



The Royal Melbourne Hospital and Western Hospital
Academic Centre
University of Melbourne

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

HONOURS PROJECTS 2011

Medical Research — Bench to Bedside



Affiliations:

The Royal Melbourne Hospital, The Western Hospital, The Royal Women's Hospital, National Ageing Research Institute (NARI), The Walter and Eliza Hall Institute of Medical Research (WEHI), The Peter MacCallum Institute, The Centre for Molecular Imaging, The Burnet Institute-Centre for Population Health, Ludwig Institute for Cancer Research, CSIRO Molecular and Health Technologies, Florey Neuroscience Institute

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Listed below are brief outlines of the projects being offered in 2011.
For further information, contact the supervisors on the numbers and email addresses as listed.

AGEING

1. A model of epileptogenesis in Alzheimer's disease

Supervisors: A/Professor Patrick Kwan, Professor Terence O'Brien
Project Site: Department of Medicine (RMH/WH)
Contact: Patrick Kwan: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong. patrickkwan@cuhk.edu.hk
Terence O'Brien: Department of Medicine (RMH/WH).
obrientj@unimelb.edu.au

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

Project Overview

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

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

Research plan

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

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

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

Supervisors: Professor Terence O'Brien, Associate Professor Chris Hovens, Dr. Nigel Jones, Dr. Dennis Velakoulis.

Project Site: Departments of Medicine, Surgery and Psychiatry, The Royal Melbourne Hospital, University of Melbourne

Contact: Prof Terence O'Brien: obrientj@unimelb.edu.au; Associate Professor Chris Hovens: chovens@unimelb.edu.au, Dr. Nigel Jones: ncjones@unimelb.edu.au, Dr. Dennis Velakoulis: dennis.velakoulis@mh.org.au.

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

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

1. That treatment with sodium selenate is effective at suppressing spontaneous seizures in rat models of acquired epilepsy (i.e. post-kainic acid status epilepticus and fluid percussion injury);
2. That treatment with sodium selenate is effective at inhibiting epileptogenesis and neurodegeneration following a range of acquired brain insults in rat models (i.e. kindling, post-kainic acid status epilepticus and fluid percussion injury).
3. Treatment with sodium selenate will mitigate the increased tissue expression of total and phospho-tau following a brain insult, with and without the development of epilepsy.

The outcomes of this project will advance the pre-clinical development of this approach, building on a sound basic science rational and strong preliminary data. Selenate has already been demonstrated to be safe and well tolerated in a 6 month Phase I trial in humans with prostate cancer, meaning a positive result from these studies has the potential to be expediently translated into clinical studies. In addition this project has relevance for epilepsy secondary to sporadic neurodegenerative conditions such as Alzheimer's disease.

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

National Ageing Research Institute (NARI)

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

3. Exploring nutrition needs of older people with chronic illness and their carers

Supervisors: Dr Irene Blackberry and Dr Briony Dow
Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
Contact: Dr Iren Blackberry T: 8344 3373 E: i.blackberry@unimelb.edu.au
Dr Briony Dow T: 8387 2639 E: b.dow@nari.unimelb.edu.au

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

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

4. Vitamin D to help with Bone and Muscle Health

Supervisors: Dr Cassandra Szoeki
Project Site: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
Contact: Dr Cassandra Szoeki T: 61 3 8387 2224 F : 61 3 9387 9384
E: cszoeki@unimelb.edu.au / Cassandra.szoeki@mh.org.au
Women's Healthy Ageing Project (WHAP),
National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

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

Opportunities:-

- i) Internationally re-known cohort and Research Team each with international recognition. (Prof, J Wark, Prof L Dennerstein, Prof D Ames, Dr C Szoeki)
- ii) Already have measures collected (no hard yards and thesis easily achievable in time frame)
- iii) Publication within one year
- iv) Treatment potential with commercial opportunities – candidate with experience in media and interest in commercialisation preferred.

5. A simple blood test to determine progression of osteoarthritis

Supervisors: Dr Cassandra Szoeki

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

Contact: Dr Cassandra Szoeki T:61 3 8387 2224 F : 61 3 9387 9384

E: cszoeki@unimelb.edu.au / Cassandra.szoeki@mh.org.au

Women's Healthy Ageing Project (WHAP),

National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Osteoarthritis is a significant and disabling condition which predominantly affects those over the age of 50. This demographic is rapidly increasing but the current treatment options for osteoarthritis are limited. Studies on quality of life and economics demonstrate the enormous burden which osteoarthritis places on individuals and our community. There is a new blood test CTX11, which has been reported as a late breaking abstract at an international meeting. It is said to be able to predict (20:1) progression of osteoarthritis in a small cohort. This assay has the potential therefore to predict (at 20 times power) those patients at risk of osteoarthritis progression. We have 224 women with X-Rays of hand and knees scored for evidence of radiological osteoarthritis using a validated scale from an international cohort of women. With funding to obtain CTX11 assay and analysis between the levels and XR measures we could test the potential of this novel assay to identify those with osteoarthritis.

Major benefits from this study are:-

- i) Internationally re-known cohort of the Melbourne Women's Midlife Health Project (MWMHP).
- ii) Research Team each with international recognition. (Prof. F Cicuttini, Prof L Dennerstein, Prof D Ames, Dr C Szoeki)
- iii) X-Rays already conducted. Blood available for assay at same time as X-Rays
- iv) Publication within one year
- v) A test to identify people with this condition early. This is important area of study as we only have prevention treatments and treatment for symptoms available for osteoarthritis.

6. Possible new treatment option for cognitive decline

Supervisor: Dr Cassandra Szoeki

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

Contact: Dr Cassandra Szoeki T:61 3 8387 2224 F : 61 3 9387 9384

E: cszoeki@unimelb.edu.au / Cassandra.szoeki@mh.org.au

Women's Healthy Ageing Project (WHAP),

National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Dementia and cognitive impairment cause significant disability, morbidity and mortality within our ageing community and current therapies are inadequate. The emerging therapies, even if successful, will be limited by both cost and side effect profiles. Population-based prevention strategies are required now more than ever to reduce the burden of disease in our community. DHEAS is a hormone produced by the adrenal gland and a precursor for both androgens and estrogens. A recent study published this year showed that high DHEAS levels were associated with better performance on cognitive studies. This study is criticized for having no mood measures and the DHEAS levels were done 2 years before the cognitive measures not at the same time. We have data available on 257 women with a full battery of cognitive tests and serum taken at the same time as well as validated mood scales. We need funding to perform DHEAS levels on this serum and analyse the results. DHEAS has the potential to be used for therapy.

Major benefits from this study are:-

- i) Internationally re-known cohort of the Melbourne Women's Midlife Health Project (MWMHP).
- ii) Research Team each with international recognition.
- iii) Publication within one year
- iv) Treatment potential for a condition currently without good therapy options

7. Comparison of event-related potentials (ERP) responses using two different auditory stimulus models in healthy young adults and healthy elderly adults

Supervisor: Dr Bruce Barber

Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Contact: Dr Bruce Barber T: 8387 2618/0423 292 792 E: b.barber@nari.unimelb.edu.au

Event-related potentials (ERP) have a role in evaluating aspects of brain function underlying perception, attention and cognition. The ERP P300 is a response that occurs approximately 300 milliseconds after a stimulus has been presented. It is regarded as an index of short term memory processing. Typically the P300 response is elicited using the standard tone/oddball stimulus paradigm. A different stimulus model recommended for cognitively impaired populations uses just a single tone stimulus. It is used in such populations because it is a simpler, more accessible task that elicits ERP wave forms even in the absence of an overt response to stimuli such as a button press. However, the ERP response to the single tone stimulus has some, as yet, unquantitated differences to that of the standard tone/oddball stimulus model.

This study will make a direct comparison of the ERP responses to the standard tone/oddball and the single tone stimulus models to in a group of healthy young adults and a group of cognitively intact, healthy elderly persons. The study will provide quantitative evaluation of the amplitude, latency and topographic distribution of the ERP sequence in response to the two stimulus models.

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

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

8. The needs of stroke survivors and primary care physicians in rural communities

Supervisors: Dr Jacques Joubert and Professor David Ames

Project Site: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Contact: Tel: +61 3 8387 2305 or +61 0419 780 448

Email: jacquesjoubert@bigpond.com.au

Stroke is the second leading cause of death in developing countries and the leading cause of disability. Rural and remote populations are disadvantaged in access to high quality, timely evidence based healthcare. With a rapidly increasing ageing population worldwide, finding strategies to reduce the burden of stroke on society, are increasingly important. NARI currently supports a large clinical research project in secondary stroke prevention aimed at the primary care level and based in designated metropolitan divisions of general practice. The investigators have performed pilot research in rural Victoria to better understand the needs of stroke survivors and primary care physicians in rural divisions and to potentially advise on effective translation of evidence based models of care into the rural sector.

Using the data from the pilot ‘NEEDS’ study, this study seeks to determine the feasibility of conducting a large multi center randomized controlled research study across multiple practice divisions and amongst culturally diverse populations in both rural and remote regions of Australia.

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

ALCOHOL

9. Media reporting on alcohol in Victoria since 2007

Supervisor: A/Professor Paul Dietze, Head, Alcohol and Drugs Research Group, Centre for Population Health, Burnet Institute and Professor Robin Room, University of Melbourne

Project Site: Centre for Population Health, Burnet Institute

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

From 2007 onwards there has been a dramatic increase in the amount of media reporting on alcohol and alcohol-related issues in the Victorian community. The aim of this project will be to document and analyse the content of this media reporting with a view to describing the main issues examined and better understand the place of key players (eg alcohol industry, researchers, government) and their role in the media portrayal of alcohol

ARTHRITIS AND INFLAMMATION RESEARCH

Arthritis and Inflammation Research Centre

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

We employ a variety of techniques and strategies including gene-based strategies (for example, micro-array technology) to understand disease causation, protein-based strategies (including proteomics, immunoprecipitation, cell transfection) to study the cellular signal transduction pathways associated with disease, and mouse models and clinical material to analyse disease in vivo. Key components of the biology involve an analysis of how macrophage lineage cells are altered during inflammatory disease, how at a molecular level these cells survive, proliferate, differentiate or are activated, and how to down-regulate the cellular functions aberrant in disease. There is some emphasis on growth factor biology/biochemistry and on signal transduction pathways implicated strongly in human arthritis, cancer and stem cell biology.

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

Supervisor: Dr Andrew Cook

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Andrew Cook T: 8344 3290 Email: adcook@unimelb.edu.au

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

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

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

Supervisor: Dr Andrew Cook

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Andrew Cook T: 8344 3290 Email: adcook@unimelb.edu.au

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

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

12. The role of inflammation in mesenchymal stem cell differentiation

Supervisor: Dr Derek Lacey and Prof John Hamilton

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Derek Lacey T: 8344 3292 Email: dlacey@unimelb.edu.au

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

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

13. The role of Wnts in Arthritis

Supervisor: Dr Derek Lacey, Dr Andrew Cook and Prof John.Hamilton

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Derek Lacey T: 8344 3292 Email: dlacey@unimelb.edu.au

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

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

14. The role of a novel therapeutic target in Arthritis

Supervisor: Dr Derek Lacey, Dr Andrew Cook and Prof John Hamilton

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Derek Lacey T: 8344 3292 Email: dlacey@unimelb.edu.au

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

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

15. The role of Wnts in Macrophages

Supervisor: Dr Derek Lacey, Dr Glen Scholz and Prof John Hamilton

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Derek Lacey T: 8344 3292 Email: dlacey@unimelb.edu.au

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

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

16. The role of a novel therapeutic target in Macrophages

Supervisor: Dr Derek Lacey, Dr Glen Scholz and Prof John Hamilton

Project Site: Arthritis Research and Inflammation Centre, Department of Medicine (RMH/WH), University of Melbourne

Contact: Dr Derek Lacey T: 8344 3292 Email: dlacey@unimelb.edu.au

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

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

17. The impact of over-expression and under expression of tissue Plasminogen Activator on epilepsy progression in mice

Supervisors: Dr Nigel Jones, Professor John Hamilton, Professor Terence O'Brien

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, The University of Melbourne

Contacts: Dr. Nigel Jones T: 8344 6729 E : ncjones@unimelb.edu.au

Professor John Hamilton T: 8344 5480 E: jahami@unimelb.edu.au

Professor Terence O'Brien T: 8344 5490 E: obrientj@unimelb.edu.au

Background: The processes governing the development of limbic epilepsy are not well understood, but a growing body of literature supports the role of inflammatory mediators in this disease process. One such molecule is tissue Plasminogen Activator (tPA), a clinically used clot-busting enzyme which also has profound effects on cellular physiology in brain regions relevant to temporal lobe epilepsy. These effects, including modulation of cognitive processes, and influencing synaptic connectivity, provide strong rationale to promote tPA as an enzyme which may be involved in development of epilepsy.

Research Plan: The current proposal will investigate the role of tPA signalling in a mouse model of temporal lobe epilepsy. Using genetically engineered mice which are bred to either express an abundance of tPA, or BSC HONOURS PROJECTS 2010 BENCH TO BEDSIDE - MEDICAL RESEARCH 11 a complete lack of tPA, we will determine the direct role of tPA on epilepsy progression. These experiments will incorporate the amygdala kindling model of limbic epilepsy in mice bred in the laboratories of our collaborators. The second aspect of the project will attempt to ascertain the mechanisms by which tPA might influence the progression of disease using immunocytochemical techniques.

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

This project is also listed under Epilepsy and Neuropharmacology

18. Retinal Vascular Calibre and Cardiovascular Disease in Patients with Autoimmune Disease

Supervisor: Dr Sharon Van Doornum

Project Site: Department of Medicine (RMH/WH)

Contact: Dr Sharon Van Doornum T: 8344 3144 E: svd@unimelb.edu.au

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

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

In this study you will investigate the prevalence of retinal vascular abnormalities in a cohort of patients with autoimmune disease, compare this with age and gender matched population controls, and correlate the findings with measures of disease activity, cardiovascular risk factors and arterial stiffness.

The project offers students an opportunity to develop research skills including literature review, effective communication with patients (recruitment, informed consent, clinical assessment), quantitative and qualitative data analysis and epidemiological study skills.

ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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

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

19. Src kinases, lung inflammation and lung cancer

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

Project Site: Department of Pharmacology, University of Melbourne

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

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

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

This project is also listed under Cancer

20. Genetic and pharmacologic approaches to dissect lung inflammation and lung cancer

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

Project Site: Department of Pharmacology, University of Melbourne

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

Chronic obstructive pulmonary disease (COPD) is an incurable and often fatal inflammatory lung disease, and is a known risk factor for lung cancer. We have a number of animal models of inflammatory lung disease, including mice with activating mutations in Src family kinases, and mice with deleterious mutations in the inositol phosphatase SHIP-1 or the protein tyrosine phosphatase SHP-1. The aim of this project is to use genetic approaches to identify genes that predispose to inflammatory lung disease, and pharmacologic methods to reverse establish disease. Skill acquisition: In vivo disease models, quantitative PCR, cell culture, histology, FACS analysis of cell populations; immuno-affinity purification of proteins, immune regulation and transduction biochemistry.

This project is also listed under Cancer

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

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

Project Site: Department of Pharmacology, University of Melbourne

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

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

and unique range of existing genetically modified mutant mice, which would be important in developing possible novel avenues of treatment.

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

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

Supervisors: A/Prof Margaret Hibbs (Ludwig Institute), Professor Gary Anderson

Project Site: Department of Pharmacology, University of Melbourne

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

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

Skill acquisition: In vivo disease models, viral culture and characterisation lung function measurement, quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; basic T cell immunology, ELISA and Western blotting.

23. Regulatory T cells and myeloid suppressor cells in asthma and COPD

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

Project Site: Department of Pharmacology, University of Melbourne

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

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

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

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

Supervisors: Dr Steve Bozinovski and Professor Gary Anderson

Project Site: Department of Pharmacology, University of Melbourne

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

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

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

25. **Skeletal muscle failure in COPD**

Supervisors: Dr Michelle Hanson and Professor Gary Anderson
 Project Site: Department of Pharmacology, University of Melbourne
 Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

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

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

Supervisors: Professor Gary Anderson, A/Prof Margaret Hibbs, DR Steve Bozinovski and Professor Bruce Levy, (Harvard Medical School, Boston USA)
 Project Site: Department of Pharmacology, University of Melbourne
 Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

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

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

27. **TH17 cells in lung disease**

Supervisors: Professor Gary Anderson and A/Prof Margaret Hibbs
 Project Site: Department of Pharmacology, University of Melbourne
 Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

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

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

28. **Novel molecular mechanisms of tumour evasion in COPD (emphysema) and lung cancer**

Supervisor: Dr Steven Bozinovski
 Co-Supervisor/s: Dr Ross Vlahos, Professor Gary Anderson
 Project Site: Department of Pharmacology, University of Melbourne
 Contact: E: bozis@unimelb.edu.au, T: 8344 4221, F: 8344 0241

Project Description: COPD (Chronic Obstructive Pulmonary Disease / Emphysema) and lung cancer are leading causes of death worldwide and will continue to be a major health burden for decades to come. COPD is also recognised to be major risk factor for lung cancer, and interestingly this can occur independently of smoking status, which implicates shared molecular pathways. Myeloid Suppressor cells are thought to contribute to tumour evasion by impairing the actions of cytotoxic T cells. This project will investigate known molecular pathways in COPD previously described in our laboratory and explore their significance in lung cancer susceptibility. A range of molecular and cell biology methods will be implemented including phenotyping of macrophage lineages defective in COPD and the characterisation of myeloid cell populations important in tumour evasion in relevant disease models.

Skill acquisition: Quantitative PCR, cell and tissue culture, histology, FACS analysis of cell populations; basic T cell immunology, ELISA and Western blotting, In vivo disease models and viral culture.

29. Role of anti-oxidants in COPD (emphysema)

Supervisor: Dr Ross Vlahos

Co-Supervisor/s: Dr Steven Bozinovski & Prof Gary Anderson

Contact: E: rossv@unimelb.edu.au, T: 8344-4221, F: 8344-0241

Project Site: Dept of Pharmacology, Level 8, N814

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

LUNG REGENERATION LABORATORY

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

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

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

30. The role of adult lung stem cells in lung injury and repair

Supervisor: A/Professor Ivan Bertoncello

Co-Supervisor: Dr Jonathan McQualter (jlmcq@unimelb.edu.au)

Project Site: Department of Pharmacology, Level 8 (N808), Medical Building,

Contact: E: ivanb@unimelb.edu.au T: 8344 6992 F: 8344 0241

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

31. The role of the HGF/Met signaling in regulating adult lung stem cells

Supervisor: Dr Jonathan McQualter

Co-Supervisor: A/Professor Ivan Bertoncello (ivanb@unimelb.edu.au)

Project Site: Department of Pharmacology, Level 8 (N808), Medical Building

Contact: E: jlmcq@unimelb.edu.au T: 8344 8509 F: 8344 0241

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

32. Characterisation of the lung epithelial stem cell niche

Supervisor: A/Professor Ivan Bertoncello

Co-Supervisor(s): Dr Rosa McCarty (rmccarty@unimelb.edu.au)

Project Site: Department of Pharmacology, Level 8 (N808), Medical Building

Contact: E: ivanb@unimelb.edu.au T: 8344 6992 F: 8344 0241

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

BIOLOGY — BONE

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

Supervisors: Profesor John Wark, Dr Peter Simm, Professor George Werther, Dr Sandra Petty

Project Site: Department of Medicine (RMH/WH)

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

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

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

34. **Hallux valgus: is it by nature or by nurture? A twin study**

Supervisor: Professor John Wark,

Project Site: Department of Medicine (RMH)

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

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

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

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

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

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

Project Site: Department of Medicine (RMH)

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

Dr Paul Wraight E: Paul.Wraight@mh.org.au

Foot disorders are a major cause of morbidity and hospitalization in patients with diabetes, with aetiological factors including vascular insufficiency, neuropathy and predisposition to infection. These

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

This project has three main objectives:

- 1) To determine whether individuals with diabetes-related foot complications are at an increased risk of bone loss, with a corresponding increase in morbidity/fractures.
- 2) If an association is identified between diabetes-related foot complications and bone loss, to identify contributing factors for this bone loss.
- 3) To develop a risk stratification tool in order to identify those individuals who are at highest risk of developing significant bone loss/morbidity/fractures.

This study may lead to improved outcomes in diabetic patients with this important cause of morbidity, poor quality of life and high health care costs. It is proposed to recruit 50 consecutive patients under the care of the RMH Diabetic Foot Unit to assess bone mineral measures during the management of their diabetes-related foot complications. Regional bone mineral density will be measured using dual energy Xray absorptiometry and peripheral quantitative computed tomography in all patients on entry to the study and at 6 months. Patients will be assessed for known and putative risk factors for both local and systemic bone mineral loss including features which may be novel to the management of their foot complication.

Students undertaking this novel project will gain substantial experience in the design and implementation of an original clinical research study, in patient recruitment, and data collection, management, analysis and interpretation.

36. The relationship between cartilage and trabecular bone microstructure in older adults

Supervisors: Associate Professor Robin Daly, Dr Christine Bailey

Project Site: Department of Medicine, Western Hospital

Contact: Associate Professor Robin Daly T: 8345 6924 E: rdaly@unimelb.edu.au ; Dr Christine Bailey T: 8345 7164 E: cbailey@unimelb.edu.au

Aims: To establish the relationship between trabecular bone microarchitecture and knee structure (tibial bone size, cartilage defects and cartilage volume) measured by MRI (magnetic resonance imaging) in a cohort of older adults aged 60+ years.

Background: The interaction between bone and cartilage in the knee joint is believed to be central to the onset and progression of knee osteoarthritis (OA), a major public health problem for which there is currently no treatment. It is known that the *size* of bone is increased in people with knee OA, which has been associated with cartilage deterioration. However, whether or not the *microarchitecture* of bone influences knee OA is unknown. This project will investigate if greater trabecular bone microarchitecture in the knee joint is associated with less bone expansion and healthier cartilage. This is important to study because interventions targeting bone structure could consequently be developed to treat and prevent knee OA.

Research Plan: Men and women aged 60 years and over will be invited to have an MRI scan of their knee and complete detailed medical and lifestyle questionnaires. Cartilage volume, cartilage defects, bone size and trabecular bone microarchitecture properties will be assessed using specially developed image analysis software. The student will be involved in analysing MRI scans and entering, analysing, and writing up data.

Skills Learned: Trabecular bone microarchitecture analysis, data management, statistical analysis, and data presentation in oral and written forms.

37. Enhancing fracture risk prediction in osteoporosis

Supervisors: Professor John Wark, Ms Susan Kantor and Dr Andrew Briggs
Project Site: Department of Medicine, The Royal Melbourne Hospital, University of Melbourne, Parkville Campus
Contact: Prof. John Wark: jdwork@unimelb.edu.au; Ms Susan Kantor skantor@unimelb.edu.au, Dr Andrew Briggs: A.Briggs@curtin.edu.au

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

Aims and Methods: This project will involve recruiting and evaluating several patient groups using this novel approach to osteoporosis assessment. Once validated, this methodology will allow more reliable identification of patients at high fracture risk. The ultimate aim is to refine diagnostic methods for the improved care of osteoporosis patients.

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

Supervisors: Professor John Wark, Dr Ashwini Kale and Susan Kantor
Project Site: Department of Medicine, The Royal Melbourne Hospital, University of Melbourne, Parkville Campus
Contact: Prof. John Wark: jdwork@unimelb.edu.au; Ms Susan Kantor skantor@unimelb.edu.au, Dr Ashwini Kale: akale@unimelb.edu.au

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

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

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

Supervisors: Professor John Wark, Ms Susan Kantor
Project Site: Department of Medicine, University of Melbourne, Parkville Campus
Contact: Prof. John Wark: jdwork@unimelb.edu.au; Ms Susan Kantor: skantor@unimelb.edu.au

Background: Bone density measurement by dual energy Xray absorptiometry (DXA) is currently the most useful way of assessing bone strength and an individual's fracture risk. However, at a population level, most low trauma fractures occur in people who have DXA bone density values below the young normal range but above the range defined as osteoporosis (so-called "osteopenia"). While DXA has a number of attractive attributes, it is not able to assess bone biomechanical indices nor to selectively

measure the density of trabecular and cortical bone. These bone properties contribute to the risk of fracture and can be assessed using peripheral quantitative computed tomography (peripheral QCT).

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

40. Improving the bone outcomes for patients with diabetes-related foot problems

Supervisors: Dr Paul Wraight, Professor John Wark and Ms Susan Kantor
 Project Site: Department of Diabetes and Endocrinology, Royal Melbourne Hospital,
 Department of Medicine, University of Melbourne, Parkville Campus
 Contact: Dr Paul Wraight: Paul.Wraight@mh.org.au, Prof. John Wark:
jdwork@unimelb.edu.au; Ms Susan Kantor: skantor@unimelb.edu.au

Background: Foot complications are a major cause of disability, hospitalization and cost in patients with diabetes. Individuals managed for diabetes-related foot complications may be more likely to develop significant bone mineral loss thus contributing to an increased fracture risk during the course of their treatment. Not only do these individuals share similar risk factors to the general population but aspects of their therapy are likely to be further contributing to this risk. For example, all individuals are managed with pressure off loading devices for varying lengths of time and this treatment not only reduces weight-bearing exercise but also increases the risk of mechanical falls. Mechanical falls are known to be more prevalent in individuals prone to developing foot complications, with our own data demonstrating that 30% of all patients had a fall in the 12 months prior to developing a foot complication. It is likely that poor calcium intake and low vitamin D levels (from reduced outside activities) also contribute to bone loss. Further contributing factors are likely and these may include the presence of infection (with 20-25% of individuals having pedal osteomyelitis), prolonged hospitalisations, co-existence of other diseases (including diabetes itself) and medications.

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

41. The young female health initiative (YFHI)

Supervisors: Professor John Wark, Professor Suzanne Garland, Dr Ashley Fletcher and Dr Yeshe Fenner
 Project Site: Department of Medicine, University of Melbourne, Department of Microbiology and Infectious Diseases, RWH, Parkville Campus
 Contact: Prof. John Wark: jdwork@unimelb.edu.au; Prof Suzanne Garland: Suzanne.Garland@thewomens.org.au, Dr Ashley Fletcher: Ashley.fletcher@mcri.edu.au, Dr Yeshe Fenner: yeshe.fenner@gmail.com

Background: Young women are often regarded as future “gatekeepers” of health in our society, yet are grossly under-represented in population-based health studies. The behaviours they adopt are likely to potentially influence their own future health trajectories and those of their partners and families.

Aims of project: The aim of this major new study is to obtain a better understanding of health-related behaviours, their determinants and their impact on health indices in 2,000 16 to 25 year-old females. Unlike any studies previously conducted, the inter-relationships between multiple health domains will be a particular focus of this research.

Methods: Web-based information and communication technologies will be used in recruitment and retention of subjects, data collection and to evaluate education and other forms of intervention. Current pilot studies suggest that this approach will be highly effective and a range of further pilot studies will be undertaken to refine and validate these novel and powerful methodologies.

This project offers the opportunity to be involved in one of several aspects of this exciting new project. For example, currently being designed are studies to look into the relationship between physical activity, mood and mental health in young women. However, studies involving bone and joint health, nutrition, sexual and reproductive health, obesity, metabolic and cardiovascular health are also planned and provide opportunities for suitable projects.

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

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

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

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

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

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

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

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

BIOLOGY —WOMEN'S HEALTH

43. Endometrial angiogenesis and vascular maturation

Project leader: Dr Jane Girling

Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital

Email: Jane.E.Girling@gmail.com

The development of new blood vessels (angiogenesis) is important for normal functioning within the endometrium (lining of the uterus) during the menstrual cycle. It is also an essential component of numerous clinically important processes, including wound healing and tumour growth and spread. A further component of blood vessel development is the recruitment of vascular mural cells including pericytes and vascular smooth muscle cells. Mural cells provide physical support for the vessels, as well as having an important role in regulating angiogenesis and vessel function. There is emerging evidence that endometrial angiogenesis and vessel maturation occur by different mechanisms when driven by oestrogen as opposed to progesterone. There is also evidence that abnormal angiogenesis contributes to endometrial breakthrough bleeding, a common and troublesome gynaecological disorder suffered by many women, particularly those using progestin-only type contraception. Three mouse models have been developed to examine the effects of oestrogen, progesterone and long-term progestin treatment on endometrial angiogenesis and vessel maturation. Projects will be available to manipulate these models and further investigate the different mechanisms controlling endometrial vascular development.

44. Lymphatics in the endometrium

Project leader: Dr Jane Girling

Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital

Email: Jane.E.Girling@gmail.com

While the location of various blood vessel types has been well characterized in the endometrium, the scientific literature on uterine lymphatics is not extensive. This is despite the known and hypothesised importance of lymphatic vessels to pathologies such as endometrial cancer, endometriosis and adenomyosis. Using recently developed markers specific to lymphatic endothelial cells, we have accurately described the location and density of uterine lymphatic vessels in human and mouse uterine tissue. Large numbers of lymphatics were observed in the basalis region (adjacent to the muscle layers) of the human endometrium, with only small numbers of vessels in the functionalis. In contrast, few if any lymphatics were observed in the mouse uterus. Projects will be available to investigate the mechanisms by which oestrogen, progesterone and progestins regulate endometrial lymphatic vessel growth and the interaction of these steroids with the key lymphangiogenic growth factors VEGF-C and VEGF-D.

45. Endometriosis

Project Leaders: Prof Peter Rogers and Dr Jane Girling

Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital

Email: peter.rogers4@gmail.com or Jane.E.Girling@gmail.com

Endometriosis is a disease where endometrial tissue grows outside the uterus, most commonly on the organs and tissues of the peritoneal cavity. Endometriosis can cause severe pain, associated with peritoneal inflammation, fibrosis and adhesions. It has been estimated that 8-10% of women in their reproductive years suffer from endometriosis. Endometriosis is a complex disease that is difficult to study. The aim of this project is to develop a mouse model of endometriosis that can then be used as part of ongoing studies with endometrial stem cells, as well as for functional studies of genes identified as playing a role in endometriosis through genetic studies.

46. **Growth and development of uterine fibroids**

Project leaders: Prof Peter Rogers, Dr Marina Zaitseva and Prof Martha Hickey
 Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital
 Email: peter.rogers4@gmail.com; mzaitseva@hotmail.com or
martha.hickey@thewomens.org.au

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

47. **Mechanisms of abnormal uterine bleeding in Implanon users**

Project leader: Prof Martha Hickey
 Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital
 Email: martha.hickey@thewomens.org.au

Long-acting progestin only contraceptives such as Implanon commonly lead to abnormal uterine bleeding. The mechanisms underlying this bleeding are not fully understood, but appear to include increased local production of reactive oxygen species which may be due to changes in endometrial perfusion. This project will further investigate how Implanon affects the endometrium by measuring endometrial perfusion using a laser Doppler probe in women before and after insertion of the long-acting contraceptive implant Implanon

48. **Management of anxiety in women during the menopause transition**

Project leaders: Dr Christina Bryant and Prof Martha Hickey
 Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital
 Email: martha.hickey@thewomens.org.au

Affective disorders (depression and anxiety) are more common in women going through the menopause transition (MT) than in younger reproductive aged women. Cognitive Behaviour Therapy techniques are effective in managing anxiety but have not been trialed in women going through the menopause transition. This study will develop a CBT program for anxiety in women during the MT and test the efficacy of this program in a randomized controlled trial compared to usual care. The setting will be in the menopause clinic at the Women's and this will be a collaborative project with the Psychology department

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

Supervisors: Professor Terence O'Brien and Professor Frank Vajda, Epilepsy and Neuropharmacology Group, The Department of Medicine: The Royal Melbourne Hospital, Associate Professor Les Sheffield, The Murdoch Children's Research Institute
 Project Site: The Department of Medicine (RMH/WH)
 Contacts: Professor Terence O'Brien T: 8344 5479 E: obrientj@unimelb.edu.au
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 A/Professor Les Sheffield E: les.sheffield@ghsv.org.au, The Murdoch Childrens Research Institute.

It is long been recognised that women with epilepsy who become pregnant while taking an anti-epileptic drug (AED) have an increased risk of having a foetus or infant with a birth defect (BD). This is particular high for valproate. Despite the increased risk associated with taking AED in pregnancy,

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

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

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

This project is also listed under Pregnancy Research

CANCER

50. Development of a diagnostic test for gastric cancer

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

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

Contact: A/Professor Alex Boussioutas T: 03 8345 6252 E: alex@unimelb.edu.au Dr Rita Busuttil T: 03 9656 1287 E: Rita.Busuttil@petermac.org

Gastric cancer (GC) is the fourth most common cancer globally and 7th in incidence in Australia. Unfortunately, in Australia as well as in other Western countries GC is diagnosed at advanced stages during endoscopic biopsy, giving patients a 5-year survival of less than 20%. Advanced stage GC is directly correlated with the T-stage of a cancer. T-stage is a measure of the invasion of the cancer through the gastric cell wall and, at more advanced stages, into adjacent structures. Currently information regarding the T-stage of the tumor can only be accurately obtained after surgery and cannot help with decisions related to the primary surgical procedure or the role of neo-adjuvant therapy. Genomic analysis in our laboratory has identified SFRP4 as the gene most highly correlated T-stage. It was also found that the expression level of SFRP4 was specifically elevated in cancer and not benign conditions of the stomach suggesting it would be a very sensitive and specific diagnostic. Moreover the higher the expression level of SFRP4 higher the level of invasion of the cancer. SFRP4 expression levels are also correlated with progression free survival with low expression being associated with lower rates of recurrence and ultimately with better prognosis. This project aims to develop a diagnostic test to detect the SFRP4 levels in a patient's blood. As well as being able to diagnose GC this non-invasive test could aid clinicians in improved prognostication of cancer to guide therapy and as a clinical aid to avoid unnecessary procedures for patients that could ultimately affect quality of life.

51. Validation of candidate genes involved in the progression of gastric cancer

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

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

Contact: A/Professor Alex Boussioutas T: 03 8345 6252 E: alex@unimelb.edu.au Dr Rita Busuttil T: 03 9656 1287 E: Rita.Busuttil@petermac.org

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

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

52. Glioma stem cells: biology and molecular targets

Supervisor: Dr Andrew Morokoff, Dr Kate Drumm, Dr Giovanna D'Abaco

Project Site: Department of Surgery, Royal Melbourne Hospital

Contact: Dr Andrew Morokoff T: 9342 7703 E: morokoff@unimelb.edu.au / Andrew.morokoff@mh.org.au

Gliomas are highly invasive brain tumours with an extremely poor survival because of their highly invasive nature and high recurrence rate. Recently, a subpopulation of cells (CD133+) with stem cell-like properties have been identified in gliomas and these cells are thought to be the primary cause of recurrence and treatment resistance. Furthermore, certain molecular pathways that lead to invasion, anti-apoptotic and drug resistance effects may be 'switched on' in glioma stem cells. Thus, understanding this type of cell may lead to better treatments. Thus project involves establishing stem cell cultures from surgical brain tumour specimens and growing then in special conditions as 'neurospheres'. Once the cell lines are established they will be assessed for known alterations of molecular signalling pathways and genetic mutations. This data will be collated and compared to clinical data from the corresponding patients such as time to progression and survival to form a 'genetic signature' of these tumours. This information will form the underpinning to the testing of various inhibitors against targets such as PI3K in glioma stem cells.

53. TGF- signalling and cancer development

Supervisors: Dr. Hong-Jian Zhu (and Dr. Rodney Luwor, Bo Wang, Catherine Winbanks)

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

Project Outline: Traditionally, key-lock or on-off models dominate the molecular understanding of cellular signalling and disease development, with most studies focusing on linear molecular signalling cascades. With the advent of large scale molecular techniques such as proteomics and microarrays, cross-talk between signalling networks has been implicated to play critical roles in cancer development. It challenges the physiological validity of the switch on-off model. Our lab, using molecular, cellular and gene targeted animal models as well as human patient samples, has established

that the moderation of signalling sensitivity by other pathways, rather than a black-white switch on-off, specifically of the TGF- β (Transforming Growth Factor- β) signalling pathways determines cancer progression. These findings have been published in top-ranking biomedical journals including **Nature Medicine** (11:845-52, 2005). Given the medical significance, current works in our lab are supported by 4 NHMRC and 1 Cancer Council grants totalling more than \$2 million.

This lab aims to understand the molecular fundamentals of TGF- β signalling mis-regulation and its causation effect on early tumor development and late tumor invasion and metastasis. In particular, we focus on the few major oncogenic molecular pathways' cross-talk with TGF- β signalling in various stages and types of cancer development. Concurrently, we are also devising strategies utilizing our unique molecular insights to convert tumor-causing signalling to directly tumor-killing.

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

Project A: Converting oncogene signalling to tumor killing in brain cancer

Project B: Stat3 mediated impairment of TGF - signalling in head&neck and breast cancer

Project C: Targeting TGF - signalling expansion in brain tumor invasion

Project D: Regulation of TGF - signaling by Wnt pathway in the development of colon cancer

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

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

54. Circulating endothelial cells as biomarkers for prostate cancer

Supervisor: Dr. Chris Hovens

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

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

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

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

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

55. Genetic and pharmacologic approaches to dissect lung inflammation and lung cancer

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

Contacts: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au
A/Professor Margaret Hibbs T: 9341 3155 E: Margaret.Hibbs@ludwig.edu.au

Chronic obstructive pulmonary disease (COPD) is an incurable and often fatal inflammatory lung disease, and is a known risk factor for lung cancer. We have a number of animal models of inflammatory lung disease, including mice with activating mutations in Src family kinases, and mice with deleterious mutations in the inositol phosphatase SHIP-1 or the protein tyrosine phosphatase SHP-1. The aim of this project is to use genetic approaches to identify genes that predispose to inflammatory lung disease, and pharmacologic methods to reverse establish disease.

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

This project is also listed under Asthma & Chronic Obstructive Pulmonary Disease (COPD)

56. Src kinases, lung inflammation and lung cancer

Supervisors: A/Prof Margaret Hibbs and Professor Gary Anderson

Project Site: Department of Pharmacology, University of Melbourne

Contacts: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au
A/Professor Margaret Hibbs T: 9341 3155 E: Margaret.Hibbs@ludwig.edu.au

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

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

This project is also listed under Asthma & Chronic Obstructive Pulmonary Disease (COPD)

57. The role of Wnt/ β -catenin and Stat3 signalling in cancer

Supervisors: Dr Michael Buchert, Dr Toby Phesse (Ludwig Institute)

Project Site: Ludwig Institute

Contact: T : 03 9341 3155
Dr Michael Buchert E : michael.buchert@ludwig.edu.au
Dr Toby Phesse E: toby.phesse@ludwig.edu.au

The canonical Wnt and the cytokine-activated Stat3 signalling pathways are key drivers for tumorigenesis in a variety of human tumours. In our laboratory, we have developed genetically modified mice in which both the Wnt and Stat3 signalling pathways are activated in the gastrointestinal tract. This results in the formation of tumours in the small and large intestine as well as in the stomach. In addition we are setting up a mouse model in which skin tumours can be induced chemically in mice with activated Wnt and Stat3 signalling pathways. The aim of this project is to elucidate the mechanism(s) leading to tumour formation with a focus on identifying potential avenues for reversing tumour growth/formation.

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

58. Role of the transcription factor, c-Myb in cell growth and differentiation in the vertebrate intestinal epithelium

Supervisors: A/Professor Joan Heath, A/Professor Rob Ramsay

Project Site: Ludwig Institute for Cancer Research

Contacts:

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The highly elaborate epithelial lining of the vertebrate intestine is a dynamic and self-renewing tissue system that encompasses most aspects of cell behaviour, including cell proliferation, differentiation, migration and apoptosis. To a large extent, the genetic mechanisms involved in establishing and maintaining this constantly remodelling tissue system remain a mystery. Due to its many favourable characteristics, including prolific reproduction, external development and optical transparency of embryos, the zebrafish is an ideal model for the genetic analysis of vertebrate organogenesis.

In the zebrafish intestine, three distinct cell lineages are derived from a common multipotential stem cell. These cells undergo a series of binary cell fate decisions to give rise to the enterocytes (nutrient absorbing), goblet (mucous producing) and enteroendocrine (hormone producing) cells. The mechanisms that govern these binary cell fate decisions are incompletely understood. We recently identified a new BAC transgenic line, *Tg[c-myb:YFP]*, which provides an exciting opportunity to throw light on this question. In this line, the regulatory elements of the *c-myb* gene drive strong YFP expression in an abundant population of cells scattered throughout the intestinal epithelium.

The specific aim of this project is to characterize the genetic regulation of epithelial cell growth and differentiation in the zebrafish intestine using reverse genetic approaches. Specifically, antisense morpholino oligonucleotides, targeted to *c-myb*, (a transcription factor known to play a role in intestinal development) will be injected into the yolk of 1-2 cell zebrafish embryos in order to knock-down c-Myb function over the first few days of development. The impact of inhibiting this transcription factor on intestinal epithelial cell development will be analysed in the first instance using fluorescence dissecting and confocal microscopy. Other approaches will be to examine intestinal epithelial cell development in a panel of zebrafish intestinal mutants that are currently undergoing characterization in our laboratory using positional cloning, *in situ* hybridization and immunohistochemistry. This analysis will be greatly facilitated by establishing the mutant strains onto the transgenic *Tg[c-myb:YGF]* background.

This Honours project will largely be conducted in the Colon Molecular and Cellular Biology Laboratory, Ludwig Institute for Cancer Research, Royal Parade, Parkville, where all the facilities for zebrafish developmental genetic studies are located.

59. Analysis of the APC tumour suppressor protein in 3D cell culture models

Supervisors: Dr Maree Faux, Professor Tony Burges, Ludwig Institute for Cancer Research

Project Site: Ludwig Institute for Cancer Research

Contact: Dr Maree Faux T : 03 9341 3155 E : Maree.faux@ludwig.edu.au

Colon cancer is one of the major diseases of the Western world and affects more people in Australia than any other cancer. APC mutations can be inherited, but more than 80% of sporadic colon cancers carry truncating mutations in the tumour suppressor protein APC (adenomatous polyposis coli). APC mutations are thought to be an early event in a multistep process involving the successive acquisition of genetic mutations. This suggests a key role for Apc in the maintenance of normal colonic cellular function, however, the precise mechanism of events arising from its loss of function that lead to the development of polyps and adenomas is not known. A well established role for APC is in the regulation of the Wnt signaling target β -catenin. Recent studies demonstrate that APC is also

involved in cytoskeletal regulation and is likely to play a role in cell migration, adhesion and differentiation. We have developed antibodies, recombinant proteins and cell lines for the study of different aspects of APC structure and function. We have evidence that the wild-type protein can influence cell adhesion. We believe that APC is a key mobile scaffold regulating cell adhesion and that its functions are intimately linked with its location and dynamic behaviour in the cell. The aim of this project is to investigate mutated and wt APC at the subcellular level in 3D culture models. The human colorectal cancer cell line LIM1863, containing mutated APC protein, form three-dimensional highly organised, multicellular structure organoids that resemble enclosed carcinoma tubules. Polarized MDCK epithelial cells, containing full-length APC, form three-dimensional cysts in culture. These models will be used to assess endogenous APC, as well as organoid/cyst formation in cells expressing APC-GFP and APC siRNA.

Skill acquisition: The successful BSc honours student will use a combination of molecular and biochemical techniques such as cell culture, immunostaining, confocal microscopy, transfection, and Western blot analysis.

60. Characterization of the role of Th17 cell populations in gastrointestinal cancer

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

Project Site: Ludwig Institute for Cancer Research

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

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

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

61. Using a new mouse model to understand colitis

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

Project Site: Ludwig Institute for Cancer Research

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

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

expressing a luciferase reporter construct that will allow for *in vivo* imaging of the colonic epithelium using state-of-the-art equipment.

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

62. What role do T-cells play in colitis?

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

Project Site: Ludwig Institute for Cancer Research

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

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

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

63. The role of PTEN and Stat3 signaling in cancer

Supervisors: Dr Michael Buchert, Dr Toby Phesse (Ludwig Institute)

Project Site: Ludwig Institute

Contact: 03 9341 3155
Dr Michael Buchert E: michael.buchert@ludwig.edu.au
Dr Toby Phesse E: toby.phesse@ludwig.edu.au

The tumour suppressor PTEN is one of the most commonly mutated genes in human cancer and the cytokine-activated Stat3 signalling pathways are key drivers for a wide range of human pathologies, most notably cancer. In our laboratory, we have developed genetically modified mice which carry mutations that inactivate PTEN and hyper-activate the Stat3 signalling pathway. This results in the formation of various tumours affecting different tissues, among them the gastrointestinal tract. The aim of this project is to elucidate the mechanism(s) leading to increased tumour formation in PTEN/Stat3 mutated mice with a focus on identifying potential avenues for reversing tumour growth/formation.

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

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

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

Project Site: Ludwig Institute for Cancer Research

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

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

References: Jenkins B, Ernst M *et.al.*, (2005) Nature Medicine; Ernst *et.al.*, (2008) J Clin Invest; Bollrath J, Putoczki T, Ernst M *et.al* (2009) Cancer Cell

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

65. Regulation of Stat3 – mediated Tumor Progression

Supervisors: Dr Rodney Luwor

Project Site: Department of Surgery, Royal Melbourne Hospital

Contact: T : 9342-7703 E : rluwor@unimelb.edu.au

During physiological processes the intracellular protein Signal Transducer and Activator of Transcription 3 (Stat3) is activated by many growth factors and cytokines (e.g. EGF) resulting in entry into the nucleus and transcription of many genes involved in a multitude of cellular processes. However, uncontrolled or un-attenuated stat3 phosphorylation/activation results in cancer initiation, progression and metastasis of many tumour types. Therefore, understanding how stat3 is regulated or controlled within the cell is pivotal for cancer biology and may allow greater scope for therapeutic intervention into stat3-driven tumourigenesis. Recently, we showed that EGFR-driven stat3 phosphorylation and transcriptional activity is regulated by EGFR internalisation indicating that EGFR activates stat3 while it traffics through the cell in the endosomal pathway. Therefore this project aims to locate where the EGFR phosphorylates Stat3 within the cell utilizing a panel of siRNA targeting proteins essential for EGFR trafficking.

Skills acquisition: Cell biology techniques including Cell transfections, western blotting, immunofluorescence staining and confocal microscopy, luciferase reporter assays and potentially animal handling and injecting.

66. Investigation of novel tumour suppressor gene and oncogene candidates for colorectal cancer

Supervisors: Dr Anuratha Sakthianandeswaren, Dr Oliver Sieber

Project Site: Ludwig Institute for Cancer Research

Contact: Dr Oliver Sieber, T : 03 9341 3168, E : oliver.sieber@ludwig.edu.au

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

Skill acquisition: The successful BSc honours student will acquire competence in a number of molecular biology techniques including cell culture, PCR, gene expression analysis, high-resolution melting curve analysis, DNA sequencing and protein detection techniques.

67. Synchrotron radiotherapy for the treatment of cancer

Project leaders: Prof Peter Rogers and Dr Jeff Crosbie

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

Email: peter.rogers4@gmail.com or Jeff.Crosbie07@optusnet.com.au

The synchrotron produces near-parallel x-ray beams that are up to ten billion times more intense than those currently used for radiotherapy in the treatment of cancer. This provides novel opportunities for spatially fractionating the beam to treat tumours. Normal tissues appear to be resistant to spatially fractionated radiation, with survival following doses up to a hundred times greater than with conventional radiation. Conversely, tumours can be readily destroyed using spatially fractionated radiation, although the molecular and cellular mechanisms behind this susceptibility are currently unknown.

This project will utilise the new Australian Synchrotron to investigate the molecular and cellular mechanisms that underpin the response of normal and tumour cells to spatially fractionated radiation in mouse models.

68. Menopausal symptoms after cancer

Project leader: Prof Martha Hickey

Project Site: Department of Obstetrics & Gynaecology, Royal Women's Hospital

Email: martha.hickey@thewomens.org.au

Treatment for breast cancer and other endocrine sensitive cancers can commonly induce menopausal symptoms. These symptoms can impact negatively on quality of life and sexual function. This project will be based at the menopause and cancer (MSAC) clinic at the Women's hospital, and will investigate the relationships between menopausal symptoms and sexual function in cancer patients. The project will include a collaboration with the Breast Cancer Network Australia (BCNA)

69. Effect of Src Phosphorylation on the biological function of E-Cadherin

Supervisors: Bruno Catimel and Tony Burgess

Project Site: Ludwig Institute for Cancer Research

Phone: 9341 3155

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E-Cadherin and β -catenin are important cytoplasmic components of the classical cadherin adhesion complex that forms the adherens junction and mediates epithelial cell-cell interactions. β -catenin binds to both cadherins and α -catenin, which connects the cadherin complex to the actin cytoskeleton. β -catenin is also a key signalling molecule in the canonical Wnt signalling pathway that controls cell production and differentiation during normal development and tumorigenesis. In the absence of Wnt signaling, β -catenin that is not associated with a cadherin complex is phosphorylated at the N-terminal Ser/Thr residues by a degradation complex containing axin, adenomatous polyposis coli (APC), casein kinase I, and GSK3 β , then ubiquitinated by beta-TrCP, and degraded by the proteasome. However, in the presence of Wnt signal, the degradation complex is disrupted and the phosphorylated β -catenin binds to a cytoplasmic complex, translocates into the nucleus, where it interacts with transcription factors.

The cytoplasmic domain of E-cadherin has been shown to display metastasis/tumour suppressor activity, probably by sequestering β -catenin. The E-cadherin/ β -catenin complex is disrupted by tyrosine phosphorylation of β -catenin by receptor associated tyrosine kinases and cytoplasmic tyrosine

kinases (e.g. src). E-cadherin/ β -catenin complex formation is promoted by β -catenin phosphorylation by casein kinase II, and disrupted by dephosphorylation by protein tyrosine phosphatases (e.g. PP2A). Ser/Thr phosphorylation of E-cadherin also modulates the binding to beta-catenin and the strength of cell–cell adhesion. Src phosphorylation of E-Cadherin appears to reduce its affinity for β -Catenin. Src is known to interact with components of the focal contacts and the adherent junctions for cell migration. Src is also frequently over-expressed and/or activated in human colorectal carcinoma (CRC), and its increased activity has been associated with a poor clinical outcome. Src regulates growth, survival, and invasion of some colonic carcinoma cell-lines *in vitro*.

This project aims to characterise the role of src phosphorylation on the biological function and cellular localisation of E-cadherin and β -catenin during Wnt signalling. The specific src phosphorylation sites in recombinant E-Cadherin will be determined and the effect of specific phosphorylation on the β - Catenin interaction will be determined. Antibodies directed against specific E-cadherin tyrosine phosphorylation sites will be generated and used to characterise the phosphorylation status of E-Cadherin in normal and cancerous colonic carcinoma cells with normal or elevated levels of src. Mass spectrometry proteomic analyses will also be available for these studies. Proteomic analyses will be used to identify protein complexes that interact with E-Cadherin and β -catenin after src phosphorylation. Biological studies (e.g. adhesion, invasion) will be performed to assess the effect of src phosphorylated E-cadherin on cellular processes associated with metastasis.

Skill acquisition: The successful BSc honours student will use cell culture, production of recombinant protein domains, biochemical techniques, biosensor analysis, proteomic studies, fluorescent confocal microscopy and biological assays for adhesion, migration and invasion.

LUDWIG INSTITUTE FOR CANCER RESEARCH MELBOURNE–AUSTIN BRANCH:- Oncogenic Transcription Laboratory:

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

70. Targeting *BRAF* mutant colon cancers

Supervisors: John M Mariadason, Ludwig Institute for Cancer Research, Austin Hospital, Lvl 7, Harold Stokes Building, 145-163 Studley Road, Heidelberg, Vic, 3084.
Co-supervisor: Dr Jayesh Desai, Ludwig Institute for Cancer Research, Royal Melbourne Hospital
Project Site: Ludwig Institute for Cancer Research, Oncogenic Transcription Laboratory, Austin Hospital
Contact: T: 61 3 9496 3068 E: john.mariadason@ludwig.edu.au F: 61 3 9496 5334. E: Jayesh.Desai@ludwig.edu.au
<http://www.ludwig.edu.au/centre/research/Mariadason-lab.htm>

Activating mutations in the *BRAF* oncogene are found in approximately 10% of patients with metastatic colon cancers. These patients tend to have a poor prognosis and have limited treatment options once they fail chemotherapy. The development of new treatments for these patients is therefore urgently needed. Drugs which target and inhibit mutant *BRAF* have recently been developed, and have shown remarkable clinical activity in *BRAF* mutant melanoma. Clinical activity of these drugs in colon cancer has also been observed, however response rates are significantly less than those

observed in melanoma. One proposed explanation for this difference is the presence of concurrent mutations in the PI3K/PTEN pathway in colon tumours, which reduces the dependence of the tumour on *BRAF*, and thus sensitivity to *BRAF* inhibitors. In this project a panel of *BRAF* mutant colon cancer cell lines will be screened for response to *BRAF* inhibitors using the MTS and FACS-based assays, to identify colon tumours sensitive and resistance to these drugs. The impact of concurrent mutations in the PI3K/PTEN pathway on response to *BRAF* inhibitors will then be determined. Should mutations in PIK3CA/PTEN be found to impact response, the effect of dual targeting of BRAF and PI3K signalling on tumour growth will be determined by combination treatment with BRAF and PI3K-inhibitors. Should PIK3CA/PTEN mutations not impact response to BRAF inhibitors, alternative mechanisms of response will be examined by gene expression profiling of sensitive and resistant cell lines treated with these drugs. This thesis is designed to provide the student with insight into the genetic basis of cancer, an understanding of the treatment strategies used in cancer and exposure to translational cancer research. This Hons project will be conducted in the Oncogenic Transcription Laboratory, Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg.

71. **Role of villin in colon cancer metastasis**

Supervisors: John M Mariadason, Ludwig Institute for Cancer Research, Austin Hospital, Lvl 7, Harold Stokes Building, 145-163 Studley Road, Heidelberg, Vic, 3084.
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<http://www.ludwig.edu.au/centre/research/Mariadason-lab.htm>

We have recently discovered a subset of colon cancers in which the cytoskeletal protein, villin, is completely absent. Remarkably, loss of villin occurs selectively in colon cancers with a characteristic known as “microsatellite instability” or MSI. Cancers with this characteristic are less likely to metastasize and have a better outcome. This honours project will examine the transcriptional mechanism by which loss of villin expression occurs in colon cancer. Specifically, the role of the Cdx-1 and HNF1 transcription factors in regulating villin expression will be explored. First, whether Cdx-1 and HNF1 expression correlates with villin expression will be examined by immunohistochemistry in a panel of colon cancer cell lines and primary colon tumors by real time PCR and immunohistochemistry. Second, the effect of over and underexpression of Cdx-1 and HNF1 on villin promoter activity and expression will be tested by transient transfection of these genes into colon cancer cells. Third, the impact of mutating Cdx-1 and HNF1 binding sites in the villin promoter by site-directed mutagenesis will also be tested, and binding of these factors to the villin promoter examined by ChIP analysis. The project will provide the student with a sound introduction to fundamental concepts in cancer biology, and experience in cell and molecular biology. This Hons project will be conducted in the Oncogenic Transcription Laboratory, Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg.

CARDIOLOGY

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

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

Heart failure (HF) is a major cause of morbidity and mortality among older adults constituting a significant burden on health-care systems. The underlying mechanism of HF is incompletely understood. It has been well recognized that activation of stress-related nerve system, sympathetic nerve system (SNS) and its responding receptors, β -adrenergic receptors (β -AR), are important for the heart to respond to physiological stress. However, tonic and chronic activation of β -AR contributes significantly to symptom worsening and progression of cardiac dysfunction and chamber dilatation leading to HF. Angiogenesis, a physiological process involving the growth of new blood vessels from

pre-existing vessels, is key factor crucially involved in the preserving of cardiac function and developing cardiac hypertrophy and its impairment leads to HF. Whereas both events, tonic/chronic β -AR activation and impaired cardiac angiogenesis, are well known to be important factors in heart disease development and progression, the connection between them and how they synergistically contribute to the progression of HF remain unknown.

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

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

COLORECTAL MEDICINE AND GENETICS

73. Bioinformatics in colorectal cancer genetics and prevention

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

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

74. Modifier genes in Lynch Syndrome

Supervisor: Professor Finlay Macrae, Dr Garry Hannan, CSIRO
 Project Site: Royal Melbourne Hospital, Parkville, and CSIRO, North Ryde, Sydney
 Contact : Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

In cooperation with the CSIRO, we are searching for new genes that modify the mismatch repair genes responsible, when mutated, for hereditary non polyposis colorectal cancer (Lynch Syndrome). This

involves further collaboration with the International Society for Gastrointestinal Hereditary Tumours, to secure the 4000 DNAs from carriers throughout the world. The project will involve understanding and assisting in a Genome Wide Association Study using an Illumina and/or Affymetrix platform in Sydney, and in assisting collating the targeted phenotypes of the carriers. Collaborations with the US National Institutes of Health Colon Cancer Family Study (with the Centre for Genetic Epidemiology, University of Melbourne) are available. This project will suit candidates interested in the interface between bioinformatics and clinical research, and is supported by substantial expertise in both these areas.

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

Supervisors: Professor Finlay Macrae Head, Colorectal Medicine and Genetics, Professor Richard Cotton, Director, Genomic Disorders Research Institute, University of Melbourne

Project Site: Dept of Colorectal Medicine and Genetics, RMH; or GDRC, Alan Gilbert Building, Uni of Melb.

Contact: Tel: 61 3 9347 0788 E: Finlay.macrae@mh.org.au

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

76. **Confocal endomicroscopy**

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics

Project Site: Royal Melbourne Hospital, Parkville

Contact: Tel: +61 3 9347 0788 E: finlay.macrae@mh.org.au

Aim: To assess distribution of disease in patients with known or historical microscopic colitis,

Inclusion: Clinical need for colonoscopy in patients with known microscopic colitis

Dysplasia in Ulcerative colitis and Barrett's Oesophagus

Intervention: Confocal Endomicroscopy

Correlation with conventional histology; diagnostic accuracy compared with random biopsy protocols

77. **Biogrid and IBD data basing**

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics

Project Site: Royal Melbourne Hospital, Parkville

Contact: Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

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

78. **Capsule Colonoscopy as a Screen for Colorectal Cancer**

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics

Project Site: Royal Melbourne Hospital, Parkville

Contact: Tel: +61 3 9347 0788 Email: finlay.macrae@mh.org.au

Capsule Colonoscopy is being introduced into Australia late in 2010. After ingestion of the device, the colon is visualized through a wireless capsule CCD device which transmits images to a receiver worn

by the patient. The Department will be the Australian lead the first two Capsule Colonoscopy projects. One is testing its capability on comparison with colonoscopy in an average risk population, and the other will tests its capacity in clinical scenarios where colonoscopy is relatively contraindicated o has failed. Assistance in performing the procedures and documenting the results of the project will be the core of this project. .

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

Supervisor: Professor Finlay Macrae, Head, Dr Suresh Sivanesan

Project Site: Royal Melbourne Hospital, Royal Brisbane, Royal Adelaide and Sir Charles Gardiner Hospitals

Contact: Tel: +61 3 9347 0788 E: finlay.macrae@mh.org.au

This is a randomised controlled trial of a new resistant starch preparation capable of releasing large quantities of butyrate for chemoprevention in the colon. The trial will measure adenoma formation of FAP patients through their regular surveillance, comparing activity with placebo study agents. In partnership with CSIRO.

CSIRO MOLECULAR AND HEALTH TECHNOLOGIES

80. **Acetyl CoA carboxylase- A target for control of obesity and diabetes**

Supervisor: Dr Lance Macaulay

Project Site: CSIRO Molecular and Health Technologies

Contact: Dr Lance Macaulay T: 9662-7335 E :: Lance.Macaulay@csiro.au

Central adiposity is associated with insulin resistance and is predictive of diabetes. Fat synthesis and breakdown is controlled in part by different forms of acetyl CoA carboxylase, ACC1 (essential for life) and ACC2 respectively. Animals in which ACC2 is deleted/inhibited are leaner and able to tolerate high fat diets, confirming this protein as a therapeutic target. This project seeks :to characterise the human carboxyl transferase (hCT) domain of ACC2. This will be accomplished by cloning several CT domain proteins, the development of assays to measure the activity of this domain including characterisation of metabolite regulators amenable for screening ACC2 inhibitors, as well as the initiation of protein crystallisation trials. The project will involve molecular biology in the cloning of various CT domain constructs of ACC2 for expression studies, cell based assays and recombinant protein production for in vitro investigation of these interactions. The project will therefore provide a rounded experience in protein chemistry and cell and molecular biology.

81. **Calmodulin dependent kinase kinase: A target for control of obesity and diabetes**

Supervisor: Dr Lance Macaulay

Project Site: CSIRO Molecular and Health Technologies

Contact: Dr Lance Macaulay T: 9662-7335 E :: Lance.Macaulay@csiro.au

Recent studies have identified calmodulin dependent kinase kinase (CamKK) as a kinase that regulates AMPK activity, the key enzyme controlling energy balance of the cell. We have expressed CamKK and now wish to explore its potential in controlling obesity related conditions including diabetes. The student project has been developed to express various domains of CamKK and screen for inhibitors of the enzyme using inhibitor libraries developed in our Division as part of CSIROs Preventative Health Flagship program. The project will involve cloning of protein domains, recombinant protein production, crystallography for structure determination and development of protein and intact cell screening assays for inhibitor analysis. The project will therefore provide a rounded experience in protein chemistry, cell and molecular biology.

These projects form part of a program run through CSIRO and SVIMR with Lance Macaulay and Bruce Kemp aimed at understanding the molecular links between diet and exercise that are important

for maintaining health and protecting the body from age onset diseases that include obesity, diabetes, hypertension, cardiovascular disease and cancer.

DERMATOLOGY

82. **ABCC6 and the pathogenesis of aneurysms**

Supervisor: Dr. George Varigos, Professor Grant Morahan and Dr Aaron Robinson

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

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

Pseudoxanthoma elasticum (PXE) is a genetic disease affecting connective tissues, caused by mutations in the gene encoding the membrane transporter ABCC6. Defects in the *ABCC6* gene can lead to mineralisation and subsequent fragmentation of elastin containing fibres in connective tissues. PXE primarily affects tissues such as the skin, causing yellowish papular lesions, but additionally has been shown to involve vascular and other organ pathology.

Although diagnoses of PXE based on dermatological presentations are rare, recent data arising from preliminary studies have suggested that *ABCC6* may play a much more widespread and significant role in the pathogenesis of vascular disease. Due to the impact of vascular pathology on the community, along with the acute health risks of rupture of aneurysms, understanding the role of ABCC6 in the pathophysiology of vascular disease is important. Additionally, as more becomes known about the pathogenesis of PXE, new opportunities for developing therapeutics become available. These may also be relevant for treatment of vascular pathology. Accordingly, we propose to investigate genetic polymorphisms in a cohort of aneurysm samples. This study will involve the following:

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

Samples will then be retrieved and prepared for histological and genetic analysis.

Histological analyses would involve staining and microscopy to examine samples for various hallmark features of PXE (such as tissue mineralisation), Genetic analysis of tissue samples would be employed to examine the correlation between various polymorphisms of *ABCC6* and pathology.

Skill acquisition: A variety of molecular biological and histological techniques, such as preparation of DNA from tissue samples, along with PCR and DNA sequence analysis, sectioning and staining of tissue samples for histological analysis, and microscopic evaluation of tissue samples.

ELECTROPHYSIOLOGY

83. **Epilepsy and Fracture Risk – Cellular electrophysiology**

Supervisors: Dr. Sandra Petty, Prof. Eleanor Mackie, Prof John Hamilton. Project collaborators: Dr. Elisa Hill and Dr. Marian Todaro.

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

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

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

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

84. Epilepsy and Fracture Risk – Bone Cell Electrophysiology

Co-Supervisors: Dr. Sandra Petty, Prof. Eleanor Mackie, Dr. Elisa Hill

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

Contacts: Dr. Sandra Petty T: 83443262 E: pettys@unimelb.edu.au ;
Prof. Eleanor Mackie T: 8344 7357 E: ejmackie@unimelb.edu.au ; Dr Elisa Hill E: elhill@unimelb.edu.au

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

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

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

85. Investigating inhibitory synaptic function in a mouse model of Autism

Supervisors: Dr Elisa Hill & Professor Terence O'Brien.

Project Site: Department of Medicine, University of Melbourne

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

Specifically, the project will investigate:

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

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

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

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

86. How do Anti-Epileptic Drugs Work?

Supervisor: Dr Chris French

Project Collaborators – Prof T O'Brien, Prof D Williams

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Website: http://sites.google.com/a/hfbg1.net/crf_lab/

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

87. How do Antipsychotic Drugs Trigger Seizures?

Supervisor: Dr Chris French

Project Collaborators – Prof T O'Brien, Prof D Williams

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

Contact: Dr Chris French T: 8344 3276 E: frenchc@unimelb.edu.au

Website: http://sites.google.com/a/hfbg1.net/crf_lab/

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

88. Multi-Electrode Recording in the Rat Brain

Supervisor: Dr Chris French

Project Collaborators – Prof T O'Brien, Dr P O'Brien

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Website: http://sites.google.com/a/hfbg1.net/crf_lab/

Although immense advances have occurred in recording electrical signals from the CNS, these observations tend to be of single cells in a matrix of many millions of neurons and hence give very limited information about how the whole highly interconnected network functions. One solution to this problem is to use banks of tetrodes, bundles of four 10-20 micron diameter electrodes to record many cells simultaneously, either from a single region or from different parts of the brain. Up to 32 electrodes can be implanted with our system, and sophisticated spike detection and analysis algorithms are available to organize the complex multiple signals recorded. This recording technique can also be easily adapted to exploring epileptiform discharges in models of both focal and generalised epilepsy (including drug effects), which will be the main aim of this project. This project provides opportunity to learn cutting-edge electrophysiological and computing analysis techniques for assessment of function of the mammalian nervous system.

ENDOCRINOLOGY, DIABETES & OSTEOPOROSIS

89. Correlation of vitamin D concentrations with measures of fat mass and insulin sensitivity in normal and obese subjects.

Supervisors: Prof Peter R Ebeling, Dr Claudia Gagnon

Project Site: Department of Medicine, Western Hospital.

Contacts: Professor Peter Ebeling T: 8345 6429 E: peterre@unimelb.edu.au;

The research study aims to correlate serum vitamin D concentrations with measures of fat mass and insulin sensitivity in normal and obese subjects, and obese patients with type 2 diabetes. This research project consists of recruiting subjects with normal BMIs and normal glucose tolerance (control group) and obese subjects (BMIs over 30 kg/m²) with normal glucose tolerance (first group), with impaired glucose tolerance (second group) and with type 2 diabetes mellitus (third group) recruited from the obesity clinic, the sleep apnoea clinic, and other sites at the University of Melbourne.

Primary endpoints: Prevalence of vitamin D deficiency (25-OH vitamin D < 25 nmol/L) and vitamin D insufficiency (25-OH vitamin D below 75 nmol/L) in each of the three groups.

Secondary endpoints: Correlation between 25-OH vitamin D levels and insulin sensitivity measured by HOMA-IS index. Correlation between 25-OH vitamin D levels and fat mass (measured by DXA).

EPILEPSY AND NEUROPHARMACOLOGY

90. Expression of efflux multidrug transporters in temporal lobe as a biomarker for outcome after surgery for pharmacoresistant temporal lobe epilepsy.

Supervisors: A/Professor Patrick Kwan, Professor Terence O'Brien, Dr Mark Cook

Contact: Patrick Kwan: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong. patrickkwan@cuhk.edu.hk; Terence O'Brien: Department of Medicine (RMH/WH). obrientj@unimelb.edu.au; Mark Cook: Department of Medicine (SVH). markjcook@me.com

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

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

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

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

Research plan

The project will study fresh human brain tissues frozen upon resection from patients with pharmacoresistant TLE and stored at the biobank at RMH, SVH and the Chinese University of Hong Kong. mRNA and protein levels of P-glycoprotein and other efflux transporters will be quantified. Their levels will be correlated with postsurgery outcome of the patients.

Acquired skills will include molecular biology techniques such as mRNA and protein extraction, quantitative RT-PCR, western blotting.

Reference

1. Kwan P, Li HM, Al-Jufairi E, Abdulla R, Gonzales M, Kaye AH, Szoek C, Ng HK, Wong KS, O'Brien TJ. Association between temporal lobe P-glycoprotein expression and seizure recurrence after surgery for pharmacoresistant temporal lobe epilepsy. *Neurobiol Dis* 2010;39:192-7.

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

Supervisor: Dr Chris French

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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

92. Does a novel mutation in the rat Cav3.2 T-type Ca²⁺ channel gene increase burst firing of neurons in vivo in a rat model of genetic absence epilepsy?

Supervisors: Dr. Kim Powell, Professor Terence O'Brien

Project Site: The Department of Medicine (RMH/WH), The Royal Melbourne Hospital, The University of Melbourne.

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

Voltage-gated calcium (Ca²⁺) channels are believed to play a critical role the generation of the hypersynchronous oscillatory thalamocortical activity that underlies absence seizures. Mutations in the Cav3.2 T-type Ca²⁺ channel gene have been reported in patients with childhood absence epilepsy (CAE) patients. Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are widely used model of absence epilepsy. In this model, Cav3.2 mRNA expression and T-type Ca²⁺ currents³ are elevated in the reticular nucleus of the thalamus (nRT), and we have shown similar elevations in the cortex. An increasing body of evidence, including from our laboratory, indicates that the seizures in GAERS originate focally in the somatosensory cortex. It is also known that the thalamus plays a critical role in allowing the seizures to occur, the basis of which is pathological oscillatory thalamocortical activity. Together this data implicates the Cav3.2 channel in the pathogenesis of this disease although whether functional abnormalities in the channel play a causative role in absence epilepsy is unknown. Linking an absence phenotype to a mutation in this channel would provide a priori case for a causative role. To this end we have identified that GAERS carry a homozygous single nucleotide missense mutation in a highly conserved region the III-IV linker domain of the Cav3.2 T-Type Ca²⁺ gene (R1584P).

Importantly, with our Canadian collaborators, we have shown that this mutation is dependent upon exonic splicing for its functional consequences to be expressed in-vitro (i.e. it requires the presence of exon 25 [Ca_v3.2 (+25)] to produce significantly faster recovery from channel inactivation and greater charge transference during high frequency bursts). This gain-of-function mutation, the first reported in the GAERS polygenic animal model, has a novel mechanism of action.

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

93. Evaluation of Dynamin Inhibitors as Novel Therapies for Epilepsy

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

Project Site: The Department of Medicine (RMH), Melbourne, and the Department of Physiology, Children's Medical Research Institute, Sydney.

Contact: Prof Terence J. O'Brien T: 8344 5479 E: obrientj@unimelb.edu.au

Professor Phil Robinson E: probinson@cmri.com.au

Dr. Nigel Jones T: 8344 6729 E: ncjones@unimelb.edu.au

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

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

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

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

Supervisor: Professor Terence O'Brien, Dr Damian Myers, Prof Rod Hicks, and Dr Nigel Jones

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

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Closed-head traumatic brain injury (TBI) is a common condition that has dramatic and often long-lasting impacts on the patient and their family. The annual incidence of significant TBI in developed countries has been estimated to be 1/1000

One of the dramatic and disabling long-term consequences of TBI is the development of post-traumatic epilepsy (PTE), which occurs in up to 25% of patients with moderate to severe injuries. With penetrating brain injuries the incidence is over 50%.

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

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

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

Several projects are available that include techniques such as small animal MRI and positron emission tomography (PET), video-EEG monitoring and histological techniques to investigate neural network changes associated with seizure onset after head trauma; another project area involves the study of neurocognitive and neurobehavioural testing to study the consequences of traumatic brain injury; advanced confocal microscopy and fluorescence imaging techniques.

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

Project 1: A study of the neurocognitive and neurobehavioural changes that occur after closed-head traumatic brain injury;

Project 2: Structural and functional changes in the brain monitored by FDG-PET and MRI after closed-head traumatic brain injury;

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

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

95. **Investigations into the role of neuropeptide y in a genetic rat model of absence epilepsy**

Supervisor: Prof Margaret Morris and Prof Terence J O'Brien.

Project Site: Department of Medicine (RMH) and Department of Pharmacology, University of New South Wales.

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

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

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

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

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

Skills: Small animal handling and neurosurgery (electrode implantations, microinjection catheter implantations), rat electroencephalography recordings, brain perfusion, fixation and histological preparation, immunohistochemistry.

96. **A model of functional disconnections to study the pathophysiology of psychosis and epilepsy**

Supervisor: Dr Nigel Jones and Prof Terence J O'Brien.

Project Site: Department of Medicine (RMH)

Contact: Dr Nigel Jones T: 8344 6729 E: ncjones@unimelb.edu.au

Functional disconnections in cortico-thalamo-cortical (CTC) systems, the neuronal circuits of attention, cognition and perception, are thought to underlie dysfunctions of conscious integration such as those seen in schizophrenia. More than 80% of the neurons that make up the CTC systems are glutamatergic. There is considerable evidence to suggest that NMDA-type glutamate receptors are implicated in the pathophysiology of schizophrenia. Non-competitive NMDA receptor antagonists (PCP, ketamine, MK-801), at subanaesthetic doses, induce cognition impairment, schizophreniform psychosis, hallucinations, and exacerbate both positive and negative symptoms in schizophrenic patients. In rodents, ketamine produces a wide spectrum of abnormal behaviour relevant to schizophrenia. The neuronal mechanisms underlying transient disruption in NMDA receptor function remain to be determined. CTC circuits generate coherent synchronized gamma frequency (30-80 Hz) oscillations during conscious brain operations. Disruption of cognition-related coherences of gamma oscillations between cortical areas is a major functional abnormality in schizophrenic patients. It has been shown that patients with generalised epilepsy have increased baseline (i.e. between seizures) gamma activity on the EEG compared to non-epileptic control subjects. Work in our laboratory in the Department of Medicine has demonstrated that the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a well validated animal model of genetic generalized epilepsy, display a range of behavioural and emotional abnormalities that are consistent with those seen in models of schizophrenia-like psychosis. These rats, and their non-epileptic counterparts (NEC rats), have been respectively selectively breed for the presence or absence of the epileptic phenotype. The co-segregation of the psychiatric behavioral and epileptic phenotypes over more than 60 generations suggests an aetiological link between the two. This project will also explore the hypothesis that GAERS have an abnormal response of cortical gamma activity to the administration of NMDA

antagonists. If true, this would provide a neurophysiological correlate for the link between the epilepsy and schizophrenic like phenotypes in GAERS.

Note: this project is also listed under Neuropsychiatry and Stress Biology

97. Antiepileptic drugs and effects on bone health

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

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

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

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

Project 1: AED-induced changes in bone macrostructure, microstructure and bone strength: AIM:

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

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

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

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

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

Supervisor: Prof. Terence O'Brien and Prof. Margaret Morris

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

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

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

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

99. Sodium Channels in Epilepsy

Supervisors: Dr Chris French, Prof Terence O'Brien

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Laboratory Overview. The O'Brien Laboratory in the Department of Medicine, University of Melbourne, has a wide range of research activities related to the neurological disorder epilepsy. Projects include molecular biological studies, *in vivo* and *in vitro* electrophysiology, advanced imaging techniques, animal behaviour models, pharmacogenomics as well as comprehensive clinical

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

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

100. Epigenetic regulation of gene expression in epilepsy

Supervisors: Dr Nigel Jones, Dr Kim Powell

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne.

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Dr. Kim Powell T: 8344 3261 E: kpowell@unimelb.edu.au

Background: Epigenetics describes the way chromatin/DNA structure can influence gene expression. This relatively new field of molecular biology is well-advanced in cancer research, but has received little to no attention with respect to neurological conditions such as epilepsy. Changes in gene expression are heavily implicated in the disease process of epilepsy (referred to as epileptogenesis) which turns a normal healthy brain into an epileptic brain, and epigenetic mechanisms are strong candidates to mediate such gene expression changes. This program seeks to investigate epigenetic changes associated with epilepsy to determine whether such modifications in chromatin structure contribute to epileptogenesis. We are currently focussing on three genes.

Research Project 1: DNA methyltransferase (DNMT) gene expression

In mammalian cells, DNA methylation is catalysed by two classes of DNMTs. DNMT1 controls maintenance methylation and DNMT3 are the *de novo* methyltransferases. This project will measure DNMT mRNA and protein expression levels and DNA methylation in the hippocampus at different time points following seizures in the amygdala kindling animal model of temporal lobe epilepsy.

Research Project 2: Brain-Derived Neurotrophic factor (BDNF).

BDNF is heavily implicated in both epilepsy and neuronal plasticity (a form of neuronal reorganisation thought to be crucial in the development of disease). Previous research has shown also that expression of this gene can be epigenetically regulated to influence learning, and also may be a mechanism by which the ketogenic diet successfully treats epilepsy. This project will examine the chromatin structural alterations (DNA methylation and histone acetylation) at the promoter regions of BDNF and determine their influence on BDNF gene expression in epilepsy, and also explore whether pharmacological modification of these sites can impede/reverse the process of epileptogenesis.

Research Project 3: Reelin.

Reelin is a guidance molecule implicated in brain development. It is also implicated in epilepsy, with reelin down-regulation thought to be responsible for pathological hallmarks of the disease, such as dentate granule cell dispersion. This project will examine Reelin expression and DNA methylation at the Reelin promoter region, and relate these changes to alterations in behaviour and seizure frequency in epileptic animals compared with controls.

Skills: Small animal handling; behavioural testing for anxiety/depression related behaviours and cognitive function; animal models of epilepsy; small animal surgery and EEG recording; extensive molecular biology techniques, including real-time qPCR, Western blotting, and techniques specific for epigenetic analysis (bisulfite conversion of gDNA and Methylation Specific PCR).

101. Imaging neurogenesis using Magnetic Resonance Spectroscopy

Supervisors: Dr Nigel Jones, Dr Dennis Velakoulis, Professor Gary Egan

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne.

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Professor Gary Egan E: gary.egan@florey.edu.au

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

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

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

102. The impact of over-expression and under-expression of tissue Plasminogen Activator on epilepsy progression in mice.

Supervisors: Dr Nigel Jones, Professor John Hamilton, Professor Terence O'Brien

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, The University of Melbourne

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Background: The processes governing the development of limbic epilepsy are not well understood, but a growing body of literature supports the role of inflammatory mediators in this disease process. One such molecule is tissue Plasminogen Activator (tPA), a clinically used clot-busting enzyme which also has profound effects on cellular physiology in brain regions relevant to temporal lobe epilepsy. These effects, including modulation of cognitive processes, and influencing synaptic connectivity, provide strong rationale to promote tPA as a enzyme which may be involved in development of epilepsy.

Research Plan

The current proposal will investigate the role of tPA signalling in a mouse model of temporal lobe epilepsy. Using genetically engineered mice which are bred to either express an abundance of tPA, or a complete lack of tPA, we will determine the direct role of tPA on epilepsy progression. These experiments will incorporate the amygdala kindling model of limbic epilepsy in mice bred in the laboratories of our collaborators. The second aspect of the project will attempt to ascertain the mechanisms by which tPA might influence the progression of disease using immunocytochemical techniques.

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

This project is also listed under Arthritis & Inflammation Research

103. Using a new mouse model of severe epilepsy to discover new antiepileptic drugs

Supervisors: Dr Chris Reid & Dr Steve Petrou

Project Site: Florey neuroscience Institutes (Howard Florey Building)

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Dr Steven Petrou T: 8344 1957 E: spetrou@unimelb.edu.au

Dravet syndrome is a severe form of epilepsy that is very difficult to treat and often results in death (http://www.ninds.nih.gov/disorders/dravet_syndrome/dravet_syndrome.htm). Our group has developed a new mouse model of the disease that is based on a human mutation. The mouse has all the major symptoms seen in patients with the disease. Some antiepileptic drugs reduce seizures in patient while others make the disease worse. We want to test these antiepileptic drugs on the mouse to see if they have the same 'pharmaco-therapeutic' profile as humans with the disease. This will validate the model potentially making it a powerful tool with which to test new and hopefully more effective antiepileptic treatments for Dravet syndrome.

104. Stopping Epilepsy before it starts

Supervisors: Dr Chris Reid & Dr Steve Petrou

Project Site: Florey neuroscience Institutes (Howard Florey Building)

Contact: Dr Chris Reid T: 8344 1954 E: careid@unimelb.edu.au

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Idiopathic generalised epilepsy is a common form of epilepsy with a strong genetic component. Advances in gene discovery suggests that genetic profiling will allow us to predict what chance an individual has of getting epilepsy. In an exciting recent discovery our group has shown that the impact of an epilepsy mutation in early brain development can increase the chance of adults having seizures (Chui et al Annals of Neurology 2008). Therefore, if we can stop the impact of the epilepsy mutation in early development we may be able to stop epilepsy from ever occurring. This project has two parts. First, to administer antiepileptic drugs in the early part of brain development and see if we can reverse the impact of an epilepsy mutation. Second, to record early brain activity in a mouse model of idiopathic generalised epilepsy that is based on a human epilepsy mutation. This will determine what may be going wrong with the brain in the early developmental time window. Together, projects outlined here will help devise new therapeutic strategies that may allow us to stop epilepsy from ever occurring in susceptible patients.

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

Supervisors: Dr Jeremy Kennard, Dr Kim Powell, Professor Terence O'Brien
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Professor Terence O'Brien T: 8344 5479 E: obrientj@unimelb.edu.au.

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

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

106. The effect of down regulating TARP and AMPA receptor on seizure expression in Genetic Absence Epilepsy Rats from Strasbourg

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

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

The specific aims of this project are:

- To measure protein expression (membrane vs. cytosol) of the TARPs ($\gamma 3$, $\gamma 4$ and $\gamma 8$) in juvenile pre-epileptic and adult epileptic GAERS and to correlate with seizure expression
- To determine if down regulating stargazin and AMPA receptor expression (using siRNA) has any effect on the seizure phenotype in GAERS
- To investigate if there are common transcription factor(s) to all the TARPs that may influence gene transcription

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, real time PCR).

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

Supervisors: Dr Jeremy Kennard, Professor Terence O'Brien, Prof Phil Robinson (University of Sydney)
 Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital
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Project Overview: The Epilepsy and Neuropharmacology Research group is currently investigating novel anti-epileptic drugs that act to inhibit **dynamin**. This protein is critical to the rapid recycling of synaptic vesicles required for excessive neurotransmitter release that occurs during epileptic seizures. Dynamin activation is regulated through calcium-dependent dephosphorylation of key serine residues in the protein's C-terminal region. Using mass spectrometry techniques, it is possible to determine the extent to which dynamin is phosphorylated at these different residues. In this way, the activation of dynamin can be assayed.

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

Specifically, this project will entail

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

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

108. Investigating Ca_v3.2 splice variant expression and the therapeutic potential of Ca_v3.2 Ca²⁺ channel blocking drugs in suppressing absence seizures in a polygenic rat model of idiopathic generalized epilepsy

Supervisors: Dr Kim Powell, Prof Terry O'Brien

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Project Overview: Absence seizures, one of the most common seizure types in humans with idiopathic generalised epilepsy (IGE), are generalised non-convulsive events characterised by recurrent episodes of staring with unresponsiveness. Aside from a few genes discovered in rare families where the epilepsy has a monogenic inheritance, the underlying genetic causes of the common IGEs are still largely unknown, but presumed to be polygenic, with more than one genetic variation contributing to the phenotype. In an important, well characterised model of IGE with absence seizures, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), our group has discovered a single nucleotide missense mutation in the highly conserved III-IV linker region of the Ca_v3.2 T-type Ca²⁺ gene (R1584P) which correlates with seizure expression in GAERS double-crossed with NEC rats (F2 generation).

Research Project 1:

Ethosuximide, a first line drug to treat patients with absence epilepsy, is commonly believed to act via effects on T-type Ca^{2+} channels. However side effects such as drowsiness, ataxia and blurred vision are common and some patients (20%) are refractory to its effects. Importantly there is some controversy as to whether it truly acts to suppress absence seizures specifically via effects on T-type Ca^{2+} channels. Our collaborators from Neuromed Pharmaceuticals (Vancouver, Canada) have developed novel selective T-type Ca^{2+} channel antagonists. Two selective $\text{Ca}_v3.2$ channel blockers were highly effective at suppressing seizures in GAERS compared to vehicle treatment (DMSO) and standard doses of the two drug most commonly used to treat absence seizures in clinical practice, ethosuximide and valproate.

Therefore the specific aims of this project are:

- To investigate whether the $\text{Ca}_v3.2(\text{R1584P})$ mutation affects the seizure suppression ability of selective $\text{Ca}_v3.2$ channel blocking drugs in double crossed F2 animals.
- To investigate whether T-type Ca^{2+} channel antagonists are effective at suppressing seizures when administered intra-cortically or intra-nRT in GAERS and F2 animals, and whether this is influenced by the $\text{Ca}_v3.2(\text{R1584P})$ mutation genotype.

Research Project 2:

Our collaborative group have also identified two $\text{Ca}_v3.2$ splice variants in rat thalamus (\pm exon 25) located only 13 residues downstream from the $\text{Ca}_v3.2(\text{R1584P})$ mutation site and demonstrated that channels containing the +exon 25 splice variant and the $\text{Ca}_v3.2(\text{R1584P})$ mutation are faster to recover from inactivation and have greater charge transference during high-frequency burst firing (as is seen during absence seizures).

The specific aims of this project are:

- To investigate the cellular expression of $\text{Ca}_v3.2$ splice variant expression in thalamocortical brain regions of NEC and GAERS, and the relationship to the $\text{Ca}_v3.2(\text{R1584P})$ mutation genotype using double crossed NEC and GAERS (F2 generation).

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

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

Supervisors: Dr Kim Powell, Dr Jeremy Kennard, Dr Elisa Hill, Prof Terry O'Brien

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Project Overview: Epilepsy is associated with an increased risk of sudden unexplained death (SUDEP), possibly due to cardiac arrhythmias, although the precise mechanism remains unknown. SUDEP is considered the most important direct epilepsy-related mode of death and accounts for up to 30% of all deaths in the epilepsy population, being particularly prevalent amongst young patients with uncontrolled or drug-resistant, frequent and severe generalized tonic-clonic seizures.

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

marked in the process of pathological cardiac hypertrophy and heart failure. Thus these ion channels are attractive candidates for investigating molecular mechanisms of SUDEP.

The specific aims of this project are:

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

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

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

Supervisors: Dr. Marian Todaro, Mr. Slave Petrovski, Prof Terence O'Brien
 Project Site: The Comprehensive Epilepsy Program, Department of Neurology, The Royal Melbourne Hospital.
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This study aims to investigate the individual responses of patients who developed a rash or drug-induced hepatitis due to an anti-epileptic drug (AED), and link this information to the genetic profile of each patient – in particular that for the human leukocyte antigens (HLA). The results will help to identify genetic markers that could predict when a patient is at risk of having side effects with a particular medication.

Previous experience has shown that individuals vary greatly in their responses to drugs. Although medication is effective and well tolerated in most patients side-effects can necessitate treatment changes. One of the most common, and potential serious, types of side effects to anti-epileptic drugs is hypersensitivity reactions - including generalised skin rashes, Steven Johnson Syndrome (SJS), and drug-induced hepatitis. It has been shown that genetic factors play an important role in determining an individual's response to medication. Recently, the occurrence of SJS in Asian patients taking carbamazepine has been repeatedly associated with the carriage of a particular HLA antigen, HLA-B*1502. However, this association does not persist in non-Asian populations and HLA associations in other populations, or with other types of AED-induced hypersensitive reactions, have not yet been identified. Understanding why responses vary has the potential to improve the safety and effectiveness of medical treatment for various conditions.

This project will utilize an international unique cohort of more than 400 patients who have been prospectively enrolled and followed following starting treatment with an AED for the first time. The HLA profiles of patients who developed hypersensitivity reactions will be compared with those who took the same drug but did not develop any such reactions. The goal of this research is to eventually allow the choice of medication to be tailored to an individual's specific genetic profile.

Skills to be learned: Human genomics, immunogenetics, bioinformatics, clinical phenotyping, multivariate statistics.

111. Investigation into neurodevelopmental mechanisms predisposing individuals towards comorbid ADHD, autism spectrum disorders (ASD) and epilepsy

Supervisor: Dr Krista Gilby
 Project Site: Department of Medicine (RMH)
 Contact details: E: kgilby@unimelb.edu.au;

Aims: (1) To identify patterns of developmental gene expression supporting a seizure-prone versus – resistant phenotype, and (2) to determine whether corrections in developmental gene expression patterns can produce a more normal developmental trajectory in seizure-prone animals.

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

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

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

112. Comparing myelination patterns during neurodevelopment in a seizure-prone (FAST) versus seizure-resistant (SLOW) phenotype

Supervisors: Dr. Krista Gilby, Dr. Nigel Jones

Project Site: Department of Medicine (RMH)

Contact details: E: kgilby@unimelb.edu.au; ncjones@unimelb.edu.au

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

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

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

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

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

Supervisors: Professor Terence O'Brien, Professor John Wark, Professor Keith Hill and Professor Patricia Desmond.
Project Site: Departments of Medicine and Radiology, The Royal Melbourne Hospital, University of Melbourne
Contact: Prof Terence O'Brien: obrientj@unimelb.edu.au; Prof. John Wark: jdwork@unimelb.edu.au; Prof. Keith Hill: keith.hill@nh.org.au; Prof. Patricia Desmond: PatriciaDesmond@mh.org.au.

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

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

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

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

114. Neuroanatomical determinants of susceptibility in a model of genetic epilepsy

Supervisors: Verena C Wimmer, Steven Petrou, Ion Channels and Disease Group, Florey Neuroscience Institutes, The University of Melbourne, Parkville, 3010.
Project Site: Florey Neuroscience Institutes, The University of Melbourne, Parkville.
Contact: Verena Wimmer E: vwimmer@florey.edu.au

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

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

will improve our understanding of pathogenic mechanisms in GGE with implications for therapy and diagnosis.

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

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

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

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

Epilepsy is the most common disorder of the Central Nervous System with ~60 million people affected worldwide. It is not a single disorder but includes aetiologies ranging from purely genetic to acquired conditions such as seizures resulting from head trauma. The common feature of “the epilepsies” is highly synchronized activity of large numbers of neurons.

Interestingly, recent research suggests a *common functional pathway* of both inherited and acquired seizure disorders: several studies have mechanistically linked functional changes in hyperpolarization activated currents (I_h) to inherited *and* acquired epilepsy. I_h regulates dendritic excitability which is a key determinant of neuronal excitability. On a molecular level, I_h is exclusively mediated by *hyperpolarization activated cyclic nucleotide gated channels* (HCN-channels).

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

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

IMAGING

116. Molecular Neuroimaging

Supervisors: Drs. Brad Moffat, Chris Steward and Soren Christensen

Project Site: The Brain Imaging Laboratory, Department of Radiology, Level 2, 1B building, Royal Melbourne Hospital.

Contact: Dr Brad Moffat T: 9342 8340 E: brad.moffat@mh.org.au

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

Project A: Image fusion of Fluoro-ethyl-tyrosine positron emission tomography and Diffusion MRI in Brain Tumour Patients

Project B: Perfusion imaging of stroke using blood oxygen level dependent and dynamic susceptibility MRI.

Project C: Absolute quantification of glutamate using MR spectroscopy.

Project D: Perfusion MRI of Brain Tumour Patients

Project E: Optimisation of diffusion tensor MRI techniques for clinical assessment of white matter integrity.

Project F: Optimisation of functional MRI paradigms for imaging the visual cortex.

117. Network Activity in Brain Tissue Recorded with Combined Calcium and Voltage-Sensitive Dye Imaging and Electrophysiology

Supervisor: Dr Chris French

Project Collaborators – Prof T O'Brien, Prof D Williams

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

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Website: http://sites.google.com/a/hfbg1.net/crf_lab/

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

INFECTIOUS DISEASES AND IMMIGRANT HEALTH

118. Monitoring the efficacy of a training program in gastroenterology in the Pacific

Supervisors: Professor Finlay Macrae

Project Site: Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital

Contact: Professor Finlay Macrae T: +61 3 9347 0788 E: finlay.macrae@mh.org.au

Diseases in the GI tract are common in the South Pacific. GI Endoscopy access is limited, and training even less available. In association with the World Gastroenterology Organization, we have recently introduced a training program in gastroenterology to support postgraduate training in gastroenterology at the Fiji School of Medicine, with expertise provided from Australia. The project is designed to monitor the effects of this across the South Pacific, through documentation of higher levels of service delivery in the region, epidemiology of disease detection (eg helicobacter pylori) and skills' acquisition by graduates of the program that can be applied in remote communities in the South Pacific with high GI disease burdens. The applicant would be required to visit South Pacific regions to assess qualitatively and quantitatively, disease burdens and the provision of services to address these needs, with a view to reports for Faculty, the Gastroenterological Society of Australia, the World Gastroenterology Organization and the Australian Government (AusAid).

Supervisor: Professor Finlay Macrae

Dept of Colorectal Medicine and Genetics The Royal Melbourne Hospital

119. Prevalence and management of infectious diseases and nutritional disorders in refugees and immigrants living in Melbourne

Supervisors: Dr. Karin Leder/A/Prof Beverly Biggs

Project Site: Department of Medicine (RMH/WH), Royal Melbourne Hospital

Contact: A/Professor Beverly Biggs T: 8344 3256/7 E: babiggs@unimelb.edu.auWeb link: www.internationalhealth.unimelb.edu.au**Overview of the Immigrant and International Health Group**

The Immigrant and International Health Group in the Department of Medicine, University of Melbourne, have research activities in the area of infectious diseases and nutritional disorders in immigrants and refugees in Melbourne, and in women and children living in rural India and Vietnam. The group works closely with the Victorian Infectious Diseases Services at the Royal Melbourne Hospital and the Nossal Institute for Global Health.

Project Overview

Appropriate screening of recently arrived immigrants/refugees to Australia can be complex as there are multiple medical, social and psychological issues to consider. Additionally, there are knowledge gaps regarding the optimal approach to some diseases, especially for infections for which the prevalence in immigrants is unknown. A good example can be seen with *Helicobacter pylori* infections. Often the presence or absence of symptoms is used to determine whether screening for *H. pylori* is performed, and this is the approach recommended in the Guidelines for diagnosis and management of infections in recently arrived refugees recently released by the Australasian Society of Infectious Diseases. However, routine population-based screening and treatment for *H. pylori* in particularly high-risk population settings has recently been advocated. Many immigrants come from highly endemic countries for *H. pylori*, but few data exist regarding the prevalence of *H. pylori* among immigrants. Moreover, clearly establishing whether or not relevant symptoms are present can be difficult, especially in immigrants in whom multiple pathologies and language barriers are common.

The successful honours applicant would be involved in performing research to optimise immigrant screening protocols, including (but not necessarily limited to) establishing a prospective prevalence study of *H. pylori* among various immigrant sub-groups seen at the Royal Melbourne Hospital.

120. Audit of Patient's Knowledge of Hepatitis B

Supervisors: Dr Karin Leder, A/Professor Beverley Biggs, Dr Caroline Marshall

Project Site: Victorian Infectious Diseases Service, Royal Melbourne Hospital

Contact: A/Professor Beverly Biggs T: 8344 3256 E: babiggs@unimelb.edu.auWeb link: www.inthealth.unimelb.edu.au

Background: Anecdotally, we know that patients often do not fully understand or remember what they have been told about the implications of having a chronic infection with Hepatitis B. This is true of many English-speaking patients, but is likely to be further exacerbated when explanations about the infection are done via an interpreter, as occurs for many immigrants/refugees. Furthermore, there is no standardised explanation about chronic hepatitis B given by doctors. In our clinic, we see many patients originating from Africa and Burma of whom between 14% and 19% have chronic hepatitis B infection. Standard management often involves 6-monthly blood tests and 6-12 monthly liver ultrasounds to monitor the status of infection, and only a small subset of patients are eligible for any specific treatment. This in itself may be confusing for patients

Aim:

1. To describe the different potential clinical outcomes following hepatitis B infection
2. To observe the interaction between clinic doctors and patients with hepatitis B infection
3. To determine the diversity in the ways that clinic doctors explain implications and management of chronic hepatitis B infection to patients

4. To determine the understanding a defined number of immigrant/refugee patients have of chronic hepatitis B infection, including their understanding of why they are asked to undergo regular testing
5. To assess whether patients have any knowledge about information resources regarding hepatitis B
6. To use the levels of understanding observed among patients to discuss whether a standardised explanation for patients about chronic hepatitis B is required.

Methods:

1. Perform a literature review to understand about how the diagnosis of hepatitis B infection is made, and about possible implications and outcomes following infection
2. Determine what information resources about hepatitis B are available for patients
3. Attend outpatient clinics and observe the discussion about hepatitis B given by doctors to: i) patients recently discovered to have chronic hepatitis B and ii) to patients diagnosed in the past who are visiting outpatients for routine follow-up of their infection
4. Devise and deliver a questionnaire to determine the understanding different patients have of hepatitis B infection.

Outcome: The results of the survey will be used in order to discuss the level of understanding immigrants/refugee patients have of their chronic hepatitis B infection. This will enable determination of whether current explanations given to immigrants/refugees with chronic hepatitis B infection are adequate, whether patient information resources could be better utilised, and whether improved and perhaps standardised explanations are required.

121. Diet and gastrointestinal symptoms among refugee patients at a tertiary referral clinic

Supervisor: Dr Chris Lemoh, Dr Caroline Marshall, Dr Karin Leder, A/Professor Beverly-Ann Biggs

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

Contact: Dr Chris Lemoh T: 8344 6252 E: c.lemoh@pgrad.unimelb.edu.au
 Dr Caroline Marshall T: 9342 8891 E: caroline.marshall@mh.org.au
 A/Professor Beverly Biggs T: 8344 3256 E: babiggs@unimelb.edu.au

Background: Patients attending the refugee health clinic have often experienced poor living conditions with difficulties maintaining adequate and balanced nutrition. Following migration, maintaining a healthy diet may be rendered difficult by poverty, unfamiliarity with locally available foods, and cultural concepts of healthy eating. Both gastrointestinal symptoms and enteric pathogens are common in this patient population, but the contribution of dietary habits to gastrointestinal symptoms is not clear.

Aims: To describe the type and prevalence of gastrointestinal symptoms, the dietary habits and concepts of healthy eating among patients attending the refugee clinic.

Methods:

- In-depth semi-structured interviews with patients attending the refugee clinic. Interviews will be recorded, transcribed and analysed thematically to identify key themes concerning concepts of healthy eating and difficulties encountered in maintaining a healthy diet.
- One month dietary diary of eating habits of patients who participate in in-depth interviews.
- Cross-sectional survey of patients attending the refugee health clinic, measuring the type and prevalence of gastrointestinal symptoms, as well the type and prevalence of diagnosed gastrointestinal infections and diseases established through routine clinical evaluation.

Outcome: Improved understanding of patient concepts of healthy diet and difficulties encountered in maintaining healthy eating habits during resettlement in Australia will enable clinicians and clinical nutritionists to engage more effectively in promotion of healthy eating habits for refugees attending the clinic, with appropriate provision of opportunities for clinical consultation and patient information about healthy eating in Australia.

122. Patient perceptions of health care at a hospital based refugee health clinic

Supervisor: Dr Chris Lemoh, Dr Caroline Marshall, Dr Karin Leder, A/Professor Beverly-Ann Biggs

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

Contact: Dr Chris Lemoh T: 8344 6252 E: c.lemoh@pgrad.unimelb.edu.au
 Dr Caroline Marshall T: 9342 8891 E: caroline.marshall@mh.org.au
 A/Professor Beverly Biggs T: 8344 3256 E: babiggs@unimelb.edu.au

Background: Patients attending the refugee health clinic are referred by primary health care providers for investigation and management of a number of conditions that have few or no symptoms but carry risks of potentially preventable serious adverse health outcomes. Investigation and management of such conditions may result in short term physical discomfort, financial expense and psychosocial stresses for patients attending the clinic that may prejudice clinic attendance or compliance with prescribed therapy.

Aims: To understand patient concepts of the purpose and outcome of their assessment and management at the refugee health clinic.

Methods: Serial in-depth semi-structured interviews with patients attending the refugee health clinic for the first time. Interviews will be recorded, transcribed and analysed thematically to identify key themes concerning concepts concerning patient concepts of the purpose and outcome of their attendance at the refugee health clinic.

Outcome: Improved understanding by clinicians and clinic staff of patient concepts of the purpose of their assessment and management at the refugee clinic, enabling clearer explanation to patients of the purpose of the consultations, goals to be attained, and expected outcomes. It is hoped that clearer explanation to patients will result in more consistent attendance at appointments and improved compliance with prescribed therapy, as well as better patient satisfaction with the outcome of clinic consultation.

123. Targeted analysis of Victorian Sentinel Surveillance data for HIV and other STIs

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

Project Site: Centre for Population Health, Burnet Institute

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

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

124. Social networking sites for sexual health promotion to at risk populations

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

Project Site: Centre for Population Health, Burnet Institute

Contact: A/Prof Margaret Hellard. T: 03 9282 2163 Email: Hellard@burnet.edu.au
 Dr Mark Stoove E: stoove@burnet.edu.au

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

125. Advanced Epidemiological Methods: the Meta-analysis

Supervisors: A/Prof Emma McBryde and Dr Joseph Doyle, Victorian Infectious Diseases Service, Department of Medicine, Royal Melbourne Hospital.

Project Site: Victorian Infectious Diseases Service, Royal Melbourne Hospital

Contact: A/Professor Emma McBryde. T: 9342 7212 E: emma.mcbride@mh.org.au

Meta-analyses are a tool for combining data from different studies to producing a single, more powerful, estimate of effect. This project will introduce methods of reviewing the medical literature, extracting key information, and statistical approaches to synthesising data.

The student will first work with a team to update and co-author a large meta-analysis asking whether the use of HIV antiretroviral medication alters risk taking behaviour. It is an important question given plans internationally to up-scale antiretroviral use worldwide. The key concern, which can be tested more confidently by combining different studies, is that people might engage in more risky sexual behaviour if they have access to anti-HIV medication.

After this introduction, the student will undertake their own meta-analysis to answer an important clinical question relating to infectious diseases or public health that interests them. It would hopefully lead to a peer-review journal publication. For example, one topical review could test the effectiveness of different treatment regimens in recently acquired Hepatitis C.

126. Patterns of drug use and health outcomes among adult prisoners in Queensland

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

Project Site: Centre for Population Health, Burnet Institute

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

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

127. Mapping the health needs of adult prisoners

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

Project Site: Centre for Population Health, Burnet Institute

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

Prisoners as a group are characterised by profound social disadvantage, a high prevalence of infectious and chronic disease, mental illness, intellectual disability and risky drug use. These problems are not evenly distributed throughout the prisoner population, and the burden of disease is thus concentrated among those who are particularly at risk. Using data from a comprehensive assessment of more than 1300 adult prisoners in Queensland, the aim of this project will be to document the prevalence and co-

occurrence of morbidity among prisoners as a function of characteristics such as age, gender and Indigenous status. Findings will inform the on-going development of evidence-based, targeted health interventions for prisoners.

128. Monitoring and improving the health of ex-prisoners: A randomized controlled trial

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

Location: Centre for Population Health, Burnet Institute

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

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

INJECTING DRUG USE

129. Drug Trend Monitoring in Regional Victoria

Supervisor: A/Professor Paul Dietze, Head, Alcohol and Drugs Research Group, Centre for Population Health, Burnet Institute and Mr Brendan Quinn, Alcohol and Drugs Research Group, Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

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

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

130. The experience of violence among injecting drug users

Supervisor: A/Professor Paul Dietze, Head, Alcohol and Drugs Research Group, Ms Rebecca Jenkinson Centre for Population Health, Burnet Institute

Project Site: Centre for Population Health, Burnet Institute

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

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

131. The post prison release trajectories and health outcomes of people with a history of injecting drug use: a prospective cohort study

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

Project Site: Burnet Institute

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

The post-prison release period is a particularly vulnerable period for ex-prisoners with a history of injecting drug use. Recruitment and prospective data collection from a cohort of post-release prisoners with a history of injecting drug use was undertaken at the Burnet Institute and completed in 2010. Opportunities exist to utilise this database to explore the drug use and health and wellbeing outcomes of this population in the immediate post-prison release period. This data is augmented by qualitative interviews with cohort participants and key informant service providers to examine personal, social and structural factors that facilitate or impede successful drug dependence treatment outcomes in this population. This Honours project could constitute a targeted epidemiological examination of health outcomes in this cohort and/or a mixed-methods study to explore a particular aspect of the post-prison release experiences of this population.

132. Patterns of drug use and health outcomes among adult prisoners in Queensland

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

Project Site: Centre for Population Health, Burnet Institute

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

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

INNATE IMMUNITY AND HOST DEFENCE

133. Regulation of host pathogen interactions by the IRF family of transcription factors

Supervisor: Dr Glen Scholz

Project Site: Department of Medicine (RMH)

Contact: Tel: 8344-3298; Email: glenms@unimelb.edu.au

Project Description: Our respiratory and gastrointestinal tracts represent major portals for the entry of important pathogens (e.g. Influenza virus, *H. pylori* and *Salmonella*). The epithelial cells lining mucosal surfaces play a pivotal role in host defence as they express pathogen recognition receptors (e.g. Toll-like receptors) that allow them to initiate an inflammatory response upon infection. Although the inflammatory factors released by epithelial cells recruit and activate leukocytes to deal with the infection, they also contribute to the pathology of chronic inflammatory diseases (e.g. inflammatory bowel disease and asthma) and cancer (e.g. gastric cancer). In this project you will investigate how a specific member of the Interferon Regulatory Factor (IRF) family of transcription factors uniquely regulates the inflammatory response of epithelial cells to pathogens. This will involve identifying the specific genes that are regulated by the transcription factor, as well as elucidating how the activity of the transcription factor is regulated in response to specific pathogens.

Techniques: Expertise in a variety of cell biology (cell culture, ELISA assays, confocal microscopy and flow cytometry), molecular biology (Real-Time PCR, cloning, cell transfection, gene reporter assays, and siRNA-mediated gene silencing), and biochemical (protein purification, mass spectroscopy and Western blotting) techniques will be acquired.

134. Signalling cross talk by Pathogen-Recognition Receptors in the innate immune system

Supervisor: Dr Glen Scholz
Project Site: Department of Medicine (RMH)
Contact: Tel: 8344-3298; Email: glenms@unimelb.edu.au

Project Description: Pathogen-recognition receptors (PRRs) play a central role in host defence as they regulate the signalling pathways that orchestrate the inflammatory response (e.g. inflammatory cytokine secretion) of immune cells to pathogens. Importantly, pathogens can be recognised by more than one type of PRR, including both cell-surface and intracellular PRRs. Therefore, physical and/or genetic interactions between the signalling pathways that are activated by different PRRs are likely to be critical in dictating the nature of the inflammatory response to pathogen infection. In this project you will investigate how the nature of the inflammatory response depends on whether different PRRs are simultaneously or sequentially activated. This will involve investigating the effects of simultaneous and sequential PRR activation on: (i) inflammatory signalling and gene expression networks and (ii) pathogen-killing by macrophages.

Techniques: Expertise in a variety of cell biology (cell culture, ELISA assays, flow cytometry, and confocal microscopy), molecular biology (Real-Time PCR, cell transfection, gene reporter assays and siRNA-mediated gene silencing), and biochemical (Western blotting and immunoprecipitation assays) techniques will be acquired.

MALARIA

The malaria research group is offering projects on the molecular biology and immunology of malaria infection. Malaria affects young children and pregnant women most severely, causing 1 to 3 million deaths each year, and these numbers are increasing. Our group is working to understand basic mechanisms of disease and immunity to malaria.

135. Malaria parasite adhesion to the human placenta

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

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

This project is based at the Department of Medicine, Royal Melbourne Hospital, in the malaria lab that has a long-term experience of malaria parasite adhesion. The lab is made of 1 lab head, 3 post-docs (including your supervisor), 2 research assistants, 6 PhD students and 2 mid-term honour students as well as visiting scientists from all over the world.

Techniques involve (but are not limited to): malaria parasite culture, biochemistry, flow cytometry, confocal microscopy and western blotting.

136. Epigenetic control of malaria pathogenesis

Supervisor: Dr Michael Duffy, Dr Michaela Petter

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne

Contact: Dr Michael Duffy T : 8344 3267 E : mduffy@unimelb.edu.au
Dr Michaela Petter T : 8344 3267 E : mpetter@unimelb.edu.au

Various conserved and novel proteins appear to be involved in epigenetic control of transcription in *Plasmodium falciparum*, the pathogen that causes malaria. This process is critical in the regulation of antigenic variation and cytoadhesion, two pathogenic processes essential for the parasite's escape of host immunity. We are investigating a range of these proteins by transfecting parasites to express tagged proteins and by making recombinant proteins for generation of antibodies used in immunofluorescence assays, western blots, co-immunoprecipitations, chromatin immunoprecipitation etc.

137. Defining the macrophage response to malaria infected erythrocytes

Supervisor: Dr Louise Ludlow

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne

Contact: Dr Louise Ludlow T: 9282-2293 E: lludlow@unimelb.edu.au

Blood stage *P. falciparum* infected erythrocytes (iRBC) are cleared by macrophage phagocytosis. This elicits cytokine secretion which orchestrates subsequent immunity but also leads to immunopathology. These responses are modulated by antibody and complement-mediated opsonisation of iRBC. Therefore investigating how the macrophage responds to opsonised versus unopsonised iRBC is required to understand the balance between protection and pathology. Malaria infected erythrocytes activate macrophage phagocytic receptors (complement, CD36 and Fc) and innate immune receptors (TLRs). This results in the initiation of multiple signaling pathways that coordinate pro-inflammatory cytokine synthesis. The primary aim of this research is to dissect the intracellular mechanisms controlling cytokine production to facilitate development of targeted therapies.

Specific pathway inhibitors and antibodies for phosphoproteins will be used to study NF- κ B and MAP kinase signaling events. The project involves culture and purification of iRBC, isolation and culture of monocyte-derived macrophages from human blood, protein extraction and Western blot analysis.

138. Functional assays for immunity to malaria

Supervisor: Professor Stephen Rogerson

Project Site: Department of Medicine, Royal Melbourne Hospital

Contact: Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

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

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

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

139. Malaria in pregnancy: risk factors and consequences

Supervisor: Professor Stephen Rogerson

Project Site: Department of Medicine, Royal Melbourne Hospital

Contact: Prof Stephen Rogerson, T: 8343259 E: sroger@unimelb.edu.au

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

This project offers an introduction to statistical analysis of multiple data sets. Some basic knowledge of statistics would be useful for this project.

140. Characterizing new surface proteins of the malaria parasite

Supervisor: Dr Michaela Petter

Contact: T: 8344 3267 Email: mpetter@unimelb.edu.au

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne

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

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

MEDICATION SAFETY

141. Testing of the Self-Administration of Medication (SAM) tool in a rehabilitation setting

Supervisor: Professor Elizabeth Manias.

Project Site: Melbourne School of Health Sciences, Royal Park Campus, Royal Melbourne Hospital

Contact: Professor Elizabeth Manias T: 8344 9463 E: emanias@unimelb.edu.au

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

current practice in a rehabilitation ward, by determining the benefits and barriers relating to its use, and by testing the utility and validity of the tool.

MULTIPLE SCLEROSIS/NEUROLOGY

142. How do Multiple Sclerosis Risk Genes work?

Supervisors: A/Prof Helmut Butzkueven and Dr Melissa Gresle
Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, Royal Parade, Parkville
Contact: Helmut Butzkueven : butz@unimelb.edu.au

In the last three years, around 30 risk genotypes for MS have been confirmed. Many of these carry small risks (eg increasing the risk of getting MS by between 10 and 30%), and many of the risk genotypes are actually fairly common in the non-MS population. One major hypothesis explaining these results is that, in MS patients, the risk genotypes are associated with altered expression of the relevant gene. We are conducting an experiment in which people with early MS and healthy controls are genotyped for the MS risk genotypes and their immune cells are sorted into different subsets (B-cells, T-cells, NK-cells, and monocytes) and their RNA is extracted.

The major aim of this project will be to determine if risk genes alter expression of gene messenger RNA in MS, if this effect does/does not occur in healthy people carrying the same genotype, and, if positive, determine if expression of the relevant protein of interest is also altered in specific immune cell subtypes from patients carrying the risk genotype.

During this project, you will become familiar with MACS and FACS cell sorting, RNA extraction, genotyping, and will be introduced to relevant statistical and bioinformatic techniques.

Feasibility: The cell collection is well under way so that there will be no delays in relation to data availability or ethics applications.

143. Is there an NK cell abnormality in early Multiple Sclerosis?

Supervisors: A/Prof Helmut Butzkueven and Dr Melissa Gresle
Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, Royal Parade, Parkville
Contact: Helmut Butzkueven : butz@unimelb.edu.au

MS has been assumed to be a T-cell mediated autoimmune disease of the central nervous system. However, specific therapies targeting T-cells have generally been unsuccessful. Innate immune cells are increasingly identified as potentially pathogenetically important in MS (Gandhi et al, 2010), and a number of alterations in innate immunity have been observed in MS patients. In particular, multiple groups have reported alterations in natural killer (NK) cell activity or numbers in MS patients compared with healthy controls, in particular in the context of MS disease activity. Remarkably, recent data from a two phase, multiparameter cytometric profiling of 38 untreated MS patients and matched controls, analysed using an advanced computational pipeline that included comparative marker selection, non-negative matrix factorization and a support vector machine, identified only a single significant abnormality consistently associated with MS, namely a decrease in peripheral blood NK cell (CD3⁺CD8^{low}CD4⁺CD56⁺) numbers (De Jager et al, 2008). These investigators confirmed their results in two independent cohorts, comprising patients with first demyelinating events and untreated relapsing-remitting MS.

In this project, we wish to independently confirm these findings by comparing MS patients and healthy controls and characterise their NK_{cell} numbers by FACS, as well as characterizing NK cell activation using both NK cell activity gene analysis (mRNA isolation and real-time PCR quantitation) and FACS analysis techniques.

During this project, you will become familiar with FACS cell sorting, RNA extraction, real-time PCR quantitation of RNA, and will be introduced to relevant statistical and bioinformatic techniques.

Feasibility: The cell collection is well under way so that there will be no delays in relation to patient or data availability or ethics applications.

144. Investigating serum biomarkers of neurodegeneration in Multiple Sclerosis

Supervisors: A/Prof Helmut Butzkueven and Dr Melissa Gresle

Project Site: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, Royal Parade, Parkville

Contact: Helmut Butzkueven : butz@unimelb.edu.au

The majority of Multiple Sclerosis (MS) disability is thought to be caused by axonal degeneration within and surrounding inflammatory demyelinating lesions. Although this pathological process is not currently directly targeted by protective therapies, such potential drugs are in fact in advanced preclinical development. Unfortunately, a lack of a reliable and validated biomarker of axonal degeneration is preventing the commencement of clinical trials at present. In order to address this need, we are assessing the utility of recently described serum markers of neuro-degeneration in multiple sclerosis. In particular, we are concentrating on detection of serum levels of phosphorylated Neurofilament Heavy Chain (pNF-H). We have previously validated this assay as a marker of axonal degeneration in a mouse model of MS, and confirmed the presence of detectable levels in two MS sample collections from Australian patients. .

We have now obtained access to almost 1000 serum samples from US MS patients, and now wish to analyse pNF-H levels in these sera by ELISA techniques, in order to assess the relationship between serum levels of this protein and clinical/MRI markers of disease severity.

During this project, you will become familiar with serum processing, ELISA, clinical MS assessment, and will be introduced to relevant statistical

Feasibility: The serum is available and the ELISA techniques are well so that there will be no delays in relation to sample or data availability.

NEPHROLOGY

145. Significance of the relaxin receptor LGR7 in progressive kidney disease

Supervisor: Dr Tim Hewitson and Dr Chrishan Samuel

Project Site: Department of Nephrology, The Royal Melbourne Hospital and Howard Florey Institute, University of Melbourne

Contact: Dr Tim Hewitson T: 9342 7726 E: tim.hewitson@mh.org.au

The endogenous hormone relaxin, is emerging as a safe and effective novel therapy for progressive renal disease. Relaxin achieves this by inhibition of growth factors that promote the accumulation of excess matrix (scarring) and promoting regeneration by upregulating angiogenesis and inhibiting apoptosis. This project will use *in vivo* and *in vitro* models of kidney disease to examine the significance of the principal relaxin receptor LGR7. In vivo studies will compare the pathogenesis of fibrosis in normal mice and mice deficient in the LGR7 gene, while in vitro studies will utilise cells from these animals to elucidate the signal transduction mechanisms.

Skills: Knock-out model, small animal surgery, histopathology, molecular biology, cell culture.

146. Anti-fibrotic efficacy of relaxin in experimental chronic kidney disease

Supervisor: Dr Tim Hewitson and Dr Chrishan Samuel

Project Site: Department of Nephrology, The Royal Melbourne Hospital and Howard Florey Institute, University of Melbourne

Contact: Dr Tim Hewitson T: 9342 7726 E: tim.hewitson@mh.org.au

Kidney failure continues to be a major health problem worldwide. The final common pathway to all ongoing kidney disease is the accumulation of scar tissue (so-called fibrosis). Prevention or limitation of this progressive fibrosis is therefore a major clinical objective in renal medicine. Currently the best available therapies only delay the progression to end stage renal disease by a matter of months. The hormone relaxin, is an endogenous factor that protects the kidney from this process, by inhibiting TGF β signalling, a major factor promoting matrix accumulation. This project will compare the actions of relaxin to the best available therapies, to determine relative efficacy and synergies.

Skills acquired: Kidney biology, animal models, histopathology, biochemistry, molecular and cell biology.

NEUROPSYCHIATRY AND STRESS BIOLOGY

147. A model of functional disconnections to study the pathophysiology of psychosis and epilepsy

Supervisor: Dr Nigel Jones and Prof Terence J O'Brien.

Project Site: Department of Medicine (RMH)

Contact: Dr Nigel Jones T: 8344 6729 E: ncjones@unimelb.edu.au

Functional disconnections in cortico-thalamo-cortical (CTC) systems, the neuronal circuits of attention, cognition and perception, are thought to underlie dysfunctions of conscious integration such as those seen in schizophrenia. More than 80% of the neurons that make up the CTC systems are glutamatergic. There is considerable evidence to suggest that NMDA-type glutamate receptors are implicated in the pathophysiology of schizophrenia. Non-competitive NMDA receptor antagonists (PCP, ketamine, MK-801), at subanaesthetic doses, induce cognition impairment, schizophreniform psychosis, hallucinations, and exacerbate both positive and negative symptoms in schizophrenic patients. In rodents, ketamine produces a wide spectrum of abnormal behaviour relevant to schizophrenia. The neuronal mechanisms underlying transient disruption in NMDA receptor function remain to be determined. CTC circuits generate coherent synchronized gamma frequency (30-80 Hz) oscillations during conscious brain operations. Disruption of cognition-related coherences of gamma oscillations between cortical areas is a major functional abnormality in schizophrenic patients. It has been shown that patients with generalised epilepsy have increased baseline (i.e. between seizures) gamma activity on the EEG compared to non-epileptic control subjects. Work in our laboratory in the Department of Medicine has demonstrated that the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a well validated animal model of genetic generalized epilepsy, display a range of behavioural and emotional abnormalities that are consistent with those seen in models of schizophrenia-like psychosis. These rats, and their non-epileptic counterparts (NEC rats), have been respectively selectively breed for the presence or absence of the epileptic phenotype. The co-segregation of the psychiatric behavioral and epileptic phenotypes over more than 60 generations suggests an aetiological link between the two. This project will also explore the hypothesis that GAERS have an abnormal response of cortical gamma activity to the administration of NMDA antagonists. If true, this would provide a neurophysiological correlate for the link between the epilepsy and schizophrenic like phenotypes in GAERS.

Note: this project is also listed under Epilepsy and Neuropharmacology

148. Temporal lobe epilepsy, the HPA axis and depression

Supervisor: Dr Mike Salzberg, Prof Terence O'Brien

Project Site: Department of Psychiatry and Medicine

Contact: Dr Mike Salzberg T: 0417357205 E: michael.salzberg@svhm.org.au

Brief Summary: The key structures involved in mesial temporal lobe epilepsy – the hippocampus and amygdala – are critical components in the central regulation of the HPA axis. The implications of this have hardly been studied at all. Does the HPA axis function normally when someone has mesial temporal sclerosis (the usual pathology underlying TLE)? What happens to HPA axis function when a temporal lobe is excised to treat intractable TLE (temporal lobectomy)? There are good reasons to think the answers to these questions are very important for several reasons, e.g., glucocorticoids and stress have been shown in animal models of this kind of epilepsy to aggravate the disorder, to speed up its rate of development.

Project: We have a small preliminary study in progress, testing HPA function before and after temporal lobectomy. We're using the dex/CRH test, doing this about 2 weeks before and at 6 and 12 weeks after surgery. We're doing the same protocol with surgical control patients, having elective brain surgery for nonepilepsy conditions remote from the temporal lobe.

We think temporal lobectomy disinhibits the HPA axis, which may help explain the transient mood disturbance that occurs in temporal lobectomy patients in the early months following surgery.

This study will interest students interested in a topic that involves basic neuroscience and neuroendocrinology but also with a very immediate clinical relevance. It will involve contact with patients – in recruitment, obtaining informed consent, administering questionnaires and helping administer the dex/CRH test (a two hour procedure). It will also involve data analysis and writing-up in the usual way. This is at least a Masters project, preferably PhD.

149. Does stress contribute to epilepsy?

Supervisor: Dr Nigel Jones and Prof Terence O'Brien

Project Site: Department of Medicine, (RMH)

Contact: Dr Nigel Jones T: 8344 6729 E : ncjones@unimelb.edu.au

- Chronic stress is strongly linked to the development of psychiatric disturbances, such as depression and anxiety disorders. Interestingly, these disorders are prevalent in a high proportion of people suffering from epilepsy.
- Recent literature suggests that environmental exposures such as stress may also contribute to the development of epilepsy. This project aims to investigate this hypothesis, with a parallel focus on anxiety and depression-like behaviour.
- Using rat models, this study will determine whether exposure to repeated stressful situations leads to a vulnerability to limbic epilepsy. It will also study whether psychiatric disturbances are enhanced in subjects who have experienced the stress.
- The second stage of the project will investigate molecular and plasticity changes which occur after epilepsy to determine whether the stress can influence such parameters as stress receptor expression and neurogenesis.

Skills: Small animal handling and neurosurgery (electrode implantations), neurobehavioural testing and analysis, post-mortem stereology.

150. EEG assessment of high frequency oscillatory activity in a mouse model of Autism

Supervisors: Dr Elisa Hill, Dr Nigel Jones, Professor Terence O'Brien.

Project Site: Department of Medicine, University of Melbourne

Contact: Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au, Dr Nigel Jones Tel: 8344 6729, email: ncjones@unimelb.edu.au, Prof Terence O'Brien: obrientj@unimelb.edu.au

Aims of Project: This project will investigate high frequency (gamma) brain rhythms in NL3 mice using:

- iii. Baseline EEG
- iv. Following administration of low dose ketamine
- v. EEG during memory task
- vi. EEG during behavioural tasks including locomotor, anxiety tests.

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder in which the vast majority of patients show altered sensory perception. A small number of patients show extraordinary “savant” abilities in restricted areas. ASD patients demonstrate altered EEG in the gamma (30 - 80 Hz) range, frequencies which have been correlated with sensory processing function. In addition, up to 30% of ASD patients also experience seizures. NL3 mice express a mutation in the Neurologin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as enhanced spatial learning. This project will assess for alterations in baseline (no task) EEG in addition to EEG changes during behavioural tasks including locomotor, anxiety tests and learning memory tasks, and following administration of a low dose of the NMDA receptor antagonist ketamine (induces increases in EEG gamma activity and psychotic like behaviour).

Skills: Surgery for EEG in adult mice. Analysis for high frequency (gamma) oscillatory activity from EEG recordings using matlab software. Behavioural and animal handling skills.

151. Investigating the stress response in a mouse model of autism

Supervisors: Dr Elisa Hill, Assoc. Professor Anthony Hannan.

Project Site: Howard Florey Institute, University of Melbourne

Contact: Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au, Assoc. Prof Anthony Hannan Email: ajh@florey.edu.au

Aims of Project: This project will investigate behavioural aspects and markers of stress in the NL3 mouse model of autism using:

- vii. Anxiety and stress paradigms
- viii. Cortisol and c-fos levels with labelling for neuronal markers.
- ix. Ultrasonic vocalisation pattern analysis

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder characterised by impairments in social interactions, communication, and repetitive behaviour. NL3 mice express a mutation in the Neurologin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as impairments in social behaviour.

In addition to altered sociability, these mice demonstrate an aggressive phenotype and one aim of this project is to investigate possible links with an altered stress response using a cortisol assay for stress. To investigate the possibility that specific neuron types are upregulated in the stress response, a c-fos assay will be carried out following stress (isolation housing and aggression test) with double labelling immunocytochemistry for neuronal subtypes (GAD and neu-N). There is also scope to assess mice for altered communication patterns by recording ultrasonic vocalisation patterns.

Skills: Behavioural and animal handling skills. Vocalisation pattern data acquisition and analysis. Cortisol assay for stress and c-fos assay for neuronal activity.

152. Investigating effects of cannabinoids on sensorimotor gating in a mouse model of autism

Supervisors: Dr Dan Malone (Monash Institute of Pharmaceutical Sciences) and Dr Elisa L Hill (Dept of Medicine, University of Melbourne).

Project Site: Monash Institute of Pharmaceutical Sciences, Royal Pde, Parkville 3050

Contact: Dr Elisa Hill Tel: 8344 3261 Email: elhill@unimelb.edu.au
Dr Dan Malone Tel: 99039576 Dan.malone@monash.edu

Aim: to investigate the effects of pharmacological agents that modulate cannabinoid pathways (CB agonists and antagonists) on sensorimotor gating in a mouse model of autism.

Autism Spectrum Disorder (ASD) is a prevalent neurological disorder in which the vast majority of patients show altered sensory perception. ASD patients demonstrate deficits in sensory motor gating compared to controls. NL3 mice express a mutation in the Neuroligin-3 gene identified in two brothers with autism and show increased synaptic inhibition in the somatosensory cortex as well as deficits in social behaviour including decreased sociability and increased aggression. While the NL3 mutation is known to be located at the postsynapse, the increase in frequency of inhibitory synaptic events suggests a change in presynaptic release of neurotransmitter. Cannabinoids serve as retrograde inhibitory messengers (ie they travel in the reverse direction across synapses) in the brain to inhibit neuronal function and transmitter release. A disruption in this pathway could result in increased inhibition as reported in the NL3 mice and contribute to the observed behavioural phenotype.

In this project we aim to use the non-invasive PPI test in the NL3 mouse model of autism to assess for alterations in sensorimotor processing. Based on published data demonstrating altered cortical inhibition in these mice, we will also investigate effects of modulating the inhibitory cannabinoid pathway using pharmacological agents.

Skills: Behavioural and animal handling skills. Data acquisition and analysis using the Pre Pulse inhibition test for sensorimotor gating. Evaluation of behavioural effects of cannabinoids in NL3 mice and controls.

153. Mapping the human brain connectome in healthy and psychiatric populations

Supervisors: Dr Alex Fornito, Dr Andrew Zalesky, Dr Ben Harrison, A/Prof. Murat Yücel, Prof Christos Pantelis

Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience Facility, Alan Gilbert Building.

Contact: Dr Alex Fornito T: 8344 1876. E: fornitoa@unimelb.edu.au

The human brain is perhaps the most complex network found in nature, comprising 10^{11} neurons connected by 10^{13} axonal fibers. In recent years, non-invasive neuroimaging techniques, particularly magnetic resonance imaging (MRI), have occupied a central role in attempts to map this connectivity web, termed the brain 'connectome', at various spatial and temporal scales. Students working in this project will have the opportunity to use these exciting new techniques to address a variety of important questions concerning the structure and function of the human brain connectome in healthy individuals and people with psychiatric disorders. Current project topics include:

- brain network dysfunction in schizophrenia;
- the effect of chronic cannabis use on brain functional connectivity;
- brain network dysfunction obsessive-compulsive disorder;
- the effect of chronic opiate use on brain functional connectivity;
- genetic influences on human cortico-striatal networks; and
- novel statistical methods for analyzing brain networks.

Students will gain a variety of skills, including developing their understanding of the neurobiological basis of psychiatric illness, the application of statistical models to neuroimaging data, and techniques for analyzing large-scale brain networks.

154. Brain activation of adolescents during a social cognition task: an fMRI study

Supervisors: Dr Cali Bartholomeusz, Dr Sarah Whittle, Professor Stephen Wood, Professor Christos Pantelis

Contact: Dr Cali Bartholomeusz T: 8344 1878, E: barc@unimelb.edu.au

Project Site: Melbourne Neuropsychiatry Centre, Department of Psychiatry, National Neuroscience Facility, Level 2-3 Alan Gilbert Building.

Description of project: Social cognition is the domain of cognition that involves the perception, interpretation and processing of social information. Two key social cognitive processes are 'theory of mind' (ToM; the mental capacity to infer one's own and others' mental states) and attributional style

(tendencies in explaining the cause of events i.e. to the self, others or the environment). From an evolutionary perspective, the development of social cognitive abilities is essential for navigating and succeeding in the social world in which we live.

It is now known that the adolescent brain undergoes substantial changes in white and grey-matter volume as part of the normal neurodevelopmental process. Adolescence is a time of psychological change, where an individual becomes more sociable, more self-aware, and starts to develop self-concepts and a personal identity. This change in social behaviour and thinking may partly result from the maturation of the 'social brain', in particular the medial prefrontal cortex, orbitofrontal cortex, superior temporal sulcus and anterior cingulate cortex. To date, exploration of the neural underpinnings of social cognitive processes have largely focused on young children or adult populations, yet emerging evidence has recently shown a shift in brain activation during social cognitive tasks during the adolescent years.

The aim of this study is to investigate the brain activation of healthy adolescents during a ToM attribution of intentions task. The student will be responsible for recruiting participants into the study, conducting interviews and running the fMRI paradigm at the Royal Children's Hospital scanner, and will also be involved in data analysis.

155. Olfactory sensitivity in psychosis

Supervisors: Dr Debra Foley, A/Prof Warrick Brewer, Prof Christos Pantelis
Melbourne Neuropsychiatry Centre, Orygen Research Centre
Project Site: Melbourne Neuropsychiatry Centre, Sunshine Hospital.
176 Furlong Rd, St Albans
Contact: Dr Debra Foley E: dfoley@unimelb.edu.au;
Prof Christos Pantelis E: cpant@unimelb.edu.au;

Project description: Reduced olfactory sensitivity for some unique odours is found in some people with schizophrenia. The aim of this project is to test sensitivity to two smells based on a synthesis of the genetic literature for schizophrenia and olfaction. Candidate genes for schizophrenia that map to the same chromosome band location as functional odorant receptors will be examined. We aim to test if these smells discriminate patients with chronic schizophrenia from matched controls. The relationship of sensitivity for candidate odours to olfactory identification ability may reveal vulnerability for negative symptoms of schizophrenia.

156. How does Age of Illness Onset affect severity and extent of MRI Brain Structural Abnormalities in Schizophrenia

Supervisors: Prof Christos Pantelis, Dr Alex Fornito, Melbourne Neuropsychiatry Centre
Project Site: Melbourne Neuropsychiatry Centre, National Neuroscience Facility (NNF),
Alan Gilbert Building, Level 3, 161 Barry Street, Carlton South, Vic 3053
Contact: Prof Christos Pantelis E: cpant@unimelb.edu.au;
Dr Alex Fornito T: 8344 1876. E: fornitoa@unimelb.edu.au

Project description: Research at the Melbourne Neuropsychiatry Centre has demonstrated that the onset of schizophrenia is characterised by dynamic brain changes that begin prior to illness onset and progress throughout the course of the illness, particularly in frontal and temporal lobe regions. We have also demonstrated that the onset of schizophrenia is associated with pronounced cognitive changes that parallel clinical symptoms, and that these changes indicate that onset of the disease may 'arrest' normal brain maturational processes. Given that frontal and temporal brain regions continue to develop into the second and third decades of life, when the onset of schizophrenia is most common, we hypothesise that the timing of illness onset is a critical factor in determining the nature and extent of these brain changes. Specifically, we predict that later illness onset will be associated with relatively preserved neuroanatomy and cognition, due to reduced maturational disruption. By addressing this question the proposed applicant will specifically investigate issues related to normal brain maturation,

schizophrenia-specific changes, and the interaction between the two. The research will be conducted using magnetic resonance images already acquired as part of the Australian Schizophrenia Research Bank together with computerised techniques to delineate differences in brain structure and cognition.

157. Mouse model investigation of the molecular mechanisms of HIV-mediated neurodegeneration and major depressive disorder

Supervisors: Mr. Timothy Nguyen, Dr. Gursharan Chana and Prof Ian Everall

Project Site: Department of Psychiatry and Medicine, Royal Melbourne Hospital

Contact details: Dr. Gursharan Chana T: +61 (0)383 447 338 E: Gursharan.chana@mh.org.au

Description: The goal of this project is to investigate candidate molecular markers and gene pathways associated with HIV infection and major depressive disorder (MDD) in the brain. HIV infection is a global pandemic that is estimated to affect 36 million people worldwide. While highly-active antiretroviral therapy has succeeded in prolonging the lifespan of HIV positive individuals, few therapies have succeeded in protecting the CNS from the deleterious effects of HIV and nearly half of this population suffer from a psychiatric disorder, markedly reducing quality of life. In particular, MDD is significantly overrepresented in this group and previous evidence from our group and others suggest a biological basis of comorbidity.

Gp120 is an HIV protein that has been shown to incite neuroinflammation and neurodegenerative pathways in humans and in mice. Furthermore, it is proposed that elevated cortisol levels found in patients with major depressive disorder may cause significant cellular changes in the brain underlying MDD. Therefore, this project will compare and examine the combined relationship of the effects of gp120 and chronic hypercortisolemia on the cellular and genetic level in vivo by examining the brains of gp120 transgenic mice and mice chronically exposed to cortisol by histological, stereological, and gene expression analysis.

Skills: This project will involve extensive training and practice of animal brain dissection, histology, qRT-PCR, immunocytochemistry, immunoblot, stereology, and statistical analysis.

158. Cholinergic muscarinic receptor expression in the orbitofrontal cortex in mood disorders

Supervisors: Dr Andrew Gibbons and Professor Brian Dean

Project Site: The Rebecca L Cooper Laboratories, The Mental Health Research Institute of Victoria

Contact: Dr Andrew Gibbons T: 9389 2990 E: a.gibbons@mhri.edu.au

Project: Mood disorders are amongst the most prevalent psychiatric disorders in society. However, the underlying cause of these disorders remains elusive. Pharmacological evidence has long supported a role for the cholinergic system in mediating the depressive symptoms seen in major depression and bipolar disorder. However, only recently have molecular studies suggested that abnormal signalling through the cholinergic muscarinic receptors is central to the cholinergic dysfunction in mood disorders. Specifically the muscarinic M2 receptor appears to play a key role. We have recently reported decreased binding of [³H]AFDX-384, a muscarinic M2 / M4 receptor selective antagonist, in the dorsolateral prefrontal cortex of subjects with major depression and subjects with bipolar disorder, suggesting a decrease in M2/M4 receptor expression. We have also reported a decrease in the binding of [³H]4-DAMP, a muscarinic M3 receptor selective antagonist in the frontal pole of people with bipolar disorder.

We are interested in finding out whether muscarinic receptor expression is altered in other brain regions from people with mood disorders. The orbitofrontal cortex is involved in emotional response and is thought to be affected in the pathology of mood disorders. This study will use the muscarinic receptor selective radioligand antagonists [³H]AFDX-384 (M2/M4), [³H]4-DAMP (M3) and [³H]pirenzepine (M1) to examine the expression of muscarinic receptors in the Brodmann Area 11, part of the orbitofrontal cortex, from post-mortem subjects diagnosed with major depression and

bipolar disorder and matched control subjects. During this project the student will develop skills in protein biochemistry as well as learn protocols for the appropriate handling of human post-mortem tissue.

159. MRI volumetry and shape analysis in frontotemporal dementia and schizophrenia

Supervisors: Dr Dennis Velakoulis and Dr Mark Walterfang
 Project Site: Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital
 Contact: Dr Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.org.au

Background: It has been well recognised for over a century that some patients with schizophrenia develop a dementia but the nature of this dementia has remained unclear. Recent clinical, neuropathological and genetic studies have identified a previously unrecognised association between chronic schizophrenia and frontotemporal dementia. This project aims to examine whether the volume and shape changes identified in schizophrenia are quantitatively and qualitatively similar to patients with a frontotemporal dementia. In addition to demographic and diagnostic information a subset of the subjects have neuropsychological and bedside screening cognitive testing which can be correlated with brain structural volumes and shape.

Aims: To estimate and compare brain structure volume and shape in an existing database of MRI images of patients with chronic schizophrenia and frontotemporal dementia compared to control subjects.

Methods: Specific regions of interest to examine would include:

- Frontal and temporal lobes
- Orbitofrontal / dorsolateral / medial frontal cortex
- hippocampus
- Insula cortex
- Superior temporal gyrus

Depending on the region of interest the project would require the learning of methods for analysing the region and developing a reliable method for this assessment.

Outcome: To assess and compare the nature and pattern of brain changes in chronic schizophrenia and FTD.

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

Supervisors: Dr Dennis Velakoulis, Dr Chris Turnbull and Professor Terry O'Brien
 Project Site: Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital and Alan Gilbert Building, University of Melbourne
 Contact: Dr Dennis Velakoulis T: 93428750 E: dennis.velakoulis@mh.org.au

Background: Depression and epilepsy are disabling disorders that are common in the community. Both disorders have been shown to have effects on the human body's physiological response to stress. These effects have been identified in both the autonomic nervous system (responsible for immediate responses to stress) and the hypothalamic-pituitary-adrenal axis (which mediates longer-term stress responses). However, it is not known whether these effects occur through similar mechanisms, partly because previous research has not focused extensively on patients with both disorders. This project will broaden our understanding of stress physiology in these disorders by assessing stress physiology in patients who have been admitted to hospital for assessment of seizures and have one or both disorders.

Aims: To compare the effects of depression and epilepsy, particularly temporal lobe epilepsy, human physiological stress responses and to assess whether these effects are additive or have a more complex interaction

Methods: The project will measure parameters of the physiological stress response in patients who have been admitted to investigate their epilepsy. Assessment of the autonomic nervous system will use a variety of measures of heart rate variability, and the HPA axis will be measured by the level of the hormone cortisol in saliva. Clinical data will be obtained by working with the clinical team caring for the patient and involves direct patient contact.

Outcome: To better understand stress physiology in depression (a psychiatric illness) and epilepsy (a neurological disorder) by assessing their interaction.

NEUROVASCULAR

161. Aspirin Resistance in Acute Stroke Study. Phase 2

Supervisor: Dr Bernard Yan

Project Site: Department of Neurology, Royal Melbourne Hospital

Contact: Dr. Bernard Yan, Consultant Neurologist and Neurointerventionist
Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital. T: +61 3 9349 2477 / F: +61 3 9349 4489
E: bernard.yan@mh.org.au

Background: Ischaemic stroke is the third most common cause of morbidity and mortality in the western world and on the rise in developing countries. The prevention of recurrent ischaemic events is an important strategy in reducing the global health and economic burden of stroke. Anti-platelet agents, such as aspirin and clopidogrel, have been shown in multiple studies to be moderately efficacious in the secondary prevention of stroke and are currently the mainstay of therapy. However, there is emerging evidence for a differing response to anti-platelets in patients with cardiac diseases and that the prevalence of aspirin resistance is as high as 30%. Given that anti-platelets are also widely used in the stroke patient population, there is growing concern that a similar proportion of patients harbour anti-platelet resistance and therefore, are at higher risk of recurrent stroke due to unrecognised ineffectiveness of anti-platelet therapy. This has never been investigated and it is imperative that this group of stroke patients with anti-platelet resistance are identified in order for an alternative secondary stroke preventive strategy to be implemented. The purpose of this observational pilot study is to recruit, prospectively and retrospectively, patients who present with acute stroke and to test their aspirin and clopidogrel resistance status. The hypothesis is that patients with anti-platelet resistance will be at higher risk of recurrent stroke.

Hypothesis: Subjects with anti-platelet resistance have a higher incidence of recurrent ischaemic strokes compared to subjects without.

Inclusion criteria: All patients presenting with acute ischaemic stroke to the Stroke Care Unit, Royal Melbourne Hospital.

Exclusion criteria: Intracranial haemorrhage. Patients who are unable to give consent.
Sample size: N = 50.

162. Intraarterial clot burden: a predictor of recanalization post intravenous tissue plasminogen activator?

Supervisors: Dr Bernard Yan, A/Professor Peter Mitchell, Dr Richard Dowling

Project Site: Department of Neurology, Royal Melbourne Hospital

Contact: Dr. Bernard Yan, Consultant Neurologist and Neurointerventionist
Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital. T: +61 3 9349 2477 / F: +61 3 9349 4489
E: bernard.yan@mh.org.au

Background: The treatment goal of acute ischaemic stroke is to recanalize the occluded artery in order to revascularise the ischaemic penumbra, tissue surrounding the core region of infarction which

is potentially salvageable. Tissue plasminogen activator (tPA) has been shown to recanalize occluded arteries in acute strokes. Moreover, multiple studies have proven that treatment with tPA in acute stroke decreases morbidity and mortality. However, the recanalization and clinical benefits are not uniform and there is emerging evidence that a proportion of patients with “larger clot burden” in the occluded artery fails to recanalize. This has not been systemically proven. We aim to correlate clot burden and clot location with recanalization in acute stroke patients who were treated with intravenous tPA.

Hypothesis: In acute ischaemic stroke, the likelihood of arterial recanalization post intravenous tissue plasminogen activator decreases with large clot burden.

Inclusion criteria: All patients presenting with acute ischaemic stroke to the Stroke Care Unit, Royal Melbourne Hospital.

Exclusion criteria: Intracranial haemorrhage. Sample size: N = 150

163. Treatment of Arteriovenous Malformation by Onyx embolization: factors determining treatment success

Supervisors: Dr Bernard Yan, A/Professor Peter Mitchell, Dr Richard Dowling
Project Site: Department of Neurology, Royal Melbourne Hospital
Contact: Dr. Bernard Yan, Consultant Neurologist and Neurointerventionist
Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital. T: +61 3 9349 2477 / F: +61 3 9349 4489
E: bernard.yan@mh.org.au

Background: Arteriovenous Malformation (AVM) is an important cause of intracerebral haemorrhage. With the advent of microcatheter techniques, AVM's are now increasingly amenable to treatment by microcatheter guided embolization with Onyx, an embolic material. However, the determinants of treatment success have not been clearly defined. It has been postulated that higher number of arterial feeders and high arterial flow are associated with treatment failure.

Hypothesis: That number of arterial feeders and arterial flow pattern are strong predictors of embolization success for Arteriovenous Malformation

Inclusion criteria: All patients treated with Onyx embolization for Arteriovenous Malformation at Royal Melbourne Hospital.

164. Assessment of Motor Function in Acute Stroke by Wireless Accelerometer and Web-based Video Telestroke System

Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, Dr. Richard Dowling
Project Site: Department of Neurology, Department of Radiology, Royal Melbourne Hospital
Contact: A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital T: +61 3 9349 2477 / F: +61 3 9349 4489 E: bernard.yan@mh.org.au

Background: Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) in order to unblock the blocked artery.

The delivery of thrombolytic agents to acute stroke patients requires the around-the-clock availability of a stroke neurologist to clinically assess the patient. This is a critical step as there are dangerous mimics of stroke and a wrong diagnosis by a non-specialist will significantly impact upon the correct

management decision. It is of major concern that a significant number of hospitals in rural Victoria do not have access to a stroke neurologist to manage acute stroke patients.

Telestroke systems include teleconferencing infrastructure installed at the emergency department of the rural hospital (on-site) and on a laptop computer provided to the stroke neurologist (off-site). These systems allow for stroke neurologists to “remotely” assess an acute stroke patient presenting to a rural hospital via fast broadband which is readily available.

Research Plan: This pilot study aims to show the feasibility and effectiveness of a telestroke system between a comprehensive stroke centre (Royal Melbourne Hospital) and a rural health centre (Wangaratta District Base Hospital) over a test period of 12 months. We hypothesize that the telestroke system in conjunction with enhanced video abilities and body area network (with accelerometer sensors) will decrease the time delay to treatment and improve patient outcome with uninterrupted monitoring.

The patients will be monitored by a wireless accelerometer to provide continuous motor recovery remote feedback to the Stroke Neurologist using a wireless body area networks. The proposed system is very small, free of wires and decentralised. We will use off-the-shelf wireless sensor motes from Crossbow as communication and processing devices. These motes have to be programmed in terms of energy efficiency, sensing, storage, and location awareness. There is also a need to make these sensors wearable so that they are convenient to use on patients without hindering their activities. The partners have identified accelerometers as suitable sensors, which need to be integrated for remote monitoring. An active interface will be developed so that the doctor at Wangaratta and in RMH will have access to all the records. The video monitoring system currently in use lacks high resolution video which is required for seamless diagnosis. We will develop a visual sensing system incorporating remote controlling of pan/tilt/zoom (PTZ) abilities.

165. Does clinical depression increase platelet aggregation and anti-platelet resistance in patients with cerebrovascular disease?

Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, Dr. Richard Dowling
Project Site: Department of Neurology, Department of Radiology, Royal Melbourne Hospital

Contact: A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital T: +61 3 9349 2477 / F: +61 3 9349 4489, Email: bernard.yan@mh.org.au

Background: Stroke is the third leading cause of death in Australia. The prevention of recurrent strokes is an important strategy to improve health and reduce medical costs. Globally, anti-platelet agents (aspirin, clopidogrel etc) are the first-line treatment to prevent further ischaemic events (i.e. heart attacks and strokes). Current research shows that up to 30% of patients with vascular disease are anti-platelet resistant. However, the exact mechanisms of anti-platelet resistance remain elusive.

Clinical depression, in previous studies, was found to be associated with significant platelet aggregation in vivo compared with controls. Studies in ischaemic heart disease have also implicated clinical depression as an important poor prognostic factor independent of other vascular risks. Although this has not been proven, it has led to interest in the role of clinical depression in anti-platelet resistance

Research plan: We aim to investigate the prevalence of anti-platelet resistance in patients with clinical depression and in controls. We hypothesize that clinical depression is associated with higher prevalence of anti-platelet resistance. The patients will be recruited from the Department of Neurology and the controls will be age-matched. The following clinical parameters will be collected: age, gender, clinical depression, depression scale (using validated grading systems), history of vascular disease, history of previous ischaemic events, medications. Anti-platelet resistance is tested by a blood test

whereby the sample undergo optical aggregometry testing to establish the degree of anti-platelet resistance.

166. Assessment of Motor Function in Acute Stroke by Wireless Accelerometer

Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, Dr. Richard Dowling
 Project Site: Department of Neurology, Department of Radiology, Royal Melbourne Hospital
 Contact: A/Professor Bernard Yan, Neurointerventionist, Neurovascular Research Group,
 Department of Neurology, Royal Melbourne Hospital T: +61 3 9349 2477 / F:
 +61 3 9349 4489 E: bernard.yan@mh.org.au

Background: Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) in order to unblock the blocked artery.

The monitoring of motor recovery post thrombolysis is critical in selecting patients for more aggressive therapy. However, the current monitoring requires labour-intensive clinical examination. In addition, the inter-rater reliability is less than optimal. We have developed a monitoring system utilizing wireless accelerometer technology which allows continuous patient assessment. This system obviates the need for labour-intensive clinical monitoring.

Research Plan: We hypothesize that wireless accelerometer sensors will improve patient outcome with uninterrupted monitoring.

The patients will be monitored by a wireless accelerometer to provide continuous motor recovery remote feedback to the Stroke Neurologist using a wireless body area networks. The proposed system is very small, free of wires and decentralised. We will use off-the-shelf wireless sensor motes from Crossbow as communication and processing devices. These motes have to be programmed in terms of energy efficiency, sensing, storage, and location awareness. There is also a need to make these sensors wearable so that they are convenient to use on patients without hindering their activities.

167. Treatment of Arteriovenous Malformation by Onyx embolization: factors determining treatment success

Supervisors: A/Professor Bernard Yan, A/Professor Peter Mitchell, Dr Richard Dowling
 Project Site: Department of Neurology, Royal Melbourne Hospital
 Contact: A/Professor Bernard Yan, Consultant Neurologist and Neurointerventionist,
 Neurovascular Research Group, Department of Neurology, Royal Melbourne
 Hospital. T: +61 3 9349 2477 / F: +61 3 9349 4489
 Email: bernard.yan@mh.org.au

Background: Arteriovenous Malformation (AVM) is an important cause of intracerebral haemorrhage. With the advent of microcatheter techniques, AVM's are now increasingly amenable to treatment by microcatheter guided embolization with Onyx, an embolic material. However, the determinants of treatment success have not been clearly defined. It has been postulated that higher number of arterial feeders and high arterial flow are associated with treatment failure.

Hypothesis: That number of arterial feeders and arterial flow pattern are strong predictors of embolization success for Arteriovenous Malformation

Inclusion criteria: All patients treated with Onyx embolization for Arteriovenous Malformation at Royal Melbourne Hospital.

For all queries, please contact: A/Professor Bernard Yan, Consultant Neurologist and Neurointerventionist, Neurovascular Research Group, Department of Neurology, Royal Melbourne Hospital, Tel: +61 3 9349 2477 / Fax: +61 3 9349 4489 /
 Email: bernard.yan@mh.org.au

PREGNANCY RESEARCH

168. Mesenchymal stem cell and vascular endothelial cell interactions in the placental bed in human pregnancy

Supervisors: Dr Bill Kalionis and Dr Rishika Pace
Project Site: Pregnancy Research Centre, Royal Women's Hospital
Contact: 8345 3748 or 8345 3755
Email: bill.kalionis@thewomens.org.au or rapace@unimelb.edu.au

A healthy pregnancy is dependent on successful remodelling of the uterine blood vessels at the site of placental formation. This process involves replacement of maternal vascular cells with placental trophoblast cells and results in reduction in vascular resistance and increased maternal blood flow to the growing placenta. The common, serious pregnancy disorders of pre-eclampsia and fetal growth restriction have significant adverse effects on the health and well-being of mothers and their babies. During these disorders uterine blood vessel remodelling and placental perfusion is deficient. The aim of this project is to elucidate the role of mesenchymal stem cell and vascular endothelial cell interactions in the processes of uterine vascular remodelling. It is proposed that a critical role of uterine mesenchymal stem cells is to regulate the changing functions of endothelial cells during early pregnancy. It is further proposed that this important regulatory interaction is disturbed during pregnancy disorders.

Techniques: human cell isolation and culture, whole cell functional assays, PCR-based analysis, immunocytochemical analysis, Western blotting and ELISA

169. Stem cells of Reproductive Tissues: their biology and potential in regenerative medicine

Supervisors: Dr Bill Kalionis and Dr Rishika Pace
Project Site: Pregnancy Research Centre, Royal Women's Hospital
Contact: 8345 3748 or 8345 3755
Email: bill.kalionis@thewomens.org.au or rapace@unimelb.edu.au

Stem cells are precursor cells with the ability to differentiate into a variety of different cell types. Typically, stem cells are categorized into “embryonic” (which arise from embryos and have the capacity to give rise to all cell types) and “adult” (which are undifferentiated cells found amongst differentiated cells in a tissue or organ and give rise to a more restricted range of cells.). Stem cells are being used in clinical trials for regeneration and repair of bone and other tissues and even for the treatment of cancers. The placenta is a rich source of stem cells with advantages over other sources of cells. Our understanding of the biology of stem cells in the placenta is still at a rudimentary stage. The project will involve gene expression and functional analysis of a gene we believe is important in placental stem cells.

Techniques: stem cell preparation and characterisation by immunocytochemistry and FACS, RNA/DNA extraction methods, real-time PCR, siRNA and gene overexpression analysis and immunohistochemistry. Functional analyses will include proliferation, migration and differentiation assays.

170. TRAIL: a novel role in regulating chemokine production during pregnancy

Supervisor: Dr Rosemary Keogh

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: rosemary.keogh@thewomens.org.au

Remodeling of maternal uterine arteries during human pregnancy transforms them from high to low resistance vessels that lack vasoconstrictive properties. This process is essential to meet the demand for increased blood flow imposed by the growing fetus. Trophoblast cells which invade the vessels from the placenta initiate remodelling by causing apoptosis of endothelial and smooth muscle cells in the vessel walls. Tumour necrosis factor-related, apoptosis-inducing ligand (TRAIL) is a member of the TNF family of death promoting ligands and is one of the factors that trophoblast use to induce endothelial and smooth muscle cell apoptosis. A novel, non-apoptotic action of TRAIL to regulate chemokine production has recently been reported. Chemokines are important regulators of trophoblast invasion into maternal vessels. The aim of this project is to determine whether TRAIL can regulate chemokine production by vascular cells. The specific objectives are to determine 1) the effect of TRAIL stimulation on chemokine production by vascular smooth muscle and endothelial cells, 2) the receptors and signalling pathways linking TRAIL stimulation to chemokine release, and 3) the effect of TRAIL-stimulation of vascular cells on trophoblast invasion.

Techniques: tissue culture, protein arrays, western blotting, ELISA, migration and invasion assays, microscopy.

171. How do chemokines affect fetal trophoblast adhesion?

Supervisor: Dr Rosemary Keogh and Dr Padma Murthi

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: rosemary.keogh@thewomens.org.au or padma@unimelb.edu.au

Late in the first trimester of human pregnancy, cells known as trophoblast migrate from the placenta and invade the arteries of the uterine wall. As they invade, the trophoblast interact with the vessels and instigate remodelling of the vessel walls. The end result is that the arteries are transformed from narrow to wide bore vessels thus facilitating blood flow to, and from, the placenta. This is an essential process to enable the fetus to develop and grow normally. In pregnancies where this remodelling is compromised, complications can arise such as pre-eclampsia, leading to poor outcomes for both the mother and baby. This project will investigate how trophoblast cells are able to migrate into maternal vessels by examining their ability to adhere to the blood vessel wall and components of the extracellular matrix. In particular, the effect of chemokines, a subgroup of cytokines, on trophoblast adhesion will be studied. The specific objectives will be to determine 1) the matrix composition surrounding the uterine arteries, 2) the effect of chemokines on trophoblast adhesion to matrix components and 3) the effect of chemokines on trophoblast adhesion to endothelial cells.

Techniques: tissue culture, western blotting, adhesion assays, immunofluorescence and confocal microscopy.

172. Characterization of novel genes associated with the pregnancy disorder pre-eclampsia

Supervisor: Dr Rosemary Keogh, Dr Bill Kalionis, Dr Padma Murthi and Dr Maria Kokkinos

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: rosemary.keogh@thewomens.org.au, bill.kalionis@thewomens.org.au, padma@unimelb.edu.au or maria.kokkinos@thewomens.org.au

Pre-eclampsia is a common and serious disorder of human pregnancy that is associated with serious health issues for both the mother and baby. It is characterized by the onset of maternal hypertension in the latter half of pregnancy, however, the pathogenesis of pre-eclampsia is not known. In conjunction with our collaborators, we have identified 8 candidate genes that show a very strong association with the development of pre-eclampsia. The aim of this project is to characterize the expression and

function of these genes. The specific objectives will be to determine the expression and localization of these genes in maternal and placental tissue. Using this information, the function of these genes will then be investigated using a suite of cellular assays.

Techniques: Tissue preparation and culture, real time PCR, RNAi, immunolotting, immunocytochemistry and functional assays including migration, proliferation, adhesion and differentiation.

173. Progesterone receptors in trophoblast function

Supervisors: Dr Padma Murthi and Dr Rosemary Keogh

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: padma@unimelb.edu.au or rosemary.keogh@thewomens.org.au

Progesterone is critical for the establishment and for the maintenance of pregnancy, as it regulates menstrual bleeding, tissue repair and regeneration, inflammation, angiogenesis, and in late pregnancy, by interfering with arachidonic acid metabolism it contributes to uterine quiescence. The genomic actions of progesterone are mediated by two intracellular receptors, progesterone receptor A (PR-A) and progesterone receptor B (PR-B), which are both members of the nuclear receptor superfamily. The project will investigate PR mediated transcriptional control and signaling pathways that are critical for successful placental cell proliferation, differentiation, and angiogenesis, that are important for decidualization.

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

174. Role of proteoglycans in preventing thrombosis within the human placenta

Supervisors: Dr Joanne Said and Dr. Amy Chui

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: jsaid@unimelb.edu.au or achui@unimelb.edu.au

Fetal growth restriction (FGR) is a serious pregnancy complication with significant short and long term sequelae. The aetiology remains largely idiopathic, although thrombosis within the placental circulation is a frequent finding. Proteoglycans and the glycosaminoglycan (GAG) side chains display important anticoagulant properties and our recent work supports a possible association between reduced expression of these macromolecules and FGR. This study aims to investigate the differences in GAG activity within the placentae of women whose pregnancies have been complicated by FGR and those who experience uncomplicated pregnancies. If our hypothesis is confirmed, there will be the potential to develop appropriate therapeutic strategies (such as anticoagulants) which may help to prevent the development of thrombosis and thus, the complications of FGR. Given the serious life-long consequences of this complication, such intervention strategies would be regarded as well worthwhile.

Techniques: Human placental tissue collection, GAG isolation and characterisation by high performance liquid chromatography (HPLC), anticoagulant activity assays, tissue culture, PCR, western immunoblotting.

175. Transcriptional regulation of insulin signaling on placental angiogenesis in diabetes and obesity

Supervisors: Dr Padma Murthi and Dr Rosemary Keogh

Project Site: Pregnancy Research Centre, Royal Women's Hospital

Email: padma@unimelb.edu.au or rosemary.keogh@thewomens.org.au

In a pregnancy complicated by type 2 diabetes, gestational diabetes and obesity, the increased maternal insulin resistance and chronic inflammation causes fetal hyperglycemia and hyperinsulinemia. Increased fetal insulin affects feto-placental vasculature by altering expression of several pro-inflammatory cytokines and angiogenic molecules that lead to aberrant placental angiogenesis. The

molecular mechanisms governing insulin signalling on placental angiogenesis is unknown. The project will identify the transcriptional control of insulin mediated changes in placental endothelial functions in diabetes and obesity during pregnancy.

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

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

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

Project Site: The Department of Medicine (RMH/WH)

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

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

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

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

This project is also listed under Biology–Women's Health

- 177. Experience of women attending the Preterm Labour Clinic at the Royal Women's Hospital**
Supervisor: Dr Christine East, Department of Obstetrics and Gynaecology. Co-supervision will be sought from Psychological Sciences and/or Melbourne School of Population Health.
Project Site: Pregnancy Research Centre, Royal Women's Hospital
Contact: T: 8345 3718 E: eastc@unimelb.edu.au

The Royal Women's Hospital (RWH), Melbourne conducts a Preterm Labour (PTL) Clinic that specializes in the prediction and prevention of spontaneous preterm birth. The practices of this clinic centre around the concepts of cervical insufficiency and intrauterine infection as the etiological basis of spontaneous preterm birth. Women are referred to this clinic based on risk factors identified from their past obstetric and gynaecological history and are seen from approximately 14 to 26 weeks gestation, then referred back to the routine clinics for the remainder of their pregnancy.

Anecdotal evidence suggests that many of the women attending this clinic are extremely anxious, particularly those who have experienced a previous pregnancy loss. This project will consider the perceptions and experiences of women attending the PTL clinic to consider whether they might benefit from further psychological support during their pregnancy journey. Both quantitative and qualitative methodologies will be incorporated to provide some answers on this question and to direct further research efforts.

178. Women's perceptions of research participation during pregnancy, childbirth and postpartum for themselves and/or their babies

Supervisor: Dr Christine East, Department of Obstetrics and Gynaecology. Co-supervision will be sought from Melbourne School of Population Health.
Project Site: Pregnancy Research Centre, Royal Women's Hospital
Contact: T: 8345 3718 E: eastc@unimelb.edu.au

The Royal Women's Hospital (RWH) has an international reputation for high quality clinical research. At the centre of such studies are the women and their babies, who may potentially be approached to participate in numerous projects. The question of 'how many projects can one person be enrolled in' is raised from time to time at various forums, usually not arriving at any consensus or resulting in policy to direct this. A project at the RWH previously considered parents' perspectives on enrolling their children in one or more of the 17 research studies running in the neonatal nursery, from 1999 to 2001. Parents were willing to join several studies believed that their baby's participation would improve care of future babies.

The number of studies conducted at the RWH has expanded considerably in the time since this survey was conducted. It is currently unknown how many projects individual women are approached for during their pregnancy, during or following their childbirth experience or that involve enrolling their babies (often born prematurely) and whether or not this adds an inordinate amount of stress or offers support additional to that which they would otherwise receive.

The proposed project seeks to investigate women's perceptions of research participation during their pregnancy, childbirth and postpartum for both themselves and their babies. The views of both parents may also be considered. The methodology will largely be quantitative in the form of a survey, with the potential for limited qualitative exploration of emergent themes.

2010/11 KEY DATES

Aug-November 2010:	Contact potential supervisors to discuss Honours projects	(Step 1)
19 November 2010:	Closing date to submit application online for the Bachelor of Science (Honours) or Bachelor of Biomedicine (Honours)	(Step 2)
28 November 2010:	Closing date for project preference submission through HATS	(Step 3)
3 rd wk December 2010:	First round of offer letters sent by mail to students	
7 January 2011:	Closing date for acceptance/rejection by students of First Round offers	
11 January 2011:	Second round of selection and mailing of offer letters begins	
Mid-late Feb 2011:	Honours 2010 begins (check with individual Departments/Institutes for specific starting date and other details)	
14 February 2011:	Honours Program commences.	

HOW TO APPLY

Course Codes: Bachelor of Biomedicine (Honours) – **BH-BMED**
Bachelor of Science (Honours) – **BH-SCI**

Enrolling Unit: Department of Medicine (RMH/WH)

Application for Honours in the Faculty of Medicine, Dentistry and Health Sciences (MDHS) in 2011

If you wish to be considered for Honours in 2011, and you would like to undertake your project and coursework in an MDHS Department or affiliated institute, you will need to carry out a **THREE STEP PROCESS**.

STEP 1:

You will need to decide which Department or Institute(s), Supervisor(s) and Project(s) that you wish to apply for. To do this, **you must speak to potential supervisors**. Please see our Honours project book and Department of Medicine (RMH/WH) website to review our projects available for 2011.

STEP 2:

Lodge an online application by Friday 19 November 2010.

Applications for Honours are lodged to MDHS via one of the following processes:

- 1) Current Local and International University of Melbourne Students:
Apply through the **Student Portal** under the Admin Tab.
Your current University of Melbourne student ID should be used for Step 3.
- 2) Local and International non-University of Melbourne Applicants:
Apply through Future Students Graduate Study:
<http://www.futurestudents.unimelb.edu.au/grad/grad/apply/aust>

Once your results are released for your current course, obtain an official or certified copy of your academic transcript and provide this to the MDHS Student Centre, Level 1, Brownless Biomedical Library, University of Melbourne. T: 8344 5890:
<http://www.sc.mdhs.unimelb.edu.au/about/contact.html>

*It is essential that you carry out **Step 2 BEFORE** you carry out **Step 3**. Note that the closing date for the Step 2 Application is **19 November 2010**.*

STEP 3:

Lodge project preferences in HATS by **28 November 2010**.

<http://hats.mdhs.unimelb.edu.au/HATS/public/index.php>

After having decided on a project(s) and submitting your application through SIS, you will need to lodge your project preferences with MDHS through the **Honours Application and Tracking System (HATS)**: <http://hats.mdhs.unimelb.edu.au/HATS/public/index.php>

It is essential that you have already identified which projects you wish to apply for by speaking to potential supervisors (i.e. Step 1) and have applied for Honours through SIS (i.e. Step 2) **BEFORE** you carry out Step 3.

To carry out STEP 3 in HATS you will need to:

A. Enter your Application ID into HATS**B. Enter your HATS password**

HATS passwords are issued once a week. Your HATS password will be emailed to you on the Monday following the date you completed Step 2.

C. Click on Preferences then Search Projects

Use this search to make sure that the project(s) you wish to apply for are present in HATS. If you cannot find the project you are interested in, you should contact the supervisor of these projects, who will be able to take steps to have the project details entered into HATS.

D. Click on Preferences then Lodge/Update Preferences to lodge your project preferences with HATS.

You can update/change your preferences as many times as you wish. However, you must ensure that your final preference list (in order of 1-10; you must enter at least 1 preference, and you can enter up to 10) is lodged by **Sunday 28 November 2010**. This list will be supplied to Departments to allow them to carry out their selection process in early December 2010

You will receive a round one offer letter for the highest preference project you have been offered by mail before Christmas. You can choose to accept the offer or not. If you choose not to accept, you will be considered for selection by Departments for the second round of selection in mid January.

Note: The enrolling unit for the RMH/WH Academic Centre Honours Program is the **Department of Medicine (RMH/WH)**, University of Melbourne.

Example of search result for Honours project:

Project Name: Sodium channels in epilepsy
Offering Department: Medicine (RMH/WH)
Supervisor: Chris French, Terence O'Brien

Project Name	Department	Supervisor	Description
Sodium channels in epilepsy	Medicine (RMH/WH)	Chris French, Terence O'Brien	This project is carried out at the Department of Medicine (RMH/WH) through the RMH/WH Academic Centre.

For further details on 'How to Apply' please refer to the following websites:

Entry Requirements: http://www.mdhs.unimelb.edu.au/future_students/honours/entry_requirements

Faculty of Medicine, Dentistry and Health Sciences Honours 2011 :
http://www.mdhs.unimelb.edu.au/future_students/honours

Faculty of Medicine, Dentistry and Health Sciences Application Process:
http://www.mdhs.unimelb.edu.au/future_students/honours/application_process

Honours Applications & Tracking System (HATS): <http://hats.mdhs.unimelb.edu.au/HATS/public/index.php>
(You must submit your preferences in HATS to ensure your application is complete and will be considered).

Department of Medicine Honours: <http://honoursrmh.unimelb.edu.au/>

ROUND 2 APPLICATIONS

Late applications will be considered from students for ROUND 2. Please check the Department of Medicine (RMH/WH) Honours website for further details in January 2011.

STUDENT INFORMATION

RMH/WH Academic Centre Honours Information Evening:

(Departments:- Medicine, Surgery, Psychiatry, Radiology, Obstetrics & Gynaecology RWH)

Date: Tuesday 31st August
Time: 4.00 – 6.00pm
Venue: The Royal Melbourne Hospital, Ground Floor, Function & Convention Centre,
Seminar Rooms 1 & 2.
Website: <http://honoursrmh.unimelb.edu.au/>

Drinks and light refreshments provided.

RMH/WH Academic Centre Department Links

Department of Medicine (Royal Melbourne Hospital/Western Hospital)
<http://www.medrmhwh.unimelb.edu.au/>

Department of Surgery (Royal Melbourne Hospital/Western Hospital)
<http://www.surgeryrmh.unimelb.edu.au/>

Department of Psychiatry (Royal Melbourne Hospital/Western Hospital)
<http://www.psychiatry.unimelb.edu.au/>

Department of Radiology (Royal Melbourne Hospital/Western Hospital)
<http://www.melbourne-radiology.org/Staff.html>

Obstetrics & Gynaecology (Royal Women's Hospital)
<http://www.thewomens.org.au/PregnancyResearchCentre>

FMDHS HONOURS EXPO:

Faculty of Medicine, Dentistry & Health Sciences

MDHS Expo – Discover Honours 2011

Thursday 9th September 2010

3:15 to 5:15pm

Alan Gilbert Building, Executive Lounge, Level 1

Faculty of Medicine, Dentistry and Health Sciences (FMDHS) link:
<http://www.mdhs.unimelb.edu.au/>

Other Links

The Royal Melbourne Hospital: <http://www.mh.org.au/>

The Western Hospital: http://www.wh.org.au/Corporate_Information/index.aspx

The Royal Women's Hospital: <http://www.thewomens.org.au/>

National Ageing Research Institute (NARI): <http://www.mednwh.unimelb.edu.au/>

The Walter and Eliza Hall Institute of Medical Research (WEHI): <http://www.wehi.edu.au/>

Bone Marrow Research Laboratories, RMH:

http://www.mh.org.au/Royal_Melbourne_Hospital/www/353/1001127/displayarticle/bone-marrow-research-laboratories--1001331.html

The Peter MacCallum Cancer Institute: <http://www.petermac.org/>

The Burnet Institute – Centre for Population Health: <http://www.burnet.edu.au/home>

Ludwig Institute for Cancer Research: <http://www.ludwig.edu.au/>

Howard Florey Institute: <http://www.florey.edu.au/>

Florey Neuroscience Institutes: <http://www.fni.edu.au/about.html>