills acquired: This project involves patient contact, a small amount of lab work and how to interpret DNA sequence abnormalities.

Feasibility: All the techniques for this project are already available in our laboratory.

218. Small vessel disease as a marker for poorly controlled hypertension – *also offered as MBiomedSc*

Supervisors: Prof Savige, A/Prof Deb Colville
Project Site: Department of Medicine, Royal Melbourne Hospital
Contact: Prof Savige on 8344 3260 or j.savige@unimelb.edu.au

Project description: This project involves taking retinal photographs in patients with hypertension relating any small vessel disease in the retina blood pressure control. This study is to investigate whether retinal photographs might be useful in predicting blood pressure control.

Techniques to be used and skills acquired: This project involves patient contact, poor blood pressure control learning how to take retinal photographs and how to interpret retinal abnormalities.

Feasibility: Many of the medical students who have undertaken similar projects during a research year have achieved a publication from their work 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).

PHARMACOGENETICS AND PRECISION MEDICINE

219. Wearable devices for non-invasive, ambulatory seizure monitoring and prediction - *also offered as MBiomedSc*

Supervisors: Prof. Patrick Kwan, Prof. Terence O'Brien
Projects site: Department of Medicine (RMH), University of Melbourne
Contact: Prof Patrick Kwan, E: patrick.kwan@unimelb.edu.au

Project description: The development of reliable, accurate, non-invasive methodologies for continuous, long-term seizure monitoring is a critical part of the precision medicine approach in epilepsy management. While the gold standard for diagnosing and detecting seizures remains inpatient simultaneous EEG and video recording, it is costly and impractical for extended use outside the hospital setting. Conventional outpatient seizure monitoring relies on self-completing seizure diary which is inexpensive but highly inaccurate. There is a need for novel technologies that combine low cost, non-invasiveness with reliability for extended seizure monitoring. This project aims to develop an integrated wearable sensor system for the clinical management of seizures in patients with epilepsy. The device will be tested in patients admitted for inpatient video-EEG monitoring.

220. Stroke and epilepsy a bi-directional relationship? - *also offered as MBiomedSc*

Supervisors: Prof. Patrick Kwan, Prof. Bernard Yan
Projects site: Melbourne Brain Centre, The Royal Melbourne Hospital
Contact: Prof. Patrick Kwan, E: patrick.kwan@unimelb.edu.au;
A/Prof. Bernard Yan, E: Bernard.Yan@mh.org.au

Project description: Stroke is one of the leading causes of acquired epilepsy in industrialised countries. Seizures are a major complication in stroke survivors and are associated with increased mortality and poorer functional recovery. Patients with post-stroke seizures have increased risk of in-hospital complications, leading to prolonged hospitalisation. Conversely, patients with epilepsy also have an increased risk of de novo stroke, the reasons for which are unclear. Utilising our access to local and international databases, this project aims to identify the biomarkers, including clinical, genomic, and radiological factors predictive of post-stroke epilepsy and post-epilepsy stroke. The findings will shed new lights in understanding the patho-mechanisms of these disorders. The project will be based on the expanding RMH stroke database with several thousands of patients recruited, as well as the epilepsy database of new onset patients.

221. Development of a low cost, point-of-care diagnostic platform

Supervisors: Prof Patrick Kwan, Prof Stan Skafidas. Dr Jianxiong Chen
Project sites: Department of Medicine (Royal Melbourne Hospital), Centre for Neural Engineering
Contact: Prof Patrick Kwan, Department of Medicine (RMH)
E: patrick.kwan@unimelb.edu.au

Project description: Point-of-care (POC) testing is the testing at the site of patient care. It is done on patients conveniently and immediately allowing patients and doctors to receive the results quicker, making faster clinical decisions. The aim of the project is to develop a novel rapid, ultrasensitive real-time POC platform targeting molecules in blood or saliva. This will be integrated on a single chip platform. Our study is divided into 3 main projects aimed at developing and validate 1) DNA-based and 2) protein base, 3) whole cell detection, from whole blood and saliva. DNA-based study will includes developing specific DNA amplification through blood/saliva and its detection through biosensors. Protein and whole cell base study will involve detection of specific protein or white blood cells in blood or saliva through functionalised biosensor. This will be integrated on a single chip platform to facilitate a small, low cost and reliable test device.

222. Autoimmune Encephalitis – a clinical project. Which anti-epileptic is most effective in controlling autoimmune encephalitis associated seizures?

Supervisors: Dr Mastura Monif, Prof Terence O'Brien, Prof Helmut Butzkueven, Dr Katherine Buzzard
Project sites: Department of Medicine (Royal Melbourne Hospital)
Contact: Dr Mastura Monif, Department of Medicine (RMH)
E: mmonif@unimelb.edu.au

Project description: Autoimmune encephalitides are a diverse yet rare group of neurological conditions presenting with acute or subacute confusion, behavioural change, cognitive deficits and seizures. The morbidity and mortality associated with autoimmune encephalitis can be quite high with major implications to the patients as well as their family members. A proportion of autoimmune encephalitis cases are mediated by autoantibodies directed against synaptic proteins in the central nervous system. Patients with autoimmune encephalitis can present with various types of seizures. The clinical features (semiology) of these seizures and the associated EEG (electroencephalogram) abnormalities are not fully understood. Also it's unclear if escalating immunotherapy versus antiepileptic medication can be helpful in treating seizures associated with these autoimmune conditions. The aim of this study is to do a retrospective analysis of cases with autoimmune encephalitis from Royal Melbourne Hospital. We hope to characterize some of the clinical features of autoimmune encephalitis, including the semiology of seizures as well as associated laboratory and brain imaging abnormalities. Using medical records from the hospital, we will search for all the cases of 'autoimmune encephalitis' that have been previously diagnosed (meeting diagnostic criteria as per Graus et al Lancet, 2016). Various patient demographics, clinical presentation, type of seizure, EEG abnormalities, laboratory investigations (inflammatory markers, biochemistry), MRI findings, cerebrospinal fluid analysis, and any other relevant investigation (i.e., CT scans, PET scans) will be recorded. The main aim of this project is to decipher which anti-epileptic medication was associated with better response in controlling seizures? Also the effect of escalating antiepileptic therapy versus immunotherapy (therapies targeting the immune system, i.e., steroids, intravenous immunoglobulin, steroid sparing agents, plasma exchange) will be documented. Records of follow up appointments (outpatients) will be analysed to identify if the patient's condition improved, remained stable or deteriorated. This project is entirely clinical and it is designed to improve our understanding of seizures associated with autoimmune encephalitis especially focusing on treatment modalities and identifying the most effective therapies.

223. Immune self-reactivity triggered by carbamazepine-modified HLA-peptide repertoire - *also offered as MBiomedSc*

Supervisors: Prof Patrick Kwan, Dr Nicole Mifsud
Project Site: Department of Medicine (RMH), University of Melbourne, Department of Biochemistry & Molecular Biology, Monash University
Contact: Prof 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 and HLA-A*31:01 are associated with severe skin reactions caused by certain antiepileptic drugs, but little is known about the underlying mechanisms of these associations. Recent research 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 the interactions between antiepileptic drugs and these HLA alleles.

224. HLA and its association with skin rashes and drug induced hepatitis: The role of pharmacogenetics to predict anti-epileptic drug side-effects - *also offered as MBiomedSc*

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;
Prof 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 hypersensitive reactions, have not yet been identified. Understanding why responses vary has the potential to improve the safety and effectiveness of medical treatment for various conditions.

This project will utilize an international unique cohort of more than 400 patients who have been prospectively enrolled and followed following starting treatment with an AED for the first time. The HLA profiles of patients who developed hypersensitivity reactions will be compared with those who took the same drug but did not develop any such reactions. The goal of this research is to eventually allow the choice of medication to be tailored to an individual's specific genetic profile.

Skills to be learned: Human genomics, immunogenetics, bioinformatics, clinical phenotyping, multivariate statistics.

225. Pharmacogenetics: do mutations in CYP 2C19 alter the clinical effectiveness of clopidogrel in patients with cerebrovascular disease? - *also offered as MBiomedSc*

Supervisors: A/Prof Bernard Yan, Prof Peter Mitchell, A/Prof Richard Dowling
Location: Department of Neurology & Department of Radiology, Royal Melbourne Hospital
Contact: A/Prof Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital,
T: +61 3 9349 2477 / F: +61 3 9349 4489, E: 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, prasurgrel 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 Prof 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 clopidgrel 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.

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

Supervisors: Prof Terence O'Brien, Prof Frank Vajda
Epilepsy and Neuropharmacology Group, The Department of Medicine: RMH
Project Site: The Department of Medicine (RMH)
Contacts: Terence O'Brien E: obrientj@unimelb.edu.au;
Frank Vajda E: vajda@netspace.net.au;

Project Description: Identify genetic markers that predict the risk of valproate-induced birth defects. It is 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 particularly 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 soon, 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. Clinical research utilizes a cohort of >2000 pregnant women enrolled in the Australian Pregnancy Register of Antiepileptic Drugs. This is a prospective, voluntary, telephone interview based study that enrols pregnant women with epilepsy, prior to the outcome of the pregnancy being known, and follows the outcomes of their pregnancies and relates this to genomic information. Basic research investigates the effects of antenatal exposure to valproate on brain gene expression changes in babies in an animal model of epilepsy.

227. Pharmacogenomics in IBD - *also offered as* MBiomedSc

Supervisors: Prof 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.

POPULATION HEALTH

228. Health and the housing interface; the health impacts of precarious housing amongst refugees in Melbourne

Supervisors: Dr Kudzai Kanhutu, Prof Beverley Ann Biggs, Dr Joanne Gardiner,
Project Site: Doherty Institute/Royal Melbourne Hospital International and Immigrant Health Group

Cohealth community health service
Contact: Dr Kudzai Kanhutu Email: kudzai.kanhutu@mh.org.au Ph: 03 8344 3704

Project description: Victoria currently receives one third of the national refugee intake. In addition 80% of immigrants come from low and middle income countries some of whom are from refugee-like backgrounds.

Refugees and asylum seekers encounter a number of barriers to accessing suitable housing.

Currently, little is known about the frequency of precarious housing in Australian hospital and primary care based patients and the co-occurrence of underlying medical comorbidities. A recently completed scoping study involving health professional key informants has provided evidence of the sustained negative impact that precarious housing is having on the physical and mental health of our refugee clients.

We intend to perform a prospective study of our outpatient and primary care clinics to establish baseline figures on the prevalence of precarious housing in our cohort of patients from refugee backgrounds. Survey questionnaires relating to refugee clients perceptions of the impact of housing on their health will provide much needed qualitative data for the Department of Health and Humans Services and other healthcare stakeholders. In addition, participants with a lived experience of precarious housing will also be interviewed regarding what supports could enable them to achieve greater housing security.

The combination of quantitative and qualitative data sets will help to pave the way to developing organisational client focused housing policy and interventions for affected refugee clients.

Skills/techniques you will build upon:
The successful applicant will be based at the world class Peter Doherty Research Institute. The project will also afford the opportunity to work alongside clinicians in the Victorian Infectious Diseases Service, RMH refugee health team, General practitioners and allied health workers at Cohealth.
Qualitative research methodology – data collection (10 – 20 interviews) and data synthesis.
Abstract writing and presentation techniques for conference settings.
Literature review

Additional career benefits:
The student will present their findings at the Victorian Refugee Health Network Strategy day.
This forum includes representatives from the Department of Health and Human Services , the Federal Government's Department of Immigration and Border Protection and key health stakeholders from the Non Governmental Sector.
Excellent opportunity for peer reviewed journal publication.

229. Gastrointestinal disequilibrium in indigenous children residing in remote communities: correlation between prevalence of gut pathogens and a chronic inflammatory state (new)

Supervisors: Dr Siddhartha Mahanty, Prof Beverley Ann Biggs
Project Site: Doherty Institute/Royal Melbourne Hospital International and Immigrant Health Group
Cohealth community health service
Contact: Dr Siddhartha Mahanty Email: smahanty@unimelb.edu.au

Project description: Indigenous children in remote communities suffer from significantly worse health than non-indigenous children. Enteric pathogens such as S. stercoralis, soil transmitted helminths (STH) and diarrhoea-producing intestinal bacteria contribute to chronic undernutrition during early childhood potentially because of chronic inflammation driven by translocation of microbial products into the circulation. The consequences of intestinal infection with enteric pathogens and a chronic inflammatory state on the growth of Indigenous children has not been previously investigated. To investigate this relationship, we will take advantage of an ongoing study that involves a cross-sectional survey of nutritional and health metrics in all children aged two years and under (~100) living on Elcho Island, NT, where health workers have reported a high prevalence of enteric infections in the past. From blood and stool samples collected in this study we will estimate the prevalence of enteric pathogens and level of inflammatory markers in this population of young Indigenous children. Prevalence of gastrointestinal pathogens identified by our tests will be correlated with the levels of inflammatory markers, represented by C-reactive protein (CRP), and alpha-1-acid glycoprotein (AGP).

Hypothesis: Children infected with pathogenic gut bacteria and parasites suffer from chronic malnutrition due to chronic activation of inflammatory pathways resulting, in part, from translocation of pathogen production into the systemic circulation.

Study design: We will use and compare standardized, previously validated, and new, more sensitive assays to detect the presence of a number of bacterial and parasitic pathogens in stools collected from study participants. Presence of pathogens will be correlated with levels of circulating C-reactive protein (CRP), and alpha-1-acid glycoprotein (AGP), as indicators of inflammation. Methodology used: Diagnostic ELISA, immunofluorescence, and biochemical assays for acute phase reactants, statistical methods for quantitative analysis of data Envisaged role of trainee: Processing and analysis of specimen collected in the field; performance of ELISA and biochemical assays (for inflammatory biomarkers); generation of prevalence data in the study population; data analysis, presentation and manuscript preparation. Significance: A better understanding of the prevalence of gastrointestinal pathogens, and chronic inflammation in an indigenous paediatric population and their relationship to child health.

230. Life-long Exposures for Healthy Ageing – *also offered as MBiomedSc*

Supervisor: Dr Melissa Coulson, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital.
Contact: Prof Cassandra Szoeke T: 61 3 8344 1835 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.

This project will involve direct hands-on participant evaluation. You will also have the opportunity to work with a rich database with lifestyle data that spans over 20 years. As well as an opportunity for publication.

231. Iron and Fatigue – *also offered as MBiomedSc*

Supervisors: Dr Steve Simpson Jr, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital.
Contact: Prof Cassandra Szoeke T:61 3 8344 1835 E: csoeke@unimelb.edu.au

Project description: Iron deficiency is prevalent in ageing women. Studies have shown that iron deficiency results in fatigue, reduced physical performance and impaired cognition. These symptoms are commonly reported in ageing populations. The Women's Health Ageing Project is an epidemiological sampled longitudinal prospective study that contains 20 years' worth of data on a number of measures including blood, cognition, diet and lifestyle, mood and wellbeing, hormones, illnesses, bone, and genes among others. This unique resource will therefore have the potential to identify new preventive health interventions and address issues relating to social determinants of health and health inequalities through social epidemiology across two decades. Over a hundred papers on this study have been published in peer reviewed journals. The results of this study have been internationally recognised and contributed significantly to the understanding of healthy ageing. The benefits of this project are:

- Opportunity to publish
- The study has data over 20 years already collected
- Will suit a candidate with an interest in commercialisation

232. Vitamin D deficiency and balance - *also offered as MBiomedSc*

Supervisors: Prof Meg Morris, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital.
Contact: Prof Cassandra Szoeke T: 61 3 8344 1835 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 renowned Women's Healthy Ageing Project (WHAP).

Opportunities: You will have the opportunity to work with an internationally renowned cohort and research team each with international recognition.

The study has data over 20 years already collected. There is opportunity for publication. This project will suit a candidate with an interest in balance, sports physiology and physiotherapy. There will be interaction with industry partners.

233. Hepatitis B infection in Australian prisons

Supervisors: Joseph Doyle, Jessica Howell
Project Site: Burnet Institute
Contact: E: Joseph.doyle@burnet.edu.au

Project description: Risks for hepatitis B transmission are common among prisoners and routine hepatitis B vaccination is recommended for all incarcerated individuals. However, the exact prevalence of current and past hepatitis B infection and related liver disease is unknown in prisons within Victoria. Vaccination coverage among prisoners is also currently unknown. Finally, prevalence of hepatitis D, a virus that requires hepatitis B to replicate, is also unknown among prisoners.

In this study, the seroprevalence of current and past hepatitis B and D infection among prisoners and associated clinical risks for disease will be determined by retrospective analysis of a clinical database (**not sure whether there is an "official" database or just the clinical "unofficial" one at this stage). Estimates of vaccine coverage within prisons will also be made, with a view to informing health policy.

This study involves quantitative analysis of data from a clinical database (data already collected but will require cleaning).

234. Barriers to hepatocellular carcinoma screening uptake in Victoria

Supervisors: Joseph Doyle, Jessica Howell
Project Site: Burnet Institute
Contact: E: Joseph.doyle@burnet.edu.au

Project description: Hepatocellular carcinoma (HCC) is the sixth most common cancer and incidence is increasing worldwide, including in Australia. Currently, people with risk factors for hepatocellular carcinoma are recommended to have twice yearly cancer screening with liver ultrasound to detect cancer when it is small enough to provide effective treatment. However, in Victoria only half of HCC are diagnosed through screening, therefore treatment options are often limited and mortality is high.

In this study, we explore barriers to HCC screening adherence. We will examine barriers to HCC screening attendance by quantitative analysis of retrospective demographic, socioeconomic and clinical data. We will collect and analyse qualitative data from a small sample of patients with liver disease, with and without HCC, to determine perceived and actual barriers to screening adherence. Finally, we will collect cost data for the process of HCC screening to inform cost-effectiveness models.

This study involves quantitative analysis of retrospective data from clinical databases (data already collected). There will also be a qualitative component, with data collection using questionnaires, structured interviews *and potentially focus groups*. Limited field work to collect data for cost-effectiveness models will also be required.

235. Hepatitis B virus infection and immunization status among gay, bisexual and other men who have sex with men attending primary health clinics

Supervisors: Caroline van Gemert
Project Site: Burnet Institute
Contact: E: caroline.vangemert@burnet.edu.au

Project description: Gay, bisexual and other men who have sex with men (GBM) are at increased risk of hepatitis B virus (HBV) in Australia and are unvaccinated GBM are recommended to have annual HBV testing. This study involves analysis of data to determine the proportion of GBM who have been vaccinated and HBV testing among GBM.

This study involves quantitative analysis of retrospective and longitudinal data collected in a surveillance system. Data are already collected and no further data collection is required.

236. Estimation of Hepatitis B virus infection among pregnant women

Supervisors: Caroline van Gemert
Project Site: Burnet Institute
Contact: E: caroline.vangemert@burnet.edu.au

Project description: Pregnant women are recommended to have hepatitis B virus (HBV) testing conducted as part of routine antenatal testing. This study involves developing a strategy to identify pregnant women in laboratory surveillance datasets, and using this strategy to estimate HBV prevalence among pregnant women.

This study involves quantitative analysis of retrospective and longitudinal data collected in a surveillance system. Data are already collected and no further data collection is required.

237. Validation of name classification software for use in Australia to identify culturally and linguistically diverse communities

Supervisors: Caroline van Gemert
Project Site: Burnet Institute
Contact: E: caroline.vangemert@burnet.edu.au

Project description: Pregnant women are recommended to have hepatitis B virus (HBV) testing conducted as part of routine antenatal testing. This study involves developing a strategy to identify pregnant women in laboratory surveillance datasets, and using this strategy to estimate HBV prevalence among pregnant women. Most people living with chronic HBV in Australia are people from culturally and linguistically diverse (CALD) communities and were born in areas endemic for HBV, mostly from the Asia–Pacific region and Africa. It is important that people born in these countries are tested, however recording of ethnicity and/or country of birth in general practice settings is low in Australia. This study involves the validation of name classification software for use in Australia and assessment of its use as a screening tool to identify people who should be screened for HBV.

238. Understanding and responding to alcohol and other drug use among people from culturally and linguistically diverse communities

Supervisors: Dr Danielle Horyniak, Dr Peter Higgs
Project Site: Burnet Institute
Contact: E: danielle.horyniak@burnet.edu.au

Project description: One fifth of the Australian population is comprised of people from culturally and linguistically diverse (CALD) communities. Victoria, in particular, has a highly diverse population; in some regions such as Dandenong and Maribyrnong, greater than 50% of the population was born outside Australia, with residents born in over 150 different countries.

Emerging evidence suggests alcohol and illicit drug use are growing concerns among some CALD communities, particularly among young people. A key issue identified relates to limited uptake of professional support such as prevention and treatment services, with potential community and service-related barriers to care.

This project aims to improve our understanding of currently available professional support for alcohol and drug use among CALD populations and inform strategies to improve CALD populations' engagement with health services.

This project may involve one or more of the following components:

- A review and content analysis of available AOD education, health promotion and support resources available for people from CALD backgrounds
- A review of current AOD policy documents to assess how the unique needs of CALD communities are incorporated and addressed
- A review of multicultural health policy documents to identify strategies and responses to AOD use

In-depth interviews with service providers from a range of sectors (general health, AOD, multicultural health, youth) and representatives of prominent CALD communities to examine barriers and facilitators to delivering AOD services to people from CALD backgrounds

This project would be suited to a student with an interest in health policy, health service delivery and/or health disparities. Prospective students will be expected to have strong skills in communication, critical thinking and analysis.

239. Understanding the role of stigma as a barrier to alcohol and other drug and mental health help-seeking and care for people from culturally and linguistically diverse communities

Supervisors: Dr Danielle Horyniak, Dr Peter Higgs, Dr Charles Livingstone
Project Site: Burnet Institute
Contact: E: danielle.horyniak@burnet.edu.au

Project description: Australia is a multicultural society, with one quarter of the population born overseas, and one fifth of the population comprised of people from culturally and linguistically diverse (CALD) communities. Although migrants are commonly impacted by social and health inequities, they are often under-represented in health research, resulting in limited understanding of the most effective ways to improve health for this population.

Alcohol and illicit drug use and poor mental health are growing concerns among some CALD communities, particularly among young people. Stigma is commonly identified as an important barrier to help-seeking and uptake of professional support for both of these health issues. Stigma, however, is a broad term, and it is often unclear what researchers are referring to when they conceptualise stigma; stigma occurs across individual, interpersonal and societal levels, stigma can be both overt and subtle, and understanding stigma requires consideration of the ways in which stigma is both enacted and felt.

This project aims to conduct a systematic review of literature examining stigma as a barrier to help-seeking and care for alcohol and other drug use or mental health among people from CALD communities.

The goal of this review is to examine the ways in which stigma has been conceptualised and measured in the literature, and to identify the most salient types of stigma that impact people from CALD communities' help-seeking behaviours. This information will be used to inform the development of future stigma reduction interventions.

This project may incorporate both quantitative and qualitative analysis, and will be informed by the available evidence base.

This project would be suited to a student with an interest in social theory and the social and cultural determinants of health and health behaviour. Prospective students will be expected to have strong skills in communication and critical thinking and excellent attention to detail.

240. Sexting, porn, and Tinder. An investigation of education and health promotion needs and evidence

Supervisors: Dr Megan Lim
Project Site: Burnet Institute
Contact: E: megan.lim@burnet.edu.au

Project description: Access to new technologies could present novel risks to young people's sexual health. The emerging popularity of sexting, online pornography use, and dating apps has been linked in some studies to sexual risk behaviours (e.g. not using condoms). There is very little known about how to educate young people about these topics. Many previous programs have taken a fear-based approach which tends to exaggerate the risks of these behaviours and promote abstinence as the only option. This project will investigate previous campaigns, survey the opinions and needs of young people, schools, parents, and health promotion practitioners, and provide recommendations for future campaigns.

A mixed methods approach will involve content analysis and review of existing health promotion, online surveys, interviews, and focus group discussions.

241. #cleaneating #detox : assessing the quality of nutrition advice in popular social media trends

Supervisors: Dr Megan Lim, Karen Klassen
Project Site: Burnet Institute
Contact: E: megan.lim@burnet.edu.au

Project description: Social media has seen the proliferation of numerous pages dedicated to health trends such as clean eating, fitspiration, paleo, and detoxes. Some of these social media pages are developed by qualified experts, however many are created by celebrities or for-profit companies with a vested interest in promoting specific products or plans. This project aims to systematically review the content and health claims made by popular social media nutrition pages and content associated with popular health trends and hashtags.

The student will first develop a sampling strategy for systematically selecting posts from popular social media tends. They will develop a framework by which to objectively analyse posts included in the sample. For example, this will include variables describing the source of posts, the evidence base for the information presented, the types of food mentioned, and follower reactions to the posts. They will conduct qualitative and quantitative analysis of the post content.

242. Intentional overdose and attempted suicide among people who inject drugs ***also offered as MBiomedSc***

Supervisors: Prof Paul Dietze, Dr Gregory Armstrong
Project Site: Burnet Institute
Contact: E: paul.dietze@burnet.edu.au

Project description: People who inject drugs (PWID) often experience non-fatal drug overdose, many of which are intentional. However, few studies have examined these intentional overdoses and how they relate to a range of other health risk behaviours. In this study data from the Melbourne Injecting Drug User Cohort Study (MIX) will be examined to determine the extent to which intentional overdose and attempted suicide more broadly relate to broader risk behaviours (and whether these change over time in the cohort) and what impact any changes have on other outcomes such as health service utilisation.

243. Apps for Harm Reduction: Help or Hindrance?

Supervisors: Dr Danielle Horyniak, Dr Megan Lim, Prof Paul Dietze
Project Site: Burnet Institute
Contact: E: danielle.horyniak@burnet.edu.au

Project description: The use of mobile phones and other technology to promote health (mHealth) is an emerging approach for providing health education, interventions and linkage to care for a wide range of health conditions. mHealth approaches may be particularly useful for marginalised populations, who may be hard to reach using traditional health promotion and care approaches. Studies of mHealth, and in particular the use of mobile phone 'apps', have identified some concerns however, including promotion of health-harming behaviours, inaccurate information and limited real-world utility. Although emerging evidence suggests that people who use drugs report high levels of interest in mHealth technologies, little is known about currently available mHealth programs and how they are being used.

This project aims to review the availability, characteristics and potential usefulness of harm reduction apps for people who use drugs.

This project will utilize a mixed methods approach. A review will be conducted to identify currently available apps which provide harm reduction to people who use drugs. Apps will be downloaded and tested to identify key characteristics (e.g. target population, purpose of the app, type of messaging used, app features). App quality will then be assessed (e.g. whether the app was designed by experts, whether the messaging in the app is consistent with evidence and best practice).

A series of focus groups may also be conducted with people who use drugs to explore their attitudes towards harm reduction apps, potential usefulness of apps and recommendations for future apps.

Prospective students will be expected to have strong skills in communication and analysis. A commitment to working with marginalised and vulnerable populations would be an advantage.

244. Investigating the limitations associated with the snowball model "Bring your friends" / "Treat your friends" in context of the TAP study

Supervisors: Dr Peter Higgs, Dr Rachel Sacks-Davis
Project Site: Burnet Institute
Contact: E: peter.higgs@burnet.edu.au, E: Rachel.sacks-davis@burnet.edu.au

Project description: The Treatment and Prevention study (TAP) is a world first clinical trial of DAA treatment for a group of people who inject drugs (PWID). The idea is that individuals are treated for hepatitis C together with people with whom they inject drugs, in order to prevent reinfection after successful treatment.

In the TAP study participants are asked how many people they have injected with (same time and place) over the last 6 months and how many in the last month?

Despite often reporting injecting with many people participants have mostly only brought a couple of friends into the study. The following research questions are of interest:

1. From a PWID perspective, what were the limitations (social, financial, cultural and circumstantial) to TAP participants bringing their whole injecting networks to receive DAA therapy as offered in the TAP study?
2. If they were willing to participate, what factors limited their friends from participating in DAA treatment?
3. From a PWID perspective, what changes could be made or what services could be offered to facilitate the full network in seeking/participating in treatment?
4. From a PWID perspective, what attitude shifts of behavioural changes must take place to make seeking DAA favourable? What promotion strategies or changes could the health system implement to facilitate these shifts?

This mixed methods study will conduct in-depth interviews with TAP participants who have finished treatment and ask what were the things that limited their friends also coming in for treatment.

Analysis of quantitative survey data and semi structured interviews with research participants.

Must have an interest in working with marginalized populations and have strong skills in communication and basic statistics which can be developed over the course

245. Strategies to reduce malnutrition among children with allocative efficiency analyses

Supervisors: Dr Madhura Killedar
Project Site: Burnet Institute
Contact: E: madhura.killedar@burnet.edu.au Ph: 61 2 8204 0707

Project description: Malnutrition is responsible for over 3 million child deaths each year with 36 countries world-wide carrying the bulk of the burden. There are proven community-based interventions to target malnutrition; however, resources are limited, so efficient allocation of available funds for maximum effectiveness is crucial.

Optima is an allocative efficiency analysis model to inform investment choices for health interventions. This computational approach to model health outcomes is integrated with an economic and financial analysis framework and a formal mathematical optimization routine. Using Optima, data-driven analysis are conducted to underpin recommendations to inform government health funding.

The Optima Nutrition model quantifies the benefits of nutrition-based interventions that target stunting and mortality in children under-five years of age. The aim of student research projects may include:

- incorporating complex dynamics into the modelling of nutrition-based interventions,
- including the effects of hygiene programs or family-planning into the model,
- extending the model to include the dependent relationships between risk factors leading to malnutrition-based outcomes,
- examining and potentially including the impact of additional risk factors such as obesity, building upon the optimization methods, and
- applying an existing model to inform a lower-income country on better use of resources in its health and nutrition infrastructure to improve health outcomes in children.

Depending on the skills and interests of potential research students, the project will involve one or more of the following:

- becoming familiar with malnutrition literature,
- applying the Optima model to a specific country case-study, performing analysis of the effects of scaling up an intervention(s) to best meet the needs of local governments surrounding child malnutrition,
- developing analytical expression to describe complex relationships between additional health risk factors as a result of malnutrition in children,
- using Python, a programming language, to implement new features in the mathematical model to incorporation the effects of child malnutrition or to build upon approaches in optimization,
- performing analytical analysis of health outcomes and cost-effectiveness of these interventions,
- contributing to novel research, and assisting with the generation of reports and journal publications.

Prospective students will be expected to have skills in quantitative data analysis, as well as written and verbal communication. A keen interest in health outcomes, and developing mathematical modelling and programming skills is essential. Some background in epidemiology, public health, mathematics, economics, physics, or computer science is preferred.

246. Allocative Efficiency in Child Nutrition

Supervisors: Dr Ruth Pearson
Project Site: Burnet Institute
Contact: E: ruth.pearson@burnet.edu.au

Project description: Allocative efficiency in public health involves determining how to best allocate resources for maximal effectiveness.

Optima is an allocative efficiency analysis tool to inform investment decisions for health interventions, as well as for academic research. Optima is an epidemiological model of disease progression which integrates an economic and financial analysis framework with a formal mathematical optimization routine.

The Optima model is applied to determine the optimal allocation of resources to different program areas in addressing specific objectives, for example, in reducing new infections or minimizing deaths.

To date, the major successes of Optima have been in the area of HIV, but this approach has been successfully expanded to other disease areas including hepatitis C, malaria, tuberculosis, and Child Nutrition.

This project will focus on Child Nutrition and given the recent application of the Optima model in this field, there is ample opportunity to explore new areas and contribute to novel research.

Optima Nutrition is a mathematical model of Child Nutrition written in the computer programming language Python. The model tracks cohorts of children from birth to five years of age. It incorporates health effects including the incidence of diarrhoea, breastfeeding, and stunting due to poor nutrition. Cost and coverage data for interventions targeting nutritional health are incorporated in the model to derive an optimal allocation of funding for the various intervention programs.

This project will involve applying the Optima model to a specific area of research or development, for example application in a specific country or setting, or to develop a new feature. This research will require quantitative data analysis from a range of sources. It will be important to fully understand each data source so data can be accurately incorporated to inform the model. For example, when applying the model in a country setting, the available data is often incomplete or may contain errors which must be identified and accounted for.

There will be opportunity to conduct mathematical and statistical analysis using Python. The student may learn to write code to perform analyses to address research questions. They will interpret and present results, usually in the form of figures and tables. There will also be opportunity to contribute to the general code base, and/or to the underlying mathematical model, as well as to produce policy documents and present findings.

Prospective students will be expected to have skills in quantitative data analysis as well as good communication skills. A keen interest in developing mathematical modelling and programming skills is essential. Some background in applied mathematics, physics, computer science, economics, or public health is preferred.

247. Sex, drugs and rock'n'roll: Young people and risk behaviours

Supervisors: Dr Megan Lim
Project Site: Burnet Institute
Contact: E: megan.lim@burnet.edu.au

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. From 2015, we have moved the survey to an online form. 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 gambling, diet and exercise, contact with police, mental health, and smoking. There is also a series of questions concerning media use, e.g. pornography, sexting, social media and smartphones, online gambling. The student project could focus on one of these issues or a range of themes. These findings, in the context of current public health measures, will be used to advise on the design of future sexual health promotion campaigns.

In this project the student will 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. The project could also involve in-depth qualitative data collection via focus group discussions or interviews.

248. Taking a punt: Exploring gambling attitudes and behaviours among a sample of young Victorians.

Supervisors: Dr Rebecca Jenkinson and Dr Megan Lim
Project Site: Burnet Institute
Contact: E: megan.lim@burnet.edu.au

Project description: The gambling environment in Australia has changed markedly over recent years and young people are a high-risk group for experiencing gambling-related harm. While estimates of gambling prevalence among young people vary considerably, there is consensus that gambling participation is increasing among young people and that youth problem gambling rates are around 2-3 times those of adults. With increasing exposure to gambling promotion and greater opportunities to gamble, the 'normalisation' of gambling among young people is likely to continue. In order to respond to increasing concern around these issues and inform future research and policy responses, this project will explore young people's gambling behaviours and experience of negative consequences in more detail, especially with regard to participation in higher risk activities such as sports betting and pokies.

In this project the student could employ a mixed-methods approach to explore gambling attitudes, behaviours and experience of negative consequences among young people (aged 15-29 years) in Victoria. Quantitative data collected as part of the Burnet's online survey of young people's health behaviours could be utilised. In addition to gambling, this annual, cross-sectional survey explores young people's alcohol and other drug use, sexual health and behaviour, experiences of mental health problems, and social media use. The student project could also involve in-depth qualitative data collection via focus group discussions or interviews.

249. Alcohol advertising on public transport: level of exposure among children and young people

Supervisors: Dr Megan Lim and Dr Nick Scott
Project Site: Burnet Institute
Contact: E: megan.lim@burnet.edu.au

Project description: Alcohol advertising is associated with increased alcohol consumption, particularly among young people. Current regulations attempt to limit exposure of alcohol marketing to children, however, no restrictions are in place regarding advertising on public transport.

This project will include an audit of alcohol advertising on public transport. Basic modelling will be conducted using publically available public transport usage data. The project will result in a policy document advising on the potential level of exposure of children to these advertisements.

250. Trends in STI testing and positivity in priority populations in Australia *also offered as* MBiomedSc

Supervisors: Carol El Hayek, A/Prof Mark Stoove
Project Site: Burnet Institute
Contact: E: carol.el-hayek@burnet.edu.au

Project description: In the last decade, communicable disease notification systems have seen a dramatic increase in the number of notifications for chlamydia and several other STIs. Higher prevalence is commonly seen in populations that have higher sexual risk practices (such as men who have sex with men, Aboriginal and Torres Strait Islander People, Sex Workers). It is important to monitor rates of STI testing and positivity in these priority populations, as well as the general population, in order to identify emerging patterns and trends in STI epidemiology.

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmitted Infections and Blood Borne Viruses (ACCESS) project is a sentinel surveillance system that monitors STI testing and positivity in a range of priority populations. This project will use existing data collected in the ACCESS project to explore STI testing and positivity in priority population and identify factors which are associated with both testing and positivity.

This project will involve quantitative data analysis of data collected through the ACCESS project. Data analysis will involve analysis of data collected through either laboratories or general practices and family planning clinics, and supplemented with behavioural data collected in some states. Data analysis will involve calculation of testing and positivity rates for a range of STIs and factors associated with these (such as age, gender and other relevant characteristics) in priority populations (including men who have sex with men, Aboriginal and Torres Strait Islander People, Sex Workers).

251. Systematic review of HIV and other STIs among transgendered populations in middle to high-income countries. *also offered as* MBiomedSc

Supervisors: Carol El Hayek, A/Prof Mark Stoove
Project Site: Burnet Institute
Contact: E: carol.el-hayek@burnet.edu.au

Project description: Transmission risk of HIV and sexually transmissible infections (STI) has not been estimated in Australia among gender diverse populations. Only recently has there been a shift to improve the completion of gender identity and sexuality when collecting associated sexual risk behaviour locally, and other HIV and STI surveillance data. This project will involve a systematic review of existing literature to find other estimates of HIV and STI prevalence, and the methods used to derive these. Understanding how the data has been used and interpreted, in other similar settings will be important when developing and measuring our own indicators for disease risk among transgendered people.

252. Understanding risky single occasion drinking and links to harms in a cohort of young Melburnians *also offered as* MBiomedSc

Supervisor: Prof Paul Dietze, Michael Livingston, Sarah Callinan
Project Site: Burnet Institute
Contact: E: paul.dietz@burnet.edu.au Telephone: 9282 2134

Project description: Young Australians frequently engage in Risky single occasion drinking (RSOD). This drinking pattern is associated with a variety of harms including increased risk of accidents, exposure to

violence and risky sex. Most research on RSOD has focused on normative drinking behaviours within the past year rather than on the specific circumstances of RSOD.The aim of this study is to examine specific occasions of RSOD by young people to understand the specifics of drinking contexts and links to harms.

The proposed study involves analysis of quantitative data collected through the Young Risky Drinkers (YRD) study. The YRD is a representative sample of 802 young high-risk drinkers recruited across metropolitan Melbourne using Computer Assisted Telephone Interviewing (CATI) during 2012. Specific questions were asked about their most recent episode of high risk drinking. The cohort is being followed up in 2013 with a similar questionnaire. Analysis will be undertaken to characterize risky drinking occasions and use findings from these analyses at baseline to examine whether these predict subsequent experiences of harm. Findings from the project will present a unique picture of RSOD.

253. Modeling the syphilis epidemic in Victoria – *also offered as MBiomedSc*

Supervisor: Ms Carol El Hayek, Dr Nick Scott
Project Site: Burnet Institute
Contact: E: carol.el-hayek@burnet.edu.au Telephone: 8506 2303

Project description In Victoria 80% of infectious syphilis cases are in men who have sex with men (MSM). Mathematical modeling of syphilis transmission in Australian MSM suggests an effective way to reduce syphilis is to increase the frequency of testing and treatment of MSM.

In recent years, we have seen a sustained increase in routine syphilis testing among MSM at high caseload clinics alongside a decline in infectious syphilis incidence.

How much testing needs to occur in Victoria's MSM community to eradicate infectious syphilis?
This project will involve the design of a syphilis transmission schema and model for mathematically predicting infection rates. Running the model will require defining input parameters which should be based on an extensive literature review.

254. Low income as a barrier to opioid substitution therapy - *also offered as MBiomedSc*

Supervisor: Dr Peter Higgs
Project site: Alcohol & Other Drug Research, Centre for Population Health, Burnet Institute
Email: peter.higgs@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 substation 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

255. Stem cells and their Potential to Treat Clinically Important Disorders of Pregnancy - *also offered as MBiomedSc*

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: We are interested in the potential for manipulating gene expression in decidual mesenchymal stem cells as for the treatment for clinically important pregnancy disorders such as preeclampsia.

The latter stages of preeclampsia are characterised by an environment of high oxidative stress in the decidua. We have shown that decidual MSCs are abnormal in their response to oxidative stress in preeclampsia. The aim of the project is to use human cell culture models to test strategies for restoring normal oxidative stress response to abnormal, preeclampsia-affected decidual MSCs (PE-DMSCs). For example, we have shown that aldehyde dehydrogenase expression, which is required for MSCs to resist oxidative stress, is abnormally low in PE-DMSCs. We will increase expression of aldehyde dehydrogenase in PE-DMSCs using plasmid-based expression vectors and test whether resistance to oxidative stress in PE-DMSCs is restored.

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.

256. Stem Cell Microvesicle Repair of the Damaged Endothelium in Preeclampsia. - ***also offered as MBiomedSc***

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: Preeclampsia is the most significant clinical disorder of pregnancy, affecting 5% of all pregnancies. Preeclampsia is a significant cause of maternal morbidity as well as fetal morbidity and mortality. Currently, there are no early diagnostic tests or effective treatments for preeclampsia. We are interested in the potential for subcellular microvesicles shed from mesenchymal stem cells to treat the symptoms of preeclampsia.

In preeclampsia, the endothelial cells lining the vessel walls become damaged. Systemic vascular damage contributes significantly to the symptoms of preeclampsia. Microvesicles shed from stem cells contain a variety of beneficial growth factors, cytokines and microRNAs that can be delivered to damaged cells, which prevent cell apoptosis, promote cell proliferation and differentiation, and thereby assist cells in recovering from damage. The aim of the project is to identify the growth factors, cytokines and microRNAs produced by microvesicles derived from placental mesenchymal stem cells.

Techniques: Stem cell preparation and characterisation by immunocytochemistry, flow cytometry and differentiation assays, microvesicle preparation from stem cells, ultracentrifugation, microvesicle characterisation and fluorescence labelling, screening assays for microRNA, growth factors and cytokines.

257. Can dietary phytophenols prevent the development of diabetes in pregnancy? - ***also offered as MBiomedSc***

Supervisors: A/Prof Martha Lappas
Project site: Obstetrics & Gynaecology, Mercy Hospital for Women
Contact: T: 8458 4370 E: mlappas@unimelb.edu.au

Project description: Gestational diabetes mellitus (GDM) affects up to 20% of all pregnancies. It has an impact that extends well beyond pregnancy and childbirth, with the potential for lifelong morbidity or mortality for both mother and baby. Despite the enormous health-impact of this condition, little progress has been made with interventions aimed at prevention; rates of GDM are increasing in parallel with the obesity epidemic. A safe and effective intervention that can reduce the burden of GDM would be a major public health initiative. Of promise, however, is the increasing volume and quality of evidence that high fruit and vegetable intake in pregnancy is associated with a decreased risk of adverse pregnancy outcomes. Many of the beneficial effects are due to phytophenols which are natural products found in fruits and vegetables and beverages derived from plants. Thus, in this study, we will use a mouse model to determine if phytophenols can prevent the development of GDM.

Techniques: Animal work, PCR-based analysis, Western blotting and ELISA

258. Can dietary phytophenols stop preterm birth? - ***also offered as MBiomedSc***

Supervisors: A/Prof Martha Lappas
Project site: Obstetrics & Gynaecology, Mercy Hospital for Women
Contact: T: 8458 4370 E: mlappas@unimelb.edu.au

Project description: The single most important complication contributing to poor pregnancy and neonatal outcome is preterm birth. Of the 130 million babies born each year, 8 million die before their first birthday. Up to 2.7 million of these deaths are attributable to being born too early. Bacterial infection is the most common

trigger for preterm birth. It activates inflammation in placenta which can trigger the processes that lead to preterm birth. In our in vitro studies, we have shown that natural plants chemicals (i.e. phytophenols), such as luteolin which is found in celery, can reduce inflammation in the placenta. Although this data is very promising, in vivo studies are needed to determine if these plant chemicals will be useful as therapeutics to prevent preterm birth. In this project, we will induce preterm birth in mice (using bacterial infection). We will then determine if phytochemicals can prevent infection induced preterm birth. The possibility of phytophenols as therapeutic agents offers an exciting step forward into the management of a condition responsible for unequalled morbidity and mortality in infants.

Techniques: Animal work, PCR-based analysis, Western blotting and ELISA

259. Understanding changes in haemostasis during pregnancy and pregnancy complications – *also offered as MBiomedSc*

Supervisors: A/Prof Joanne Said and Dr Briony Cutts
Project Site: Melbourne Medical School, Sunshine Hospital, St Albans.
Contact: E: jsaid@unimelb.edu.au or briony.cutts@thewomens.org.au

Project description: Haemostasis in humans represents a complex balance between prothrombotic and anticoagulant proteins. During pregnancy, this balance is shifted in favour of a prothrombotic state such that pregnant women have an increased risk of developing deep vein thrombosis. This disturbance in coagulation is even more pronounced in a range of pregnancy complications. The aim of this study is to investigate the changes that occur during pregnancy, and in various adverse pregnancy conditions, using the calibrated automated thrombinoscope. This modern technology allows a global assessment of haemostasis rather than investigating individual factors. The project will be conducted in the brand new laboratories at the Centre for Health Research and Education based at Sunshine Hospital. Sunshine Hospital is the second largest maternity unit in Victoria and thus there is an ample population of pregnant women available to participate in this study. Techniques: Recruitment of patients, sample collection, thrombin generation assays.

260. The evaluation of a decision aid for women considering non-medical egg freezing – *also offered as MBiomedSc*

Supervisors: Dr Michelle Peate, Prof Martha Hickey
Project Site: Obstetrics and Gynaecology, Royal Women's Hospital
Contact: E: michelle.peate@unimelb.edu.au

Project description: There is a growing trend in developed countries for women to delay starting a family until their early 30's or later. This delay can mean that some women miss the opportunity to have children due to age-related infertility. Egg freezing can offer women the option of delaying pregnancy and lower the risk of age-related infertility. However, making choices around egg freezing and family planning is complicated, as health, financial and psychological implications for a procedure with no guarantee of success. Although increasing numbers of women are freezing their eggs, very little is known about their understanding of egg freezing and its potential impact. Nor is it known what information women need in order to make an informed decision. Declining fertility is an urgent social and economic problem in Australia and most other developed countries. The most common and potentially avoidable factor contributing to declining fertility is advanced female age. Advances in technology mean that women now have access to egg freezing to try and overcome the effects of age-related infertility. This procedure is being widely promoted by commercial providers, but is also costly and caries potential physical and emotional risks. Currently, women are relying on information from commercial providers and internet sources such unmoderated forums and blogs. There is a need for objective and evidence-based information to support decision-making. An interactive, online decision aid for women considering egg freezing for non-medical reasons has been developed. This will be the first study to develop and evaluate a decision aid in the context of non-medical egg freezing. It is anticipated that the decision aid will lead to better understanding of fertility-related issues and educated involvement in decision-making.

261. Development and evaluation of guidelines and an intervention for moving on from IVF in women with a low chance of success – *also offered as MBiomedSc*

Supervisors: Dr Michelle Peate, Prof Martha Hickey
Project Site: Obstetrics and Gynaecology, Royal Women's Hospital, Parkville
Contact: E: michelle.peate@unimelb.edu.au

Project description: Over 34,000 Australian women and couples use In Vitro Fertilisation (IVF) each year in the hope of achieving a pregnancy, of which 60% will not have a baby that year. Whilst there are guidelines and

clinical consensus around starting IVF, there is almost no evidence-based information about when to stop. The personal, social and financial consequences of continued unsuccessful attempts at IVF are profound. Consequences of continued IVF failure include cumulative psychological, financial and physical burden, and life goals being put on hold. Also, failure to engage with alternative options which may include egg or embryo donation, adoption or child free etc. Very few previous studies have addressed the reasons why women continue to undergo IVF when success is low and the reasons that clinicians continue to treat them. Additionally, there are concerns about the psychological health and wellbeing of those who have discontinued IVF without a successful pregnancy. Women who remain childless following IVF generally experience poorer psychological health, suggesting that current processes for moving on poorly manage psychological sequelae.

To our knowledge this proposal is the first internationally to address why women and clinicians continue IVF when success is unlikely. Given the burgeoning use of IVF internationally and the generous Medicare subsidy of repeated cycles of IVF in Australia, we are well placed to address this growing problem. Many developed countries offer limited state funded IVF treatment, but with strict criteria around patient age, reasons for infertility with the number of cycles generally limited to. In Australia, there are no criteria that limit government subsidies. Whilst this program optimises access to IVF, it may also lead to inefficient use of resources which are costly for the tax payer and without benefit for the unsuccessful patient. There is an urgent need to establish a consensus around "low chance of success", addressing patient and clinician reasons for continuing treatment in these circumstances and developing a high quality intervention to facilitate decision-making around treatment continuation. The Australian environment, where the role of cost in motivating the discontinuation of IVF is reduced, is ideal for the exploration of this issue. Further, with a better understanding of the support needs of this group, an intervention will be developed that we anticipate will lead to more efficient use of resources and improvements in psychological adjustment, informed choice, and improved satisfaction with their experience in the longer term.

262. EndoNeeds: Investigating the unmet physical, psychological and social needs of Australian women with endometriosis – *also offered as MBiomedSc*

Supervisors: Dr Michelle Peate, Dr Jane Girling
Project Site: Obstetrics & Gynaecology, Royal Women's Hospital
Contact: E: michelle.peate@unimelb.edu.au

Project description: Endometriosis is a disease that can affect every facet of a woman's life, interfering with her ability to work, study, care for family and enjoy a normal social life. Thus, interventions designed to reduce the impact of endometriosis must take into account the 'whole patient', rather than focusing only on medical issues. For this reason, the biopsychosocial model of care (which considers the biological, psychological and social aspects of health) is particularly relevant, and should be used for, the care of women with endometriosis.

As health care services endeavour to become more patient-centred, the use of 'patient-reported outcome measures' (PROMs) has gained importance. PROMs can be used to measure a patient's function, symptoms and quality of life, and a number of endometriosis-specific PROMs have been developed. However, most of these focus on physical symptoms and quality of life and do not address aspects of care that patients require or desire in order to obtain optimal well-being – their 'unmet needs'. A type of PROM that has been used extensively in cancer care to capture what patients feel they need to improve their well-being is the 'unmet needs' survey. A thorough review of the existing evidence reveals that only one unmet needs survey has been developed for women with endometriosis, and this focused on the informational needs of the women, in addition to exploring their experiences of the disease. In addition, it is unclear whether the survey instrument was subject to psychometric validation. What is needed is a systematic examination of unmet needs, which can be used to improve clinical care and ultimately the woman's experience of living with endometriosis.

Our project aims to combine the concepts of the biopsychosocial model of care and patient-centred care by developing and administering a survey that investigates the physical, psychological and social needs of Australian women with endometriosis, and to what extent those needs are being met.

PSYCHIATRY

263. Causes of Depressive Symptoms in Early Ageing – *also offered as MBiomedSc*

Supervisor: Dr Melissa Coulson, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke T: 61 3 8344 1835 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. Analysis will be conducted examining the consistency 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 of this study are:
1. There is opportunity for publication
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

264. Lifestyle factors and effects on mood in elderly women – *also offered as MBiomedSc*

Supervisors: Dr Stephen Campbell, Prof Cassandra Szoeke
Project Site: Healthy Ageing Program, Dept of Medicine, Centre for Medical Research, Royal Melbourne Hospital
Contact: Prof Cassandra Szoeke T:61 3 8344 1835 E: cszoeke@unimelb.edu.au

Project description: Alcohol consumption in women is becoming an increasing public health concern. Depression, the most prevalent and persistent mental disorder in women, has been shown to be related to alcohol consumption. This study examines the association between alcohol intake and depression in community-dwelling older women.

The Women's Healthy Ageing Project (WHAP) has prospective longitudinal, epidemiological data on alcohol consumption and mood of Australian women from age 45 over 25 years. This project will provide the opportunity for publication, as well as participant contact and clinical skills experience.

265. Improving methodologies and outcomes of cognitively-oriented treatments for older adults

Supervisor: Dr Alex Bahar-Fuchs
Project Site: Psychiatry, Royal Melbourne Hospital
Contact: Dr Alex Bahar-Fuchs E: alex.bahar@unimelb.edu.au

Project description: My group at the AUPOA (Academic Unit for Psychiatry of Old Age) investigates cognitively-oriented treatments (e.g., cognitive training, rehabilitation) targeting cognition, well-being, and function, in older adults. Broad themes of interest include the development of cognitively-oriented interventions incorporating emerging technologies (e.g., virtual reality), with strong theoretical underpinnings in neuroscience and behaviour-change, as well as trial design methodology and evidence synthesis. Within the older adult population, my work includes the full spectrum from cognitive and functional health, to dementia.

The following are some suggested directions to explore with prospective honours students in 2018:

1. Framework for the development of cognitive training tasks across multiple environments in the setting of virtual reality-based training.
2. The relationship between self and informant-reported mood symptoms (depression ,anxiety, apathy), adherence/engagement, and cognitive test performance before and after cognitive training.

3. Cognitive training-related practice effects in older adults with and without cognitive impairment
4. Patterns of decay in cognitive gains following cognitive training in cognitively healthy and cognitive impaired older adults
5. Modelling of change in individual task performance throughout a cognitive training intervention.
6. Olfactory identification in older adults with and without cognitive impairment and mood-related symptoms: analysis of error-types.
7. Meta-review of cognition-oriented treatments for older adults (systematic review of reviews).
8. Recruitment and retention of research participants in trials of cognition-oriented treatments: a review of methodological challenges and possible solutions. These and other relevant projects can be completed using literature reviews, analysis of existing data-sets and prospectively collected data. Further details will be discussed with suitable prospective students. If you are interested, send your CV along with a brief expression of interests to: Alex.bahar@unimelb.edu.au.

SPINAL CORD INJURY

266. Acute management of traumatic central cord syndrome

Supervisors: Dr Peter Batchelor, Dr Camila Battistuzzo
Project Site: Department of Medicine (RMH)
Contact: Dr Peter Batchelor: peter.batch@unimelb.edu.au
Dr Camila Battistuzzo: camilab@unimelb.edu.au

Project description: Acute traumatic central cord syndrome (TCCS) is the most common type of incomplete cervical spinal cord injury. TCCS is usually the result of a hyperextension injury in a patient with pre-existing narrowing of the spinal canal and can result in paralysis and permanent functional deficits. At present there is no standardized treatment for this condition, although early surgery to relieve spinal cord compression may improve neurological recovery. The aim of this project is to map the process of care of people with TCCS to determine the timing of spinal decompression surgery and factors that influence surgical decisions.

This project is part of the Immediate Cooling and Emergency Decompression (ICED) trial. You will have access to our database and opportunity to work with our national and international collaborators. We have already obtained Human Ethics Committee approval. There is opportunity for publication within one year. This project would suit a candidate with an interest in trauma, spinal surgery and acute medicine.

HONOURS AT RMH

Enrolling Department: MEDICINE RMH

HONOURS ENQUIRIES

RMH Honours Coordinator:	Dr Chris French	E: frenchc@unimelb.edu.au
RMH Honours Administrator:	Fiona Hocking	E: honours-rmh@unimelb.edu.au
		T: 61 3 8344 5479

2017/18 KEY DATES

Aug-November 2017:	Contact potential supervisors to discuss Honours projects	(Step 1)
11 September 2017:	Open date to lodge project preferences through SONIA	
10 November 2017:	Closing date to register online Honours application	(Step 2)
24 November 2017:	Closing date to lodge project preferences through SONIA	(Step 3)
22 December 2017:	First round of offer letters sent to students	
5 January 2018:	Closing date for acceptance/rejection by students of First Round offers	
10 January 2018:	Second round of offer letters sent to students	
Middle February 2018:	RMH Honours 2018 Program commences / RMH Student Orientation.	

HONOURS ENTRY REQUIREMENTS

To be eligible to enter the Bachelor of Biomedicine (Honours) or the Bachelor of Science (Honours), applicants must satisfy both:

- the Faculty of Medicine, Dentistry and Health Sciences or Faculty of Science entry requirements;
- and the requirements of the department offering the Honours program.

Please note: The minimum entry requirement is 65 (Weighted Average Mark).

HONOURS COURSEWORK

BIOM40001 – SEMESTER 1: Introduction to Biomedical Research (12.5%)

This core subject contributes 12.5% to the total mark of the Honours year and is administered through the Faculty of Medicine, Dentistry & Health Sciences.

Structure: Series of 10 x 2 hr tutorials to introduce students to processes and strategies at the core of modern biomedical research.

Assessment: *Semester 1: 2 written reports (each not exceeding 3000 words).*

MEDI40004 – SEMESTER 1: Advanced Coursework (12.5%)

This subject contributes 12.5% to the total mark of the Honours year.

Structure:	Semester 1:	Attend Seminars in Translational Medicine - thematic topics of approximately 20 lectures (1 hour each).
	Semester 1 & 2:	Attend Weekly Research Seminars. Attendance is compulsory from March to October but not assessed.
Assessment:	*Semester 1:*	*Multiple Choice Question examination covering examinable topics from the Seminars in Translational Medicine.*

MEDI40016 & MEDI40017 – SEMESTER 1 & 2: Research Project (75%)

The written thesis together with an Oral Presentation constitutes the Research Project for Semester 1 & 2 and contributes 75% to the total mark of the Honours Year.

Structure: Research Project (Thesis)

Assessment:

MEDI40016	*Semester 1:*	*Oral Presentation on project outline. Feedback only - not assessed.*
MEDI40017	*Semester 2:*	*a) Written research report (thesis) to be submitted. 80%*
		b) Formal thesis oral presentation

HOW TO APPLY - HONOURS

Course Codes:
Bachelor of Biomedicine (Honours) – **BH-BMED**
Bachelor of Science (Honours) **– BH-SCI**

Visit the website for details on HOW TO APPLY**:**
http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

2018 APPLICATIONS

If you wish to be considered for Honours in 2018, and you would like to undertake your project and coursework with Department of Medicine at RMH, The University of Melbourne (enrolling unit: Department of Medicine (RMH)), you will need to carry out a **THREE STEP PROCESS:**

STEP 1: Contact Potential Supervisor
STEP 2: Lodge an online application
STEP 3: Submit your project preference on the Honours Application and Tracking System (SONIA)

MASTER OF BIOMEDICAL SCIENCE

The Master Biomedical Science 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 MBiomedSc is a two year course that can be taken in place of Honours.

Students must complete 200 points comprising of:

Major Research Project	(Literature Review, Thesis, & Ora Presentations)	125 points
Core Discipline subject	(Introduction to Biomedical Research BIOM40001)	12.5
Discipline Subjects		37.5 points
Professional Skills		25 points

MAJOR RESEARCH PROJECT: 125 points.

- A literature review of up to 6,000 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 20,000 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.

Available Projects: For MBiomedSc projects available with the Royal Melbourne Hospital please see projects listed as available for MBiomedSc in the 2018 Honours / Master of Biomedical Science Project List Handbook: *For further details on the project please contact the supervisor listed in the handbook.*

HOW TO APPLY - MBIOMEDSC

Course Code MC-BMEDSC

1. Applications for the Master of Biomedical Science are made directly via the University online application system. Late applications can be considered for admission (but may not be eligible for competitive fee places or bursaries).
2. Talk with academic staff offering projects you are interested in. Find out what is involved. Talk to the students in the labs. Talk with the Department Masters Coordinator if you have questions about the overall course structure.
3. When you are ready to make a formal application, lodge an online – see links below on how to apply: http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/overview

You will be required to nominate a Department, Supervisor and Project, and have your prospective supervisor provide you with evidence (ie a letter or email) of their potential willingness to supervise your project. You will be required to submit this information as part of your course application.

MBIOMEDSC ENQUIRIES

School of Biomedicine E: biomedsci-gradstudent@unimelb.edu.au

USEFUL LINKS

Honours Overview: http://mdhs-study.unimelb.edu.au/degrees/honours/overview

Department of Medicine/Radiology: http://medicine.unimelb.edu.au/school-structure/medicine-and-radiology

Department of Medicine at RMH Research Groups:
http://medicine.unimelb.edu.au/research-groups/medicine-and-radiology-research/royal-melbourne-hospital

Honours and Master of Biomedical Science Coursework:
http://medicine.unimelb.edu.au/school-structure/medicine-and-radiology/study/honours

Honours and Masters Current Student Resources
http://medicine.unimelb.edu.au/school-structure/medicine-and-radiology/study/current-student-resources/honours