The Royal Melbourne Hospital

Bench to Bedside – Medical Research

THE UNIVERSITY OF MELBOURNE

GRADUATE RESEARCH PROJECTS 2018

THE UNIVERSITY OF MELBOURNE AT THE PARKVILLE PRECINCT

(RMH Departments: Medicine and Radiology, Surgery, Psychiatry, Obstetrics & Gynaecology/RWH, and affiliated institutes)

Melbourne Medical School, The University of Melbourne

Affiliations: The Peter MacCallum Cancer Centre, The Burnet Institute, Melbourne Brain Centre, Florey Neuroscience Institute, Mental Health Research Institute, Baker IDI Heart & Diabetes Institute.

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GRADUATE RESEARCH PROGRAMS AT THE PARKVILLE PRECINCT

The Melbourne Medical School's Parkville precinct offers GR Programs, combining projects from University of Melbourne Departments of Medicine and Radiology at RMH, Psychiatry, Surgery at RMH, and Obstetrics & Gynaecology (RWH), along with other affiliated institutions. These institutes include The Peter MacCallum Cancer Centre, The Burnet Institute, and Baker IDI Heart & Diabetes Institute.

We have expertise in a very wide range of basic, applied and clinical methodologies and offer a unique experience for students. Not only do students master the research field of their project, but they have the opportunity to learn about the bigger picture, particularly with regard to leadership and responsibility, and the importance of the interface between research and medicine.

The School's research themes include:

- Ageing
- Cancer in Medicine
- Cardiometabolic
- Child Health in Medicine
- Infectious Diseases and Immunity
- Integrated Critical Medicine
- Musculoskeletal
- Neuroscience and Psychiatry
- Women's Health

HOW TO APPLY LINKS

http://mdhs-study.unimelb.edu.au/future-graduate-researchers
http://futurestudents.unimelb.edu.au/admissions/applications/research

Search for GR programs

There are a range of research degrees offered at Masters and Doctorate level, whereby students undertake a specific research project under the supervision of research staff at The Royal Melbourne Hospital/RWH. The programs include PhD and other doctorates, MPhil and other masters by research. Please refer to: http://mdhs-study.unimelb.edu.au/degrees

Overview and Entry Requirements

PhD: http://mdhs-study.unimelb.edu.au/degrees/doctor-of-philosophy/entry-requirements#entry-requirements
Doctor of Medical Science: http://mdhs-study.unimelb.edu.au/degrees/doctor-of-medical-science/entry-requirements#entry-requirements
Master of Philosophy: http://mdhs-study.unimelb.edu.au/degrees/master-of-philosophy/entry-requirements#entry-requirements
Master of Surgery: http://mdhs-study.unimelb.edu.au/degrees/master-of-surgery/overview

Find a Supervisor

You can either contact the supervisors listed in this booklet or refer to the Find an Expert link at: http://www.findanexpert.unimelb.edu.au/

For details of the research groups at the Parkville precinct, please refer to:
http://medicine.unimelb.edu.au/research/department-research-summaries
http://medicine.unimelb.edu.au/research/research-groups

SCHOLARSHIPS

GR Scholarships link

http://mdhs.unimelb.edu.au/study/scholarships/graduate-research-scholarships

Scholarship eligibility

http://mdhs.unimelb.edu.au/study/scholarships/graduate-research/scholarship-eligibility

SCHOLARSHIP KEY DATES

Application Timelines - 4 major rounds

http://mdhs.unimelb.edu.au/study/scholarships/grad-res-scholarships/key-dates

ENQUIRIES

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PARKVILLE PRECINCT DEPARTMENT LINKS:

Department of Medicine & Radiology:

http://medicine.unimelb.edu.au/research-groups/medicine-and-radiology-research

Department of Surgery:

http://medicine.unimelb.edu.au/research-groups/surgery-research

Department of Psychiatry:

http://medicine.unimelb.edu.au/research-groups/psychiatry-research

Department of Obs & Gyn:

http://medicine.unimelb.edu.au/research-groups/obstetrics-and-gynaecology-research

GRADUATE RESEARCH PROJECTS 2018

THE UNIVERSITY OF MELBOURNE AT THE ROYAL MELBOURNE HOSPITAL

Listed below are brief outlines of some of the projects being offered in 2017-2018.
For further information, contact the supervisors on the numbers and email addresses as listed.

DEPARTMENT OF MEDICINE AND RADIOLOGY

@AgeMelbourne

Group Leader: Professor Andrea B Maier **T:** + 61 3 8387 2137 **E:** Andrea.Maier@unimelb.edu.au
Location: Level 6 North, Royal Melbourne Hospital, 300 Grattan St, Parkville. **W:** Personal web page

1. Inter- and intra-individual pattern of diseases

Professor Andrea Maier, Professor Cassandra Szoeke **T:** + 61 3 8387 2137
E: Andrea.Maier@unimelb.edu.au **Location:** Level 6 North, Royal Melbourne Hospital, 300 Grattan St.

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 for the ageing process.

2. The intra-individual rate of ageing

Professor Andrea Maier, Dr. Esmee Reijnierse **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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. The underestimated power of human muscle

Professor Andrea Maier **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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. Prerequisite: conduct epidemiological studies / interventions, epidemiological/statistical skills, good communication skills, capacity to work in a multidisciplinary team.

4. Refining the comprehensive geriatric assessment

Professor Andrea Maier, Dr. Esmee Reijnierse **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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 the same extensive CGA, the 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.
Prerequisite: epidemiological/statistical skills, write journal articles, good communication skills, capacity to work in a multidisciplinary team.

5. Muscle health and nutritional needs during recovery from acute disease

Professor Andrea Maier, Dr. Esmee Reijnierse **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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. The 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. Three 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. The blood pressure drop makes you fall

Professor Andrea Maier, Dr. Esmee Reijnierse **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

(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.

7. Essence of Senescence

Professor Andrea Maier, Dr. Camilla Tuttle **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

Cellular senescence, the process by which cells lose their ability to divide is a well-established mechanisms of ageing and age-related diseases. A number of ageing associated senescent biomarkers have been identified (e.g. p16INK4a 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.

8. Proteostasis and Muscle Regeneration

Professor Andrea Maier, Dr. Camilla Tuttle **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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.

9. Cellular Senescence as a Biomarker of Ageing

Professor Andrea Maier, Dr. Camilla Tuttle **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

The increasing aging population has led to national and international healthcare systems being inundated with geriatric patients. Currently elderly patients are assessed and managed using a Comprehensive Geriatric Assessment (CGA). The CGA is a clinical tool comprising multiple domains that predict the risk of morbidity and mortality in older adults. However, the current CGA contains limited biological diagnostic options, owing largely to the complexity of the human body and ageing process. Multiple disease presentations incorporating several organ systems has led to challenges in determining whether biological/biomedical science changes are a cause or consequence of the disease/aging process. Nine molecular hallmarks of aging are currently recognised, one of which is cellular senescence. Cellular senescence - a defensive mechanism in response to molecular damage - accumulates with age. Recently it has been shown that removal of senescent cells by 'senolytics' rejuvenates body function in animal models. How senescent cells contribute to the human aging process is not well defined. In addition, whether increased numbers of senescent cells contribute to a cascade of age-related disease pathologies is also unknown and the basis for future therapeutic innovations. Aims: This PhD project will investigate the role senescent cells play in ageing and the age-related disease pathology of a geriatric cohort. In the first two years, the PhD candidate will isolate senescent biomarkers of interest associated with clinical features of ageing and age-related diseases in geriatric cohorts. In the second and third years, the PhD candidate will establish the underlying causal pathway between isolated biomarker(s) of interest and ageing. Research Environment: @AgeMelbourne Research Group, led by Professor Andrea Maier, conducts innovative, translational and multi-disciplinary research in Gerontology and Biogerontology. The group's mission is to prolong the healthy lifespan of an individual by the prevention of age-related diseases. Ageing is the major risk factor of age-related diseases resulting in multimorbidity of the majority of the population aged 60 years and over. Understanding the basis of the human ageing process and its influence on age-related diseases is the starting point for establishing targeted interventions. @AgeMelbourne is currently conducting four large, longitudinal, studies examining the clinical and biological phenotypes of geriatric populations in inpatient and outpatient settings. All @AgeMelbourne studies demonstrate a strong translational component that is, improving diagnostics and therapies for age-related diseases based on a solid methodological and biological understanding. The @AgeMelbourne Research Group includes an internationally-recognised and dedicated team of academic research staff and students with a diverse background of clinical research skills and knowledge, making it an

exciting and inspiring group to work with.

10. Comprehensive Geriatric Assessment in Geriatric Evaluation and Management Clinics

Professor Andrea Maier, A/Prof Kwang Lim **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

Elderly patients generally present to hospitals with complex health problems. A Comprehensive Geriatric Assessment (CGA) allows for a proper treatment plan and long-term follow up and is therewith a critical component of characterising older patients, involving a multidisciplinary assessment of psychological, cognitive, gait/balance, nutrition, spiritual, social, and biomedical factors. The CGA is based on the premise that systematic evolution of these factors can lead to the identification of treatable health issues and optimisation of patient outcomes. However, the CGA is not well defined and a standardised version has not been developed. Aims: This PhD project will evaluate patients at the Royal Melbourne Hospital's Geriatric Evaluation and Management (GEM) clinic with an extensive CGA. In this longitudinal cohort study, approximately 1,000 patients will be recruited over two years and followed-up for six months. The primary aim of this study is to characterise the descriptive epidemiology of geriatric inpatients in the GEM clinic and assess what factors are associated with post-discharge health outcomes such as mortality, readmissions, and major clinical events. Because a wealth of data on patient characteristics will be collected, the broad scope of this data will allow us to explore a variety of possible secondary aims as they relate to characteristics and outcomes of geriatric inpatients. Modifiable risk factors will be targeted by dedicated interventions. Research Environment: @AgeMelbourne Research Group, led by Professor Andrea Maier, conducts innovative, translational and multi-disciplinary research in Gerontology and Biogerontology. The group's mission is to prolong the healthy lifespan of an individual by the prevention of age-related diseases. Ageing is the major risk factor of age-related diseases resulting in multimorbidity of the majority of the population aged 60 years and over. Understanding the basis of the human ageing process and its influence on age-related diseases is the starting point for establishing targeted interventions. @AgeMelbourne is currently conducting four large, longitudinal, studies examining the clinical and biological phenotypes of geriatric populations in inpatient and outpatient settings. All @AgeMelbourne studies demonstrate a strong translational component, that is, improving diagnostics and therapies for age-related diseases based on a solid methodological and biological understanding. The @AgeMelbourne Research Group includes an internationally-recognised and dedicated team of academic research staff and students with a diverse background of clinical research skills and knowledge, making it an exciting and inspiring group to work with.

11. Sarcopenia and nutritional needs during recovery from acute disease

Professor Andrea Maier, Dr. Esmee Reijnierse **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

It is estimated that the number of people aged 60 years and older worldwide will triple over the next 30 years. However, the increase of an individuals' lifespan is accompanied by an accumulation of age-related diseases associated with diminishing health and functional independence. 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. The importance of sarcopenia has been underlined with its recognition as an independently reportable chronic disease (ICD-10-CM code M62.84) in October 2016. 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. Aims: This PhD project will investigate the triangular relationship between muscle health, energy expenditure and nutritional status in patients admitted to geriatric rehabilitation wards. In the first and second year, the PhD candidate will collect data on the geriatric rehabilitation wards and perform data analysis of the observational study. In the second and third years, the PhD candidate will be involved in a randomized

controlled trial and assist in the nutritional intervention based on the results of the observational study. Research Environment: @AgeMelbourne Research Group, led by Professor Andrea Maier, conducts innovative, translational and multi-disciplinary research in Gerontology and Biogerontology. The group's mission is to prolong the healthy lifespan of an individual by the prevention of age-related diseases. Ageing is the major risk factor of age-related diseases resulting in multi-morbidity of the majority of the population aged 60 years and over. Understanding the basis of the human ageing process and its influence on age-related diseases is the starting point for establishing targeted interventions. @AgeMelbourne is currently conducting four large, longitudinal, studies examining the clinical and biological phenotypes of geriatric populations in inpatient and outpatient settings. All @AgeMelbourne studies demonstrate a strong translational component that is, improving diagnostics and therapies for age-related diseases based on a solid methodological and biological understanding. The @AgeMelbourne Research Group includes an internationally-recognised and dedicated team of academic research staff and students with a diverse background of clinical research skills and knowledge, making it an exciting and inspiring group to work with.

12. Towards a biological geriatric assessment

Professor Andrea Maier, Dr. Camilla Tuttle **T**: + 61 3 9342 2635 **E**: andrea.maier@mh.org.au
Location: University of Melbourne, RMH, Department of Medicine and Aged Care

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 tools. The consequence is that CGAs are not comparable and that the causal mechanisms of the geriatric condition 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 (BGA) being predictive for relevant outcomes and sensitive and specific for change over time. The BGA will be based on the nine molecular hallmarks of aging currently recognized. Aims: This PhD project will investigate the role of the molecular hallmarks of ageing in age-related disease pathology in different populations (healthy to diseased). In the first two years, the PhD candidate will investigate the association of hallmarks of ageing with disease pathology combining molecular and epidemiological techniques, followed by validation of (parts of the) BGA in diseased populations. Research Environment: @AgeMelbourne Research Group, led by Professor Andrea Maier, conducts innovative, translational and multi-disciplinary research in Gerontology and Biogerontology. The group's mission is to prolong the healthy lifespan of an individual by the prevention of age-related diseases. Ageing is the major risk factor of age-related diseases resulting in multimorbidity of the majority of the population aged 60 years and over. Understanding the basis of the human ageing process and its influence on age-related diseases is the starting point for establishing targeted interventions. @AgeMelbourne is currently conducting four large, longitudinal, studies examining the clinical and biological phenotypes of geriatric populations in inpatient and outpatient settings. All @AgeMelbourne studies demonstrate a strong translational component that is, improving diagnostics and therapies for age-related diseases based on a solid methodological and biological understanding. The @AgeMelbourne Research Group includes an internationally-recognised and dedicated team of academic research staff and students with a diverse background of clinical research skills and knowledge, making it an exciting and inspiring group to work with.

ACRF Translational Research Laboratory

GROUP LEADER: Professor David S Ritchie **T:** +61 3 9342 2520 **E:** david.ritchie@mh.org.au
Location: Royal Melbourne Hospital **W:** Personal web page

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

Joanne Davis, David Ritchie, Nick Huntington **E:** david.ritchie@mh.org.au **W:** Personal web page

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.

Bone and Mineral Research Group

GROUP LEADER: Professor John D Wark **T:** +61 3 83443258 **E:** jdwark@unimelb.edu.au
W: Personal web page

14. Improving Vitamin D status and related health in young women: The Safe-D study – Part B

Prof. John D Wark **T:** +61 3 8344 3258 **E:** jdwark@unimelb.edu.au
Location: Department of Medicine (Royal Melbourne Hospital) University of Melbourne Parkville.

Vitamin D deficiency is an important health risk for young women, particularly during child-bearing years. Vitamin D deficiency is also associated with increased risk of many chronic health conditions including cardiovascular disease, poor bone and muscle health, mental ill-health and infection. Part B of the Safe-D study aims to investigate the safest and most effective way to increase vitamin D levels in vitamin D deficient young women. This study is a randomised controlled trial (RCT) to measure the effectiveness of (1) a behavioural intervention (using mobile-based application to encourage safe levels of sunlight exposure) and (2) 1000 IU per day vitamin D supplementation to increase vitamin D levels and a wide range of health outcomes over 12 months.

15. A critical analysis of Sunsmart behaviour in young Australian women

Prof John Wark, Prof George Varigos, Prof Suzanne Garland **T:** +61 3 8344 3258
E: jdwark@unimelb.edu.au **W:** Personal web page
Location: Department of Medicine, (RMH) Parkville Campus
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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

16. Air pollution may impair vitamin D status in young Victorian women

Prof John Wark, Ms Alexandra Gorelik **T:** +61 3 8344 3258 **E:** jdwark@unimelb.edu.au
Location: Department of Medicine, (RMH) Parkville Campus

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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

17. Dietary habits and mental health in females aged 16-29

Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik **T:** +61 3 8344 3258
E: jdwark@unimelb.edu.au **W:** Personal web page **Location**: Department of Medicine, (RMH)

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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

18. Metabolic health of females with Type 1 Diabetes aged 16-25 years

Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik **T:** +61 3 8344 3258
E: jdwark@unimelb.edu.au **Location**: Department of Medicine, (RMH) Parkville Campus

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. Suitable for Honours, MDRP, MBiomedSc, or Masters by Research studies.

19. Vitamin D status and multiple health outcomes in females aged 16-25 years participating in a randomized controlled trial

Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik **T:** +61 3 8344 3258
E: jdwark@unimelb.edu.au **W:** Personal web page

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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

20. Vitamin D status and multiple health outcomes in females aged 16-25 years participating in a randomized controlled trial

Prof John Wark, Prof Suzanne Garland, Ms Alexandra Gorelik **T:** +61 3 8344 3258
E: jdwark@unimelb.edu.au **W:** Personal web page
Location: Department of Medicine, (RMH) Parkville Campus

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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

21. Longitudinal analysis of health outcomes in 16-29 year old females

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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. Suitable for Honours, MDRP, MBiomedSc, MPH, Masters by Research, or PhD studies.

22. Bone health and its long-term predictors post-bone marrow transplantation

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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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

23. Monitoring for atypical femoral fracture (AFF) risk

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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. Suitable for Honours, MDRP, MBiomedSc, MPH, or Masters by Research studies.

Boussioutas Laboratory: Gastrointestinal Cancer

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

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Location: Peter MacCallum Cancer Centre

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.

25. Functional characterization of candidate genes involved in the progression of gastric cancer

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Location: Peter MacCallum Cancer Centre

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 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 model systems.

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.

26. Role of the Tumour Microenvironment in Gastric Cancer

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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 have 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.

CORe Unit (Clinical Outcomes Research Unit)

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27. Long-term disability outcomes in multiple sclerosis

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Prevention of irreversible disability is currently the most important goal of disease-modifying therapy for multiple sclerosis. Only limited information is available regarding the long-term impact of the available immunomodulatory therapies. Moreover, the information about the effectiveness
of these therapies at various disease stages is lacking. Finally, there is currently no therapy approved for treatment of progressive multiple sclerosis phenotypes. This program studies accumulation of disability in different disease phenotypes and during different stages of multiple sclerosis. It focuses on the ability of disease modifying therapies to ameliorate accumulation of irreversible disability.

28. Evaluation of different treatment strategies in multiple sclerosis

A/Prof Tomas Kalincik **T:** +61 3 9342 4404 **E:** tomas.kalincik@unimelb.edu.au
Location: Melbourne Brain Centre, Royal Melbourne Hospital

The results of randomised clinical trials provide key evidence for regulatory approvals of disease modifying drugs in multiple sclerosis. However, evidence-based long-term clinical management of multiple sclerosis can only come from expertly conducted cohort studies. Two themes are of particular importance to neurologists and their patients: A comprehensive head-to-head evaluation of the available disease-modifying therapies and the role of the available disease-modifying therapies in different pathways of disease management.

This program compares effectiveness of the available disease-modifying therapies for multiple sclerosis in the context of the whole patient population, including patients typically excluded from clinical trials. Furthermore, it investigates the interactions between disease/patient characteristics and the effectiveness of different DMTs. Finally, it examines management strategies common in real-world clinical practice but typically omitted from the design of clinical trials, such as treatment switch or discontinuation.

29. Phenotypic characterisation of multiple sclerosis

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Multiple sclerosis is a disease with a broad spectrum of clinical and subclinical presentations. Our understanding of their patterns (such as frequency and topography of clinical relapses, radiologically apparent brain damage, neurological disability and cognitive impairment) is limited. New metrics enabling more detailed, in-depth phenotypisation of the disease (such as volumetric MRI or accessible instruments for screening of cognitive function) are now becoming available for use in clinical practice. This program broadens our understanding of multiple sclerosis phenotypes. It studies the patterns and impact of clinical relapses, disability trajectories, quantitative (volumetric) MRI changes and cognitive function, with emphasis on the prognostic value of the identified patterns. It also implements volumetric MRI in clinical practice and establishes its translational value at the individual patient level.

30. Personalised therapy for multiple sclerosis

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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 clinical relapses and relapse-related disability accrual.

Despite the rapid development of pharmacotherapy, 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 multiple sclerosis phenotype and treatment response. From the patients' perspective, any time spent on disease modifying therapies with suboptimal individual effect translates into ongoing loss of capacity. While an enormous effort is being invested into developing new, more potent therapies, it is of paramount importance that use of the currently available therapies is optimised.

31. Precision therapy for multiple sclerosis

A/Prof Tomas Kalincik **T:** +61 3 9342 4404 **E:** tomas.kalincik@unimelb.edu.au
Location: Melbourne Brain Centre, Royal Melbourne Hospital

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.

Epilepsy and Neuropharmacology

Professor Terence O'Brien **T:** + 61 3 8344 5490 **E:** obrientj@unimelb.edu.au
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32. Identifying Predictors of Death in Patients with Epileptic and Psychogenic Seizures

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Location: The Department of Medicine, The Royal Melbourne Hospital

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

33. Sodium Selenate as a Disease Modifying Treatment for Probable Behavioural Variant Fronto-temporal Dementia

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Location: The Department of Medicine, The Royal Melbourne Hospital

Frontotemporal dementia (FTD) is generally due to abnormalities either in a protein called tau (45%) or a protein called TDP-43 (45%). In both types of FTD the protein aggregates into 'clumps' that block brain cell function. There are currently no treatments for either type of FTD. Our group has successfully run several research trials using a drug called sodium selenate that prevents the aggregation of tau in brain cells. We have shown that sodium selenate is safe in humans and that it has measurable benefits in Alzheimers disease (a different type of dementia to FTD). This study is an early phase study in which participants with FTD receive sodium selenate and are followed over 12 months. During this period standardised measurements of safety, cognition and neuroimaging (MRI, PET) will be undertaken.

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

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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.

35. Plasma biomarkers for epileptogenesis and epileptic seizures

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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.

36. M2 Polarization of microglia as a new approach targeting temporal lobe epilepsy

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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.

37. Neuropharmacological strategies for disease modification and prevention of the development of epilepsy

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Location: The Department of Medicine, The Royal Melbourne Hospital, and The Melbourne Brain Centre.

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

38. Biomarkers of epileptogenesis and epilepsy disease progression

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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.

39. The role of microparticles in traumatic brain injury.

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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.

40. Microglial activation and neurological disease.

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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.

41. The contribution of P2X7R and microglial activation in the neurological deficits of temporal lobe epilepsy.

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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.

42. Monocytes in Multiple Sclerosis

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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.

43. Barriers to early epilepsy diagnosis and the impact of diagnostic delay
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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.

Epilepsy and Precision Medicine

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44. Development of a low cost, point-of-care diagnostic platform
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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.

45. Developing highly sensitive point-of-care molecular diagnostic devices malaria eradication
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Detection of very low-density malaria infection i 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 fulfill diagnostic gaps required for malaria elimination.

46. Acquired epilepsy in Alzheimer's disease

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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.

47. Management and prognosis of first seizure and newly diagnosed epilepsy

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Seventy million people have epilepsy with 34–76 per 100,000 developing the condition every year. To formulate rational treatment plans, it is important to understand the different clinical courses and patterns of response to antiepileptic drugs, ideally by following outcomes from the point of treatment initiation. This project will perform analysis focusing on patients presenting with first seizure and their response to the initial therapies and their relationship with long-term treatment outcomes and development of pharmacoresistance in newly treated epilepsy patients. The student will be involved in recruiting and following up eligible patients. Basic knowledge and skills in biostatistics is preferred.

48. Wearable devices for non-invasive, ambulatory seizure monitoring and prediction

Professor Patrick Kwan, Professor Terence O'Brien
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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.

49. Clinical utility and cost-effectiveness of genomic sequencing for epilepsy

Professor Patrick Kwan **E**: patrick.kwan@unimelb.edu.au
Genetic variants have been found to cause epilepsy as well as affect how people respond to treatment. Whole exome sequencing is a new method of genetic testing that has the advantage of being able to screen all the genes in a person. Currently it is mainly being used for research purposes. The purpose of this prospective study is to find out whether genomic sequencing offers value for money when used in the clinical setting to help diagnose people with epilepsy.

50. Predictors and mechanisms of cutaneous adverse drug reactions: a multi-omic approach

Professor Patrick Kwan, Dr Alison Anderson
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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.

51. Long-term Prognosis of Antiepilpetic Drug Therapy in People with Newly Diagnosed and Treated Epilepsy

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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.

52. Treatment Gap in People with Newly Diagnosed Epilepsy in Australia

Professor Patrick Kwan, Dr Ben Chen **E:** patrick.kwan@unimelb.edu.au **E:** chen.z@unimelb.edu.au

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.

53. Cognitive and emotional phenotypes of generalised epilepsies

Dr Genevieve Rayner, Dr Charles Malpas **E:** genevieve.rayner@florey.edu.au

The evolving understanding of epilepsy is that it is a disease that propagates along and alters brain networks; often the same brain networks that subserve cognitive or emotional processes (Rayner, Epilepsy Curr, 2017). As such, network disease in epilepsy may give rise not only to the principal problem of seizures, but also to

cognitive and psychological comorbidities (Scheffer et al., Epilepsia, 2017). Patients deemed to have a generalised epilepsy show a diversity of seizure types and pathogenic mechanisms, but all typically show generalized spike-wave activity on EEG. While there is a robust body of evidence attributing distinct profiles of cognitive deficits to different focal epilepsy syndromes, less is known about the cognitive and emotional processing of patients with generalised epilepsies. The clinical consensus seems to be that many of these patients are unimpaired by clinical standards, and so comprehensive studies of their behavioural profiles are rare. However, there is growing evidence that a subset of these patients do perform worse than healthy controls in some domains (Elger et al., Lancet Neurology, 2004), although the lack of systematic data on this topic renders it unclear which patients with generalised epilepsy are most vulnerable to cognitive and emotional decrement, and if there are distinct phenotypes of cognitive and emotional decrement within this population. The scope of this project would support both a Masters and PhD candidate. Cognitive and emotional processing will be measured using the brief iPad-based NIH Toolbox with patients recruited from multiple Comprehensive Epilepsy Programs across Melbourne, with supervision from experts in neurology and neuropsychology.

Gastroenterology

54. Locus Specific Databases in Hamartomatous polyposis syndromes

Professor Finlay Macrae E: finlay.macrae@mh.org.au **Location**: The Royal Melbourne Hospital

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.

55. Barrett's Oesophagus

Professor Finlay Macrae and Dr Andrew Metz E: finlay.macrae@mh.org.au **Location**: RMH

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.

Hamilton Laboratory

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56. Molecular signaling pathways controlling gene expression during chronic disease progression

Dr Adrian Achuthan **T:** +61 3 8344 3298 **E:** aaa@unimelb.edu.au **W:** Personal web page
Location: Dept of Medicine, Royal Melbourne Hospital

Inflammation is increasingly being seen to have a significant impact on many chronic diseases such as arthritis, cancer, Alzheimer's disease, obesity/type II diabetes and heart diseases. The socio-economic

burden of inflammatory diseases is enormous both in terms of direct health care costs and indirect non-health care costs.

Granulocyte macrophage-colony stimulating factor (GM-CSF) is a prosurvival factor for monocytes/macrophages, but also act as a proinflammatory cytokine. Thus, GM-CSF has been targetted in a number of clinical trials associated with inflammation. However, this may lead to undesirable side-effects, such as infections, given its role in prosurvival of immune cells. We are examining GM-CSF-mediated molecular signalling pathways controlling the expression of inflammatory genes critical for the progression of such inflammatory diseases.

57. Elucidating molecular signaling pathways controlled by anti-inflammatory steroids

Dr. Adrian Achuthan and Prof. John Hamilton **T:** +61 3 8344 3298 **E:** aaa@unimelb.edu.au
Location: Dept of Medicine, Royal Melbourne Hospital

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 identify 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 glucocorticoid-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).

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

Dr. Adrian Achuthan and Professor Stephen Rogerson **T:** +61 3 8344 3298 **E:** aaa@unimelb.edu.au
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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.

59. The role of granulocyte macrophage colony stimulating factor (GM-CSF) in arthritis and inflammation

Associate Professor Andrew Cook **T:** +61 3 8344 3290 **E:** adcook@unimelb.edu.au
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Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the population. We have shown that GM-CSF is important for the development of several models of inflammation and

arthritis. Furthermore, blockade of GM-CSF is effective at reducing arthritis severity and arthritic pain. Phase 1 clinical trials are now underway in human rheumatoid arthritis. However, we still do not completely understand how GM-CSF is acting during inflammation and arthritis. We are investigating the role of GM-CSF in inflammatory and arthritic pain and disease, including how GM-CSF interacts with other mediators and what downstream events GM-CSF is controlling during inflammation.

60. The role of Interferon Regulatory factors in Arthritis

Dr Andrew Cook, Prof John Hamilton and Dr. Ming-Chin Lee
Associate Professor Andrew Cook **T:** +61 3 8344 3290 **E:** adcook@unimelb.edu.au
Location: Department of Medicine, Royal Melbourne Hospital

Macrophages are key cells involved in the destruction of joints during rheumatoid arthritis. In this project you will investigate how the transcription factors, called interferon regulatory factors (IRFs), control gene expression in macrophages during inflammatory models of arthritis. You will also determine if targeting IRFs would be a beneficial treatment for arthritis. You will be cutting tissue sections and measuring the expression of these novel proteins. You will be inducing murine models of arthritis, 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 models.

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.

61. The role of a novel macrophage inflammatory mediator in arthritis

Dr Andrew Cook, Prof John Hamilton and Dr. Ming-Chin Lee
Associate Professor Andrew Cook **T:** +61 3 8344 3290 **E:** adcook@unimelb.edu.au

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.

Healthy Ageing Program

GROUP LEADER: Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
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62. Lifestyle Factors for Healthy Ageing

Dr Helen Brown, Professor Cassandra Szoeke
Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
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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 morbidity and quality of life in health and ageing. 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.

63. Multimorbidity and ageing women

Dr Lucy Busija, Professor Cassandra Szoeke
Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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 within one year and suits a candidate with an interest in a number of disease areas.

64. Physical Activities for Healthy Ageing

Dr Steve Simpson Jr, Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au

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.

65. Diet and Healthy Ageing

A/Professor Allison Hodge, Professor Cassandra Szoeke
Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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, small sample sizes, and most have examined the Mediterranean diet. 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 diets on cognitive performance and health. 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.

66. Patterns of Violence in Australian Women – A twenty year follow up Study

Dr Kelly Hand, Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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

67. Social and physical activities in ageing women

Dr Helen Brown, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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

68. Lipoproteins and Cardiovascular Risk from Mid- to Late-life in Women

Dr Stephen Campbell, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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. Hormone Therapy and Cardiovascular Disease in Postmenopausal Women

Dr Alicia Goodwill, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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.

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.

70. Nutrient intake and mental health

A/Professor Allison Hodge, Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
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There is increasing evidence to suggest that diet may play an important role in short- and long-term mental health. Research has found that a regular diet that is rich in fresh, unprocessed, nutrient-dense foods – particularly a Mediterranean-style diet – is associated with better mental health, and reduced risk of depression. Given that mental health is one of the greatest contributors to non-communicable disease burden, this is a growing area of research. This project will examine the impact of diet from mid- to late-life on mental health for a cohort of healthy Australian women. A major benefit 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.

71. Lifestyle Factors and Cognitive Health

Dr Helen Brown, Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

Several studies have described the benefit of lifestyle change for healthy ageing and cognitive improvement. 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:
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 suit a candidate with an interest in neuropsychology

72. Early detection of cognitive decline and disease

Dr Stephen Campbell, Professor Cassandra Szoeke **T:** +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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.

73. Life-long exposures for Healthy Ageing

Dr Melissa Coulson, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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 health. This project will involve direct hands-on participant evaluation. 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 and opportunity for publication.

74. Iron and Fatigue

Dr.Steve Simpson Jr, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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 industry partnerships.

75. Vitamin D deficiency and balance

Professor Meg Morris, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

Low levels of vitamin D are relatively common in older women Australian, which is concerning given that vitamin D is essential for the maintenance of healthy bone and muscle. There is evidence to suggest that vitamin D may also be important for the maintenance of balance in women. This project will examine the relationships between vitamin D and balance in non-elderly postmenopausal 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 already collected data over 20 years and 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.

76. Causes of Depressive Symptoms in Early Ageing

Dr Melissa Coulson, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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.

77. Lifestyle factors and effects on mood in elderly women

Dr Stephen Campbell, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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 morbidity and quality of life in health and ageing. 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.

78. Anxiety and neurodegeneration in preclinical Alzheimer's Disease

Dr Stephen Campbell, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
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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.

79. The effect of anxiety on cardiovascular risk in healthy ageing women

Dr Alicia Goodwill, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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

80. The importance of diet in health

Dr Allison Hodge, Professor Cassandra Szoeke T: +61 3 8344 1835 **E:** cszoeke@unimelb.edu.au
Location: Centre for Medical Research, Royal Melbourne Hospital

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.

International and Immigrant Health

GROUP LEADER: Professor Beverley-Ann Biggs T: +61 3 8344 3256 **E:** babiggs@unimelb.edu.au
Location: Level 5, Room 5054, Peter Doherty Institute, Parkville **W:** Personal web page

81. Does weekly iron supplementation increase iron uptake in pregnant Vietnamese women, and improve maternal and infant health?

Professor Beverley-Ann Biggs T: +61 3 8344 3256 **E:** babiggs@unimelb.edu.au
Location: Level 5, Room 5054, Peter Doherty Institute, Parkville **W:** Personal web page

This project examined the impact of weekly iron supplementation provided to women during pregnancy on maternal anaemia, infant birth weight, and infant growth and development in the first six months, and on maternal antenatal and postnatal depression and well-being. Data was collected on social and demographic factors as well as wealth index and nutrition profile. Evidence from this study that an intermittent iron supplementation approach is suitable for use in Vietnam in pregnant women living in areas where rates of anaemia and iron deficiency have reduced over the last few years. This approach has the potential to vastly increase compliance and effectiveness of iron supplementation in pregnancy, reduce rates of iron deficiency anaemia, and improve birth weight, and infant development.

Jones Laboratory: Epilepsy and Behaviour

82. Serotonin in epilepsy

Group Leader: Associate Professor Nigel Jones T: +61 3 9035 6402 **E:** ncjones@unimelb.edu.au
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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.

83. Does stress contribute to epilepsy?

Associate Professor Nigel Jones T: +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

Chronic stress is strongly linked to the development of psychiatric disturbances, such as depression and anxiety disorders. Interestingly, these disorders are prevalent in a high proportion of people suffering from epilepsy. Recent literature suggests that environmental exposures such as stress may also contribute to the development of epilepsy. This project aims to investigate this hypothesis, with a parallel focus on anxiety and depression-like behaviour. Using rodent models, this study will determine whether exposure to repeated stressful situations, either early in life or in adulthood, 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.

84. Does stress contribute to epilepsy?

Associate Professor Nigel Jones **T:** +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

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. This research will open up avenues for new therapies for seizures which may be appropriate for many different epilepsy patients.

85. Functional disconnections and the pathophysiology of psychosis

Associate Professor Nigel Jones **T:** +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

Functional disconnections in cortico-thalamo-cortical (CTC) systems, the neuronal circuits of attention, cognition and perception, are thought to underlie 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.

86. Role of specific interneuron types in cognitive behaviour

Associate Professor Nigel Jones **T:** +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

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.

87. NMDA receptor antagonists and cognitive dysfunction

Associate Professor Nigel Jones **T:** +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

NMDA receptors are ion channels involved in many aspects of neural communication and neural plasticity. 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.

88. Antidepressants in epilepsy

Associate Professor Nigel Jones **T:** +61 3 9035 6402 **E:** ncjones@unimelb.edu.au

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.

Melbourne EpiCentre

Group Leader: Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au
Location: Royal Melbourne Hospital **W:** Personal web page

89. Development of early warning systems for hypoglycaemia

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

Prof. Paul is developing methodologies and techniques to analyse continuously monitored blood glucose levels in patients with diabetes, with the aim of developing a system to warn patients about incipient hypoglycaemia or hyperglycaemia.

90. Evaluation of cardio-metabolic effects of Incretin-based therapies in type 2 diabetes

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

Prof. Paul is leading this major research project to evaluate the cardio-metabolic effects of GLP-1 receptor agonists and DPP-4 inhibitors. The initial findings from this study have already gained attention from the international research community with considerable media coverage, and he was invited at international clinical conferences to present the initial findings. The first study on the possible association of treatment with GLP1 RA Exenatide with cardiovascular risk, in comparison to treatment with insulin, has been published in Cardiovascular Diabetology (2576 accesses since published in January 2015).

91. Evaluation of the obesity paradox in diabetes: A longitudinal case-control study of half a million patients

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

Prof. Paul is leading an NHMRC funded large comparative longitudinal case-control study to understand the possible reasons behind the observed “obesity paradox” in patients with type 2 diabetes. This study is based on half-a-million subjects with complete clinical, prescription, medical and event history data from 1990 to 2014, with a median follow-up period of 9 years.

92. Hypoglycaemia and its consequences

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

In collaboration with Novo Nordisk, Amylin Pharmaceuticals and University of Leicester, Prof. Paul is leading a research project to evaluate the risk factors associated with mild-moderate and severe hypoglycaemia, and the long-term consequences of hypoglycaemia.
The first real-world based study evaluating the cardiovascular consequences of hypoglycaemia in both type 1 and type 2 diabetes patients was published in Diabetes Care 2015; 38: 316-22. The possible risk factors associated with hypoglycaemia differentiated between patients treated with insulin and incretin-based therapies was published in Journal of Diabetes 2015; 7: 60-7

93. Pathophysiology of glycaemic and cardiovascular risk factors in diabetes

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

Prof. Paul is leading a research program to evaluate the long-term effects of glycaemic and other risk factors on cardiovascular and mortality risks in patients with diabetes. This programme of studies is based on the

longitudinal electronic data on about 2.5 million patients with diabetes and non-diabetic controls, from primary care and ambulatory care databases of UK and USA.

94. The Dementia Care Pathway for use in acute care

Associate Professor Dina LoGiudice **E:** dclogi@unimelb.edu.au
W: Personal web page **Location:** Royal Melbourne Hospital, Parkville

The aim of this study is to develop a Dementia clinical pathway for use in acute hospitals, to implement it in two hospitals in Victoria, Australia and to evaluate the implementation and impact of the pathway on clinical outcomes.

Dementia is a major health and social challenge, and is one of Australia's National Health Priority Areas. Over 350,000 Australians are estimated to be living with dementia, and this number is expected to continue to grow (Alzheimer's Australia, 2016). People with dementia are high users of hospital services, with 25% having at least one hospital stay each year (Australian Institute of Health and Welfare, 2013). In hospital, people with dementia have poorer outcomes compared to people without dementia, including longer length of stay and are greater risk of in-hospital complications including falls, pressure injuries, delirium and death (Bail et al., 2013; Tropea et al., 2016). Studies have also shown hospitalised people with dementia are not always receiving best practice or quality dementia care (Sampson et al., 2006; Wenger et al., 2007).
Improving the quality of dementia care in hospitals and associated outcomes is imperative. To assist clinicians in delivery of best practice dementia care in hospital, we proposed to develop a multidisciplinary Dementia Care Pathway (the pathway) for use on acute medical wards at two hospitals in Victoria, Australia. Care or clinical pathways "…are structured multidisciplinary care plans used by health services to detail essential steps in the care of patients with a specific clinical problem. They aim to link evidence to practice and optimise clinical outcomes whilst maximising clinical efficiency" (Rotter et al., 2010).

Emergency departments and general medical units will be the focus of the pathway activities as this is where the majority of people with dementia present and are admitted to at the two hospital sites. Multidisciplinary staff including medical, nursing, pharmacy and allied health staff from these departments will be involved in the pathway project activities. The pathway project will include: assessing current practice, identifying barriers and facilitators to implementation of best practice dementia care, developing a new pathway document to fill gaps in current practice, selecting and tailoring implementation strategies, pilot implementation at two sites and evaluating the pathway (process and outcome evaluation).

95. Therapeutic Inertia & Risk Burden in Type 2 Diabetes

Professor Sanjoy Paul **T:** +61 3 9342 8772 **E:** Sanjoy.Paul@mh.org.au

With funding support from Novo Nordisk, Prof. Paul is leading a research project to evaluate the therapeutic inertia and risk burden in patients with type 2 diabetes. These studies are based on primary care and ambulatory care large population level databases from UK and USA.

The initial findings have already gained international attention, with the first study reporting the consequences of delay in intensification of treatment for glycaemic control on cardiovascular risk recently published in Cardiovascular Diabetology (2015, 14:100; 3715 accesses since published online in August 2015). His interview during EASD conference on this study can be seen in here.

Molecular Epilepsy

Group Leader: Dr Kim Powell T: +61 3 9035 6394 E: kpowell@unimelb.edu.au
W: Personal web page

96. Investigating molecular and physiological determinants of Sudden Unexplained Death in Epilepsy in acquired and genetic animal models of epilepsy and in epileptic patients.

Dr. Kim Powell, Dr. Pablo Casillas-Espinosa, Prof. Terry O'Brien **T**: 9035 6394
E: kpowell@unimelb.edu.au

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

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. 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 $Ca_v3.1$ and $Ca_v3.2$ 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)).

Aims

1. To investigate the molecular mechanisms contributing to the cardiac dysfunction on genetic and acquired animal models of epilepsy.
2. To investigate whether patients with chronic epilepsy have alterations in cardiac electrophysiology and ion channel expression compared to matched non-epileptic control subjects.
3. 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.
4. To investigate if by pharmacologically suppressing seizures we can alleviate the altered cardiac electrophysiological function and HCN2 and T-type calcium channel transcriptional repression
5. To investigate cardiac structure and function in genetic and acquired animal models of epilepsy.

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).

97. Does epilepsy cause a secondary cardiac channelopathy?

Dr. Kim Powell, Prof Terence O'Brien, Dr. Marian Todaro **E**: kpowell@unimelb.edu.au; obrientj@unimelb.edu.au

Location: The Department of Medicine, The Royal Melbourne Hospital and Melbourne Brain Centre.

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.

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

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

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).

99. Is telomere length associated with cardiac dysfunction in chronic epilepsy
Dr. Kim Powell **T**: 9035 6394 **E**: kpowell@unimelb.edu.au
Dr. Anne McIntosh **E: a.mcintosh@unimelb.edu.au**
Location: Department of Medicine (RMH), MBC Neurosciences Building, Parkville

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)) in human cardiac tissue from patients with epilepsy and in genetic and acquired animal models of epilepsy.

MS and Comorbidities Team

100. Movement Disorders and Cognitive monitoring in MS
Group Leader: Dr Anneke van der Walt **T:** +61 3 9342 7000 **E:** annekevd@unimelb.edu.au
Location: Melbourne Brain Centre at RMH, Level 4 C, Royal Melbourne Hospital, Grattan St. Parkville

An important ongoing project, is the implementation of a computerized cognitive test using a purpose-specific website, www.msreactor.com. The software was made available by Neurability (www.neurability.br) and was adapted for the website by A/Prof David Derby from the Florey institute of Neuroscience. The testing platform allows neurologists to quickly test a person with MS' reaction speed and working memory and results are immedialtely availble. The test is also available for self-testing allowing people with MS to test themselves at home. The goal of this study is to develop a monitoring tool that can provide information about cognitive deterioration very early in people with MS that can then help guide decisions about treatment changes as well as direct people to appropriate resources that can aide cognition. Our previous work has shown that the tests are more sensitive than research-type cognitive tests (the PASAT) to detect changes over 12 months. In collaboration with Box Hill Hospital and the MSBase group, we plan to implement msreactor in large groups of people with MS.

101. Prospective validation of acoustic speech analysis in progressive multiple sclerosis
Anneke van der Walt, A/Prof Adam Vogel T: +61 3 9342 7000 **E:** annekevd@unimelb.edu.au

Location: Melbourne Brain Centre at RMH, Level 4 C, Royal Melbourne Hospital, Grattan St. Parkville

Speech production problems (dysarthria) in people with MS are common and can affect quality of life. New technologies allow for detailed acoustic analysis of speech patterns that are closely correlated with MS disease stage and MRI volumetric data. In addition, pilot data collected in our clinic demonstrates a close correlation between acoustic changes and upper limb dexterity in MS. This project will be a prospective clinical study implementing a novel, app-based, voice recording system in a cohort of patients with progressive (SPMS and PPMS). Clinical data will be recorded in the MSBase and volumetric MRI data will be prospectively collected.

MS Biology, Genomics and Prognostics Group

102. Prediction of long-term disease outcomes in people with Multiple Sclerosis or Clinically Isolated Syndromes

Dr Vilija G. Jokubaitis **T:** +61 3 9342 4404 **E:** vilija.jokubaitis@unimelb.edu.au
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Location: Melbourne Brain Centre, Royal Melbourne Hospital

MS outcomes are highly variable amongst individuals, ranging from very mild, with no significant persistent disability, to very severe, and even fatal disease within a few years. Therefore, one of the principal objectives in the care of people with MS is to prevent or reduce the accumulation of permanent neurological disability. At present, the ability to predict a person's likely MS outcome at first diagnosis is limited. This relative inability to predict future disability outcomes is a great opportunity lost. Better prediction could lead to a more individualised risk/benefit ratio evaluation for different therapies, and ultimately improve quality of life and productivity for patients with early MS.

This project aims to develop tools that help improve our understanding of factors that determine risk of developing irreversible neurological disability in people with MS, with a focus on clinical and paraclinical factors, pregnancy, demographics, treatment effects and environment.

103. Environmental determinants of disability accumulation in Multiple Sclerosis

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

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 assist in the implementation of an environmental impact survey into the international MSBase registry. Further, it will utilise existing 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.

104. Genotype-Phenotype Correlations in Multiple Sclerosis

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

MS is a complex polygenic and environmentally determined disease. MS risk has been linked to over 200 single nucleotide polymorphisms (SNPs), each with average increased odds of developing MS within the range of 1.1-1.3. To date, the only replicated genetic modifier of any MS phenotype the main risk allele, HLA-DRB1*1501, which confers reduced age of onset. The best evidence to-date for a genetic basis underlying phenotypic outcomes comes from a small number of cross-sectional genome-wide association studies *a priori* dedicated to a search for severity signals. These studies have had modest success in cumulatively identifying 109 *putative* modulators disease outcome. Critically however, a functional dichotomy between genes involved in susceptibility and those that regulate severity has been reported, the latter having an over-representation of signals related to CNS and embryonic development, and cellular respiration. Therefore, strong preliminary evidence exists that genetic variation does influence phenotypic outcomes, however this remains to be validated. This PhD project will utilise genetic data that is linked to a global observational cohort to identify genotype-phenotype correlations with (1) clinical phenotypes (2) MRI phenotypes. Further, genetic variants will be incorporated into prognostic models to determine whether they exert an independent effect on disease outcomes.

Outcomes and impact
The identification of genetic predictors of MS phenotype will have a significant impact on MS management, with the capacity for rapid translation in to clinical practice through the development of a genetic test of disease outcome. It will inform risk/benefit decision-making when selecting appropriate therapies for individuals, and thus maximise quality of life and reduce economic burden. Biologically, success in genetic analyses will provide insight into the molecular mechanisms of MS progression.

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. Within the MSBase observational cohort study, we have formed a special interest group to examine genetic predictors of disease outcome. This group comprises 11 centres that have the capacity to undertake genetic studies. Here, our cohort comprises 8,574 patients, with 60,000 patient-years of follow-up with visits occurring on average every 6 months.

105. Impact of pregnancy on long-term outcomes in women with multiple sclerosis – assessment of mechanism

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

Data suggests that pregnancy in women with MS may exert long-term health benefits, with comparisons of women with and without pregnancy (but otherwise equivalent disease at a baseline time point) demonstrating 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 Victoria, 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.

106. Impact of pregnancy on long-term outcomes in women with multiple sclerosis

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

Data suggests that pregnancy in women with MS may exert long-term health benefits, with comparisons of women with and without pregnancy (but otherwise equivalent disease at a baseline time point) demonstrating less accumulation of disability in those who have had pregnancies. However, past studies have been limited by data quality issues and availability of large data sets. Here, using data from the MSBase registry, we aim to determine whether pregnancy during MS does indeed have long-term impact on disease outcomes. Whether 1) gravidity, parity, or both affect disease outcomes, 2) whether pregnancy is only beneficial early in disease course 3) if beneficial effects of pregnancy are limited to a time window, 4) whether pregnancy is beneficial in patients with certain MS phenotypes and not others.
This PhD project will suit someone with a strong statistical background and/or interest. It will involve the development of complex statistical models utilising clinical outcomes data and environmental data derived from the international MSBase Registry.

Outcomes and impact
Determination of pregnancy impacts on long-term outcomes in women with multiple sclerosis will allow more appropriate counselling of women with MS about the impact of pregnancy on their disease course and therefore enable evidence-based decision making with regards to family planning.
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.

107. Pharmacogenomic studies in Multiple Sclerosis

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

Multiple sclerosis, an autoimmune, neurodegenerative condition, is the most common cause of non-traumatic neurological disability in young adults. At present twelve immunomodulatory or immunosuppressive therapies with varying levels of treatment efficacy are approved for the treatment of MS in Australia (13 globally). All drugs have been shown to reduce relapse rates in clinical trials, and some have also been shown to have disability progression and MRI benefits. However, individuals are known to have variable responses to these therapies, and can be classed as treatment responders, intermediate responders and non-responders. This project aims to identify genetic markers of treatment response to three of the newer, and more commonly prescribed MS drugs; the monoclonal antibody against ^{3}a4-integrin, natalizumab, the sphingosine-1-phosphate receptor modulator, fingolimod, and the monoclonal antibody targeted against the B-Cell antigen CD20, rituximab.
This PhD project will utilise genetic data that is linked to a global observational cohort to identify genetic markers of treatment response and non-response.

108. Environmental determinants of disability accumulation in Multiple Sclerosis

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

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 assist in the implementation of an environmental impact survey into the international MSBase registry. Further, it will utilise existing clinical outcomes data and environmental data derived from the international MSBase Registry to identify environmental determinants of disease outcome.

109. Determining predictors of post-partum relapse in women with MS

Dr Vilija Jokubaitis **T:** +61 3 9342 4404 **E:** vilija@unimelb.edu.au
Location: Melbourne Brain Centre, Level 4 Centre, Royal Melbourne Hospital

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.

Neural Dynamics Laboratory

110. Effects of Drugs on Cognition-Related Brain Wave Signals in the Rat

Dr Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au
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It is increasingly recognised that the rhythmic signals recorded with the electroencephalogram (EEG), or "brain waves" are not just the "noise" of neural activity, but are probably frequency specific channels through which cognition related signalling occurs, including memory encoding. High frequency ("gamma") brain wave activity has been associated with higher cognitive activity in humans and animals, and is disrupted in psychosis and schizophrenia.

A largely neglected area of study in this area is the role of voltage-gated ion channels that have a significant role in the generation of neuronal and network rhythmicity. In this project, signals related to cognitive processing, including gamma frequency oscillations and place cells will be recorded with microelectrode arrays. The effects of antipsychotic drugs and some related compounds, including potassium and sodium channel modulators, will be examined.

This project has considerable potential to reveal how psychoactive drugs work at the whole brain level, and provide clues for better therapies.

111. Electrophysiological Properties of Human Brain Neuronal Tissue

Dr Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au

Almost all electrophysiological observations of neural normal function, drug responsiveness and abnormal states such as epilepsy in have been performed on rodent brain tissue. It is becoming clear, however, that human tissue has significant differences from rodent brain.
This project presents an almost unique opportunity to study human brain tissue at the single neuron and network level by utilising tissue taken in the course of neurosurgical procedures. Individual neurons are prepared by enzymatic dissociation, and recorded with patch electrodes. Network properties are recorded using intact brain slice.

For this project, the main aims are to identify the properties of voltage gated ion channels, in particular sodium and potassium currents. An area of special interest is the HERG channel subtype, which is likely to play an important role in brain function, but almost completely uncharacterised in any neural system.

112. How do Anti-Epileptic Drugs Work?

Dr Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au

Despite many years of use and research, it is still not clear how even some of the oldest forms of antiepileptic drugs (AED's) work. What 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.

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

Dr. Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au

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 that actually develops epeileptic discharges. 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.

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

Dr Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au

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. We have developed a unique method to model AED effects which will be used in these simulations. The programs "Neuron" and Matlab are 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**.**

An extension of this project is to study cognitive phenomena in realistic "conductance" based models using a form of distributed "Hopfield" network structure that depend on intrinsic oscillations in the theta (4-8 Hz) and gamma (30-80Hz), as observed in vivo.

115. Electrophysiology of Human Brain Tissue

Dr Chris French **T:** +61 3 8344 3276 **E:** frenchc@unimelb.edu.au

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.

Rogerson Laboratory

116. Antibody to PfEMP1: role in immunity to malaria in children and pregnant women

Group Leader: Professor Stephen Rogerson **T:** +61 3 8344 3259 **E:** sroger@unimelb.edu.au
W: Personal web page **Location:** Department of Medicine at the Doherty Institute.

Plasmodium falciparum erythrocyte membrane protein 1 is the major binding ligand and major antigen expressed on the surface of infected red blood cells, and is a major target of human immunity. Our work is aiming to identify PfEMP1 types that are associated with specific disease syndromes, and to characterise antibody responses that protect against particular pfEMP1 types and particular disease syndromes.

We use a variety of assays to measure antibody against PfEMP1 types and correlate this with exposure to, or protection from, malaria syndromes. These include malaria in pregnant women, and severe malaria in young children. Assay types include ELISAs; luminex assays (to measuure antibody to multiple PfEMP1 protein fragments simultaneously), assays to measure antibody toPfEMP1 expressed on the surface of infected red blood cells; and antibodies that opsonise infected cells for uptake by phagocytic cells.
Our aim is to identify protective correlates of immunity, and assays that can be deployed tomeasure immunity to PfEMP1 in the context of protection against malaria disease.

117. Innate immune responses to Plasmodium falciparum infected erythrocytes

Professor Stephen Rogerson **T:** +61 3 8344 3259 **E:** sroger@unimelb.edu.au
Location: Department of Medicine, Doherty Institute, Building 248, the University of Melbourne

The project takes place in Melbourne and in Blantyre, Malawi. Our aims are:

1. To determine whether parasite binding phenotype helps drive the innate immune response to Plasmodium falciparum infected erythrocytes
2. To discover whether binding phenotype and gene expression of clinical isolates influences cytokine secretion in vivo and in vitro. We are collecting malaria parasites from Malawian children with severe or mild malaria, and will examine the immune responses they generate from white blood cells.
3. To compare the proportions of different monocyte subsets and their uptake of malaria infected cells, using samples from children with severe and mild malaria. Follow up studies after recovery are also done.
4. To understand the roles of intermediate monocytes in clearance of malaria and cytokine response, and its possible importance in severe malaria.

Our outcome of interest is an improved understanding of how host and parasite combinations increase risk of severe malaria.

118. Is there a role for adipose (fat) tissue in malaria?

Dr Elizabeth Aitken **E:** elizabeth.aitken@unimelb.edu.au **W:** Personal web page
Location: Peter Doherty Institute for Infection and Immunity, Building 248, The University of Melbourne

We know that fat tissue may affect how the immune system fights the malaria parasite because it can produce lots of hormones and cytokines which regulate the immune response, nfortunately we don't know what role fat tissue plays in the immune response to malaria. Also we know that malaria parasites like to stay in the fat tissue but we don't know how this may change the fat tissues structure or function. With these points in mind our main aim is to characterise how fat tissue plays a role in the immune response and pathology of malaria.

119. Development of an ultra-sensitive non-invasive point-of-care immunosensor for malaria elimination

Prof. Stephen Rogerson, Prof. Patrick Kwan, Prof. Stan Skafidas
Professor Stephen Rogerson, **E**: sroger@unimelb.edu.au; Patrick Kwan, **E**: patrick.kwan@unimelb.edu.au
Location: Doherty Institute, Dept. Medicine (RMH), Centre for Neural Engineering, University of Melbourne

Detection of very low-density malaria infection is essential for malaria elimination, but current diagnostics are insensitive and/or costly. Supported by the Bill & Melinda Gates Foundation, this project aims to develop 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 fulfill diagnostic gaps required for malaria elimination. Our pilot data suggest superior sensitivity that can detect protein at levels three logs lower than conventional malaria rapid diagnostic tests (RDTs), and two logs lower than next generation IDTs (Infection Detection Tests).

120. Hiding out in the Placenta. Investigating how glycosaminoglycans can modulate the immune system during malaria and pregnancy.
Dr Louise Randall and Professor Stephen Rogerson E: louise.randall@unimelb.edu.au **T**: 8344 2181
Location: Doherty Institute, Department of Medicine (RMH), Centre for Neural Engineering, UoM.

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.

Burnet Institute

121. Investigating the acquisition and maintenance of immunity to malaria in infants and pregnant women
A/Prof Freya Fowkes, Professor James Beeson
E: freya.fowkes@burnet.edu.au; james.beeson@burnet.edu.au
Location: Burnet Institute

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

122. Understanding the targets and mechanisms of human immunity to malaria
Professor James Beeson, Dr Jack Richards E: james.beeson@burnet.edu.au **;** Richards@burnet.edu.au
Location: Burnet Institute

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

123. Vaccines against malaria
Professor James Beeson, Dr Jack Richards E: james.beeson@burnet.edu.au **;** Richards@burnet.edu.au
Location: Burnet Institute

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

124. Identifying targets and mechanisms of the acquired immunity to severe malaria in children
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E: sroger@unimelb.edu.au **Location**: Burnet Institute

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

125. Healthy Mothers, Healthy Babies in Papua New Guinea – The impact of Nutrition, Malaria and STIs on pregnant women and infants
Professor James Beeson, Associate Professor Freya Fowkes, Dr Philippe Boeuf
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Location: Burnet Institute

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 Government, 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

126. Development of novel point-of-care diagnostics tests and surveillance tools
Professor James Beeson, Dr Philippe Boeuf, Associate Professor David Anderson
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Location: Burnet Institute

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

127. Developing new assays to identify mechanisms of human immunity to malaria
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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

128. To examine genetic variants of Nfkb1 as a biomarker of poor maternal health
Dr Raffi Gugasyan, Dr Philippe Boeuf, Associate Professor Freya Fowkes
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Location: Burnet Institute

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.

129. Healthy Mothers, Healthy Babies: Maternal nutrition and inflammation and their impact on pregnancy outcomes

Professor James Beeson, Dr Philippe Boeuf
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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 on maternal nutritional status 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 Healthy 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

130. The impact of malaria control measures on the acquisition of immunity to malaria

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Location: Burnet Institute

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

131. Novel serological and molecular tools for malaria surveillance and intervention

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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.

132. Developing new antimalarial drugs that block protein trafficking and host cell modification in malaria parasites

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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 unknown. 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 red blood 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.

133. Epidemiology of malaria transmission in Papua New Guinea

Dr Leanne Robinson, Associate Professor Freya Fowkes
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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.

134. Immunity to malaria in children and pregnant women
Associate Professor Freya Fowkes freya.fowkes@burnet.edu.au **Location**: Burnet Institute

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

135. Understanding malaria transmission and immunity to inform malaria elimination
Prof James Beeson E: james.beeson@burnet.edu.au **Location**: Burnet Institute

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

136. Antibody engineering to study responses mediating protective immunity to malaria and other infectious diseases
Dr Jack Richards, Professor James Beeson jack.richards@burnet.edu.au; james.beeson@burnet.edu.au
Location: Burnet Institute

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.

137. Understanding the acquisition and maintenance of antibodies against malaria
Dr Jack Richards, Dr Leanne Robinson, Professor James Beeson
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Location: Burnet Institute

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.

138. Mechanisms of transmission-blocking immunity against malaria
A/Prof Siddhartha Mahanty, Prof Stephen Rogerson **E:** smahanty@unimelb.edu.au

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 complex process that requires the parasite to overcomes immune defences in both hosts. Antibodies directed against sexual stages of Pf can directly inhibit growth of sexual stages (gametocytes). The extent of antibody-mediated immunity against Pf gametocytes, the sexual stage in humans, and the functional properties of antibodies that can block transmission, are not well understood. The goal of this project is to characterize immune mechanisms underlying transmission blocking immunity mediated by antibodies to sexual stage parasites in human malaria. To investigate these mechanisms, we will identify malaria-infected individuals who have antibodies to gametocytes and gametocyte-derived antigens of Pf and determine the biophysical and functional properties of anti-gametocyte antibodies that confer transmission-blocking properties. A better understanding of the mechanisms of transmission blocking immunity will facilitate the development of vaccines aimed blocking transmission – an "altruistic" vaccine. 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 biophysical

and functional properties (characterizing properties such as IgG isotypes, receptor binding, opsonisation, phagocytic efficiency, NK cell activation, cytokine stimulation and parasiticidal activity). The functional characteristics will be correlated with transmission blocking activity to identify the most closely correlated properties. Methodology employed: ELISA, flow cytometry, immunofluorescence, antibody subclass analysis, opsonisation, bead phagocytosis assays, NK activation, statistical methods for quantitative analysis of data.

Savige Laboratory

139. New therapies for inherited renal disease – chaperones, stem cells and other agents

Prof Judy Savige, Dr Dongmao Wang **T: 8344 3260 or** jasavige@unimelb.edu.au
Location: University Department of Medicine, Royal Melbourne Hospital

Alport syndrome is an inherited renal disease that results in end-stage renal failure, hearing loss, and ocular abnormalities. Forty % of cases are due to missense and 40% to nonsense mutations. The aim of this study is to investigate treatments that can be used for these types of different mutations, using cell lines derived from patients. The aim is to derive the optimum dose, and to understand the mechanisms by which these agents have their effect. They will then be used in a pilot study in patient to determine the effect on the rate of deterioration in renal function.

140. New genes for inherited renal disease

Prof Judy Savige, Dr Dongmao Wang **T: 8344 3260 or** jasavige@unimelb.edu.au
Location: University Department of Medicine, Royal Melbourne Hospital

Many causes of renal failure are due to inherited renal disease but the genes have not been identified yet. The aim of this study is to identify the mutant genes in some of our families and then to prove that the mutations are pathogenic using laboratory based assays.

Semple Laboratory: Developmental Neurotrauma

141. Neuroimaging and neuropathological biomarkers of social dysfunction after paediatric brain injury

Bridget Semple **E:** bridget.semple@unimelb.edu.au

Social behaviour problems are a common and debilitating consequence of traumatic brain injury in children, and a key contributor to poor quality of life for survivors. However, mechanisms underlying the emergence or persistence of social deficits after injury remain poorly understood, particularly in the context of ongoing brain maturation throughout childhood. Damage to the social brain network, a distributed circuit of frontal temporo-limbic brain regions, is hypothesised to underlie problems with social behaviours and communication that emerge after brain injury in both humans and animal models. Using a clinically-relevant mouse model of traumatic injury to the paediatric brain, this project will therefore evaluate whether disruption of white matter integrity in the social brain network is integral to the manifestation of social deficits after early life brain injury. Using advanced neuroimaging modalities and post-mortem immunohistochemical staining, we will evaluate the developmental trajectory of key white matter tracts in mice as they age after a paediatric brain injury compared to uninjured controls, aiming to identify in vivo neuroimaging biomarkers predictive of long-term social behaviour deficits.

Stroke Imaging and Treatment

142. EXTEND-IA TNK

Group Leader: Associate Professor Bruce Campbell **T:** +61 3 9342 4408 **E:** bcam@unimelb.edu.au
W: Personal web page
Location: MBC@RMH, 4th floor, Main Block, Royal Melbourne Hospital

A clinical trial comparing two different clot-dissolving medications in ischemic stroke patients planned for endovascular stroke treatment. EXTEND-IA TNK randomizes patients to alteplase 0.9mg/kg versus tenecteplase 0.25mg/kg The primary outcome is the rate of reperfusion prior to endovascular treatment. https://www.clinicaltrials.gov/ct2/show/NCT02388061

Stroke Research Group

143. Saving Brain and Changing Practice in Stroke

Project Lead: Professor Stephen Davis **T:** +61 3 9342 8448 **E:** stephen.davis@mh.org.au
W: Personal web page **Location:** Level 4 Centre, Royal Melbourne Hospital.

Stroke is a massive global health challenge. With 17 million new strokes each year and 6 million deaths, stroke is a leading cause of chronic disability. Stroke is the second commonest cause of death worldwide and the leading cause of death in 39% of countries. We have shown that effective acute stroke therapies modify the dynamic evolution of stroke pathophysiology. Following arterial occlusion, most patients have a mismatch between the region of the irreversibly injured ischemic core and the surrounding region of hypoperfused but salvageable brain. This ischemic penumbra is the target of acute stroke therapy. Reperfusion strategies that attenuate infarct growth include IV tPA and now endovascular thrombectomy for large artery occlusion. Our pathophysiological research has confirmed the principle that 'time is brain', and hence our overall research strategy will now focus on the patient journey from the time of acute stroke pre-hospital through to recovery.

144. Rapid point of care diagnosis of stroke: development of GFAP biomarkers

A/Prof. Bernard Yan, Professor Patrick Kwan **E**: Bernard.Yan@mh.org.au
E: patrick.kwan@unimelb.edu.au **W:** Personal web page

Stroke is the leading cause of disability and the third leading cause of death in the industrial world. In the United States alone each year some 600,000 patients suffer from an ischaemic stroke each year, and about 25% die within the first month. GFAP is a cytoskeletal filament found almost exclusively in astrocytic cells within the central nervous system. Under physiological conditions GFAP is typically not at detectable levels in the blood . When astrocytes are damaged they undergo astrogliosis, during which GFAP production markedly increases. When this damage becomes terminal, astrocytes undergo necrosis and cytolysis, spilling their contents into the extracellular milieu. In ICH, shear stress and mechanical forces during haematoma expansion result in instant astrocyte necrosis and destruction of the blood-brain barrier, with subsequent translocation of GFAP into the blood. The release of GFAP occurs much more slowly in AIS, with serum GFAP levels peaking between 48 and 96 hours after onset15. These distinct patterns have allowed several studies to investigate GFAP biomarkers to differentiate AIS and ICH. Some of these studies have also correlated GFAP concentrations with stroke severity, haematoma volume, or outcome in ICH, indicating that GFAP may also be of prognostic value An accurate, rapid, and portable diagnostic GFAP biomarker assay is of great potential value in pre-hospital stroke care. First, it would differentiate between AIS and ICH, allowing for expedited triage assessment and subsequent diversion to the most appropriate stroke centre. Second, it would allow ambulance personnel to initiate potentially lifesaving treatment that would have otherwise been delayed until a radiological diagnosis is confirmed.

145. Intensive continuous monitoring of motor function in acute stroke: development of a broadband-based wearable motion detector (STROKE WATCH 3)

A/Prof. Bernard Yan, Professor Stephen Davis **T:** +61 3 9342 8448 **E:** stephen.davis@mh.org.au
E: Bernard.Yan@mh.org.au **W:** Personal web page

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.

The National Centre for Antimicrobial Stewardship (NCAS)

146. Optimising the Use of Antifungal Agents

Dr. David Kong **E**: david.kong@monash.edu

Invasive Fungal Diseases (IFDs) are associated with high mortality and are costly to treat. Indeed, immunocompromised patients (e.g. lung transplant or cancer patients) are at risk of contracting IFD. For these reasons and to prevent the emergence of 'multi-drug resistant' fungal infections, antifungal medicines should be used appropriately and in a cost-effective manner. This PhD will focus on a number of important aspects related to the use of antifungals in patients [e.g. recipients with bone marrow or solid organ transplant (e.g. liver or lung transplants), HIV/AIDS or cancer, fungal keratitis]. Successful candidate will have the opportunity to investigate one or more of the following areas: a) The managements and outcomes of invasive fungal diseases. b) The pharmaco-economics of using high cost antifungal medicines in immunocompromised patients. c) Investigate the pharmacokinetics/pharmacodynamics of antifungal medicines. d) Antifungal stewardship and prescribing practices in Australian and other healthcare setting. This PhD will be undertaken in-collaboration with relevant clinicians who are based in Australian hospitals (e.g. National Centre for Infection in Cancer, Peter MacCallum Cancer Institute, The Alfred, Westmead Hospital, NHMRC's National Centre for Antimicrobial Stewardship) and may be extended to those overseas. Successful candidate will have the opportunity to gain skills in one or more areas depending on his/her preference for viz. clinical or non-laboratory research, laboratory-based research, or combination of laboratory and non-laboratory research. The project will generate important data to optimise the use of antifungal medicines.

The Vascular Bionics Laboratory

147. Development of a Minimally Invasive Chronic Neural Interface

Group Leaders: Dr Nicholas Opie and Dr Thomas Oxley **E:** nicholas.opie@unimelb.edu.au
Location: Dept. of Medicine and Radiology, Clinical Sciences Building, Royal Melbourne Hospital

Brain computer interfacing is a rapidly expanding field of research. The technology allows communication between the external environment and the complex biological signaling of the brain. Significant advances have been accomplished to date with groups demonstrating willful thought control over a number of prosthetic devices. Despite these achievements, many interface systems fall prey to the body's foreign body responses which render the device inoperable after a number of years.

Our team has designed and tested a novel interface prototype which can be implanted into a cerebral blood vessel without the need to perform a craniotomy. Our technology and delivery methodology mitigates the severe risks associated with craniotomy, circumnavigates chronic inflammatory responses, and dramatically reduces the long-term possibility of infection.

The Vascular Bionics Lab are currently progressing towards a first-in-human trial. We are conducting pre-clinical studies directed towards patient safety, chronic biocompatibility and device efficacy. It is our hope to improve the risk to benefit ratio of a neural interfaces and make it a worthwhile option to those suffering paralysis.

148. Development of a Brain-Machine-Interface Training Paradigm
Dr Nicholas Opie and Dr Thomas Oxley **E:** nicholas.opie@unimelb.edu.au

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.

Translational Traumatic Brain Injury Laboratory

149. Biomarkers of brain concussion in Australian Rules Footballers
Dr. Sandy Shultz, Prof. Terence O'Brien, Prof. Andrew Kaye **E**: sshultz@unimelb.edu.au
Location: Department of Medicine RMH, Melbourne Brain Centre, Kenneth Myer Building

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).

Neuroimaging

Group Leader: Professor Patricia Desmond **T:** +61 3 9342 8398 **E:** patricia.desmond@mh.org.au
W: Personal web page
Location: Department of Radiology, Royal Melbourne Hospital

150. Non-Invasive Imaging of High-Flow Arteriovenous Intracranial Shunts
Prof Roland Bammer, Prof Patricia Desmond
E: roland.bammer@unimelb.edu.au **E: Patricia.Desmond@mh.org.au**

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.

151. Phantom Development for Longitudinal Multi-Center Clinical Trials

Prof Roland Bammer, Prof Patricia Desmond
E: roland.bammer@unimelb.edu.au **E: Patricia.Desmond@mh.org.au**

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.

152. An Economics Study of Specialized Radiology Practices

Prof Roland Bammer, Prof Patricia Desmond
E: roland.bammer@unimelb.edu.au **E: Patricia.Desmond@mh.org.au**

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.

Diabetes

153. Investigating the effect of a proactive inpatient diabetes team assisted by networked blood glucose technology in high risk cardiology inpatients.

Dr. Spiros Fourlanos, Dr. Mervyn Kyi **E: spiros.fourlanos@mh.org.au**

A new RMH proactive model of diabetes care has been devised. This study aims to evaluate the effect of proactive care using an inpatient diabetes team (IDT) intervention, assisted by networked blood glucose meter technology, to deliver proactive and safe diabetes care in cardiology inpatients. This IDT intervention will provide early and rapid assessment in all high risk diabetes inpatients admitted to the cardiology wards aiming to avoid extremes of glycaemia ie. hypoglycaemia (blood glucose < 4.0 mmol/L) and hyperglycaemia (blood glucose >15.0 mmol/L). The proactive IDT intervention will aim for a 50% decrease in adverse glycaemic days (ie. any inpatient day where the blood glucose is < 4 or >15 mmol/L).

DEPARTMENT OF PSYCHIATRY

Melbourne Neuropsychiatry Centre Research

Research Overview

Melbourne Neuropsychiatry Centre conducts world leading research with focus on specific streams in Psychiatry/Psychology and Neuroscience. An overview of the research interest streams within the centre and the project work being carried out by our research groups can be found listed under RESEARCH PROJECTS and on the Centre website http://www.psychiatry.unimelb.edu.au/mnc

154. Depression and Anxiety Neuroscience

RESEARCH GROUP LEADER: Associate Professor Ben Harrison **T:** + 61 3 834 41959
E: habj@unimelb.edu.au **W:** Personal web page **Location:** Level 03, Room 345, Alan Gilbert Building

Research Overview

Our aim is to develop integrated models based on affective neuroscience for treatment-oriented research and discovery in mood and anxiety disorders.

155. Testing a dynamic neural model of impaired medial prefrontal cortex function in youth depression

A/Prof Ben Harrison & A/Prof Chris Davey **E: habj@unimelb.edu.au**
Location: Melbourne Neuropsychiatry Centre, Department of Psychiatry

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 clinical - including treatment response characteristics - of the depressed participants will be examined in detail.

156. A neural systems model of fear dysregulation in anxiety disorders

A/Prof Ben Harrison & A/Prof Chris Davey **E: habj@unimelb.edu.au**
Location: Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne.

People with anxiety disorders experience fear that is excessive and disproportionate to their current circumstances – they have difficulty regulating their fear responses. Recent work by our team has shown that successful fear regulation relies on the coordinated activity of an extended 'ventromedial prefrontal cortex system' that mediates adaptive emotional responses to perceived threat and safety signals. This project will combine functional magnetic resonance imaging, psychophysiological monitoring and advanced brain connectivity analysis, to develop a unified neural systems model of human fear regulation that will be applied to the study of three clinical anxiety disorders in young people. We will test the hypothesis that these disorders are characterised by mostly common alterations of this underlying neural system. The capacity of the model to predict clinical outcomes over a 12-month period will also be assessed. This project will represent the most comprehensive neuroscientific study of fear regulatory processes in people with anxiety disorders. Its results may inform the discovery of novel brain systems targets with direct relevance to the optimisation of treatments.

157. A brain model of disturbed self-appraisal in social anxiety disorder

A/Prof Ben Harrison & A/Prof Chris Davey **E: habj@unimelb.edu.au** **E: c.davey@unimelb.edu.au**
Location: The National Centre of Excellence in Youth Mental Health

An essential characteristic of people with social anxiety disorder (SAD) is that they feel threatened by the criticism of others, and during social interactions respond by focusing excessively on themselves. This disturbance in self-appraisal processes is associated with marked anxiety, and is one of the features of SAD

that is targeted by cognitive behavioural therapy (CBT). The aim of the proposal is to examine such a brain model of disturbed self-appraisal in SAD, and to determine whether it can identify participants who are likely to respond to CBT. Participants in our study will be young people (16-25 years of age) with SAD who are presenting for treatment for the first time. They will be recruited from local headspace centres, and will be matched with a group of healthy control participants. They will undergo baseline functional magnetic resonance imaging (fMRI) before commencing a 10-week course of CBT, and will be scanned again at the completion of treatment. We will employ an advanced supervised machine-learning methodology to determine the predictive value of the brain model in evaluating the likelihood of treatment response. The results of the study promise to better align therapy approaches with brain mechanisms in SAD, with the aim of advancing the development of brain-based biomarkers that can guide mental health treatments.

158. A brain based model of anxiety sensitivity in panic disorder
A/Prof Ben Harrison & A/Prof Chris Davey **E: habj@unimelb.edu.au**
Location: Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne.

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.

159. Imagining Brain Development in the Childhood to Adolescence Transitions Study
A/Prof Sarah Whittle, Dr. Julian Simmons **T**: swhittle@unimelb.edu.au; **W**: Personal webpage

We are seeking an enthusiastic and motivated candidate for a PhD project beginning in the first half of 2018. The project is a joint initiative of the Melbourne Neuropsychiatry Centre (Department of Psychiatry) and the Melbourne School of Psychological Sciences, The University of Melbourne, and the Murdoch Childrens Research Institute, Victoria, Australia. The candidate, supervised by Dr. Sarah Whittle, will be required to contribute to a unique ongoing longitudinal study that aims to investigate the association between puberty, brain development, and mental health, from late childhood to mid-adolescence. The successful candidate will have the opportunity to craft a thesis topic that suits their interests, and may utilise a range of data being collected, including structural and functional imaging, hormonal, environmental (e.g., parenting), and mental health data. The successful applicant should have an undergraduate and/or honours degree in a relevant field, have excellent results (first class honours or equivalent) and/or have relevant research experience. Experience in clinical interviewing, endocrinology, &/or structural or functional MRI analysis will be looked upon favourably.

160. Bugs and Brains: The Gut and Mental Health Study
Dr. Julian Simmons, A/Prof Sarah Whittle **T:** +61 3 9035 8318 **E:** jgs@unimelb.edu.au
W: Personal web page **Location:** Redmond Barry Building University of Melbourne Mebourne

We are seeking an enthusiastic and motivated candidate for a PhD project beginning in the first half of 2018. The project is a joint initiative of the Melbourne School of Psychological Sciences, the Melbourne Neuropsychiatry Centre (Department of Psychiatry), the Melbourne Dental School and the Department of Biochemistry and Molecular Biology, The University of Melbourne, Victoria, Australia. The candidate, supervised by Dr. Julian Simmons, will be required to contribute to a unique study that aims to investigate the association between mental health, gut health, and the microbiome, in adults. The successful candidate

will have the opportunity to craft a thesis topic that suits their interests, and may utilise a range of data being collected, including bacterial, hormonal, immune, metabolite, and gut and mental health data. The successful applicant should have an undergraduate and/or honours degree in a relevant field, have excellent results (first class honours or equivalent) and/or have relevant research experience. Experience in clinical interviewing, microbiology, endocrinology, immunology, bioinformatics, &/or metabolomics will be looked upon favourably.

161. The worldwide ENIGMA MDD consortium: detecting robust imaging markers of depression
Dr. Lianne Schmaal and Dr. Chris Davey **T**: 0393422886 **E**: lschmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne

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/

The overall aims of the ENIGMA MDD consortium are to 1) identify robust imaging markers of MDD, 2) establish the neurobiological correlates underlying variation in disease profile and disease course, and 3) identify the genetic factors affecting neurobiological alterations in MDD using available genome-wide data, and relate the genetic risk profile to the implicated brain circuits. Currently, 31 research sites from around the world are participating in ENIGMA MDD and sharing neuroimaging data.

The PhD 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) and genetic data, organising and harmonising databases, communicating with members of the consortium, 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.

162. Understanding the heterogeneity of youth depression using machine learning methods
Dr. Lianne Schmaal and Dr. Chris Davey **T**: 0393422886 **E**: lianne.schmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne

The conventional approach to diagnosing MDD does not reflect the complexity and heterogeneity of the disorder, and consequently, reproducible neurobiological and genetic studies remain elusive. Depression is a complex heterogeneous disorder and the diagnostic label of MDD based on the classificatory systems of the DSM and ICD is likely to encompass biologically distinct phenotypes with different aetiologies and different optimal treatment strategies. This project aims to disentangle phenotypic heterogeneity of youth depression by integrating neurobiological information with clinical and behavioural data using machine learning techniques.

This project (or potentially PhD project) will use functional magnetic resonance imaging (fMRI) and data on symptom dimensions. The student will be involved in the acquisition of the neuroimaging and clinical data, processing of neuroimaging data and using machine learning methods to stratify the patients. Patients will be recruited from Orygen Youth Health and headspace centres. 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.

163. Understanding brain correlates of cognition in psychosis

Dr Tamsyn Van Rheenen and Dr Vanessa Cropley **E**: tamsyn.van@unimelb.edu.au
W: https://findanexpert.unimelb.edu.au/display/person706069

We are seeking an academically high-performing student with a background in psychology, psychophysiology and/or neuroscience to be involved in an exciting new PhD study exploring brain correlates of cognitive deficits in individuals with bipolar disorder and schizophrenia. The project will be conducted in the context of a collaboration between the Melbourne Neuropsychiatry Centre at the University of Melbourne, the Brain and Psychological Sciences Research Centre of Swinburne University and the Monash Alfred Psychiatry Research Centre of Monash University and the Alfred Hospital in Melbourne, Australia. The candidate, supervised by Dr Tamsyn Van Rheenen, Dr Vanessa Cropley and Professor Susan Rossell, will be required to contribute to a larger neuroimaging study of severe mental illness that utilises various magnetic resonance imaging and neurophysiological techniques. This will involve assistance with data collection (at Swinburne University), data analysis and manuscript preparation. The successful candidate will have the opportunity to craft a specific research question aligned to their interests utilising the resting state neuroimaging and behavioural data collected as part of this project. The successful applicant should have an undergraduate and/or honours degree in a relevant field and have good results (first or upper second class honours or equivalent). Prospective PhD and combined PhD/Masters students are encouraged to apply. Research experience in clinical interviewing, neurocognitive testing and neuroimaging analysis will be looked upon favourably. Students with their own scholarship funding are welcomed.

164. Understanding emotional information processing in bipolar disorder

Dr Tamsyn Van Rheenen **E**: tamsyn.van@unimelb.edu.au

We are seeking an academically high-performing student with a background in psychology, psychophysiology and/or neuroscience to be involved in a PhD study exploring emotional information processing in individuals with bipolar disorder. The project will be conducted in the context of a collaboration between the Melbourne Neuropsychiatry Centre at the University of Melbourne, the Brain and Psychological Sciences Research Centre of Swinburne University and the Monash Alfred Psychiatry Research Centre of Monash University and the Alfred Hospital in Melbourne, Australia. The candidate, supervised by Dr Tamsyn Van Rheenen, Dr Vanessa Cropley, Prof Susan Rossell and Prof Christos Pantelis, will be required to contribute to a larger neuroimaging study of severe mental illness that utilises various magnetic resonance imaging and neurophysiological techniques. This will involve assistance with data collection (at Swinburne University), data analysis and manuscript preparation. The successful candidate will contribute to a project aimed at understanding top-down and bottom-up integration of emotional information in bipolar disorder, and ascertaining the impact that structural brain disturbances have for the coordination of brain function during such information processing. The successful applicant should have an undergraduate and/or honours degree in a relevant field and have good results (first or upper second class honours or equivalent). Prospective PhD and combined PhD/ Masters students are encouraged to apply. Research experience in clinical interviewing, neurocognitive testing and neuroimaging analysis will be looked upon favourably. Students with their own scholarship funding are welcomed.

165. Neuroimaging in schizophrenia/bipolar disorders

Dr Tamsyn Van Rheenen **E**: tamsyn.van@unimelb.edu.au

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.

166. Neuroimaging in schizophrenia-spectrum disorders
Dr Vanessa Cropley, Dr Tamsyn Van Rheenen, Dr Andrew Zalesky T: (03) 8344 1876
E: vcropley@unimelb.edu.au; **Dr Tamsyn Van Rheenen E:** tamsyn.van@unimelb.edu.au
Location: Melbourne Neuropsychiatry Centre, The Alan Gilbert Building, 161 Barry Street, Carlton South

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.

167. Understanding the neural circuitry underpinning emotional information processing in bipolar disorder
Dr Tamsyn Van Rhenen, Dr Vanessa Cropley, Prof Christos Pantelis E: tamsyn.van@unimelb.edu.au
Location: Melbourne Neuropsychiatry Centre, and Department of Psychiatry

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.

168. Risk and resilience in schizophrenia from the perspective of brain networks
Dr Andrew Zalesky, Dr Vanessa Cropley T: (03) 8344 1876 E: vcropley@unimelb.edu.au

Schizophrenia is a debilitating neuropsychiatric disorder ranked among the world's top-ten leading causes of death and disability. To date, most research in schizophrenia has focused on identifying genetic, biochemical, neurobiological, and cognitive risk factors that may lead to the illness. However, there is increasing recognition for the need to identify putative factors conferring resilience to developing the disorder. This project will use state-of-the-art neuroimaging techniques to investigate neuroimaging-based resilience endophenotypes associated with schizophrenia. Specifically, the project will investigate brain networks, which are a comprehensive description of the brain's internal wiring. Advances in magnetic resonance imaging (MRI) have now enabled reliable mapping of an individual's white matter network or connectome. The study will investigate brain networks in patients affected with schizophrenia, their unaffected siblings and healthy comparison subjects. Resilience endophenotypes will be identified by comparing ill individuals with their unaffected family members. The student will be involved in the development and/or application of neuroimaging tools from a brain network perspective.

169. Understanding the heterogeneity of youth depression using machine learning
Dr. Lianne Schmaal and Dr. Chris Davey T: 0393422886 E: lianne.schmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, UoM

The conventional approach to diagnosing MDD does not reflect the complexity and heterogeneity of the disorder, and consequently, reproducible neurobiological and genetic studies remain elusive. Depression is a complex heterogeneous disorder and the diagnostic label of MDD based on the classificatory systems of the DSM and ICD is likely to encompass biologically distinct phenotypes with different aetiologies and different optimal treatment strategies. This project aims to disentangle phenotypic heterogeneity of youth depression by integrating neurobiological information with clinical and behavioural data using machine learning techniques.

This project (or potentially PhD project) will use functional magnetic resonance imaging (fMRI) and data on symptom dimensions. The student will be involved in the acquisition of the neuroimaging and clinical data, processing of neuroimaging data and using machine learning methods to stratify the patients.

Patients will be recruited from Orygen Youth Health and headspace centres. 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.

170. The worldwide ENIGMA MDD consortium: detecting robust imaging markers of depression
Dr. Lianne Schmaal and Dr. Chris Davey T: 0393422886, E: lschmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, University o Melbourne

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/

The overall aims of the ENIGMA MDD consortium are to 1) identify robust imaging markers of MDD, 2) establish the neurobiological correlates underlying variation in disease profile and disease course, and 3) identify the genetic factors affecting neurobiological alterations in MDD using available genome-wide data, and relate the genetic risk profile to the implicated brain circuits. Currently, 31 research sites from around the world are participating in ENIGMA MDD and sharing neuroimaging data.

The PhD 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) and genetic data, organising and harmonising databases, communicating with members of the consortium, 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.

171. World-wide data-sharing to detect neurobiological alterations in MDD: the worldwide ENIGMA Major Depressive Disorder consortium

Dr. Lianne Schmaal T: 0477550490 E: lschmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, UoM.

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/

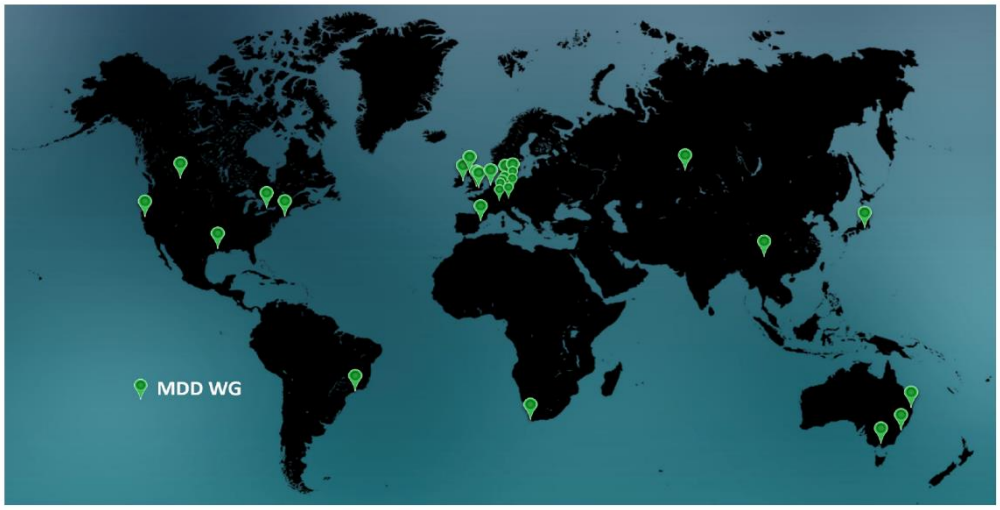

Figure 1: World map of institutes participating in the ENIGMA MDD working group

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 PhD 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) and genetic data, 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.

172. Identifying novel subtypes of youth depression and anxiety using machine learning methods
Dr. Lianne Schmaal, Dr. Chris Davey, Dr. Ben Harrison T: 0477550490 E: lianne.schmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, University of Melbourne

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.

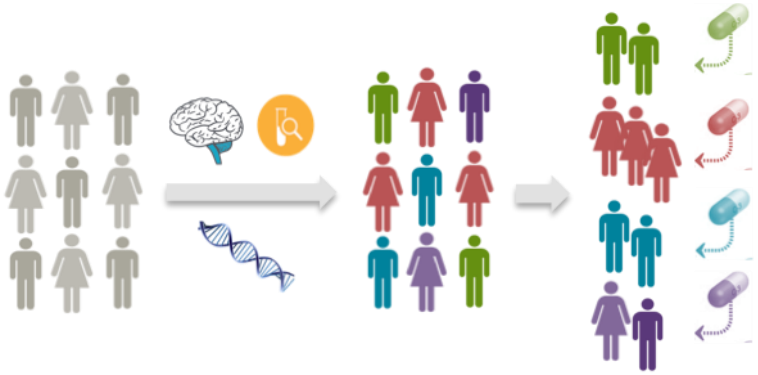

Figure: Identifying novel subtypes of youth depression and anxiety based on neurobiological and clinical characteristics

The PhD student 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. The student will report results in 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.

173. Neurobiology of Suicide Thoughts and Behaviours in Youth with Mental Disorders
Dr. Lianne Schmaal, T: 0477550490, E: lschmaal@unimelb.edu.au
Location: Orygen the National Centre of Excellence in Youth Mental Health, UoM.

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 PhD 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. The student will help organise and harmonise databases, communicate 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, (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.

174. Multimodal machine learning approaches to predicting outcome in early psychosis
Prof Stephen Wood **E**: S.J.Wood@bham.ac.uk or sjwood@unimelb.edu.au
Location: Orygen

PRONIA is an EU FP7 and NHMRC funded study that is looking to use machine learning techniques to improve the prediction of various clinical outcomes in people presenting with first episode psychosis. Initial efforts have focused on single modalities of data; for example, structural neuroimaging, or neurocognitive

performance. However, it is believed that greatly improved accuracies will be possible if multimodal analyses can be conducted that combine the relevant information from the unimodal data. This PhD project will work closely with the local investigators, Prof Stephen Wood & Prof Christos Pantelis, as well as the co-ordinating centre in Munich led by Dr Nikos Koutsouleris.

Academic Unit for Psychiatry of Old Age (AUPOA)

175. INDIGO Study: physical activity and goal-setting intervention for sedentary older adults at risk of cognitive decline

Prof Nicola Lautenschlager **E:** nicolatl@unimelb.edu.au **W:** AUPOA

Cognitive decline is common in old age. In Australia 1400 new cases of dementia are diagnosed each week with Alzheimer's Disease being the most common cause. Physical Activity (PA) appears to be one of the strongest factors to delay or prevent cognitive decline. Despite this, physical inactivity has been shown to increase with age. Changing this sedentary behaviour is difficult, and groups with health problems face an even greater challenge. However, it has been reported that motivators such as self-efficacy (confidence to exercise safely), the ability to set individual PA goals and enjoyment of the PA increase adherence.

The INDIGO Study is a single-blind randomised controlled trial based on the CONSORT guidelines. The primary aim of INDIGO is to determine whether a home-based physical activity intervention with individual goal setting and peer mentors can significantly increase PA levels in older adults who do not engage in leisure time physical activity and are at increased risk of developing Alzheimer's disease.

176. RAndomised trial to imProve the quality of lIfe of people with Dementia (RAPID)

Prof Nicola Lautenschlager **E:** nicolatl@unimelb.edu.au

Depressive symptoms are common and undermine the quality of life of people with Alzheimer's disease (AD). Cholinesterase inhibitors and antidepressants have all but no effect on the mood of patients, and their use is associated with greater risk of adverse events compared with placebo. The use of traditional psychotherapeutic interventions, such as cognitive behavioural therapy, is hindered by the presence of cognitive impairment.

Cognitive bias modification (CBM) is a novel, simple and safe intervention that targets attentional and interpretative biases associated with anxiety, dysphoria and depression. CBM operates through implicit learning systems, which are spared until late in the course of the dementia illness. Pilot data from Western Australia Centre for Healthy Ageing indicates that the use of CBM is feasible and, most likely, an efficacious treatment for people with depression in AD (DAD). Moreover, CBM is safe and unlikely to be associated with significant adverse events in this vulnerable population.

RAPID is a parallel, double-blind, controlled randomised trial. RAPID aims to examine the presence of attention and interpretation biases in people experiencing Alzheimer's disease, and investigate if the use of CBM for two weeks is associated with a reduction of depressive symptoms and/or improved quality of life. It is hoped that the RAPID trial will provide high quality evidence of efficacy in this important clinical area.

177. The Stand Up & Go Study: Physical activity and sitting time reduction program for older community members

In Australia 1400 new cases of dementia are diagnosed each week with Alzheimer's Disease being the most common cause. Physical Activity (PA) appears to be one of the strongest factors to delay or prevent cognitive decline. Despite this, physical inactivity has been shown to increase with age. Prolonged sitting is now also acknowledged as a public health issue, with strong evidence that increased levels of sedentary behaviour are associated with cardiovascular disease, diabetes, and more recently, poor cognition. The Stand Up & Go study is combining a PA program with a targeted program to reduce sitting time in vulnerable older adults who experience one or more major risk factors for cognitive decline (insufficiently active and T2DM). The aim of this pilot study is to investigate whether the participants can adhere successfully to such a combined

intervention in comparison to a stand-alone PA program. If successful, the combined physical activity and sitting reduction intervention represents a safe, easily accessible, affordable and highly translatable program and the results of a future larger RCT could inform clinical practice guidelines.

Melbourne Clinic Research

178. ARCADIA: Nutraceutical and Lifestyle Medicine Mental Health Research Group

A/Prof Jerome Sarris **E: jsarris@unimelb.edu.au**

ARCADIA is a specialised nutraceutical and lifestyle medicine mental health research group within The Professorial Unit based at The Melbourne Clinic. ARCADIA holds collaborations with The University of Melbourne, Swinburne University and the National Institute of Complementary Medicine (NICM) at Western Sydney University. Our vision is to enhance the treatment of mood and anxiety disorders by leading the research of nutraceuticals (pharmaceutical-grade standardised nutrient or plant-based medicines) and lifestyle medicine in the field of psychiatry. The group is part of the broader research unit focusing on the key areas of psychopharmacology, pharmacogenomics, and brain stimulation.

The group is conducting several NHMRC-funded double-blind randomised control trials using nutraceuticals in the treatment of mental disorders such as unipolar depression, generalised anxiety disorder, and obsessive compulsive disorder. A major focus of this research includes the study of pharmacogenomics, to examine genetic markers of treatment response and the prediction of efficacy and tolerability of these agents. We are also passionate about researching the emerging area of lifestyle medicine, and the application of diet, exercise etc. to enhance both physical and mental health.

Results of our ongoing NHMRC and collaborative industry-funded clinical studies continues to advance the treatment of depressive and anxiety disorders. This research is aimed at enhancing the education and clinical treatment of mental disorders, as well as growing public knowledge of these approaches.
Details of our current research studies can be found here: https://www.arcadia-research.com/

179. Therapeutic Innovations in Affective Disorders

The group based at the Melbourne Clinic is focused on research in treatments for affective disorders in the areas of psychopharmacology, pharmacogenomics, lifestyle interventions, integrative mental health models, nutraceuticals, and brain stimulation. The clinical research areas include major depressive disorder, bipolar disorder, treatment resistant mood disorder, anxiety disorders and related disorders.

Currently the research unit is conducting several double-blind randomised control trials (RCTs) using conventional and novel pharmacotherapies for affective and anxiety disorders. Interventions studied include both pharmaceutical psychopharmacological agents and nutraceuticals. A major focus of the unit's research includes the study of pharmacogenomics, to examine potential genetic markers of treatment response and the prediction of efficacy and tolerability. Of note, one of the key focus is nutraceutical and lifestyle medicine mental health research, and the unit is involved in several NHMRC-funded multi-centre projects testing novel nutraceutical compounds to improve mood or reduce anxiety in people with psychiatric disorders (see Arcadia research group).

The Melbourne Clinic Professorial Unit is involved in a number of collaborations in Victoria, nationally and internationally in Asia, Europe, and the USA.

St Vincent's Mental Health Research

Chair of Psychiatry, St Vincent's Mental Health Unit, Department of Psychiatry University of Melbourne
Professor David Castle **T:** 61 3 92134751 **E:** david.castle@svha.org.au
Location: Level 2 42, Nicholson Street, Fitzroy, Victoria **W:** Personal web page

Austin Health Research

Chair of Psychiatry, Austin Health

Professor Richard Kanaan **T:** +61 3 94963351 **E:** richard.kanaan@unimelb.edu.au
W: Personal web page

180. The neuropsychiatric consequences of androgen deprivation

Professor Richard Kanaan Richard.kanaan@unimelb.edu.au
Location: Department of Psychiatry, Austin Health, Heidelberg, VIC 3084

Patients with prostate cancer are often treated with androgen-deprivation therapy (ADT), which dramatically reduces their testosterone but is also responsible for some significant side effects, including on mood and cognition. Recent evidence suggests that, in men, some important biological actions attributed to testosterone are mediated via its metabolite, estradiol. We will conduct a randomized, placebo-controlled trial in 130 men receiving ADT to investigate whether selective restoration of estradiol is sufficient to prevent the side effects. This project in particular will examine the mood and cognition of the patients undergoing ADT and see whether they respond to estradiol replacement, using a combination of clinical and neuropsychological assessment, and functional and structural neuroimaging.

Centre for Women's Mental Health Research

181. Building Early Attachment and Resilience (BEAR) Study – evaluation of group intervention programs for parents with risk factors for attachment disorders.

Prof. Louise Newman **T**: 83452070 **E**: louise.newman@thewomens.org or
Dr Angela Komiti **T**:90357122 **E**: angelaak@unimelb.edu
Location: RWH and RMH

The primary aim of the BEAR study is to evaluate the efficacy of two psychologically- based interventions for infants of 'at risk' mothers (experiencing mental health problems) in order to promote the development of mother/infant attachment and therefore foster the development of resilient children. The interventions are: [1] the Mindbabybody program – a mindfulness-based program delivered in the antenatal period, focused upon decreasing maternal stress and anxiety by increasing self- awareness and acceptance through meditation-based practices, and [2] the Parenting with Feeling program- an attachment-based group parenting program delivered in the postnatal period, focused upon improving parental self-representation, emotional understanding and attachment relationship with their child. These two programs have been designed to help parents with mental health issues, improve their emotional responsiveness to their infants to foster secure attachment relationships between parents and child which in turn promote resilience for both groups. Recruitment for the study commenced mid-2015 and is ongoing.

182. Safe Mothers-Safe Babies – developing a screening tool and intervention program for pregnant women at risk of domestic violence.

Prof. Louise Newman **T**: 83452070 **E**: louise.newman@thewomens.org or
Dr Angela Komiti **T**: 90357122 **E**: angelaak@unimelb.edu
Location: RWH and RMH

PROJECT DETAILS: The Safe Mothers, Safe Babies project has been developed with the overall aim of improving identification and intervention approaches for women during pregnancy and the perinatal period who are at risk of, or experiencing interpersonal violence. It is recognised that this is a significant problem and a major contributor to stress and anxiety during pregnancy with significant implications for both the mother and for foetal development and infant outcome. The program components include both an antenatal (MindBabyBody) and postnatal group (Parenting with Feeling) intervention programs. The research component will include a trial of the intervention program in this particular cohort and incorporate the NBO (Newborn Behavioural Observation) as part of the group program with the aim of enhancing parent-infant interaction and relational outcome. The study is projected to commence mid-2017.

Mindful Research

183. Child and Adolescent Mental Health

Director, Mindful: A/Professor Alessandra (Sandra) Radovini **T:** +613 9371 0203
E: radovini@unimelb.edu.au **Location:** Mindful, Centre Gat 1 Building C, 50 Flemington Street Tranvancore
W: Personal web page

Psychosocial Research Group

Professor Carol Harvey **T:** +61 3 9355 9826 **E:** c.harvey@unimelb.edu.au
Location: Ground Floor, 130 Bell Street, Coburg, Vic, 3058 **W:** Personal web page

184. Carers of People Living with Psychosis

Carers of people living with a mental illness are often peripheral in the clinical setting, or considered only in relation to the person living with the mental illness. Our research group is investigating the health and wellbeing and needs of carers of people living with a mental illness and the effectiveness of services designed to meet these needs.

185. Employment and Vocational Occupation

Various employment-related and occupation-focussed research projects have been conducted and continue to be conducted by our group, especially researching programs which provide employment support, including social firms, for people living with severe mental illnesses (SMI). Much of this work has been carried out in partnership with Social Firms Australia (SoFA) and also Professors Ellie Fossey (Monash University), David Castle (University of Melbourne), Marc Corbiere (Université du Québec à Montréal (UQAM), Canada) and Susan Rossell (Swinburne University).

186. Ripple

Ripple: researching evidence based interventions to improve the mental health of vulnerable young people living in out of home care by strengthening the therapeutic capacities of their carers.
This NHMRC Partnership grant led by Professor Helen Herrman (Orygen Research Centre) is researching evidence-based interventions to improve mental health for young people (aged 12-17) in out-of-home care. Out-of-home care (OoHC) refers to the care of children and young people removed from their families by the state because of abuse, neglect or other adversities. Young people in OoHC are highly vulnerable to mental ill-health and associated problems with relationships, education and meaningful activity. Typically, they also have poor access to mental health services. The 5-year project aims to deliver evidence-based mental health support and care across the health and community service system relevant to these young people in Victoria, principally through strengthening the therapeutic capacities of their carers.

187. Single Session Family Consultation

The project concerned the implementation of Single Session Family Consultation in four Headspace centres to improve the extent and quality of family inclusion in care for young people with mental health difficulties. The project was conducted within headspace centres which assist young people who are having mental health difficulties. The Bouverie Centre was contracted to provide consultancy services to implement SSFC in headspace and Psychosocial Research Centre staff conducted the evaluation. An existing Family Inclusive Practice model, Single Session Family Consultation (SSFC), was introduced at four headspace centres across South Australia and Victoria. The evaluation adopted a mixed methods Action Research methodology to address the question of how to best implement and sustain family inclusive practice within headspace.

188. Survey of High Impact Psychosis (SHIP)

The Survey of High Impact Psychosis (SHIP) is the second prevalence study of psychotic mental illness across Australia and was conducted in 2010. It involved an indepth analysis of factors influencing the daily lives of people living with psychosis, with a focus on those amenable to change. Analysis of data from the second national survey of psychosis is continuing: 50 articles (published or in press/submission) have already been generated by PRC staff and/or their collaborators. Publications generated within PRC have included experiences of housing, relationships and work and study among SHIP participants as well as services delivered by the non-governmental sector.

Trauma Research Group

Director, Phoenix Australia Centre for Posttraumatic Mental Health
Professor David Forbes **T:** +61 3 9035 5599 **E:** dforbes@unimelb.edu.au
Location: Level 3, Alan Gilbert Building, 161 Barry Street, Parkville, Vic 3010 **W:** Personal web page

189. Posttraumatic Nightmares

Dr Andrea Phelps **Professor David Forbes**

Phoenix Australia - Centre for Posttraumatic Mental Health, (Phoenix) in collaboration with Austin Health Veterans Psychiatry Unit, conducted an early pilot trial of imagery rehearsal (IR) therapy in 2001. The success of this trial has led to investigation of the nature of the phenomenon of posttraumatic dreams – whether they are better understood and treated as intrusive symptoms of PTSD or as dreams that have become stuck in a cycle of chronic repetition.

190. Traumatic Injury Research

Associate Professor Meaghan O'Donnell **E:** mod@unimelb.edu.au

This program of research began in 2003 in a collaboration between Phoenix Australia and The Alfred Hospital in a study that investigated the mental health outcomes of survivors of injury. The success of this study resulted in two publications in the prestigious American Journal of Psychiatry, and a NHMRC Career Development Award. This study led to the establishment of a large multi-site cohort study in collaboration with University of New South Wales, University of Adelaide and University of Melbourne. The study has followed over 1000 injury survivors over 10 years being funded by consecutive NHMRC Program Grants. We have published over 70 peer review papers in the area of mental health and injury.

191. Veteran and Military Mental Health

Dr Andrea Phelps **Professor David Forbes**

Military service is associated with a unique set of experiences that have implications for mental health. These experiences include operational deployment to conflict zones, peacekeeping deployments and humanitarian missions following disaster. This body of research is conducted as a series of competitively funded and commissioned projects and in collaboration with the Departments of Veterans Affairs and Defence. It examines four key themes:

1. Common mental health outcomes following these experiences, including an examination of the clinical phenomenology of these mental health sequelae, and how these may differ from those following non military trauma
2. Organisational, environmental and individual risk and resilience factors that influence mental health outcomes following military experiences
3. Pathways to care for military veterans and uptake and engagement with clinical services.
4. Interventions and service models for delivery of care to veterans with military related mental health problems.

DEPARTMENT OF SURGERY

Brain Tumour Biology and Therapies

Head of Research Group: Professor Andrew H. Kaye **T:** +61 3 8344 5492 **E:** a.kaye@unimelb.edu.au
W: Personal web page **Location:** Department of Surgery, The Royal Melbourne Hospital

Molecular Mechanisms of Tumour Resistance Laboratory

Dr. Rodney Luwor **T:** 8344 3027 **E:** rluwor@unimelb.edu.au **W:** Personal web page
Location: Level 5, Clinical Sciences Building, Royal Melbourne Hospital

Approximately 2000 Australians are expected to be diagnosed with brain cancer and about 1500 Australians will die this year. The most severe form of brain cancer, Glioblastoma (also known as GBM or grade IV astrocytoma) is the most common primary tumour of the central nervous system and is classified as one of the most aggressive. Surgery to remove the bulk of the tumour followed by standard treatment of radiotherapy and chemotherapy (mainly using the chemotherapeutic temozolomide) is the usual treatment regimen used for these patients. However, the residual tumour cells unable to be removed by surgery are often resistant to this treatment leading to rapid tumour reccurence and an overall poor survival rate of less than 15 months post surgery.

Therefore, there is a urgent need to further understand the critical molecular mediators of tumour recurrence and tumour resistance to therapy and more importantly overcome this resistance with novel therapeutics. Our laboratory particularly focuses on both these critical questions. This project will definitively analysis the molecular systems that mediate resistance to the current therapeutics used to treat glioblastoma utilising primary and established glioblastoma cell lines, genetic and patient-derived xenograft animal models and patient tumour tissue. Specifically, we will use a combination of large scale genome wide and phospho-proteomic analysis, cell and molecular biology based studies and bio-informatics approaches to achieve this goal. Furthermore, our laboratory will identify novel agents that can overcome this resistance isolating agents that are effective in the treatment of glioblastoma patients. Overall, this project is expected to yield important novel biomarkers for resistance to current therapeutic agents used clinically for the treatment of glioblastoma.

192. Regulation of invadopodium function and involvement in cancer cell invasion

Dr Stanley Stylli **T:** 61-3-90355236 **E:** sstylli@unimelb.edu.au **W:** Personal web page
Location: Department of Surgery, The Royal Melbourne Hospital; Level 5, Clinical Sciences Building

A property shared by several types of tumour cells is an ability to form structures known as invadopodia. These are dynamic actin-dependent, membrane protrusions which proteolytically degrade extracellular matrix (ECM) substrates via the activities of numerous proteases. Invadopodia have been observed in tumour cell lines derived from various cancers including breast cancer, melanoma, prostate cancer, colon cancer, glioma and head and neck cancers, just to name a few. It is a continually evolving field and our aim is to undertsand how invadopodia are formed and regulated.

193. The role of invadopodia in glioma invasion and response to therapeutics

Dr Stanley Stylli **T:** 61-3-90355236 **E:** sstylli@unimelb.edu.au
Location: Department of Surgery, The Royal Melbourne Hospital; Level 5, Clinical Sciences Building

Malignant gliomas caused approximately 2.3% of cancer-related deaths in the USA with over 22,000 new patients expected annually. The most prevalent form of glioma and the tumour with the worst prognosis is the glioblastoma multiforme (GBM,WHO grade IV). The prognosis for patients with GBM tumours remains poor with a median survival of only 14.6 months, after receiving the current standard treatment consisting of surgery, radiotherapy and temozolomide. The characteristic of all gliomas is their extensive infiltration, which thwarts efforts to completely remove or ablate these malignant cells.

A property shared by several types of tumour cells is an ability to form structures known as invadopodia. These

are dynamic actin-dependent, membrane protrusions which proteolytically degrade extracellular matrix (ECM) substrates via the activities of numerous proteases. We have observed invadopodia in glioma cell lines and primary tumour cells derived from ex vivo cultured GBM specimens, suggesting a role for invadopodia in glioma invasion.

Cancer Signalling Research Laboratory

194. Molecular mechanism of cancer metastasis, targeted therapy and immunotherapy

Dr Hong-Jian Zhu **T:** +61 3 8344 3025 **E:** hongjian@unimelb.edu.au
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PROJECT DETAILS: 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 these "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 are 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 covers from basic understanding of how at molecular level exosomes delivers tumourigenic TGF-β signalling, particularly in the context of tumour microenvironment to new therapeutic strategy and theraies for treatment of verious type 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 forefront cancer research and to achieve excellent novel results in a relative short time frame (9-10 months).

Project A: Discovering TGF-□ signaling-driven 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 in research, perseverance in problem solving.

Prostate Cancer Research Group

Professor Christopher Hovens **E:** chovens@unimelb.edu.au
Location: Room 515/ Level 5, Clinical Sciences Building, Department of Surgery, RMH

195. Integrated Genomics of metastatic, lethal Prostate Cancer

A/Prof Chris Hovens and Dr Niall Corcoran **T**: 9342 7703/4 **E**: cbhovens@gmail.com
Location: Department of Surgery (RMH), 5th Floor, Clinical Sciences Building and Prostate Cancer, Epworth Hospital, Richmond

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.

Ultrasound Education Group

Co-director: Professor Colin Royse

196. Arterial grafting for coronary artery revascularisation

Professor Colin Royse **T:** 0408467548 **E:** roysec@unimelb.edu.au **W:** Personal web page
Location: Ultrasound Education Group, Department of Surgery, University of Melbourne, Level 6 Centre for Medical Research, Royal Parade, Parkville VIC 3052

Professor Alistair Royse, a cardiothoracic surgeon, undertakes research into coronary bypass surgery. He was one of the pioneers for the utilization of the radial artery as a conduit in coronary artery surgery. The radial artery has been used at the Royal Melbourne Hospital since 1994. This included the use of complex novel grafting strategies including sequential grafting methods and the joining of arteries together (composite or Y grafts) which led to technique and outcome publications during 1998-2002. This innovation led to rapid and significant change to clinical practice in the mid 1990s, the use of the radial artery grafts rising from 5% to 85% in 1997, and total arterial revascularisation increasing from 5% to 68%. These figures have remained constant since 1997. By comparison, in the United States and Europe, total arterial revascularization is only 5 - 6%, and use of the radial artery only about 4%.

Late clinical follow up has found that there is a survival advantage to total arterial revascularisation as well as use of the radial artery and a complex reconstruction (Y graft).

Frequent symptom-driven and other preoperative angiograms performed at a minimum of more than 10 years postoperative reveal no progressive atherosclerosis over time as is present with saphenous vein grafts. Some prospective research-driven angiograms reveal no arterial conduit atherosclerosis more than 10 years postoperative. Indeed, all arterial grafts appear to behave similarly and appear to be resistant to late atherosclerosis formation. There are three ongoing studies on patient's at least 10 years postoperative:

1. Patients who received all three conduits (a mammary artery, radial artery and saphenous vein), assessed by angiography;
2. Clinically indicated angiography where a radial artery has been used and
3. Survival and quality of life data on coronary bypass patients.

197. Postoperative Quality of Recovery

Professor Colin Royse **T:** 0408467548 **E:** roysec@unimelb.edu.au
Location: Ultrasound Education Group, Department of Surgery, University of Melbourne, Level 6 Centre for Medical Research, Royal Parade, Parkville VIC 3052 **W:** Personal web page

Professor Colin Royse has developed a novel assessment tool that can asses the quality of recovery after surgery that can be repeated at multiple time-points including after discharge home from hospital. This tool is increasingly becoming popular for evaluation of surgery and as a valuable research tool. Professor Royse is the chair of the Postop QRS committee and overseas many projects and higher research degree students in this rapidly growing area of research.

Central to the practice of perioperative medicine and patient centred care are the abstract ideals of quality and recovery, neither of which have a universally accepted definition or assessment tool. Recovery definitions have progressed from an historical emphasis on short-term restitution of purely physiological parameters to a multidimensional concept, which includes physiological, nociceptive, emotive, functional and cognitive domains. With an ageing, ambulant perioperative population and an increasing understanding of the interplay between physiological stress and neurophysiology, there is increased importance of cognitive assessment. Current recovery assessment tools vary in their validation and differ in their assessment of recovery as a dichotomous vs. continuous variable, and at the individual vs. group level. Ideally, quality of recovery would be defined as a return of a patient's function to their own baseline or better and assessed in multiple domains and over multiple time points. The ideal recovery assessment tool would allow real-time assessment of recovery with facility to identify in which sub-domain recovery has failed, in both individual patients and at a population level, thus allowing both clinical time critical interventions and research applications.

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

Gynaecology Research Centre

198. Identification and function of genes that increase risk for endometriosis

Professor Peter Rogers T: 8345 3706 **E:** parogers@unimelb.edu.au **W:** Personal web page
Location: Royal Women's Hospital

Endometriosis is a common, oestrogen-dependent condition associated with menstrual pain, chronic pelvic pain and infertility. It is thought to affect 7% of women of reproductive age in Australia, increasing to 35-50% of women with chronic pelvic pain and fertility problems. Medical treatment options have limited effectiveness, and surgical intervention may not prevent later recurrence. The personal and healthcare costs associated with endometriosis are high. In an Australian report, direct medical and surgical costs for endometriosis were estimated at $6 billion per annum for adult women (based on 1 in 10 adult women having endometriosis, $10,000 per woman). For adolescent girls, direct costs were estimated at $600 million.

199. Menstrual concerns in young women: the father's perspective (DADs Study)

Dr Yasmin Jayasinghe T: 8345 3721 **E:** yasmin.jayasinghe@unimelb.edu.au
W: Personal web page **Location:** Royal Women's Hospital

Menstrual pain not only impacts on the individual girl/woman, but also on her family. Conversely, the attitudes of the family towards menstrual pain may have a significant impact on how the girl/women views, understands and manages her symptoms. To date, there is no literature available that considers the father's perspective of menstrual pain. Information on the father's perspective may help identify specific areas where education may help a father support and advocate for his daughter. Ultimately, understanding men's views more generally may help overcome current taboos surrounding menstruation and dysmenorrhoea.

200. Preparing for clincial trials of synchrotron microbeam radiation therapy for cancer treatment

Professor Peter Rogers T: 8345 3706 **E:** parogers@unimelb.edu.au **W:** Personal web page
Location: Royal Women's Hospital

Microbeam radiation therapy (MRT), using X-rays generated by a synchrotron facility, is a novel, preclinical form of radiotherapy that shows promise of providing a major advance in cancer control if successfully translated to clinical practice. Given that up to 50% of cancer patients receive radiotherapy, and that radiotherapy and surgery remain the major treatment modalities that achieve loco-regional control of cancer, the significance of developing MRT as a new treatment paradigm cannot be understated. In particular, the apparent tolerance of normal tissues to MRT-induced radiotoxicity holds promise of a greatly improved therapeutic index with this treatment modality, opening the way to significantly improved patient outcomes.

201. What is the contribution of embryo-endometrial asynchrony to implantation failure?

Professor Peter Rogers T: 8345 3706 **E:** parogers@unimelb.edu.au **Location:** Royal Women's Hospital

The synchronized development of a viable embryo and a receptive endometrium are critical for successful implantation to take place. By convention, the time when the blastocyst first attaches and starts to invade into the endometrium, has been defined as the 'window of implantation'. The term 'window of implantation' can be misleading when it is used to imply that there is a single critical window in time that determines whether implantation will be successful or not. Embryo maturation and endometrial development are two independent continuous processes. Implantation occurs when the two tissues fuse and pregnancy is established. A key concept in understanding this event is developmental 'synchrony', defined as when the early embryo and the uterus are both developing at the same rate such that they will be ready to commence, and successfully continue implantation at the same time. Many different events including controlled ovarian hyper-stimulation as routinely used in IVF, can potentially disrupt embryo-endometrial synchrony. There is some evidence in humans that implantation rates are significantly reduced when embryo-endometrial development asynchrony is greater than 3 days (+/- 1.5 days).

202. Investigation of genes associated with increased risk of endometriosis
Prof Peter Rogers, Dr Sarah Holdsworth-Carson, Dr Premila Paiva E: parogers@unimelb.edu.au
Location: Department of Obstetrics and Gynaecology, Royal Women's Hospital

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.

203. EndoNeeds: Investigating the unmet physical, psychological and social needs of Australian women with endometriosis.
Dr Michelle Peate, Dr Jane Girling E: michelle.peate@unimelb.edu.au Location: Royal Women's Hospital

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.

Hickey Research Group

204. Impact of risk-reducing bilateral salpingo-oophorectomy on non-cancer outcomes in young high-risk women: a multicentre prospective study.
Professor Martha Hickey T: 8345 3715 E: hickeym@unimelb.edu.au W: Personal web page
Location: Research Precinct, Level 7, The Royal Women's Hospital, Cnr Grattan Street and Flemington Road

Surgical menopause due to bilateral oophorectomy (surgical removal of both ovaries) in pre-menopausal women is the commonest cause of premature and early menopause. Despite this, there is currently very little information about the short- and long-term health consequences of surgical menopause, although these are thought to be more problematic than natural menopause.

This 2-year prospective observational study will measure key physical and psychological outcomes of surgical menopause in pre-menopausal women choosing to have cancer risk-reducing bilateral oophorectomy due to high familial and/or high inherited risk of ovarian and breast cancer. We are focussing on this high-risk population because: (1) a growing number of women are discovering they carry pre-disposing genetic mutations (such as BRCA1/2) and are electing to have risk-reducing surgery, and (2) these women are otherwise well, and so will provide a clear picture of the effects attributable to surgical menopause. The measured outcomes include menopausal symptoms, sexual function, bone turnover and density (fracture risk), cardio-metabolic health, mental health and sleep quality. The effects of age and lifestyle will be controlled for by the inclusion of a comparison group of age-matched, pre-menopausal women who are not planning to undergo surgical menopause. The study is anticipated to provide new and clinically important information that will address the gap in existing evidence and inform new international evidence-based guidelines for surgical menopause. Such information can be used to better inform clinicians and women considering surgery, and also to optimise the post-operative clinical management of symptoms and disease prevention.

Obstetrics, Nutrition and Endocrinology Group

205. Can dietary phytophenols improve pregnancy outcomes?

Associate Professor Martha Lappas **T: 8458 4370** **E:** mlappas@unimelb.edu.au
W: Personal web page **Location:** Mercy Hospital for Women

Preterm birth and GDM are seemingly disparate conditions but linked by common pathways in their pathogenesis. They affect up to 20% of all pregnancies but have 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 both these conditions, little progress has been made with interventions aimed at prevention. Rates of preterm birth remain static, whilst GDM is increasing in parallel with the obesity epidemic. A safe and effective intervention that can reduce the burden of preterm birth and GDM would be a major public health initiative. There is increasing volume and quality of evidence that high fruit and vegetable intake in pregnancy is associated with a decreased risk of adverse pregnancy outcomes . For example, consumption of a diet rich in fruits, vegetables and whole grains (Dietary Approaches to Stop Hypertension (DASH) diet) in pregnant women with GDM had beneficial effects on their metabolic profile. Many of these beneficial properties have been attributed to the potent anti-inflammatory properties of phytophenols. There are, however, no studies that have assessed dietary phytophenols in preterm birth or GDM. In this project, in vitro and in vivo studies will be used to test the hypothesis that dietary phytophenols can delay preterm birth and prevent the development of GDM, and improve fetal outcome in both these conditions.

206. Understanding the pathogenesis of gestational diabetes

Associate Professor Martha Lappas **T: 8458 4370** **E:** mlappas@unimelb.edu.au **W:** Personal web page
Location: Mercy Hospital for Women

Gestational diabetes mellitus (GDM) affects up to 20% of all pregnancies but have 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 GDM, little progress has been made with interventions aimed at prevention. An efficacious medical therapeutic that can prevent the development of GDM would be a major advance. Such treatments do not exist and their development is hampered by the fact the pathophysiology of GDM is incompletely understood. Current therapy for GDM is largely “glucocentric”, with the major therapeutic goal being achievement of glucose levels as close to normal pregnancy values as possible. However, these current therapies do not target inflammation, which is critical to both disease pathogenesis and long-term outcome in GDM.

This project will investigate whether major regulators of inflammation such as sirtuin 1 (SIRT1) are involved in the pathophysiology of GDM.

207. Understanding what triggers birth? New opportunities for prevention of early delivery
Associate Professor Martha Lappas **T**: **8458 4370** **E**: **mlappas@unimelb.edu.au**
Location: Mercy Hospital for Women

Within the discipline of reproductive biology, our understanding of one of the most fundamental biological processes is lacking – the cellular and molecular mechanisms that govern BIRTH. This lack of understanding limits our ability to reduce the incidence of labour complications. The incidence of labour complications including: preterm labour; cervical incompetence; and post-date pregnancies has not diminished in decades. The key to improving the management of human labour and delivery is an understanding of how the multiple processes that are requisite for a successful labour and delivery are coordinated to achieve a timely birth. Processes that include the formation of: contraction associated proteins [CAPs]; inflammatory mediators [eg cytokines]; uterotonic phospholipid metabolites [eg prostaglandins]; and the induction of extracellular matrix remodelling.

New approaches that identify and target the upstream regulators of multiple labour-associated processes are required if better management of labour is to be achieved. Over the last decade, my studies have identified a number of "master regulators" of the mechanisms that govern birth. My in vitro data has made it increasingly clear that a suite of regulators (e.g. nuclear factor-κB, NF-κB; peroxisome proliferator activated receptors, PPARs; activator protein, AP-1; sirtuin 1, SIRT1) coordinate the timely expression of the terminal effector pathways of labour and delivery. These master regulators may represent novel intervention points for developing therapeutics to reduce the incidence of preterm birth and related perinatal morbidity and mortality. In this project, we will thoroughly characterise their role in preterm birth and investigate their potential as a therapeutic intervention to prevent preterm labour using a mouse model of preterm birth.

Paediatric and Adolescent Fertility Preservation Taskforce

208. Fertility preservation in children and teenagers with cancer
Dr Yasmin Jayasinghe **T: 8345 3712** **E:** yasmin.jayasinghe@unimelb.edu.au
W: Personal web page **Location:** Royal Women's Hospital

Over 80% of children, adolescents and young adults (AYA) diagnosed with cancer survive to adulthood. Fertility impairment is a major survivorship consideration. We know from follow-up studies of childhood cancer survivors that infertility may affect long-term wellbeing, relationships and life decisions. We now understand that lack of information about the impact of cancer treatments on fertility can increase distress and anxiety in young people. International bodies now recommend discussion of fertility risks and options prior to cancer treatment.

Fertility Preservation poses unique clinical challenges in children as it is considered experimental. It also poses ethical challenges around consent and beneficence for the young person. Fertility preservation is time sensitive as it is best undertaken prior to the administration of chemotherapy or radiotherapy. Discussions often occur around one or two days after diagnosis of cancer, which is a stressful time. Ovarian tissue collected from children prior to cancer treatment can be stored for many years, and tissue may survive for some years after transplantation back into the body years later. There have been isolated reports in children of return of ovarian function after transplantation. Over 70 pregnancies have been reported worldwide, but only one from tissue from a child. For boys testicular tissue collection may be undertaken, but at present mature sperm from this tissue has not been produced. Lack of governance over paediatric and adolescent Fertility Preservation, creates burdens for families and health providers. Unfortunately detailed national guidelines do not exist to guide clinicians in this complex area of practice. The Royal Children's Hospital Melbourne developed a multidisciplinary collaborative Paediatric Adolescent and Young Adult Fertility Preservation Taskforce in conjunction with the Royal Women's Hospital in 2012. The aims of the taskforce are to integrate the collective wisdom of families of children with cancer and experts from a range of disciplines (Paediatric Gynaecology, Oncology, Endocrinology, Reproductive Medicine, Ethics, Legal, Sociology, Paediatric Surgery), in order to

develop clinical pathways and policies around paediatric and adolescent fertility preservation; to guide referrals to Clinical Ethics Committees around fertility preservation; to improve patient-provider communication; to design academic programs which collect safety and efficacy data, and information on long-term acceptance by cancer survivors; and to educate health providers and the community.

Royal Women's Hospital Department of Maternal Fetal Medicine Pregnancy Research Centre

209. Fetal Welfare Assessment

Director: Prof Shaun Brennecke **T: 8345 3703** **E:** s.brennecke@unimelb.edu.au
W: Personal web page **Location:** Research Precinct Level 7, Royal Women's Hospital

Project 1. There is currently an epidemic of caesarean sections performed in Australia and overseas. Although many caesarean sections are performed for concerns about fetal welfare, the majority of babies are shown to be well at birth, meaning that the operation, with its inherent short- and long-term risks, could have been avoided, without compromising the baby's health. This project is a world-first randomised trial of fetal scalp blood sampling for lactate estimation during labour, with a view to reducing the caesarean section rate for apparently non-reassuring fetal status.

Project 2. It would be very helpful to be able to accurately monitor babies' movements in the womb so that we could help the few babies who need it, and so prevent poor outcomes. Mothers feel their babies moving, but it is often difficult for them to detect all the movements that do occur. The best way of measuring babies' movements is during an ultrasound. This is, however, expensive and means that the pregnant mother needs to lie still for about half an hour to have this testing done. These may become tests that is easier to use and predicts outcomes as well or better than current monitoring methods.

210. Labour & Delivery

Research Clinician: Dr Penny Sheehan **T: 8345 3752** **E:** Penny.Sheehan@thewomens.org.au
W: Personal web page **Location:** Research Precinct Level 7, Royal Women's Hospital

Project 1. What triggers labour

The process of birth is thought to be controlled by hormonal factors produced by tissues within the womb. The aim of this project is to investigate one of these hormones, in particular, a metabolite of progesterone called 5-beta-dihydroprogesterone. This study will help to improve our understanding of how normal labour occurs and may provide insight into how to prevent it from occurring prematurely. Blood samples are collected from women before, during and after labour, and also from women in premature labour and before term but not in labour. Tissue samples from the womb are also collected at the delivery of babies by Caesarean section for investigation using various molecular biology techniques.

Project 2. Failure to progress in labour - electrophysiological and molecular studies

Failure of the muscle of the uterus to contract strongly during labour results in protracted and exhausting labour and, in a significant percentage of cases, necessitates caesarian delivery. The aim of this study is to elucidate the mechanisms that may be responsible for the weak uterine contractions that underlie ineffective labour. Failure of the uterus to contract normally at term, ineffective labour, necessitates the intervention of caesarian delivery in as many as 5-10% of first pregnancies. Administration of oxytocin may augment weak uterine contractions and resolve ineffective labour in some cases. However, in many cases, successful vaginal delivery is not achieved by oxytocin infusion. The causes of ineffective labour remain obscure. In our recent studies of uterine contractility in tissues form a subset of the in-labour group appeared to divide the ineffective labour tissues further into three groups. One group contracted weakly to applied oxytocin. In another group, contractions were anomalously suppressed by prostaglandins that are normally strongly excitatory. The smooth muscle cells in tissues of the third group had unusually negative transmembrane potentials, making contractions difficult to achieve in the face of a wide range of stimuli. Elucidation of the mechanisms underpinning the failure to contract by these tissue is the main aim of this project.

211. Placental Stem Cells

Deputy Head of Research, Director Head of the Stem Cell Laboratory

Dr Bill Kalionis T: 8345 3748 E: bill.kalionis@thewomens.org.au **W:** Personal web page
Location: Research Precinct Level 7, Royal Women's Hospital

Stem cells have been isolated also from a variety of adult and embryonic sources. Currently, stem cells for research are taken from the umbilical cords of newborn babies, bone marrow of children or adults, or aborted fetuses, or discarded test-tube embryos.

However, these sources have a number of limitations. Umbilical cord blood contains only small numbers of stem cells and extraction of bone marrow requires a painful needle and a very close match between donor and recipient to prevent rejection. Moreover, the use of embryos and fetal tissue as stem cell sources is extremely contentious.

Recently, the placenta has been shown to be a plentiful, non-controversial source of stem cells. It therefore may have a number of advantages over traditional methods of preparing stem cells.

Our aim is to develop methods to harvest and characterise stem cells from the placenta so as to provide a safe non-controversial alternative to the harvesting of embryonic or fetal stem cells. These placental stem cells will be used to develop novel therapies in our field of Obstetrics and Gynaecology. In addition, through collaborative interactions with other medical researchers, these stem cells will be used to develop novel therapies to treat a wide range of other significant human diseases and disorders.

Our research group has extensive experience in studying placental functions and specific placental cell types. We enjoy an excellent international reputation for innovative and leading edge placental research.

Medicine Pregnancy Research Centre

212. Pre-eclampsia - Eclampsia

Director: Prof Shaun Brennecke T: 8345 3703 E: s.brennecke@unimelb.edu.au
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Pre-eclampsia (PE) is the most common serious medical disorder of human pregnancy. Particularly in their first pregnancy, pregnant women can suffer from high blood pressure, kidney dysfunction leading to leakage of protein into the urine, swelling of hands, feet and face, and, in severe cases, dizziness, headaches and difficulties with vision. This condition is called pre-eclampsia. If left untreated, it can lead to convulsions and other life-threatening problems for both mother and baby. Pre-eclampsia only occurs when a woman is pregnant, and currently, the only cure for it is to end the pregnancy, even if the baby is not yet ready for birth.

In Australia, mild pre-eclampsia occurs in 5-10% of pregnancies and severe pre-eclampsia in 1-2% of pregnancies. Pre-eclampsia and complications associated with this condition account for 15% of direct maternal mortality and 10% of perinatal mortality. Pre-eclampsia is the indication for 20% of labour inductions and 15% of Caesarean sections. It also accounts for 5-10% of preterm deliveries. Worldwide, pre-eclampsia and its complications kill many tens of thousands of women and their babies each year.

213. Preterm Labour

Senior Research Fellow: Dr Harry Georgiou T: +61 3 8345 3708 E: harrymg@unimelb.edu.au
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Being born too early is a common problem and a major cause of infant morbidity and mortality. Healthcare costs are enormous as many survivors will have at least one major disability. A reliable screening test that identifies women at risk of premature birth is currently lacking.

Preterm birth (birth before 37 completed weeks' gestation) is a significant problem occurring in 5-20% of all deliveries. Most developedcountries including Australia report an increasing trend in the incidence of premature birth. Being born too early is the major cause of perinatal morbidity and mortality and accounts for the majority of neonatal deaths. Recent medical advances have increased survival rates, particularly for the

extremely premature baby, but the associated morbidity for these survivors remains significant where up to one-quarter will have at least one major disability. Healthcare costs for the short and long-term care of these infants is enormous.

The lack of a rapid and reliable screening test to identify women who are at risk of developing preterm labour further limits the early detection of disease onset and the implementation of preventive therapies. We have previously identified and evaluated a number of putative biomarkers found in human vaginal fluid that are associated with preterm labour onset. Using this data, predictive models have been generated and the ability of these biomarkers to predict labour have been investigated.

The Psychosocial Health and Wellbeing Research (emPoWeR) Unit

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214. The evaluation of a decision aid for women considering non-medical egg freezing

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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.

215. Development and evaluation of guidelines and an intervention for moving on from IVF in women with a low chance of success

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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.

Victorian Infant Collaborative Study Group

216. Impact of Extreme Prematurity or Extreme Low Birthweight on Young Adult Health and Well-being
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We are assessing physical, socio-emotional and mental health of extremely preterm (EP, <28 weeks' gestation) or extremely low birthweight (ELBW, <1000 g) young adults born in the era after surfactant was introduced into clinical practice.

The participants comprise the Victorian Infant Collaborative Study 1991-92 (VICS 91-92) cohort, a unique geographic cohort of all (n=297) EP/ELBW infants survivors born in the state of Victoria in 1991-92, and 262 contemporaneously recruited matched NBW controls. A wealth of perinatal information, and data from longitudinal follow up at ages 2, 5, 8 and 18 years are already available.

217. Health-related risk behaviour in adolescence
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VICS research is one of Australia's flagship research areas since the 1980s, with over 50 publications on the long-term outcomes of very tiny or preterm infants in Victoria since that time.

Much of the burden of disease and social adversity in adulthood is linked to long-standing patterns of behaviour and lifestyle. These patterns of behaviour often have their origins in adolescence. Using repeated measures from questionnaire, physical and biological data collected in the Western Australia Pregnancy (Raine) Cohort, we will model pathways of health risk indicators (problem behaviour, injury, overweight, physical inactivity, substance use, sexual risk behaviour) from childhood through adolescence, and then use these trajectories to quantify the risks of adverse health and social outcomes in adulthood, collected via Raine and the WA Data Linkage system.

218. Priorities and needs of women living with advanced cancer
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Location: The Royal Women's Hospital

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.

219. Biomarkers of human papillomavirus-related cancers

Dr. Alyssa Cornall, Prof Suzanne Garland **E** alyssa.cornall@mcri.edu.au

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.