THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital and Western Hospital
Clinical Departments Cluster
University of Melbourne

Bachelor of Science (Degree with Honours)

HONOURS PROJECTS 2010

Medical Research — Bench to Bedside

The Royal Melbourne Hospital

Western Health
Caring for the West

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), Bone Marrow Research Laboratories, RMH, The Peter MacCallum Cancer Institute, The Centre for Molecular Imaging, The Burnet Institute–Centre for Population Health, Ludwig Institute for Cancer Research, CSIRO Molecular and Health Technologies, Howard Florey Institute, Florey Neuroscience Institutes

TABLE OF CONTENTS

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Listed below are brief outlines of the projects being offered in 2010.
For further information, contact the supervisors on the numbers and email addresses as listed.

AGEING

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:

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

Supervisors: Dr Irene Blackberry and Dr Briony Dow
Location: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
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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.

2. Implementation of 'Nintendo Wii' amongst older people in aged care facilities

Supervisors: Dr Liz Cyarto and Dr Irene Blackberry
Location: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
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Nintendo Wii is a technology that provides a new opportunity for older people to engage in physical activity. Anyone of any age or level of skill can pick up and play games on the Wii console. Using the motion-sensitive remote, the player actually swings the golf club or tennis racquet. Given that many residents of aged care facilities may no longer be able to participate in these activities due to physical limitations (e.g. lacking the strength to lift and throw a bowling ball), the exercise intensity of playing Wii Sports may be sufficient to provide health benefits. Anecdotal evidence from aged care facilities indicates that using Nintendo Wii has improved the health of residents.

The overall aim of the project is to determine the feasibility, acceptability and sustainability of implementing 'Nintendo Wii' in improving health for older people in aged care facilities. This project will provide older people with structured group sessions using the Nintendo Wii system. Pre and post study design will be used for outcomes including cardiovascular endurance, CVD risk factors, depressive symptoms, social, loneliness and quality of life. A focus group will be conducted after the follow-up period has been completed to explore barriers and enablers of such implementation in residential care setting.

Training will be available for using all equipment associated with the project. The project offers students an opportunity to develop quantitative and qualitative research skills including literature review, quantitative data analysis, qualitative data analysis, interview skills, and working with residents of residential care.
Note: this project is subject to successful funding application.

3. Vitamin D to help with Bone and Muscle Health

Supervisors: Dr Cassandra Szoeke
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E: cszoeke@unimelb.edu.au / Cassandra.szoeke@mh.org.au
Women's Healthy Ageing Project (WHAP),
National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

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 Szoeke)

ii) Already have measures collected (no hard yards and thesis easily achievable in time frame)
iii) Publication within one year
iv) Treatment potential with commercial opportunities – candidate with experience in media and interest in commercialisation preferred.

4. A simple blood test to determine progression of osteoarthritis

Supervisors: Dr Cassandra Szoeke
Location: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
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E: cszoeke@unimelb.edu.au / Cassandra.szoeke@mh.org.au
Women's Healthy Ageing Project (WHAP),
National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.

Osteoarthritis is a signific 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 Szoeke)
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.

5. Possible new treatment option for cognitive decline

Supervisor: Dr Cassandra Szoeke
Location: National Ageing Research Institute, 34-54 Poplar Road, Parkville, Vic 3052.
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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

6. 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
Location: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
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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.

7. The needs of stroke survivors and primary care physicians in rural communites

Supervisors: Dr Jacques Joubert and Professor David Ames
Location: National Ageing Research Institute (NARI), 34-54 Poplar Rd., Parkville, 3052.
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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.

A HEALTHY START TO LIFE: PREGNANCY RESEARCH

8. Pre-eclampsia: women's perceptions of their experience

Supervisors: Dr Christine East, Prof Shaun Brennecke
Location: Department of Obstetrics & Gynaecology, Royal Women's Hospital, University of Melbourne
Contact: Dr Christine East E: 8345 3718 E: eastc@unimelb.edu.au

This project seeks to consider women's experiences of pre-eclampsia, a condition associated with elevated blood pressure, proteinuria, seizures (eclampsia) and potentially substantial morbidity for mother and baby, in the later half of pregnancy. The only known cure is delivery of the baby and placenta. Women often approach pregnancy with no expectation of the potential severity of this disorder and may be faced with deteriorating health and urgent interventions that can have serious short- and long-term medical and psychological effects. A major focus of this project will be women's experiences with severe pre-eclampsia or eclampsia, particularly how much prior knowledge they had of its potential emergence and how they felt during the process of diagnosis and progression of illness to birthing and beyond. The successful honours student candidate would require previous clinical experience and/or training in the equivalent of psychological theory and methodologies.

Skill acquisition: Quantitative and qualitative survey and interview techniques and analysis.

9. Ambulatory fetal activity monitoring

Supervisor: Dr Christine East
Location: Department of Obstetrics & Gynaecology, Royal Women's Hospital, University of Melbourne
Contact: Dr Christine East T: 8345 3718 E: eastc@unimelb.edu.au

This project considers the movements of healthy and compromised fetuses. Many women become concerned about their unborn baby's movements during pregnancy and it is well established that compromised babies move less than healthy babies. In this project we record fetal movements using an Ambulatory Fetal Activity Monitor, which uses accelerometers that detect motion (like those in an iPhone or Nintendo Wii). Analyses performed in this project will focus on movements made by both healthy and compromised fetuses, a unique potential generated by this project, as no similar technology has previously been available to record fetal activity during usual and/or prolonged maternal activity.

Skill acquisition: Quantitative and comparative analyses.

10. Role of proteoglycans in preventing thrombosis within the human placenta

Supervisors: Dr Joanne Said and Dr Gayathri Rajaraman
Location: Pregnancy Research Centre, The Royal Women's Hospital
Contact: Dr Joanne Said T: 8345 3717 E: jsaid@unimelb.edu.au,
Dr Gayathri Rajaraman T: 8345 3753 E: graja@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 their 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.

11. Mesenchymal stem cell and vascular endothelial cell interactions in the placental bed in human pregnancy

Supervisors: Dr Neil Gude and Dr Bill Kalionis
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Neil Gude T: 8345 3751 E: neil.gude@thewomens.org.au
Dr Bill Kalionis T : 8345 3748 E: bill.kalionis@thewomens.org.au

A healthy pregnancy is dependent on successful remodelling of the uterine blood vessels at the site of placental formation. This process involves replacement of maternal vascular cells with placental trophoblast cells and results in reduction in vascular resistance and increased maternal blood flow to the growing placenta. The common, serious pregnancy disorders of pre-eclampsia and fetal growth restriction have significant adverse effects on the health and well-being of mothers and their babies. During these disorders uterine blood vessel remodelling and placental perfusion is deficient. The aim of this project is to elucidate the role of mesenchymal stem cell and vascular endothelial cell interactions in the processes of uterine vascular remodelling. It is proposed that a critical role of uterine mesenchymal stem cells is to regulate the changing functions of endothelial cells during early pregnancy. It is further proposed that this important regulatory interaction is disturbed during pregnancy disorders.

Techniques: human cell isolation and culture, whole cell functional assays, PCR-based analysis, immunocytochemical analysis, Western blotting and ELISA

12. Stem cells of Reproductive Tissues: their biology and potential in regenerative medicine

Supervisor: Dr Bill Kalionis and Dr Rishika Pace
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Bill Kalionis T : 8345 3748 E: bill.kalionis@thewomens.org.au
Dr Rishika Pace T: 8345 3748 E: 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 that 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.

13. How do chemokines affect fetal trophoblast adhesion?

Supervisor: Dr Rosemary Keogh
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Rosemary Keogh E: rosemary.keogh@thewomens.org.au

Late in the first trimester of human pregnancy, cells known as trophoblast migrate from the placenta and invade the arteries of the uterine wall. As they invade, the trophoblast interact with the vessels and instigate remodelling of the vessel walls. The end result is that the arteries are transformed from narrow to wide bore vessels thus facilitating blood flow to, and from, the placenta. This is an essential process to enable the fetus to develop and grow normally. In pregnancies where this remodelling is compromised, complications can arise such as pre-eclampsia, leading to poor outcomes for both the mother and baby. This project will investigate how trophoblast cells are able to migrate into maternal vessels by examining their ability to adhere to the blood vessel wall and components of the extracellular matrix. 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.

14. Do the aminopeptidases ARTS-1 and LNPEP regulate trophoblast functions?

Supervisor: Dr Rosemary Keogh
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Rosemary Keogh E: rosemary.keogh@thewomens.org.au

Pre-eclampsia is a common and serious disorder of human pregnancy that is associated with serious health issues for both the mother and baby. It is characterized by the onset of maternal hypertension in the latter half of pregnancy. However, the pathogenesis of pre-eclampsia is not known. In a normal pregnancy, cells known as trophoblast invade the arteries in the uterine wall and replace the endothelial and smooth muscle cells. This dilates the arteries and facilitates an increase in blood flow to the placenta to allow the fetus to grow and develop. In pre-eclamptic pregnancies, this invasion is limited with consequent reduced remodelling of the arteries and a restriction of maternal placental blood flow.

Genetic analysis has identified candidate genes that encode animopeptidase enzymes that may be involved in the development of pre-eclampsia. The aim of this project is to characterize the function of these aminopeptidases (ARTS-1 and LNPEP) in regulating trophoblast cell functions. The specific objectives will be to determine 1) the localization of ARTS-1 and LNPEP in trophoblast cells, 2) if ARTS-1 and LNPEP regulate trophoblast migration and invasion and 3) if ARTS-1 and LNPEP regulate trophoblast survival.

Techniques: tissue culture, RNAi, western blotting, immunofluorescence and migration and proliferation assays.

15. Regulation of pregnancy hormone chorionic gonadotropins in human pregnancy disorders

Supervisors: Dr Padma Murthi and Dr Niro Pathirage
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Padma Murthi E: padma@unimelb.edu.au
Dr Niro Pathirage E: npa@unimelb.edu.au

A critical step in establishment of human pregnancy is the invasion of the uterus wall by extravillous cytotrophoblasts (EVCT) during the first trimester. It is well established that human chorionic gonadotropin (hCG) is secreted by the endocrine syncytiotrophoblast (ST) into the maternal compartment. We have preliminary studies to show that invasive EVCT also produce hCG, suggesting a possible role in the modulation of trophoblast invasion. This project will investigate the role of transcription factors in the regulation of hCG in normal placental development and in disorders of pregnancy such as fetal growth restriction and pre-eclampsia.

Techniques: cell and molecular biology, immunoblotting, immunohistochemistry, functional assays including proliferation, migration and invasion.

16. Identification of factors that regulate placental angiogenesis

Supervisors: Dr Padma Murthi, Dr Niro Pathirage and Dr Rosemary Keogh
Location: Pregnancy Research Centre, Royal Women's Hospital
Contact: Dr Padma Murthi E: padma@unimelb.edu.au
Dr Niro Pathirage E: npa@unimelb.edu.au

Angiogenesis or new blood vessel formation is co-ordinated by placental trophoblast cells and endothelial cells. Aberrant placental angiogenesis is associated with complications of pregnancy disorders such as fetal growth restriction and pre-eclampsia. This project will identify factors that are released by trophoblast cells on endothelial cell function such as proliferation, migration and network formation.

Techniques: cell and molecular biology, immunoblotting and immunohistochemistry.

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.

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

Supervisor: Dr Andrew Cook
Location: 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.

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

Supervisor: Dr Andrew Cook
Location: 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.

19. The role of inflammation in mesenchymal stem cell differentiation

Supervisor: Dr Derek Lacey and Prof John Hamilton
Location: 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

20. The role of Wnts in Arthritis

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

21. The role of a novel therapeutic target in Arthritis

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

22. The role of Wnts in Macrophages

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

23. The role of a novel therapeutic target in Macrophages

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

24. Host pathogen interactions and mucosal inflammation

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

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 inflammation (e.g. Crohn's disease, ulcerative colitis, 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 working out how the activity of the transcription factor is regulated in response to specific pathogens.

Skill acquisition: a variety of cell biology (e.g. tissue culture, ELISA assays, FACS analysis, and confocal microscopy), biochemical (e.g. affinity purification of proteins and Western blotting), and molecular biology techniques (e.g. Real-Time PCR, cloning, transfection of cells, and siRNA-mediated gene silencing).

25. How macrophages use SNAREs to capture and kill microbial pathogens

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

The phagocytosis and killing of pathogens by macrophages, as well as their secretion of inflammatory cytokines (e.g. TNF), is crucial for effective host defense. These key immune functions of macrophages depend upon the highly coordinated intracellular trafficking of vesicles from one compartment to another (e.g. trafficking of phagocytosed pathogens to lysosomes for killing). SNARE proteins are small, membrane-anchored proteins that directly control the membrane fusion events which are necessary for vesicle trafficking. In this project you will investigate how particular SNARE proteins mediate pathogen killing and inflammatory cytokine secretion by macrophages. You will also investigate if SNARE proteins are targeted by virulence factors from important human pathogens (e.g. Salmonella, Legionella, and Mycobacterium) in order to usurp the immune functions of macrophages.

Skill acquisition: a variety of cell biology (e.g. tissue culture, ELISA assays, FACS analysis, and confocal microscopy), biochemical (e.g. affinity purification of proteins and Western blotting), and molecular biology techniques (e.g. Real-Time PCR, cloning, transfection of cells, and siRNA-mediated gene silencing).

26. Regulation of inflammation and cancer by SNARE proteins

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

Following their activation, many cell-surface receptors (e.g. growth factor receptors) are internalized and then trafficked through the endocytic pathway, finally arriving at the lysosome where they are degraded. Such degradation of receptors is thought to be important in limiting their signalling activity. Aberrant trafficking of receptors through the endocytic pathway could therefore potentially result in prolonged signalling and hence altered cellular responses (e.g. prolonged inflammatory responses, cellular hyperproliferation, etc.). SNARE proteins are small, membrane-anchored proteins that directly control the membrane fusion events which are necessary for intracellular vesicle trafficking through the endocytic pathway. In this project you will establish if specific SNARE proteins dictate the biological response of cells to inflammatory stimuli and growth factors by regulating the intracellular trafficking of key signalling receptors.

Skill acquisition: a variety of cell biology (e.g. tissue culture, ELISA assays, FACS analysis, and confocal microscopy), biochemical (e.g. affinity purification of proteins and Western blotting), and molecular biology techniques (e.g. Real-Time PCR, cloning, transfection of cells, and siRNA-mediated gene silencing).

27. 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
Location: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, The University of Melbourne
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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 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 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.

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

Supervisor: Dr Sharon Van Doornum
Location: 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 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.

29. Src kinases, lung inflammation and lung cancer

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

30. 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)
Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au
A/Prof 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.

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

Supervisor(s): Dr. Andrew Jarnicki and Prof. Gary Anderson
Location: Department of Pharmacology, University of Melbourne
Contacts: Dr Andrew Jarnicki T: +61-3-9341-3148 E: jarnicki@ludwig.edu.au
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 remodeling 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.

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

Supervisors: A/Prof Margaret Hibbs (Ludwig Institute), Professor Gary Anderson
Location: Department of Pharmacology, University of Melbourne
Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au
A/Prof Margaret Hibbs T: 9341 3155 E: Margaret.Hibbs@ludwig.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 re most unregulated in COPD when viruses infect the lungs. A major ficus 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.

33. Regulatory T cells in asthma and COPD

Supervisors: A/Prof Margaret Hibbs and Professor Gary Anderson
Location: Department of Pharmacology, University of Melbourne
Contact: Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au
A/Prof Margaret Hibbs T: 9341 3155 E: Margaret.Hibbs@ludwig.edu.au

Regulatory T cells (Tregs) are a newly discovered set of cells that limit immune responses in therefore prevent tissue damage. There is now a suspicion that Tregs 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.

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

Supervisors: Dr Steve Bozinovski and Professor Gary Anderson
Location: 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 spontaneous 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.

35. Skeletal muscle failure in COPD

Supervisors: Dr Michelle Hanson and Professor Gary Anderson
Location: 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.

36. Identification of Lyn regulated proteins using proteomics

Supervisor: A/Prof Margaret Hibbs, Professor Gary Anderson
Location: Ludwig Institute
Contact: A/Prof Margaret Hibbs T: 9341-3155 E: Margaret.Hibbs@ludwig.edu.au

The Lyn protein tyrosine kinase plays an essential role in the immune system and is critical for a wide variety of processes including B cell development, dendritic cell maturation and function, mast cell responses, and macrophage developmental programming and activation. Using standard biochemical approaches, we have identified some substrates of the Lyn kinase; these proteins are modified post-transcriptionally, and this process is dependent on the presence or absence of an active Lyn kinase. The aim of this project is to identify additional Lyn-regulated genes in macrophages derived from Lyn mutant mice using proteomics technology. The proposed experiments are aimed at identifying important novel proteins that are critical regulators of macrophage development, activation and innate immune responses.

Skill acquisition: Cell culture, histology, Western blotting, immuno-affinity purification of proteins, 1D & 2D gels for protein pattern analysis, advanced proteomics (SELDI-ToF, MS/MS).

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

Supervisors: Professor Gary Anderson, A/Prof Margaret Hibbs and Professor Bruce Levy, (Harvard Medical School, Boston USA)
Location: 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.

38. TH17 cells in lung disease

Supervisors: Professor Gary Anderson and A/Prof Margaret Hibbs
Location: 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.

Lung Stem Cell Biology/Bertoncello Lab

The broad interest of the Lung Stem Cell Biology 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. Our long-term goal is to investigate the role of stem cells in lung homeostasis, and identify factors regulating their regenerative potential as a prerequisite to the development of therapeutic strategies to attenuate lung disease and regenerate the injured lung.

Our group is a member of the Adult Stem Cell Program funded by the Australian Stem Cell Centre Collaborative Stream Initiative which comprises a national network of high calibre scientists with internationally recognised leadership in adult stem cell biology focused on working collaboratively to address key areas that will allow significant acceleration of stem cell research.

The laboratory performs cutting edge research using flow cytometry-based cell separative strategies, novel three-dimensional cell culture assays and in vivo transplantation to identify and characterize stem/progenitor cells in the adult lung. Current projects offered in the laboratory aim to elucidate the mechanisms by which epithelial and mesenchymal stem/progenitor cells contribute to homeostasis in the lung and how they are regulated by the microenvironmental niche in which they reside.

39. Defining the lineage specificity of adult lung epithelial stem/progenitor cells

Supervisors: Dr Jonathan McQualter, Professor Gary Anderson, A/Professor Ivan Bertoncello
Location: Department of Pharmacology, University of Melbourne
Contact: A/Prof Ivan Bertoncello E: Ivan.Bertoncello@stemcellcentre.edu.au,
Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

We have developed a novel 3D culture assay based on the epithelial-mesenchymal-matrix interactions in the lung which enables the identification of lung epithelial stem/progenitor cells by their colony-forming potential *in vitro*. We have identified a population of epithelial stem/progenitor cells which generate colonies comprising airway, alveolar, or mixed lung epithelial cell lineages *in vitro*, suggesting for the first time that an epithelial stem/progenitor cell hierarchy exists in the adult lung. This project will advance on these cell culture techniques to identify the cues that regulate the survival, self-renewal and lineage specificity of different stem/progenitor cell subsets.

40. The response of lung epithelial stem cells in animal models of lung injury

Supervisors: Dr Jonathan McQualter, Professor Gary Anderson, A/Professor Ivan Bertoncello
Location: Department of Pharmacology, University of Melbourne
Contact: A/Prof Ivan Bertoncello E: Ivan.Bertoncello@stemcellcentre.edu.au,
Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

This project will analyze the temporal pattern of depletion and recovery of lung epithelial stem/progenitor cells following lung injury by exploiting the selective toxicity of drugs which impair lung function. Cell culture analysis of the proliferation, self-renewal and lineage specificity of lung epithelial stem/progenitor cells at various stages of injury and repair will provide valuable insights into the role in endogenous epithelial stem cells in regeneration and repair of the adult lung.

41. The role of lung stromal cells in the regulation of lung epithelial stem cell proliferation and differentiation

Supervisors: A/Professor Ivan Bertoncello, Professor Gary Anderson, Dr Rosa McCarty
Location: Department of Pharmacology, University of Melbourne
Contact: A/Prof Ivan Bertoncello E: Ivan.Bertoncello@stemcellcentre.edu.au,
Professor Gary Anderson T: 8344 8602 E: gpa@unimelb.edu.au

This project will analyse the different lung stromal cell populations which comprise lung epithelial stem cell niches and compare their ability to regulate lung epithelial stem/progenitor cell proliferation and differentiation. Cell culture assays will be used to determine how lung stromal cells alone, or together with growth factors and matrix proteins affect the lung epithelial regeneration.

BONE BIOLOGY

42. Antiepileptic medication and bone health: Is quantitative ultrasound a reliable monitoring test for AED-associated bone disease

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Aims: To assess quantitative bone ultrasound (QUS) measures compared with dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) in subjects taking anti-epileptic drugs (AEDs) and their non-AED exposed twins or siblings

Background: Epilepsy is the most common serious chronic neurological disease. Most people with active epilepsy take an AED for many years to prevent seizures. Patients taking AEDs have high rates of bone fractures. The reasons for this major adverse effect are likely multifactorial, including an effect of the AEDs resulting in bone fragility. Decreased bone mineral density (BMD) and increased rates of osteoporosis have been demonstrated in people taking long-term AEDs. QUS is a convenient, economical method with potential utility to monitor patients for osteoporosis and fracture risk

Research Plan: Patients aged over 18 years, taking AED for >12 months, who have a same-sex twin (or sibling within 3 years of their age) will be identified, and offered participation. This project forms a sub-study of the *AED Twin and Sibling Bone Health Study.* The student will also be involved in recruitment of study participants, and conducting study visits.

Skills learnt: Patient interviewing techniques, quantitative ultrasound techniques, blood sample taking, and data management and analysis.

43. 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
Location: 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.

44. Determinants of osteoporosis, falls and fracture risk: twin studies

Supervisor: Professor John Wark, Dr Rosemary Wong
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Many projects are available within this large, multi-disciplinary program of research into determinants of growth and development, and osteoporosis risk, and involve female twins over a wide age range. Available projects include physiology, biochemistry, nutrition, epidemiology and biostatistics and genetics.

Osteoporotic fractures cluster in families and so may falls. We aim to study genetic and environmental determinants of gait and balance in young twins. The study may help explain why hip fractures run in families. We have identified important relationships between lean body mass, fat mass and bone mineral density (a key predictor of fracture risk) in women. In this project we will explore how regional soft tissue composition predicts bone mass.

We, and others, have demonstrated in randomised, controlled trials that dietary calcium supplementation augments the gain in bone in adolescent girls. In this project, we will evaluate the extent to which the bone gained is retained after supplementation is ceased: this will give insight into the potential benefits of additional dietary calcium in augmenting peak bone mass in young women.

We have a large cohort of female twins studied longitudinally before and during puberty. We now plan follow-up studies after completing growth so that we can evaluate genetic and environmental determinants of bone mass and bone strength.

Our research and that of others has shown a strong association between cigarette smoking and low bone mass/risk of fractures. We will explore the mechanisms by which smoking affects bone health. Recently described biomechanical properties of the proximal femur may help to explain hip fracture risk.

We will use classical twin research methods to study genetic and environmental determinants of these parameters.

45. Bone health in Asian Australians

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

There are important ethnic differences in osteoporotic fracture risk. To date, osteoporosis risk factors, bone mineral density and fracture rates are almost unstudied in Australians of Asian ethnic background. This project is intended to redress this lack of important information.

Example using well-established research methods we will compare osteoporosis risk factors, bone density and bone ultrasound in Australians of Asian and Caucasian ethnic background also seeking effects of migration on these factors.

46. Glucocorticoids and bone loss

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Patients treated with glucocorticoids for their anti-inflammatory, immuno-suppressive effects often suffer severe bone loss and fractures. Early recognition of susceptible patients would help in the prevention and treatment of this form of osteoporosis. In this project, the roles of transmission ultrasound and loss of lean body mass in predicting early glucocorticoid-induced bone loss will be evaluated prospectively.

47. The epidemiological study of bone health in Asian—Australians

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

There are important ethnic differences in osteoporotic fracture risk. To date, osteoporosis risk factors, bone mineral density and fracture rates are almost unstudied in Australians of Asian ethnic background. This project is intended to redress this lack of important information.

Example - using well-established research methods we will compare osteoporosis risk factors, bone density and bone ultrasound in Australians of Asian and Caucasian ethnic background also seeking effects of migration on these factors.

48. AED Pharmacogenetic AED bone health

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

A prospective study of patients attending first seizure clinic or private rooms, who are commencing AED treatment for the first time. Patients who attend first seizure clinic or private rooms and are diagnosed with another disorder, or are not commenced on treatment may be enrolled as control subjects.

First visit is within 3 months of starting AED, next visit at two years later. Potential to study at 5 years if funding allows. Currently no balance testing available for this study.

Bone Biopsy will be available as an optional sub study, but is not expected to be required prior to the two year follow up, where subjects who have experienced low-trauma fracture or have low BMD since starting AED therapy will be offered participation. Some of these patients will be enrolled in COMET study (sponsored by UCB), and can be billed for bone tests accordingly.

49. Konquest bone health study

Supervisor: Professor John Wark, Professor Terence O'Brien
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au
Professor Terence O'Brien T: 8344 5479 E: obrientj@unimelb.edu.au

A study commencing at time of first substitution of medications for epilepsy where the original treatment has not controlled the seizures adequately. Patients will have bone measurements (DXA, pQCT, turnover markers) done 3 months after change of meds (Levetiracetam, Carbamazepine or Sodium Valproate) and again at one year.

50. Predictors of glucocorticoid induced bone loss

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Patients treated with glucocorticoids for their anti-inflammatory, immuno-suppressive effects often suffer severe bone loss and fractures.

Early recognition of susceptible patients would help in the prevention and treatment of this form of osteoporosis. In this project, the roles of transmission ultrasound and loss of lean body mass in predicting early glucocorticoid-induced bone loss will be evaluated prospectively.

51. Improving the prediction of vertebral fracture risk in osteoporosis

Supervisor: Professor John Wark, Dr Andrew Briggs
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Vertebral fractures account for many of the low-trauma fractures seen in osteoporosis and impact significantly on health-related quality of life. The prediction of vertebral fracture risk therefore is very important for the appropriate diagnosis and treatment of osteoporosis. Dual energy Xray absorptiometry (DXA) is the best available clinical tool to measure bone mass and therefore infer skeletal status. Although DXA can be used to aid in the diagnosis and treatment of osteoporosis, its

capacity to provide reliable information about vertebral fracture risk is limited. Individuals with osteoporosis show marked differences in the prevalence of vertebral fractures where areal BMD is comparable. Similarly, individuals with secondary osteoporosis from glucocorticoid therapy are at a significantly higher risk of sustaining a vertebral fracture compared to BMD-matched controls. In both clinical scenarios – primary and secondary osteoporosis – neither patients at risk of sustaining an incident vertebral fracture nor those at risk of entering the vertebral fracture cascade can be readily identified with standard DXA parameters.

Our pilot data suggest that this limitation may be attributable partly to standard-DXA parameters relying solely on a gross measure of vertebral BMD, for example total spine BMD. We have demonstrated that measurement of subregional areal BMD on lateral spine scans can better discriminate between fracture and no-fracture individuals in the context of idiopathic osteoporosis. The aim of the current study is to extend our pilot work to a larger clinical study to provide more robust clinical data. Ultimately, the application of subregional BMD measurement may provide greater diagnostic sensitivity for vertebral fragility in primary and secondary osteoporosis.

Students undertaking this novel project will work with an outstanding research team and gain wide-ranging experience in clinical research including the application of state-of–the-art technology, patient recruitment and data collection techniques, data management and biostatistics, and research translation. They will also help to improve the care of patients with osteoporosis, a common and potentially-debilitating condition.

52. Is regular table tennis activity associated with increased bone and muscle strength and improved balance in elderly Asian men and women

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Osteoporosis is “a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture” (1). While there are an estimated 1.2 billion people worldwide with osteoporosis, more than 50% of them reside in the Asia-Pacific region with approximately half a million people of Chinese extraction in Australia alone (2). This public health burden will increase significantly over the next 20 years due to ageing of the population (3).

Physical exercise may have beneficial effects on bone mass, muscle strength and balance in the elderly (4-6). Regular weight-bearing exercise for at least one hour per week is associated with increased bone mineral density (BMD) in the normal population (7).

Tai Chi exercise appears to have a beneficial effect on BMD at multiple sites (8, 9). Post-menopausal Chinese women had a greater increase in hip BMD following a combination of calcium supplementation and an exercise programme compared to those receiving calcium supplementation alone (9). Similar findings have been previously reported in non-Chinese women (10). “Keep-Fit” classes involving high-impact exercise two to three times a week maintained muscle strength and increased femoral BMD in men and women aged 50 years and older (11). Significant strength increases after one year of progressive resistance exercises were evident in elderly women and parallelled BMD changes (12). A high-intensity weight-bearing exercise program for patients with rheumatoid arthritis was effective at slowing down hip BMD loss (13). These studies suggest that anti-gravity exercise may be an osteogenic stimulus leading to increased bone mass, thereby reducing fracture risk.

There appear to be no published studies investigating the effects of table tennis activity on BMD or other measures of fracture risk. Table tennis exercise is not excessively strenuous and is therefore suitable for elderly people. Little financial outlay is required as minimal specialised equipment is

necessary, unlike gymnasium-based interventions. Moreover, table tennis encourages socialisation. Table tennis is the "national sport" of China and is therefore a culturally-acceptable form of exercise in many communities in the Asia-Pacific region. These factors may favour both uptake of and compliance with table tennis as an exercise intervention compared with more formal gymnasium-based interventions.

53. Optimising the bone response to dietary calcium: a physiological approach

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

This study aims to identify the type of variable calcium diet that optimises bone mass, density and strengths. This unique approach suggests that a moderate dietary calcium diet followed by a period of high calcium intake is beneficial for bone health. This proof of concept application will utilise the rat as a model to generate data that would directly translate into functional food development for human diary products. This research may lead to the generation of novel functional foods in the form of 'dairy product packs'. Consumers would drink mild (or eat yogurt) from a :moderated calcium pack' for 5 days followed by a 'high calcium pack' for 5 days. The approach is based on the physiological effect of reduced calcium intake up regulating fractional intestinal calcium absorption. The "primed" intestine will respond to an increased calcium load with enhanced calcium absorption, creating a greater positive calcium balance than would be predicted from the same "steady state" intake. This novel approach will encourage increased dairy intake and be of significant benefit to the Dairy Industry as our strong new evidence from this program of research provides the foundation for the novel marketing strategy.

Low birth weight is associated with adult hypertension, diabetes and obesity as well as reduced bone mass and osteoporosis. We have shown that uteroplacental insufficiency, which restricts nutrients and oxygen supply before birth and lactational nutrition after birth in rats, causes fetal and postnatal growth restriction. These rat pups then develop high blood pressure, increased adiposity and insulin resistance later in life.

The aim of this study is to use cross-fostering techniques in the rat to determine whether restricted nutrition before birth via the placenta, or after birth via lactation, increases the risk of having reduced bone density and growth. Bone changes will be quantified using dual-energy X-ray absorptiometry (DXA) for bone mass, bone mineral density, bone mineral content and soft tissue composition and peripheral quantitative computed tomography (pQCT) for bone strength and lean mass. In addition, the relationship between skeletal development and key bone plasma markers will be assessed. In this project students will undertake state-of-the-art measurements of bone mass and bone strength.

54. Quitline Cohort Study

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Currently the research group is working on a number of studies investigating the association between smoking and bone health. The aims of the studies are to investigate the effects of smoking cessation on bone health in males and females and to examine the reversibility of smoking-associated loss of bone mineral density (that is, the risk of developing osteoporosis)

Osteoporosis is a common condition where bones are thin and this leads to fractures. It affects mostly women after the menopause, but it also affects men and people with some medical conditions. Because there are now effective treatments for osteoporosis, it is important to make the diagnosis early.

Fractures cause pain, disability, deformity and especially after a hip fracture, loss of independence so that you may not be able to live with your family anymore, for example. We can measure how thin or thick your bones are by measuring the density of your bones.

Lifestyles are important determinants of the risk of developing osteoporosis. Cigarette smoking is a key lifestyle risk factor for osteoporosis and is important particularly because it is potentially modifiable. Loss of bone density (bone thinning) has been reported at all medically important sites such as the lower back and hip, the bones where most osteoporotic fractures occur. These losses of bone increase an individual's risk of developing osteoporosis. These reductions in bone mass have been reported in both men and women across the life span. Smoking is associated with a 30-40% increase in lifetime hip fracture risk. Of all the hip fractures that occur in the community 6-12% of hip fractures may be caused by smoking. That means that for every 100 hip fractures, 6 – 12 of these fractures could have been prevented if people did not smoke. When people stop smoking we want to see if bone density increases, reversing the loss of bone and reducing the risk of having a fracture. By investigating the reversibility of smoking associated bone loss we hope to provide essential information to guide individual patient management aimed at preventing smoking-related fracture and to support public health approaches to quitting smoking and improving bone health.

55. AED Twin and sibling bone health study

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

A study of twins and siblings, of same gender, siblings aged within 3 years of each other, where one has been taking AED for any indication for more than 12 months. DXA, pQCT, bone turnover markers are done at baseline (time of enrolment) and again two years later. Balance testing is done at first visit. Fat Distribution study is in progress. Patients can be enrolled via ATR, media referral, specialist referral and epilepsy clinics referral.

Bone biopsy is available as an optional sub-study where the AED user has a history of low-trauma fracture or low BMD (ethics approval pending). Mary Sakellarides will be doing a sub study looking at pQCT and US in this group.

56. The effect of anti-epileptic medication on indices of bone health and risk factors for falls and fracture: a twin/sibling pair study

Supervisor: Professor John Wark, Professor Terence O'Brien, Professor Keith Hill
Location: Department of Medicine (RMH)
Contact: Prof John Wark T: 9342 7109 E: jdwark@unimelb.edu.au
Prof Terence O'Brien T: 8344 5479 E: obrientj@unimelb.edu.au

Aims: To utilise the University of Melbourne *Twin and Sister Longitudinal Bone Health Study* methodology to compare bone mineral density (BMD), biochemical indicators of bone turnover and balance function in subjects taking anti-epileptic drugs (AEDs) with their non-AED exposed twin or sibling.

Background: Epilepsy is the most common serious chronic neurological disease in the community, affecting up to 3% of the population in a lifetime. Most people with active epilepsy are required to take an anti-epileptic drug (AED) for many years, and often lifelong, to prevent the harmful effects of seizures. Patients taking AEDs have high rates of bone fractures.

The reasons for this are likely multifactorial, including a direct effect of trauma from the seizures as well as an effect of the AEDs resulting in bone fragility and balance impairments (increasing falls

risk). A number of studies have demonstrated decreased bone mineral density (BMD), increased rates of osteoporosis and greater fracture rates in women with epilepsy who have been taking long-term AEDs. However, these studies have been limited by inadequate controls, use of cross sectional design, and lack of adjustment for other BMD determinants. Moreover, the mechanisms by which AEDs might be associated with decreased BMD and increased bone fragility are not well understood.

Research Plan: This study will utilise the University of Melbourne *Twin and Sister Longitudinal Bone Health Study* methodology to investigate the effects of the long-term use of AEDs for epilepsy on BMD, indices of bone turnover, vitamin D and mineral levels, and measures of balance function. Women who have been using AEDs for >12 months will be identified and compared with their co-twin or matched sister for the above variables.

The study will provide important data on the extent of the effect of AED use on BMD, gait and balance function and potential fracture risk. It has the potential to provide novel insights into the mechanisms underlying the effect of AEDs on BMD, and for the identification of specific types of AEDs that may have greater/less risks.

57. Smoking—discordant twins: follow-up studies

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

A number of studies address the association between smoking and bone health. The aims of the studies are to investigate the effects of smoking on bone health and to examine the reversibility of smoking-associated loss of bone mineral density (that is, the risk of developing osteoporosis). Osteoporosis is a common condition where bones are thin and this leads to fractures. Lifestyle factors are important determinants of the risk of developing osteoporosis. Cigarette smoking is a key lifestyle risk factor for osteoporosis and is important particularly because it is potentially modifiable. Loss of bone density (bone thinning) has been reported at all clinically-important sites such as the lumbar spine and hip. Smoking is associated with a 30-40% increase in lifetime hip fracture risk. Of all the hip fractures that occur in the community 6-12% may be caused by smoking. That means that for every 100 hip fractures, 6 – 12 of these fractures could have been prevented if people did not smoke.

We want to investigate that extent to which bone loss is ongoing in people who choose to continue smoking. When people stop smoking we want to see whether bone density increases, reversing the loss of bone and reducing the risk of having a fracture. By investigating the reversibility of smoking associated bone loss we hope to provide essential information to guide individual patient management aimed at preventing smoking-related fracture and to support public health approaches to quitting smoking and improving bone health.

In this project students use the powerful twin study design to conduct a follow-up study of twin pairs who are discordant for smoking and who have previously attended our centre for baseline measures of bone mineral measures and a range of hormones and bone turnover markers. Changes in measures of bone health will be assessed and the role of smoking/smoking cessation in determining changes in bone health will be evaluated.

In this novel project students will gain experience in twin study design, implementation of clinical research studies, data collection, management and analysis, and interpretation of twin research data.

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

Supervisor: Professor John Wark,
Location: 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.

59. Lifecourse choices in young women

Supervisor: Professor John Wark,
Location: Department of Medicine (RMH)
Contact: Professor John Wark T: 9342 7109 E: jdwark@unimelb.edu.au

Behaviours and lifestyle choices of adolescent females have far reaching consequences that impact on health, well-being and productivity in adult life. We aim to perform a longitudinal, community-based study of females aged 16-25 years. Our aim is to provide epidemiological evidence in key national priority areas where lifelong patterns are established during adolescence and young adulthood: obesity and metabolic health, sexual and reproductive health, bone health and mental health. If you are interested in one or more of these health research areas, and are eager to learn how to engage in all aspects of a medical research study, from study design, interviewing and consenting participants, collecting, cleaning and analysing data, and importantly, translating your new knowledge into a scientific communication, then this project is for you!

Suitable projects include:

The association between metabolic syndrome and disordered eating in a community sample of young Victorian women. Supervisors: Prof John Wark, Dr Yasmin Jayasinghe, Dr Elya Moore.

To investigate the association of bone mineral density and bone strength measures with weight, soft tissue composition, and the metabolic syndrome using peripheral quantitative CT and dual energy Xray absorptiometry. Supervisors: Prof John Wark, Dr Yasmin Jayasinghe, Dr Elya Moore.

60. 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.
Location: 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.

BONE MARROW RESEARCH

61. Analysis of a novel family of genes crucial for the neural tube development and wound healing.

Supervisors: Dr Tomasz Wilanowski and Prof Stephen Jane
Location: Bone Marrow Research Laboratories, Royal Melbourne Hospital
Contacts: Dr Tomasz Wilanowski T: 9342 8125 E: wilanowski@wehi.edu.au,
Professor Stephen Jane T: 9342 8641 E: jane@wehi.edu.au

Our research team studies a highly conserved family of mammalian genes, the Grainyhead family. Knockout studies in mice have shown that these genes play essential roles in a range of developmental events including neural tube closure and embryonic wound repair (Nature Medicine 9: 1513-1519, 2003; Science 308: 411-413, 2005). The Grainyhead genes encode transcription factors which act through target genes to mediate their effects. The project offered here will involve identification of Grhl target genes relevant to neural tube closure and wound healing. This is likely to have impact on

the treatment of children with spina bifida, and in the development of new approaches to wound repair.

Skills - Molecular biology, cell culture, knockout models, bioinfomatics, and more

62. Studying the role of self-renewal in causing T cell leukaemia

Supervisors: Dr Matthew McCormack, Dr David Curtis
Location: Bone Marrow Research Laboratories, RMH
Contacts: Dr Matthew McCormack T: 9342 8948 E: mccormack@wehi.edu.au
Dr David Curtis T: 9342 8444 E: dcurtis@wehi.edu.au

Project description: Whilst transcription factor Lmo2 is a principle oncogene in human T cell leukaemia, its cellular effects on T cell development remain poorly defined. We have recently shown that Lmo2 causes long-term persistence of early T cells via the process of self-renewal. This process involves early T cells replicating themselves whilst retaining the ability to mature, and normally never occurs during T cell development. This project will establish *in vitro* model systems for studying self-renewal caused by Lmo2 and test whether inhibition of various signalling pathways can interfere with this process. This will identify potential therapeutic approaches for preventing leukaemia development.

63. Identifying target genes of Lmo2 in haemopoietic (blood) stem cells

Supervisor: Dr Matthew McCormack, Dr David Curtis
Location: Bone Marrow Research Laboratories,RMH
Contacts: Dr Matthew McCormack T: 9342 8948 E: mccormack@wehi.edu.au
Dr David Curtis T: 9342 8444 E: dcurtis@wehi.edu.au

Project description: The transcription factor Lmo2 has crucial roles in haemopoietic (blood) stem cell development and T cell leukaemia. With regard to blood development, the critical targets of this transcription factor remain poorly defined. Using microarray analysis of T cells overexpressing Lmo2 we have shown that Lmo2 induces expression of several genes that are normally only expressed in haemopoietic stem cells (HSCs). This implies that Lmo2 normally regulates these genes in HSCs. This project will use molecular and cellular techniques to demonstrate the regulation of key HSC genes by Lmo2.

64. bHLH factors and Haemopoietic Stem Cell cycling

Supervisor: Dr David Curtis
Location: Bone Marrow Research Laboratories, RMH
Contact : Tel: 9342-8444 Email: dcurtis@wehi.edu.au

Project description: Haemopoietic stem cells (HSC) are primitive cells that maintain the blood system throughout life. To achieve this there must be tight control of HSC cycling such that most HSCs are in a "quiescent" or non-dividing state. Restriction of HSC cycling is achieved by factors that govern the entry of HSCs into the cell cycle. One such regulator is p21, also known as cyclin-dependent kinase inhibitor 1A (CDKN1A). p21 serves as a negative regulator of HSC cycling by regulating the activity of cyclin-dependent kinase proteins. However, the factors that regulate p21 activity are largely unknown. We have data suggesting that the bHLH factors, Scl and Lyl1 are important repressors of p21. HSCs in mice lacking Scl or Lyl1 show a 3-fold reduction in HSC cycling, and this correlates with increased p21 expression. HSCs lacking both Scl and Lyl1 cannot grow and we hypothesize that this is due to high levels of p21. The aims and experiments of this project may include

i. Determine cell cycle status and p21 levels of Scl/Lyl1 deficient HSCs using RT-PCR and in vivo labelling with BrdU.

ii. Determine the response of Scl/Lyl1-deficent mice to cell cycle-dependent cyctotoxics.
iii. Generate *in vitro* assays for deletion of Scl to assess early changes in gene expression.
iv. Use an *in vitro* promoter assay to determine if Scl and Lyl1 repress p21.
v. Perform ChIP assay using a 'stem cell' line to determine if Scl and Lyl1 can bind to the p21 promoter and if so characterise other protein partners.
vi. Perform knockdown experiments of p21 using lenti-viral RNAi and genetic approaches to determine if this can rescue the growth defects of Scl/Lyl1-null HSCs.

65. Analysis of a novel family of genes crucial for prevention human skin diseases

Supervisors: Dr Charbel Darido and Professor Stephen Jane
Location: Rotary Bone Marrow Research Laboratories, Royal Melbourne Hospital
Contact: Dr Charbel Darido T: 9342 8125 E : darido@wehi.edu.au
Professor Stephen Jane T: 9342 8641 E: jane@wehi.edu.au

Our research team discovered and studies a highly conserved family of mammalian genes, the Grainyhead family. Knockout studies in mice have shown that these genes play essential roles in a range of developmental events involving the skin, including wound repair, and barrier formation (Nature Medicine 9: 1513-1519, 2003; Science 308: 411-413, 2005). They may also be important in the context of skin cancer. Grainyhead genes encode transcription factors which act through target genes to mediate their effects. The project offered here will involve identification of Grhl target genes relevant to skin diseases. This is likely to have impact on the treatment of a range of human diseases including skin barrier defects wound healing and and cancer.

Skills - A wide range of skills will be taught including molecular biology, cell culture, knockout models, and bioinfomatics. This is an ideal project for a student who wishes to pursue higher studies in the future. Two positions are available.

66. Modulating apoptosis in myelodysplasia

Supervisors: Dr Chris Slape and Dr David Curtis
Location: Bone Marrow Research Laboratories, Royal Melbourne Hospital
Contacts: Dr Chris Slape T: 9342-8948 E: slape@wehi.edu.au
Dr David Curtis T: 9342-8444 E: dcurtis@wehi.edu.au

Project description: Myelodysplasia is the most common hematologic malignancy with limited effective therapies. The major clinical problems of MDS are low blood counts requiring blood transfusions and antibiotics for recurrent infections. Studies of human MDS suggest that aberrant cell death (apoptosis) is central to the cause of low blood counts. We have generated transgenic mouse models of human MDS that have low blood counts. The aims of this project are to determine the mechanism(s) of apoptosis in transgenic mice and translate these findings to cases of human MDS.

Techniques: This project uses genetically modified mouse strains, retroviral expression systems as well as human samples. Techniques learnt will include mouse handling/breeding/drug administration, tissue harvesting, cell culture, DNA and RNA isolation, gene expression analyses including quantitative RT-PCR and Western blotting, flow cytometry and cell sorting.

Significance: This work will form the pre-clinical data for subsequent human clinical trials in MDS.

67. Drug therapies targeting the cancer stem cell

Supervisors: Dr David Curtis and Dr Matthew McCormack
Location: Bone Marrow Research Laboratories, Royal Melbourne Hospital
Contacts: Dr David Curtis T: 9342-8444 E: dcurtis@wehi.edu.au
Dr Matthew McCormack T: 9342 8948 E: mccormack@wehi.edu.au

Project description: We have identified the cancer stem cell in a transgenic mouse model of acute lymphoblastic leukemia. The frequency of this abnormal stem cell can be measured using transplant assays. The aim of this project is to determine the effect of new therapuetic drugs on the cancer stem cell.

Techniques: T-cells from transgenic mice will be transplanted into wild-type mice, and then mice will be treated with various agents including the mTOR inhibtior Rapamycin, the HDAC inhibtior vorinostat and the differentiating agent arsenic trioxide. The effects of these drugs will be determined by flow cytometry and gene expression studies.

Signficiance: These studies will provide the rationale for testing of these drugs in human cases of acute lymphoblastic leukemia.

68. bHLH factors and Haemopoietic and Leukemic Stem Cell cycling

Supervisors: Dr David Curtis and Dr Matthew McCormack
Location: Bone Marrow Research Laboratories, Royal Melbourne Hospital
Contacts: Dr David Curtis T: 9342-8444 E: dcurtis@wehi.edu.au
Dr Matthew McCormack T: 9342 8948 E: mccormack@wehi.edu.au

Project descripiton: Haemopoietic stem cells (HSC) are primitive cells that maintain the blood system throughout life. To achieve this there must be tight control of HSC cycling such that most HSCs are in a "quiescent" or non-dividing state. Restriction of HSC cycling is achieved by factors that govern the entry of HSCs into the cell cycle. One such regulator is p21, also known as cyclin-dependent kinase inhibitor 1A (CDKN1A). p21 serves as a negative regulator of HSC cycling by regulating the activity of cyclin-dependent kinase proteins. However, the factors that regulate p21 activity are largely unknown. We have data suggesting that the bHLH factors, Scl and Lyl1 are important repressors of p21. HSCs in mice lacking both Scl and Lyl1 cannot grow and have p21 levels 10-fold higher than normal. We hypothesize that bHLH factors regulate the quiescence of HSCs by controlling the levels of p21. This project will study the cell cycle characteristics of HSCs lacking Scl and Lyl1. Furthermore, you will determine if reducing levels of p21 by either siRNA or using p21 knockout mice can rescue the growth defects seen in Scl/Lyl1-deficient HSCs.

Techniques: Cell cycle analyses including BrdU-labelling and Hoechst pyronin staining, siRNA and/or analysis of p21 knockout mice, DNA and gene expression techniques, cell culture, flow cytometry.

Significance: This work will provide a better understanding of regulators of stem cell growth. These findings may be important for improved uses of blood stem cells.

69. Targeting the inflammatory response of myocardial infarction to improve heart function

Supervisors: Dr David Curtis and Professor Alex Bobik
Location: Bone Marrow Research Laboratories, Royal Melbourne Hospital and Cell Biology Laboratory, Baker Heart Research Institute
Contacts: Dr David Curtis T: 9342-8444 E: dcurtis@wehi.edu.au

Project description: We have shown that mice lacking the G-CSF receptor have impaired heart function after myocardial infarction (MI) (Kanellakis et al. Circ. Res 2006). In contrast, mice lacking the GM-CSF receptor have improved heart function after MI. We postulate that these findings are due

to differences in macrophage subsets that accumulate within the infarct within the first 48 hours. This project will examine the effects of an inhibitor of GM-CSF on heart function in a mouse model of MI. **Techniques:** Analyses of myocaridal tissue using flow cytometry and gene expression methods. Assistnace with cardiac surgery including invasive cardiac catheter monitoring. Cell culture. Western blotting.

Significance: These studies will provide data essential for design of potential human trials using the inhibtior of GM-CSF.

CANCER

70. Glioma stem cells: biology and molecular targets

Supervisor: Dr Andrew Morokoff, Dr Kate Drummnod, Dr Giovanna D'Abaco
Location: Department of Surgery, Royal Melbourne Hospital
Contact: Dr Andrew Morokoff (morokoff@unimelb.edu.au) 9342 7703

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 know alterations of molecular signalling pathways and genetic mutations. This data will be collated and compard 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.

71. Circulating endothelial cells as a biomarker in brain tumours

Supervisor: Dr Andrew Morokoff, Dr Chris Hovens, Dr Kate Drummond
Location: Department of Surgery, Royal Melbourne Hospital
Contact: Dr Andrew Morokoff (morokoff@unimelb.edu.au) 9342 7703

There has been much interest recently in defining better markers of brain tumour behaviour and prognosis. At the present time, prognosis is based on histopathology grading scheme (WHO I-IV 2007) and the response of the tumour to treatment is followed on contrast-enhanced MRI. However, both of these methods have limitations, particularly in the context of post-treatment effects after both radiation therapy and especially novel chemotherapies that target angiogenesis. Endothelial cells that line tumour blood vessels apoptose and enter the blood stream, becoming detectable as Circulating Endothelial Cells (CECs) with a simple blood test. Levels of CECs have been shown to correlate with the activity of the tumour in prostate cancer, and therefore hold great promise for brain tumours, which are highly angiogenic. The project involves taking blood samples from brain tumour patients and testing for the levels of CECs by using FACS analysis. This identifies specific markers of endothelial cells such as CD31, CD45 and VEGFR2. By taking samples pre and post treatment time points, we hope to correlate the CEC level with the tumour burden and determine if this could provide more information as a clinically relevant biomarker in brain tumours.

72. Dynamin as an anti-tumour drug in gliomas

Supervisor: Dr Andrew Morokoff, Prof Terence O'Brien, Prof Phil Robinson
Location: Department of Surgery and Medicine, RMH. Department of Physiology, Children's Medical Research Institute, Sydney.
Contact: Dr Andrew Morokoff T: 9342 7703 E: (morokoff@unimelb.edu.au)
Prof Terence O'Brien E: (tjobrien@unimelb.edu.au)

Background: The group of Prof Phil Robinson at CMRI have developed dynamin inhibitors as promising treatments of epilepsy and possibly also gliomas. Gliomas are highly invasive and recurrent tumours that have a particularly poor prognosis, despite surgery, radiotherapy and chemotherapy. Novel effective treatments for glioma are desperately needed. A number of inhibitors of dynamin II (dyn-II) have been screened for anti-tumour activity against glioma cell lines and have shown positive effects.. This project aims to test these inhibitors in an in vivo animal model of gliomas. Glioma cells will be injected stereotactically into the amygdala of 8-12 week old nude mice and the animals asssessed or tumour growth and survival after treatment with or without study drug. The tumour growth will be assessed both by bioluminescence with live animal imaging (IVIS system) as well as be immuohistochemistry and volumetric brain slice analysis. The student will develop skills with animal handling, cell lines, in vivo imaging and data/statistical analysis.

73. TGF- signalling and cancer development

Supervisors: Dr. Hong-Jian Zhu (and Dr. Rodney Luwor, Bo Wang, Catherine Winbanks)
Location: Cancer Signalling Laboratory, Department of Surgery (RMH) (5th Floor, Clinical Sciences Building, The Royal Melbourne Hospital)
Contact Dr Hong-Jian Zhu T: 8344 3025 Email hongjian@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-□ (Transforming Growth Factor-□) 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-□ 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-□ 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.

74. Circulating endothelial cells as biomarkers for prostate cancer

Supervisor: Dr. Chris Hovens
Location: 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.

75. 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.

76. Src kinases, lung inflammation and lung cancer

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

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

Supervisors: Dr Michael Buchert, Dr Toby Phesse (Ludwig Institute)
Location: Ludwig Institute
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The canonical Wnt and the cytokine-activated Stat3 signalling pathways are key drivers for tumourigensis 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.

78. 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
Location: 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.

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

Supervisors: Dr Maree Faux, Professor Tony Burges, Ludwig Institute for Cancer Research
Location: 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 □-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.

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

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

81. Using a new mouse model to understand colitis

Supervisors: Dr Tracy Putoczki, A/Professor Matthias Ernst, Ludwig Institute for Cancer Research
Location: 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 statement of the art equipment.

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

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

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

83. The role of PTEN and Stat3 signaling in cancer

Supervisors: Dr Michael Buchert, Dr Toby Phesse (Ludwig Institute)
Location: Ludwig Institute
Contact: 03 9341 3155
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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.

84. 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)
Location: 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.

85. Regulation of Stat3 – mediated Tumor Progression

Supervisors: Dr Rodney Luwor
Location: Department of Surgery, Royal Melbourne Hospital
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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.

CARDIOLOGY

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

Supervisors: A/Professor Xiao-Jun Du, Dr Qi Xu, Dr Peter Kistler
Location: 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 know 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 agiogenic 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

87. Bioinformatics in colorectal cancer genetics and prevention

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics
Location: 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 furthers enhances our capacity to explore this dataset, including through after merging with a similar dataset housed at Flinders University. Another project in cooperation with the CSIRO searching for new genes that modify the mismatch repair genes reponsible, when mutated, for hereditary non pllyposis colorectal cancer (Lynch Syndrome). 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.

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?

88. 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
Location: Dept of Colorectal Medcine 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 efforts to position itself as a lead locus for the HVP

89. Dietary modulation of cancer related gene expression

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

Colon cancer is the most common internal malignancy in developed countries and its incidence in Australia is increasing. Our current studies are evaluating the cancer prevention potential of resveratrol, a phenolic compound in red wine. Participants at increased risk of bowel cancer are being randomized to a 6 week treatment with resvertarol versus placebo, with the outcome measures being the expression of cancer related genes in the lining of the bowel.

Changes in proliferation must be interpreted in context with changes in apoptosis as it is a decrease in cell death relative to proliferation that may increase the risk of DNA damage and decrease the probability of repair. Genes regulating apoptosis, either pro-apoptotic or anti-apoptotic, include bcl-2, bax and bak. Activation or suppression of these genes has been shown to be important in controlling neoplastic processes. Other key genes potentially modulated by diet along the pathway to cancer include: APC (a tumour suppressor gene); p21 (a differentiation marker); MSH2 and MLH1 (mismatch repair genes); COX-2 (inflammation and growth) and hTERT (telomerase).

Methodology has been established through our collaborators in South Carolina, who developed the techniques under a grant from the US National Cancer Institute. Rectal biopsies from our trial have been sectioned and stained with Mib-1 (for Ki-67), bcl-2, bax, and p21. Mib-1 sections have been counted and results analysed. These biomarkers are currently being analysed using an Image Analysis System with a dedicated 'Hemicrypt' macro program. Enough biopsy samples from the study remain for examination of the other biomarkers including: APC, COX-2, p21, MSH2, MSH1, bak and hTERT. These additional biomarkers tissue will be sectioned and stained before counting using the 'Hemicrypt' program.

The project will provide an unparalleled opportunity to study the expression of these cancer related genes in response to dietary intervention.

The project will provide an unparalleled opportunity to study the expression of these cancer related genes in response to dietary intervention.

90. Confocal endomicroscopy

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics
Location: 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 accutracy dcompared with random biopsy protocols

Progress: Unlimited places available, Funding: Optiscan - covers endoscopy costs and confocal
Ethics: Approved Cabrini Health

91. Biogrid and IBD data basing

Supervisor: Professor Finlay Macrae, Head, Colorectal Medicine and Genetics
Location: 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. Henry Gasko, for the Australian BioGrid, is assisting with this. http://www.biogrid.org.au

92. Functional Foods in colorectal cancer prevention

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

Evolving project. Please let me know if any interest.

93. Dietary prevention of adenomas in familial adenomatous polyposis

Supervisor: Professor Finlay Macrae, Head, Dr Suresh Sivanesan
Location: 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

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

Supervisor: Dr Lance Macaulay
Location: 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.

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

Supervisor: Dr Lance Macaulay
Location: 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

96. ABCC6 and the pathogenesis of aneurysms

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

ENDOCRINOLOGY, DIABETES & OSTEOPOROSIS

97. The relationship between abdominal aortic calcification and its progression and bone loss in middle aged and older men.

Supervisors: A/Prof Robin Daly and Prof Peter Ebeling
Location: Department of Medicine Western Hospital.
Contact: A/Prof Robin Daly T: 8345 6924 E: rdaly@unimelb.edu.au

Atherosclerosis and osteoporosis are two multi-factorial and degenerative diseases that often coexist in many older adults. While there is evidence for a shared pathogenesis between osteoporosis and atherosclerosis, few studies have been conducted in older men. The aim of this research study is to investigate the relationship between computed tomography and DXA measures of abdominal aortic calcification and its progressive on bone density and strength (and the associated age-related changes) in middle aged and older men. A secondary aim is to investigate the key determinants of the progressive of calcification and bone loss, including the influence of cardiovascular risk factors (cholesterol and lipids), body composition, diet, exercise and inflammation.

This project will use existing data from an 18-month exercise and calcium-vitamin D randomized controlled trial in 180 men aged 50 to 79 years. In this project the student will be required to assess abdominal aortic calcification from computed tomography and DXA scans. This project will also offer students a unique opportunity to develop skills in handling and analyzing longitudinal data.

98. 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
Location: 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

99. How do Anti-Epileptic Drugs Work?

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

Despite many years of use and research, it is still not clear how even some of the oldest forms of anti-epileptic drugs work. That which is known is generally based on the effects of these compounds on single neurons, rather than examining how activity of the whole inter-connected neural network of the

mammalian CNS is modulated. This project involves studying the effects of AED's at several levels of organization of the CNS – single channel (voltage-gated sodium, potassium and calcium channels), single neuron, principal neuron/interneuron dynamics, as well as glial cell effects. Patch clamp techniques are used for recording dissociated neuron and neurons in the intact brain slice, and these observations will be extended with high-speed calcium imaging with conventional microscopy as well as multiphoton techniques. This projects affords excellent opportunities for skill development in electrophysiology, pharmacology, advanced microscopy and computational neuroscience.

100. How do Antipsychotic Drugs Trigger Seizures?

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

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.
This project will be a great introduction to basic in vitro synaptic electrophysiology, whole-cell patch clamping and basic pharmacological manipulations to assess dopaminergic activity.

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

Supervisor: Dr Chris French
Location: 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.

102. Multi-Electrode Recording in the Rat Brain

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Although immense advances have occurred in recording electrical signals from the CNS, these observations tend to be of single cells in a matrix of many millions of neurons and hence give very limited information about how the whole highly interconnected network functions. One solution to this problem is to use banks of tetrodes, bundles of four 10-20 micron diameter electrodes to record many cells simultaneously, either from a single region or from different parts of the brain. Up to 32 electrodes can be implanted with our system, and sophisticated spike detection and analysis algorithms

are available to organize the complex multiple signals recorded. This recording technique can also be easily adapted to exploring epileptiform discharges in models of both focal and generalised epilepsy (including drug effects), which will the main aim of this project. This project provides opportunity to learn cutting-edge electrophysiological and computing analysis techniques for assessment of function of the mammalian nervous system.

103. ADAM22 and LGI1: role in epilepsy and synapse development

Supervisor: Dr Giovanna D'Abaco, Dr Andrew Morokoff
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Background: ADAM22 and its ligand LGI1, have been described to play diverse roles in the brain. For instance, ADAM22 knockout mice die early from seizures and ataxia and LGI1 mutations have been found in human subjects with temporal love epilepsy. LGI1 binding to ADAM22 takes place at the synaptic membrane and leads to hyper-excitability mediated by glutamate receptors. Both proteins are expressed highly during development of the hippocampus and cerebellum, however little is known about their exact role. This project aims to explore the effects of ADAM22 and LGI1 on brain an synaptic development using a number of approaches. ADAM22 -/- mice and +/- mice will be compared in panel of behavioural testing as well as histopathological brain assessment. The effect on seizures will be assessed by placing electrodes in the brain of the mice and EEG monitoring for up to 8 weeks. Furthermore, in vitro testing, eg using neuronal and synaptic differentiation assays, as well as stem cell differentiation assays will be performed in the laboratory.

104. 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 epilespy?

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Voltage-gated calcium (Ca^{2+}) channels are believed to play a critical role the generation of the hypersynchronous oscillatory thalamocortical activity that underlies absence seizures. Mutations in the $Ca_v3.2$ T-type Ca^{2+} 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, $Ca_v3.2$ mRNA expression and T-type Ca^{2+} currents[3] are elevated in the reticular nucleus of the thalamus (nRT), and we have shown similar elevations in the cortex. An increasing body of evidence, including from our laboratory, indicates that the seizures in GAERS originate focally in the somatosensory cortex. It is also known that the thalamus plays a critical role in allowing the seizures to occur, the basis of which is pathological oscillatory thalamocortical activity.

Together this data implicates the $Ca_v3.2$ channel in the pathogenesis of this disease although whether functional abnormalities in the channel play a causative role in absence epilepsy is unknown. Linking an absence phenotype to a mutation in this channel would provide a priori case for a causative role. To this end we have identified that GAERS carry a homozygous single nucleotide missense mutation in a highly conserved region the III-IV linker domain of the $Ca_v3.2$ T-Type Ca^{2+} gene (R1584P).

Importantly, with our Canadian collaborators, we have shown that this mutation is dependent upon exonic splicing for its functional consequences to be expressed in-vitro (i.e. its requires the presence of exon 25 [$Ca_v3.2$ (+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 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.

105. Neuropsychiatric, Neurocognitive, Quality Of Life and Bone Health Outcomes In Patients With Epilepsy Treated With Levetiracetam (Keppra) Verses Older AEDs As Substitution Monotherapy. (KONQUEST)

Supervisors: Dr Raju Yerra, Dr Marian Todaro, Prof Terence O'Brien
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This is an investigator initiated study that aims to compare neurocognitive, neuropsychiatric, Quality of Life (QOL) and bone health outcomes in a cohort of patients with focal epilepsy treated with Levetiracetam (LEV) as the substitution Anti Epileptic Drug (AED) monotherapy, with those in whom carbamazepine (CBZ) or sodium valproate (VPA) are started as first substitution drug. Seizure control and adverse drug effects will be compared as secondary outcome variables. This patient population was chosen as it represents a clinically important common group of patients who have not been adequately studied. Previous studies of LEV and other "new" AEDs have been performed in either medically refractory patients (who have taken multiple AEDs) or newly treated patients. If positive the results of this study will provide evidence for wider use of the new drugs as monotherapy, especially in early stages of epilepsy, and help improve the health outcomes of patients with epilepsy. With the bone health and body composition study we aim to study changes in bone health and body composition with anti epileptic drug therapy. There is increasing concern about the long-term increased risk for fracture and bone disease in patients taking long-term anti-epileptic drugs, and this study aims to determine if the newer drug (LEV) may have an advantage in this regard over the older drugs.

The study population is over 100 patients with epilepsy recruited from the Epilepsy, Neurology and First Seizure outpatient clinics of the Royal Melbourne Hospital who have failed treatment with first AED either, due to lack of efficacy or side effects. The subjects were randomised to treatment with LEV or with CBZ or VPA. If the initial AED was CBZ or PHT the subject will be randomised to LEV or VPA, and conversely if the initial AED was VPA the subject will be randomised to LEV or CBZ. Subjects are then followed for 12 months with assessment of their epilepsy, drug side-effects, mood, quality of life, cognition and bone health.

106. Evaluation of Dynamin Inhibitors as Novel Therapies for Epilepsy

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

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

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

107. Investigating the role of Stargazin and AMPA receptors in contributing to the epileptic phenotype of GAERS.

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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 is still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and how they interact to result in epilepsy remains to be determined**.** GAERS rats are a strain of rats which spontaneously develop generalized absence seizures.

AMPA receptors are ionotropic transmembrane receptors for the excitatory neurotransmitter, glutamate that mediates fast synaptic transmission in the central nervous system. Stargazin, a member of a new family of proteins called Transmembrane AMPA Receptor regulatory Proteins (TARPs), 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. Indeed research from our laboratory using a genetic animal model has linked an increase in stargazin expression in the brain to absence epilepsy. Associated with an increase in stargazin expression is an increase in AMPA receptor expression only at the plasma membrane. This would be expected to enhance neuronal excitability and therefore be potentially pro-epileptic.

The specific aims of this project are

- To correlate thalamocortical expression of stargazin with seizure expression.
- To examine for differences in expression (membrane vs. cytosol) of AMPA receptor subunits in juvenile pre-epileptic and adult epileptic GAERS and for association with stargazin expression.
- To determine if stargazin associates with a specific AMPA receptor subunit and if there is a developmental switch in this preference associated with the onset of absence seizures.
- To determine if there is a genetic cause for the increase in stargazin expression.

Skills

The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), EEG recordings and analysis, biochemical and molecular analysis (real time PCR, western blotting, multiplex ligation-dependent probe amplification analysis).

108. 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

Location: 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 neurobehvioural 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.

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

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- 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 intracerberbal 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 an 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.

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

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

111. Antiepileptic drugs and effects on bone health

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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.

112. Neurodegenerative diseases: Investigation of neuronal circuit activity using fluorescence imaging combined with electrophysiology

Supervisor: Dr Damian Myers, Dr Gareth Moorhead, Dr Chris French and Dr Chris Ryan, Department of Medicine (RMH/WH), University of Melbourne, The Royal Melbourne Hospital, CSIRO Materials Science and Engineering.

Location: Department of Medicine (RMH/WH), Royal Melbourne Hospital and the CSIRO Materials Science and Engineering Division in Clayton

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Neurodegenerative disorders such as Alzheimer's disease, stroke, brain tumors, epilepsy and traumatic brain injury have long-lasting impacts on patients and their families. Dysregulation of neuronal networks caused by such disease processes underlies the neurocognitive, neurobehavioural and neuropsychiatric changes that occur and typically involves altered neuronal circuit activity in the hippocampus and/or the thalamocortical circuits. The capacity of neuronal circuits to change and the subsequent altered function of neurons is termed neuronal plasticity. In the laboratory, this can be assessed using fluorescence-based microscopy combined with electrophysiology.

The aim of this project is to design and implement an electrode array for investigation of the perforant pathway in the hippocampus. This novel approach to study neuronal changes will be used in future studies to define hippocampal neuronal network activity in normal and disease states. A key component of this project will be validation of the electrode array measures using a traditional field recording approach. Electrophysiological recordings and neuronal activity will be combined to assess temporal changes in electrophysiological output with cell activity based on calcium ion transients measured using calcium ion-sensitive fluorescent probes.

Techniques to be used in this project include in vitro slicing of brain for the study of neuronal circuit activity and monitoring of neuronal activity using Ca^{2+}-sensitive fluorescent probes with fast sensitive CCD cameras. An electrode array will be developed with validation and preliminary experiments performed using field recordings as described previously.

This project will be conducted through the Department of Medicine at the Royal Melbourne Hospital and the CSIRO Materials Science and Engineering Division in Clayton.

113. 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
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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 valpraote administration in rats results in upregulation of expression of neuropeptide Y (NPY) in brain regions critical to the generation of generalisied 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.

114. Sodium Channels in Epilepsy

Supervisors: Dr Chris French, Prof Terence O'Brien
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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.

115. The role of Grainyhead-like genes in neural tube deficits induced by valproate

Supervisors: Professor Stephen Jane, Bone Marrow Research Laboratories; Professor Terence O'Brien, Epilepsy and Neuropharmacology Group; Professor Frank Vajda, Epilepsy and Neuropharmacology Group
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Valproate is one of the most common medications prescribed for patients with epilepsy, and is the drug of choice for primary generalised epilepsy. Additionally it is commonly prescribed for a number of non-epileptic conditions, such as bipolar disorder and chronic pain. Women chronically taking valproate for these conditions not uncommonly become pregnant despite the fact that it is established to increase the risk of major birth defects, including neural tube defects (NTD). The risk of NTD in a foetus exposed to valproate during the first trimester is greater than that for other anti-epileptic drugs. However, the mechanism by which valproate causes NTD is currently unknown. Research in the BMRL has demonstrated that a highly conserved family of mammalian genes, the Grainyhead family, play essential roles in a range of developmental events including neural tube closure (Nature Medicine 9: 1513-1519, 2003; Science 308: 411-413, 2005). The Grainyhead genes encode transcription factors which act through target genes to mediate their effects. This project aims to determine if these genes play a role in valproate induced neural tube deficit. If successful this model can be used to address a number of clinically important questions, including to design and test interventions (e.g. folate supplementation) or valproate-analogues which may reduce the occurrence of this serious drug-induced teratogenicity. The study methodology will involve feeding breeding pairs of transgenic or control mice expressing different levels grainyhead-like proteins to one of two different treatments: (i) 4g/kg of chow feed – a dose established to produce clinical relevant blood levels in mice – prior to and during pregnancy; (ii) normal chow feed. Two groups of control wild type mice will be feed each of the diets respectively. The litters will be examined for the incidence and nature of neural tube defects in the pups.

116. Epigenetic regulation of gene expression in epilepsy

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Background: Epigenetics describes the way chromatin/DNA structure can influence the 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. Epigenetic alterations are a strong candidate 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 two genes.

Research project 1: 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 2: 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 (Methylation Specific PCR, Bisulfite Specific PCR etc).

117. Imaging neurogenesis using Magnetic Resonance Spectroscopy

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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.

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

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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.

119. Neuronal networks – wired differently in epilepsy?

Supervisors: Dr Verena Wimmer and Dr Steven Petrou
Location: Howard florey Institute, Royal Parade, The University of Melbourne
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GABA receptors play an important role in mediating inhibitory transmission in the brain. One less well know aspect of GABA receptor signalling is their function in the migration of "young" neurons during embryonic development, when GABA receptors guide the neurons to their appropriate position and allow them to make the correct connections with other cells. Our group has generated a mouse model of human epilepsy which is characterized by a mutation in the GABA receptor subunit gamma2. Our mice show the same epilepsy phenotype human patients have, absence seizures. This project aims at revealing changes in the "wiring" of neuronal networks in the epileptic mouse brain due to GABA receptor dysfunction in development. We will use state-of-the-art laser scanning imaging to visualize synaptic connections and find out how the epilepsy mutation has changed their number, type and specificity. These data will be important for our understanding of how genetic mutations affect different aspects of brain function.

120. Investigating the therapeutic potential of $Ca_v3.2$ Ca^{2+} channel blocking drugs in suppressing absence seizures in a polygenic rat model of idiopathic generalized epilepsy

Supervisors: Dr Kim Powell, Professor Terence O'Brien
Location: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne
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Project Overview

Absence seizures are one of the most common seizure types in humans with idiopathic generalised epilepsies (IGE). 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. 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 Ca^{2+} gene (R1584P, *gcm*) which correlates with seizure expression in GAERS double-crossed with NEC rats (F2 generation).

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 $Ca_v3.2$ 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. Recently it has been shown that a genetic polymorphism in the sodium channel, SCN1A, has an effect on the proportion of two splice variants as well as an effect on anti-epileptic drug dosing.

Therefore the specific aims of this project are:

- To investigate whether the *gcm* affects the seizure suppression ability of selective $Ca_v3.2$ 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 *gcm* genotype.

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.

121. Investigating genetic determinants of absence epilepsy in a polygenic rat model of idiopathic generalized epilepsy

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Location: Department of Medicine (RMH/WH), Clinical Sciences Building, Royal Melbourne Hospital, University of Melbourne
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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 is still unknown. These epilepsies are presumed to be polygenic, with more than one genetic variation contributing to the phenotype, but the nature of these variations and how they interact to result in epilepsy remains to be determined**.** GAERS rats are a strain of rats which spontaneously develop generalized absence seizures.

Recent evidence implicates the $Ca_v3.2$ T-type Ca^{2+} channel in the pathogenesis of genetic absence epilepsy, although whether functional abnormalities in this channel play a causative role is unknown. We have previously reported that GAERS (a genetic rat model of absence epilepsy) carry a homozygous single nucleotide missense mutation in the highly conserved III-IV linker region of the $Ca_v3.2$ T-type Ca^{2+} gene (R1584P, *gcm*) which correlates with seizure expression in GAERS double-crossed with NEC rats (F2 generation). Our collaborative group have also identified two $Ca_v3.2$ splice variants in rat thalamus (± exon 25) located only 13 residues downstream from the *gcm* site and demonstrated that channels containing the +exon 25 splice variant and the *gcm* 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 compare mRNA expression of $Ca_v3.2$ total and splice variants in somatosensory cortex and thalamus of F2 animals at different time points during development and correlate to the number of copies of the *gcm* and seizure expression.
- To investigate the topographical expression of $Ca_v3.2$ mRNA expression (total and splice variants) in GAERS and NEC rats and F2 animals.
- To investigate the cellular expression of $Ca_v3.2$ splice variant expression in thalamocortical brain regions of NEC and GAERS, and relationship to the *gcm* genotype.

Skills

The skills expected to be learnt from this project include: Small animal handling and neurosurgery (electrode implantations), EEG recordings and analysis, biochemical and molecular analysis (real time PCR, in situ hybridization, immunohistochemistry).

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

Supervisors: Dr Chris Reid & Dr Steve Petrou
Location: 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.

123. Stopping Epilepsy before it starts

Supervisors: Dr Chris Reid & Dr Steve Petrou
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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.

124. Effects of epilepsy mutations on brain oscillations involved in learning and memory

Supervisors: Dr Verena Wimmer and Dr Steven Petrou
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Many genetic epilepsy syndromes are associated with deficits in learning and memory. To date, it is still unclear whether these deficits are a secondary effect of ongoing seizure activity or a primary consequence of the genetic mutation. We will study this question using a mouse model of human epilepsy, the so-called R43Q mouse. Patients with an R43Q mutation in the gamma2 subunit of the GABA receptor present with absence seizures which are replicated in the knock-in mouse, making it an excellent model of the human disease. GABA receptors are known to mediate inhibitory neurotransmission and they are also involved in synchronization of neurons that underlies brain waves, in particular the gamma and theta waves. These brain oscillations have been shown to be important for learning and memory. Our hypothesis is that the R43Q mutation causes epileptic seizures but independently affects gamma and theta wave generation. We will test this hypothesis using local field potential and tetrode recordings in vivo in combination with behavioral tests. These experiments will shed light on divergent effects of genetic epilepsy mutations on cognitive function

IMAGING

125. Molecular Neuroimaging

Supervisors: Drs. Moffat, Steward and Lovell
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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.

126. Orbitofrontal cortex sulcogyral patterns in early psychosis

Supervisors: Dr Cali Bartholomeusz, A/Professor Stephen Wood
Location: Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Level 2-3 Alan Gilbert Building, 161 Barry Street, North Carlton.
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This project aims to classify brain-folding patterns of the orbitofrontal cortex, in young people with a psychotic illness. Findings from this project will have implications for identification of a possible vulnerability marker for psychosis.

For individuals who develop a psychotic disorder like schizophrenia, the first episode is typically around age 20, yet pre-psychotic symptoms often emerge earlier during adolescence, a time of increased vulnerability to many psychiatric disorders. The exact reason for this is unknown, but may be related to abnormal maturation of the brain during adolescence. It is now known that the adolescent brain undergoes substantial changes in white and grey-matter volume as part of the normal neurodevelopmental process.

The orbitofrontal cortex (OFC) is an important brain region typically associated with processes such as social cognition, moral judgement/decision-making and emotional experience/regulation. The pattern of the gyri and sulci of the OFC has been found to be abnormal in adults with schizophrenia. The proposed project would extend this research by investigating young people (aged 15-25) who are in the early stages of the illness.

We have already collected structural brain imaging data, therefore the student must be interested in learning the novel OFC classification technique and analysis of Magnetic Resonance Imaging (MRI) data.

INFECTIOUS DISEASES AND IMMIGRANT HEALTH

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

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

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

Supervisors: Dr. Karin Leder/A/Prof Beverly Biggs
Location: Department of Medicine (RMH/WH), Royal Melbourne Hospital
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Web 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.

129. Prevalence of anxiety and depression among refugee patients at a tertiary referral clinic

Supervisor: Dr Chris Lemoh, Dr Caroline Marshall, Dr Karin Leder, Prof Fiona Judd; A/Professor Beverly-Ann Biggs,
Location: The Department of Medicine (RMH/WH), The Royal Melbourne Hospital ; Centre for Women's Mental Health, Royal Women's Hospital
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A/Professor Beverly Biggs T: 8344 3256 E: babiggs@unimelb.edu.au

Background: Many patients referred to the refugee health clinic have had previous traumatic experiences and face ongoing psychosocial stresses during resettlement in Australia. Undiagnosed mental illness may have a significant impact on quality of life and success of resettlement, but the proportion of patients with undiagnosed depression or anxiety disorders is not known.

Aim: To estimate the proportion of patients referred to the refugee clinic that have symptoms that fit diagnostic criteria for depression and anxiety disorders, but have not been formally diagnosed with or treated for such conditions.

Methods: The anxiety and depression modules from the Patient Health questionnaire (PHQ9; to assess depressive disorder, generalised anxiety disorder and panic disorder) will be administered to patients of the refugee health clinic who have migrated to Australia as refugees and have not previously been diagnosed with or managed for either depression or an anxiety disorder since their arrival in Australia. The proportion of patients with responses that met criteria for DSM-1V disorders will be measured. In addition, the Posttraumatic Stress Disorder Checklist- Civilian Version (PCL-C) will be used to screen for symptoms indicative of PTSD

Outcome: This study will provide an estimate of the proportion of patients referred to the refugee clinic that may benefit from formal psychiatric assessment but have not previously been identified. It will provide information that can be used to plan the provision of coordinated mental and physical health care for refugees by hospital-based and primary care services.

130. Concepts of mental health and illness among refugee patients at a tertiary referral clinic

Supervisor: Dr Chris Lemoh, Dr Caroline Marshall, Dr Karin Leder, Prof Fiona Judd, A/Professor Beverly-Ann Biggs,
Location: The Department of Medicine (RMH/WH), The Royal Melbourne Hospital, The Centre for Womens Mental Health, Royal Womens Hospital
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Background: Many patients referred to the refugee health clinic have had previous traumatic experiences and face ongoing psychosocial stresses during resettlement in Australia. Undiagnosed mental illness may have a significant impact on quality of life and success of resettlement, but the subjective experience and verbal descriptions of the symptoms of mood and anxiety disorders may be influenced by cultural background and linguistic medium of communication. Standardised screening tools used to detect depression and anxiety disorders may over- or underestimate the prevalence of these conditions in refugees from non-English speaking backgrounds. Refugees from underdeveloped countries may also have poor physical health due to lack of access to health care, poor living conditions and exposure to infectious diseases. It may be difficult to distinguish between conditions that require physical or pharmaceutical intervention, from those that require psychological intervention.

Aim: To explore concepts of health and illness among refugees from Africa and South East Asia attending a refugee health clinic, focusing particularly on the subjective distinction between symptoms of illness attributed to physical causes and those attributed to psychosocial causes.

Methods: In depth, semi-structured interviews with patients born in Africa or South East Asia who arrived as refugees and are attending the refugee health clinic. Interviews will be recorded, transcribed and analysed thematically to identify key themes concerning concepts of health and illness, and the physical and psychosocial causes to which symptoms of illness are attributed.

Outcome: Improved understanding by clinicians of concepts of health and illness among patients attending the refugee health clinic, which will provide a basis for better identification and interpretation of symptoms elicited during clinical consultation, with more appropriate investigation and management of physical and psychological symptoms.

131. 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
Location: The Department of Medicine (RMH/WH), The Royal Melbourne Hospital
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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.

132. 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
Location: The Department of Medicine (RMH/WH), The Royal Melbourne Hospital
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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.

133. Mannose-binding lectin's contribution to ocular defences against infection

Supervisors: Associate Professors Damon Eisen and Mark Daniell, Victorian Infectious Diseases Service and Department of Ophthalmology, Royal Melbourne Hospital.
Location: Victorian Infectious Diseases Service, RMH.
Contact: A/Professor Damon Eisen T :9342 8818 E: damon.eisen@mh.org.au

Mannose-binding lectin (MBL) is a pattern recognition receptor of the innate immune system that contributes to killing of a broad range of micro-organisms. Deficiency of this serum protein is common and predisposes to numerous infectious diseases. MBL is present in small concentrations in the lungs, joints and, as shown by our group, eyes if they are inflamed and probably contributes to local defences against pathogens. A recent study of fungal keratitis in murine corneas has shown that MBL is one of a handful of inflammatory pathway genes that are upregulated. Furthermore, MBL was shown to be produced locally in murine corneas which is a particularly notable finding. These data suggest that MBL is important in the local response to corneal infection. The contribution of MBL to prevention of endophthalmitis is undefined.

This honours project will explore human correlates of the murine keratitis study. Human corneal cells from cell cultures will be infected with Pseudomonas aeruginosa, a common cause of keratitis, and MBL mRNA will be measured by RT-PCR. Immunohistochemical staining of corneal rims will also be undertaken to establish whether MBL is produced locally in human corneal cells. To investigate the link between endophthalmitis and MBL deficiency both a case control study of endophthalmitis and analysis of an animal model may be undertaken.
Note: this project is also listed under Ophthalmology

134. Could aspirin improve outcomes in severe staphylococcal infections

Supervisors: Associate Professor Damon Eisen and Dr Anna Walduck, Victorian Infectious Diseases Service, Royal Melbourne Hospital and Department of Microbiology and Immunology, University of Melbourne.
Location: Victorian Infectious Diseases Service, RMH.
Contact: A/Professor Damon Eisen T :9342 8818 E: damon.eisen@mh.org.au

Aspirin is one of the most widely used medicines and it may have a novel effect in reducing the severity of infections, particularly due to Staphylococcus aureus. This gram-positive bacteria is a

common cause of severe disease in both community and nosocomial settings. Aspirin has already been shown to have benefits in-vivo and in animal models of S. aureus infective endocarditis. Here, aspirin is able to inhibit S. aureus virulence determinants such as fibronectin binding protein and alpha-toxin. Aspirin reduces the size of vegetations and the frequency of embolic events in animals with experimental S. aureus endocarditis. A recent development in staphylococcal infections is the role played by non-multiresistant MRSA or caMRSA that causes severe skin disease and necrotising pneumonias particularly in patients from the community.

This honours project will investigate other pathogenic determinants in the S. aureus agr operon particularly *lukS/F* and *spa* that encode Panton-Valentine leukocidin and protein a respectively. These are both thought to be critical to the development of severe caMRSA disease. Type strains and clinical isolates of caMRSA will be investigated to see whether aspirin is able to inhibit PVL and spa in-vitro. Animal models of necrotising pneumonia will also be investigated to see whether aspirin can improve outcomes in this devastating disease through inhibition of the virulence determinants mentioned.

135. 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
Location: Centre for Population Health, Burnet Institute
Contact: Dr Mark Stoove E: stoove@burnet.edu.au

The Burnet Institute manages the Victorian Primary Care Network for Sentinel Surveillance on BBVs and STIs on behalf the Department of Human Services. The surveillance system collects demographic and risk behaviour data from patients attending clinical sites that see high caseloads of key at 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 cohort analyses, to answer key questions relating to HIV and other STI risk and prevention. Such questions include, but not limited to, an assessment of the accuracy of self-reported HIV testing histories and an examination of socio-demographic correlates of risk behaviour and HIV and other STI transmission.

136. Patterns of drug dependence treatment and other health service utilization among post release prisoners with a history of injecting drug use

Supervisor: Dr Mark Stoove, Head HIV/STI Research Group Centre for Population Health, Burnet Institute
Location: Centre for Population Health, Burnet Institute
Contact: Dr Mark Stoove E: stoove@burnet.edu.au

Recruitment and prospective data collection from a cohort of post-release prisoners with a history of injecting drug use is currently being undertaken at the Burnet Institute. This project will involve the targeted analysis of this prospective data to examine factors related to entry and maintenance in post-release drug treatment programs in the first six months post-prison release. This data will be augmented by qualitative interviews with key informant service providers to examine personal, social and structural factors that facilitate or impede successful drug dependence treatment outcomes in this population.

137. 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
Location: Centre for Population Health, Burnet Institute
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The Burnet Institute is conducting project 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". In collaboration with the University of Melbourne and the Victorian College of the Arts, background preparation and planning for this project is being conducted in 2009 with the project "going live" during 2010. 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.

138. HIV infection in the heterosexual community – understanding the changing epidemic in Victoria

Supervisor: Dr Mark Stoove, Head HIV/STI Research Group Centre for Population Health, Burnet Institute and Dr Isabel Bergeri, Surveillance manager, Centre for Population Health, Burnet Institute
Location: Centre for Population Health, Burnet Institute
Contact: Dr Mark Stoove E: stoove@burnet.edu.au

The Burnet Institute manages a variety of HIV surveillance systems on behalf the Department of Human Services, including HIV Passive Surveillance (all notifications data) and a Sentinel Surveillance Network of Primary Care Providers (clinics that see a high caseload of at-risk populations). Recent surveillance data suggests that Victoria is witnessing a diversification of HIV epidemiology, including higher rates of notifications among heterosexual populations. An opportunity exists to work with an expert and experienced team of public health epidemiologists to examine in detail the changing patterns of heterosexual transmissions of HIV in Victoria. The project will work with existing HIV surveillance data at Burnet and elsewhere and collect new data to examine potential correlates of increasing heterosexual notifications to guide public health interventions and inform policy responses.

139. Coming of age: A study of opiate use after 50

Supervisor: Dr Peter Higgs, Centre for Population Health, Burnet Institute
Location: Centre for Population Health, Burnet Institute
Contact: Dr Peter Higgs E: peterh@burnet.edu.au/ phiggs@nchecr.unsw.edu.au

Data on both illicit opiates like heroin and licit opiates such as methadone among those aged over 50 years are scarce. The data collected on people accessing needle and syringe programs in Melbourne shows that for the period 2006-2007 those aged over 46 years made up between 5-8% of the total contacts.
This pilot study will utilise a number of research methods. These include the running of focus groups, structured surveys and in-depth interviews.

All participants will be aged over 50 years. 75 participants (half in a formal methadone program and half who are using illicit opiates only) will be recruited to the structured quantitative survey. We will

conduct about 20 in-depth qualitative interviews with participants with the aim of recruiting half from each group (licit and illicit opiates).

In Australia there has yet to be any in-depth study of the effects of methadone in maintenance doses on people who have been using it for many years. The advent of a more maintenance style pharmacotherapy program in Australia during the mid 1980s means that there are likely to be people who have been enrolled in methadone for over 20 years now.

The pilot data collected in this study will inform the development of a more in-depth study with possible funding sourced from the National Health and Medical Research Council. We also envisage that there will be peer review manuscripts developed based on the data and submitted for publication in suitable scientific journals.

Abstracts will also be developed for local and international conferences.

140. The PADIE II project: drug use, health and risky behaviour in the emergency department

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 Patterns of Alcohol and Drug Use in Emergency (PADIE II) study involved face-to-face interviews with patients who presented to the Gold Coast (QLD) hospital emergency department over a 2 weeks period, 24 hours a day, 7 days a week. In total, around 1,200 patients completed an interview exploring a range of health issues including the nature of their presentation, their alcohol and other drug use history, sexual risk behaviour, mental health and general health. This project will involve analysis of this large dataset and publication of a paper, with a focus on the links between substance use, mental health and sexual risk behaviour.

141. 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.

142. 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
Location: Centre for Population Health, Burnet Institute
Contact: A/Prof Paul Dietze. T: 03 9282 2134 E: pauld@burnet.edu.au

The aim of this project will be to investigate patterns of injecting drug use and characteristics of drug markets in a site in regional Victoria. The Illicit Drug Reporting System (IDRS), established in Melbourne in 1997 has added considerably to our understanding of patterns of injecting drug use and

harm along with the characteristics of illicit drug markets in Melbourne. However, in general the IDRS is limited to a consideration of these drug-related issues in metropolitan Melbourne. Indeed, there is little known about drug consumption in Victoria outside of metropolitan Melbourne other than in relation to tobacco and alcohol. The absence of such data presents a significant impediment to the formation of effective policy responses. The implementation of the IDRS methodology in a regional setting will provide useful information on trends in drug use in non-metropolitan Victoria.

143. 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
Location: Centre for Population Health, Burnet Institute
Contact: A/Prof Paul Dietze. T: 03 9282 2134 E: pauld@burnet.edu.au
Professor Robin Room. E: rroom@unimelb.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.

144. The experience of violence among injecting drug users

Supervisor: A/Professor Paul Dietze, Head, Alcohol and Drugs Research Group, Centre for Population Health, Burnet Institute and Ms Lucy Frankin, Alcohol and Drugs Research Group, Centre for Population Health, Burnet Institute
Location: Centre for Population Health, Burnet Institute
Contact: A/Prof Paul Dietze. T: 03 9282 2134 E: pauld@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.

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.

145. Malaria parasite adhesion to the human placenta

Supervisor: Dr Philippe Boeuf
Location: 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.

146. Epigenetic control of malaria gene expression with a focus on control of antigenic variation

Supervisor: Dr Michael Duffy, Dr Michaela Petter
Location: 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-immunopreciptations, chromatin immunoprecipitation etc.

MEDICAL BIOLOGY OF WOMEN'S HEALTH

147. A Pharmacogenomics study of the teratogenicity anti-epileptic drugs based on the prospective Australian Register for Anti-epileptic Drugs in Pegnancy

Supervisor: Professor Frank Vajda (vajda@netspace.net.au)
Location Epilepsy and Neuropharmacology Group; The Department of Medicine;
Contacts: Professor Frank Vajda E: vajda@netspace.net.au
Professor Terence O'Brien, Epilepsy and Neuropharmacology Group, The Royal Melbourne Hospital T: 8344 5479 E: obrientj@unimelb.edu.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). Despite the increased risk associated with taking AED in pregnancy, most women with epilepsy who become pregnant, or plan to do so in the near future, cannot simply cease the drugs because of the risk to the health and safety of the mother and child of uncontrolled seizures. The development of methods that would allow the prediction that a specific drug would be associated with a higher risk of a birth defect in a particular woman would be of great potential benefit. There is evidence from family and twin studies that genetic factors may play a role in determining predisposing an individual to having a child with an AED associated birth defect. The Australian Register of Anti-epileptic Drugs in Pregnancy has been established in an attempt to obtain more accurate information about the risks of

specific AEDs. This is a prospective, voluntary, telephone interview based study that enrols pregnant women with epilepsy, prior to the outcome of the pregnancy being known, and follows the outcomes of their pregnancies. The study has been running since July 1999, and to date has enrolled more than 1400 pregnant women.

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

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

NEPHROLOGY

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

Supervisor: Dr Tim Hewitson and Dr Chrishan Samuel
Location: 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

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

Supervisor Dr Tim Hewitson and Dr Chrishan Samuel
Location: 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 TGFbeta 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

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

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

151. Temporal lobe epilepsy, the HPA axis and depression

Supervisor: Dr Mike Salzberg, Prof Terence O'Brien
Location: 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.

152. Does stress contribute to epilepsy?

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

153. Altered social behaviour in a mouse model of Autism

Supervisors: Dr Elisa Hill and Assoc. Prof Anthony Hannan
Location: Howard Florey Institute, florey Neuroscience Institutes
Contact: Dr Elisa Hill T: 8344 1954 E: elisa.hill@florey.edu.au
Web: www.brainsrus.org.

Aim of Project: This project involves the study of altered behavioural characteristics in the (R451C)NL3 mouse model of Autism Spectrum Disorder.
Specifically, the project will investigate:

i. altered social behaviour, and
ii. the effect of environmental enrichment paradigms on (R451C)NL3 mice.

Autism Spectrum Disorder (ASD) is a highly prevalent neurological disorder characterised by impairments in social interactions, communication, and repetitive behaviour. Autism includes Asperger's Syndrome, Rett's syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and affects approximately 1 in 150 children in Australia. Intensive educational and behavioural intervention therapies have produced positive outcomes for children with autism. These methods include exposing children with ASD to highly stimulating environments to improve social interaction.

Standard housed (R451C)NL3 mice show decreased social tendencies in keeping with ASD symptoms. In this project, we wish to investigate the effect of environmental enrichment on these behavioural profiles. Social interaction by standard housed mice will be assessed by time spent

interacting with novel and inanimate objects and caged target mice. Subsequent analysis will assess social behaviour in (R451C)NL3 and wild type littermate mice housed in environmentally enriched paradigms (e.g. these mice will be housed in larger cages, with exposure to a variety of different enrichment objects and activities such as tunnels and running wheels). Additional behavioural testing will be conducted to assess levels of anxiety, alterations in communication and sensory modulation to further characterise the mouse model.

Skills: Mouse behavioural analysis (motor, cognitive and affective test batteries), Environmental manipulations in wild-type and mutant mice.

154. Altered cortical inhibition in a mouse model of Autism

Supervisors: Dr Elisa Hill
Location: Howard Florey Institute, florey Neuroscience Institutes
Contact: Dr Elisa Hill T: 8344 1954 E: elisa.hill@florey.edu.au
Web: www.brainsrus.org.

Aim of Project: This proposal aims to examine synaptic activity in the somatosensory cortex of the (R451C)NL3 mouse model of Autism Spectrum Disorder.

Autism Spectrum Disorder (ASD) is a highly prevalent neurological disorder characterised by impairments in communication, socialisation, restricted patterns of interests and behaviours. Autism includes Asperger's Syndrome, Rett's syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and affects approximately 1 in 150 children in Australia. As many as 30% of people with ASD also experience seizures, suggesting alterations in neuronal network function.

(R451C)NL3 mice show decreased social tendencies in keeping with ASD symptoms along with an increase in the frequency of inhibitory synaptic events in the somatosensory cortex. The observed alterations in inhibitory synapse activity may reflect changes in physiological properties of inhibitory neurons to cause subtle alterations in cortical function. Inhibitory neurons comprise a heterogeneous population and it has been suggested that a deficit in even a single subset of inhibitory neurons may contribute to the specific symptoms observed in ASD.

Skills: This project will involve the characterisation of cortical inhibitory neurons in the (R451C)NL3 mouse based on physiological and morphological properties using patch clamp electrophysiology in acute slices, biocytin labelling (histochemistry) and 3D neuronal reconstruction software.

NEUROVASCULAR

155. Aspirin Resistance in Acute Stroke Study. Phase 2

Supervisor: Dr Bernard Yan
Location: 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.

156. Intraarterial clot burden: a predictor of recanalization post intravenous tissue plasminogen activator?

Supervisors: Dr Bernard Yan, A/Professor Peter Mitchell, Dr Richard Dowling
Location: 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 benefis 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

157. Treatment of Arteriovenous Malformation by Onyx embolization: factors determining treatment success

Supervisors: Dr Bernard Yan, A/Professor Peter Mitchell, Dr Richard Dowling
Location: 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.

NURSING

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

Supervisor: Professor Elizabeth Manias.
Location: 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.

OPHTHALMOLOGY

159. Mannose-binding lectin's contribution to ocular defences against infection

Supervisors: Associate Professors Damon Eisen and Mark Daniell, Victorian Infectious Diseases Service and Department of Ophthalmology, Royal Melbourne Hospital.
Location: Victorian Infectious Diseases Service, RMH.
Contact: A/Professor Damon Eisen T : 9342 8818 E: damon.eisen@mh.org.au
Dr Mark Daniell E: mark.daniell@mh.org.au

Mannose-binding lectin (MBL) is a pattern recognition receptor of the innate immune system that contributes to killing of a broad range of micro-organisms. Deficiency of this serum protein is common and predisposes to numerous infectious diseases. MBL is present in small concentrations in the lungs, joints and, as shown by our group, eyes if they are inflamed and probably contributes to local defences against pathogens. A recent study of fungal keratitis in murine corneas has shown that MBL is one of a handful of inflammatory pathway genes that are upregulated. Furthermore, MBL was shown to be produced locally in murine corneas which is a particularly notable finding. These data suggest that MBL is important in the local response to corneal infection. The contribution of MBL to prevention of endophthalmitis is undefined.

This honours project will explore human correlates of the murine keratitis study. Human corneal cells from cell cultures will be infected with Pseudomonas aeruginosa, a common cause of keratitis, and MBL mRNA will be measured by RT-PCR. Immunohistochemical staining of corneal rims will also be undertaken to establish whether MBL is produced locally in human corneal cells. To investigate the link between endophthalmitis and MBL deficiency both a case control study of endophthalmitis and analysis of an animal model may be undertaken.
Note: this project is also listed under Infectious Diseases and Immigrant Health

KEY DATES

Aug-Nov 2009:	Contact potential supervisors to discuss Honours projects	(Step 1)
20 Nov 2009:	Closing date for Honours application through SIS	(Step 2)
29 Nov 2009, 11.000pm	Closing date for project preference submission through HATS	(Step 3)
3rd week Dec 2009	First round of offer letters sent by mail to students	
6 Jan 2010	Closing date for acceptance/rejection by students of First Round offers	
11 Jan 2010-	Second round of selection and mailing of offer letters begins	
Mid-late Feb 2010	Honours 2010 begins (check with individual Departments/Institutes for specific starting date and other details	

HOW TO APPLY

COURSE CODE: 754 BM (Biomedical Science)

ROUND 1 APPLICATIONS HAVE NOW CLOSED
Late applications will be accepted from students who wish to be considered for ROUND 2**.**

Please refer to the following websites for details on 'How to Apply' for late applications.

Department of Medicine's: http://www.medrmhwh.unimelb.edu.au/
Department of Medicine's Honours: http://honoursrmh.unimelb.edu.au/
Faculty of Medicine, Dentistry and Health Sciences Honours 2010 :
http://www.mdhs.unimelb.edu.au/future_students/honours

Please note that students must still complete Steps 1 & 2 as outlined on the MDHS website to register into the system : http://www.mdhs.unimelb.edu.au/future_students/honours/application_process

NOTE: Late applications for Honours may be made via the Student Information System and International Admissions office up to 30th January 2010.

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Application for Honours in the Faculty of Medicine, Dentistry and Health Sciences (MDHS) in 2010

If you wish to be considered for Honours in 2010, 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.** Department and Institute Honours project booklets and websites, the MDHS Honours expo, and individual information sessions held by Departments and Institutes are all ways of helping you make contact with potential Honours supervisors.

STEP 2: You must lodge an online application for Honours to the Faculty of Science through the SIS:
1) For current local students: https://sis.unimelb.edu.au/cgi-bin/course-application.pl
2) For local students who have not studied at the University of Melbourne: https://sis.unimelb.edu.au/cgi-bin/course-application.pl/register/

Once the above has been completed take a hard copy of the application to the Science Student Centre for confirmation as instructed. You need to do this whether you are a BSc, BBiomedSci or external local student. International students however will need to apply through the International Office http://www.futurestudents.unimelb.edu.au/int/

After submitting your application, you will be sent an Application ID number by email. You will need this Application ID for Step 3. It is therefore essential that you **carry out Step 2 BEFORE you carry out Step 3**. Note that the closing date for the Step 2 Application is **20 Nov 2009.**

STEP 3: 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

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) 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.

c) 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 one preference, and you can enter up to ten) is lodged by **11:00pm on Sun, 29 Nov 2009.** This list will be supplied to Departments to allow them to carry out their selection process in early December 2009.

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.

PLEASE NOTE: The Royal Melbourne Hospital / Western Hospital Clinical Departments Cluster Honours Projects are offered through 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	Medicine (RMH/WH). This project is carried out at the Department of Medicine (RMH/WH) through the RMH/WH Clinical Departments Cluster.

STUDENT INFORMATION

Student Information Session on Applying for Honours 2010

Dr Tony Hughes, Honours Coordinator in the Faculty of Medicine, Dentistry and Health Sciences (FMDHS), will present an Information session on applying for Honours and the MSc (Research Training) in MDHS. This will be held in the week following the MDHS Honours Expo
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Date: Wednesday 16th September 2009
Time: 5.15pm to 6.15pm
Venue: Sunderland Lecture Theatre, Ground floor, Medical Building, University of Melbourne

Faculty of Medicine, Dentistry and Health Sciences (FMDHS):
http://www.mdhs.unimelb.edu.au/

- HONOURS 2010:
http://www.mdhs.unimelb.edu.au/future_students/honours

- HONOURS EXPO:
http://www.mdhs.unimelb.edu.au/future_students/honours/mdhs_expo_do_honours_in_2010

Other Honours Information Sessions

1) MDHS Expo – 'Do Honours' in 2010
Wednesday 9th September 2009
3.15pm to 5.15pm
Harry Brookes Allen Museum of Anatomy and Pathology
(Level 3 Medical Building - West Wing)

2) Beyond Tomorrow – Honours Expo and Information Sessions
Thursday 10th September 2009
4.30pm – 7pm
Sidney Myer Asia building (foyer)

Over 30 departments and courses will be represented. Discuss research opportunities & career options

The Royal Melbourne Hospital and Western Hospital Clinical Departments Cluster 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

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