Eastern Hill Campus Precinct Research Projects

Note: These headings are clickable hyperlinks within this document. We encourage you to contact the supervisors in this booklet to discuss your research options here at the precinct.

Research and Research Training @ Eastern Hill Campus Precinct

The Melbourne Medical School's Eastern Hill Campus Precinct offers a wide range of exciting, cutting-edge translational research projects through the following Departments: Medicine at St Vincent's, Surgery at St Vincent's, Otolaryngology, Ophthalmology and Medical Bionics.

Students can also conduct their research in our affiliated medical research institutes as well as in the various departments/ units within St Vincent's Hospital itself.

The Precinct currently hosts around 150 – 180 Honours, Masters and Graduate Research students on both the St Vincent's Hospital and Royal Eye & Ear Hospital campuses.

Projects offered in this booklet can be tailored to suit any of the degrees available – Honours, Masters of Biomedical Science, Masters by Research or PhD.

All support services offered to students on the main university campus are available to our students, as well as additional resources such as dedicated Research Higher Degree Coordinators, a Research Training Committee for help and advice, Research Training Forum and Travel Grants for eligible research students.

The students have their own Student Society that arranges both educational and social events throughout the year such as a Student/ Supervisor BBQ as well as the Annual Retreat Weekend.

Scholarships

Students enrolled through the Precinct are eligible to apply for University of Melbourne Honours and Graduate Research scholarships, including the Faculty of Medicine, Dentistry and Health Sciences' Trust Fund Scholarships.

We also provide excellent support to help students apply for external scholarships and grants including those offered by the National Health and Medical Research Council, National Heart Foundation and other organisations.

Further Information

If you have any questions about our research projects, application process, and/ or scholarships please do not hesitate to contact us at easternhill-gr@unimelb.edu.au

Medicine Research Projects

The goal of our research is to improve the treatment of human disease. Driven by clinical questions, our work covers aspects of the basic mechanisms of biology and physiology, clinical and community-based epidemiology, and clinical trials of new therapies and devices. The core research foci have been on diabetes and its complications, kidney disorders, vascular disease, nutritional intervention, inflammation and thrombosis. New areas of activity include epilepsy research, genetics of leukaemia, infectious diseases, inflammatory bowel disease and other gastrointestinal disorders, and health bioinformatics.

Biomedical (Renal and Cardiovascular) Translational Research Group

The Renal and Cardiovascular Translational Research group is focused on developing novel compounds for the treatment of pathological inflammation and fibrosis in diabetic and non-diabetic kidney, heart and eye disease. Our projects adopt a "bench to bedside" approach where we evaluate the efficacy of novel therapies on structural and functional aspects of heart, kidney, liver and eye disease using well characterised animal models that mimic the complications seen in humans.

TREATING FIBROSIS AND INFLAMMATION TO PREVENT END-ORGAN DAMAGE IN DIABETES

Suitable for Honours or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Roy Kong**
Co-supervisors: **Dr Amanda Edgley, Dr Fay Khong, Dr Roy Kong**

For enquiries about current projects please contact:

Dr Edgley	Dr Kong	Dr Khong
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Diabetes is associated microvascular complications which lead to diabetic nephropathy, cardiomyopathy and retinopathy. Inflammation and scar tissue formation (fibrosis) contribute to the decline in organ function in both diabetic and non-diabetic disease. At present there is no effective treatment for pathological fibrosis. The Renal and Cardiovascular Translational Research group is focused on developing novel compounds for the treatment of pathological inflammation and fibrosis in diabetic and non-diabetic kidney, heart and eye disease. Our projects adopt a "bench to bedside" approach where we evaluate the efficacy of novel therapies on structural and functional aspects of heart, kidney, liver and eye disease using well characterised animal models that mimic the complications seen in humans. We can then assess the underlying mechanism of action of these compounds using specialised molecular, histopathological and imaging techniques, complemented with cell culture systems. As a team, we have contributed to the discovery of several anti-fibrotic compounds that inhibit the progression of diabetic and non-diabetic kidney disease and these compounds have been advanced into clinical trials in humans. We have a number of projects suitable for Honours or PhD students available to outstanding and enthusiastic students interested with a particular interest in pre-clinical drug development.

NON-ALCOHOLIC FATTY LIVER DISEASE – CHARACTERISING DISEASE FEATURES IN ORDER TO DEVELOP NEW THERAPIES

Suitable for Honours or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Amanda Edgley**
Co-supervisors: **Dr Fay Khong, Dr Roy Kong**

For enquiries about current projects please contact Dr Edgley
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Non-alcoholic Fatty Liver Disease is the most common chronic liver disorder in developed countries, affecting up to 30% of the population. 10-20% of NAFLD patients will progress to non-alcoholic steatohepatitis, in which inflammatory processes are activated in the liver. NASH can then progress to more advanced liver diseases, including cirrhosis and even hepatocellular carcinoma. Previous studies have demonstrated that individuals with obesity, diabetes and insulin resistance have an increased risk of NAFLD and disease progression. Currently, no effective treatments have been shown to alter the natural history of NAFLD progression. Research efforts to understand the pathogenesis of NAFLD progression are hampered by the lack of a robust animal model. Using quantitative immunohistological techniques and advanced 2D & 3D multiphoton imaging techniques, this project involves characterisation of the histological and molecular features of a high fat, high cholesterol fed animal model of NAFLD/NASH and investigation of new molecular targets that could be involved in the disease pathogenesis.

TARGETING INFLAMMATION AND FIBROSIS FOR THE TREATMENT OF RETINAL DISEASE

Suitable for PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Darren Kelly**
Co-supervisors: **Dr Amanda Edgley, Dr Fay Khong, Dr Roy Kong**

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Our group is focussed on the development of innovative therapeutic strategies for the treatment of ophthalmic disorders such as age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity, which are associated with retinal inflammation, growth of abnormal blood vessels (neovascularisation) and fibrosis. Currently, there are no effective treatment options for retinal scarring and limited therapies for neovascularisation, hence there is a high unmet clinical need for novel and cost effective products to prevent vision loss associated with neovascularisation, inflammation and fibrosis. With this focus our group, along with the biotech company OccuRx, has patented a library of new chemical entities with potent anti-inflammatory and anti-fibrotic properties to treat inflammatory and fibrotic diseases of the retina. Our projects involve investigating novel therapeutic targets and testing the efficacy of targeted therapies on the pathological (histological and molecular) features of various

eye diseases using animal models and cell culture systems. We have a number of projects suitable for PhD students that are available to outstanding and enthusiastic students interested in pre-clinical drug development. We also welcome enquiries from students interested in the business development side of the Biotech Industry in Australia.

NOVEL THERAPIES FOR TREATMENT OF CARDIORENAL DISEASE

Suitable for PhD project but could be adapted to Honours/Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Darren Kelly**
Co-supervisors: **Dr Andrew Kompa, Dr Amanda Edgley**

For enquiries about current projects please contact:

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The interaction between heart disease and kidney disease is bidirectional, indicating acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ. This interdependent relationship has come to be known as cardiorenal syndrome (CRS) for which there are limited therapeutic options. Uraemic toxins, such as indoxyl sulphate (IS), are elevated in the serum of chronic kidney disease (CKD) patients and contribute to the pathogenesis and progression of CKD and CRS by exerting deleterious effects in cardiac, renal, vascular and immune cells. The adverse effects of IS are potentially mediated by oxidative stress following activation of the aryl hydrocarbon receptor (AhR). The aim of this project is to investigate the mechanisms underlying the direct effects of uraemic toxins in vitro in cardiac, renal, vascular cells and monocytes, with a focus on actions mediated via the AhR. By inhibiting the AhR pathway, we can determine the downstream adverse effects of the receptor in each of the cell type and their potential contributory role in the progression of CRS. This project will potentially identify a novel strategy to for the treatment of patients with CRS or renal disease.

EFFECT OF URAEMIC TOXINS ON VASCULAR REACTIVITY

Suitable for Honours or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Andrew Kompa**

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Cardiovascular disease in the setting of chronic kidney disease (CKD) displays unique characteristics, primarily left ventricular (LV) hypertrophy with extensive interstitial fibrosis as well as endothelial dysfunction, arterial stiffness, calcification and inflammation, collectively termed 'uraemic cardiomyopathy'. Uraemic toxins are elevated in the circulation of patients with CKD. Indoxyl sulphate (IS) is one such uraemic toxin that has been extensively examined in cells and animal models of disease. IS has

been demonstrated to exert deleterious effects in cardiac, renal, vascular and immune cells, and in tissues from man and animal models. Recently an intracellular receptor for IS was identified, the aryl hydrocarbon receptor (AhR), which, when activated, mediates numerous biological processes including inflammation, vascular remodeling, and atherosclerosis. This project will assess the vascular reactivity of aortic vessels exposed to the uraemic toxin IS and its inhibition using selective AhR antagonists in aortic rings. Following experiments the tissue will be examined using immunohistochemistry and real time PCR. This project will potentially identify a novel agent to treat vascular and inflammatory changes in patients' with CKD.

CHARACTERIZATION OF GPR 35 IN MODELS OF CARDIOVASCULAR DISEASE

Suitable for Honours or Masters

Department: Medicine and Radiology **Location: St Vincent's Hospital**

Primary Supervisor: Dr Andrew Kompa
Co-supervisor: Dr Amanda Edgley

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G-protein coupled receptor 35 (GPR 35) expression is increased early in the hearts animal models of cardiac disease such as myocardial infarction and models of hypertrophy, and in heart failure patients. Furthermore, in neonatal cardiomyocytes exposed to hypoxia, GPR 35 expression is increased after 12 hours and this increase is mediated by hypoxia-inducible factor 1 (HIF-1). A human polymorphism for this receptor has been identified and is associated with high coronary artery calcification, a measure of subclinical coronary atherosclerosis, which has been used to predict coronary artery disease events. Evidence suggests that GPR35 may be an early marker of cardiac pathology and may also be a potential target for the development of novel therapies. This project will assess the expression of GPR 35 in archived tissues from various animal models of cardiac disease, including myocardial infarction, pressure-overload hypertrophy and diabetes using immunohistochemistry and real time PCR. Under hypoxic conditions, known to increase GPR35, cell culture experiments utilising cardiac cells will be performed in the absence and presence of selective GPR 35 antagonists to determine the effect on GPR 35 gene expression, as well as determine effects on collagen synthesis and hypertrophy using proline and leucine incorporation assays respectively.

VALIDATION OF 2 PHOTON IMAGING OF FIBROSIS IN MODELS OF KIDNEY, LIVER AND EYE DISEASE

Suitable for Honours or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Supervisors: **Dr Andrew Kompa, Dr Amanda Edgley**

For enquiries about current projects please contact:

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Inflammation and scar tissue formation (fibrosis) contribute to the decline in organ function in both diabetic and non-diabetic disease. At present there is no effective treatment for pathological fibrosis. The Renal and Cardiovascular Translational Research group is focused on developing novel compounds for the treatment of pathological inflammation and fibrosis in diabetic and non-diabetic kidney, heart, liver and eye disease. This project will validate a the use of a new quantitative 2D & 3D multiphoton imaging system (Genesis®200, Histoindex) to assess fibrotic scar formation in archived tissue from experimental models of kidney, heart, liver and eye disease. The quantification of collagen via multiphoton imaging will be cross-referenced to traditional measures of collagen quantification via immunohistochemical staining techniques and molecular analysis.

Clinical Epilepsy Epidemiology Research Group

Group Leader: A/Prof Wendyl D'Souza

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Our research group is focused on clinical epilepsy epidemiology, electrophysiology and co-morbidity. Particular research emphasis is currently on neural networks in Idiopathic Generalised Epilepsy and health outcomes of epilepsy using privacy preserving data linkage techniques. In addition, our strong clinical epilepsy emphasis allows unprecedented access to invasive epilepsy monitoring techniques and interpretation of brain wave recordings for seizure localisation, detection and prediction utilising cutting edge techniques.

Our group's main aims are to better understand the prognosis of epilepsy especially outcomes of modifiable public health significance (e.g. psychiatric, injury, cognition, mortality). Our ongoing clinical interest maintains this focus on immediate translation of our research findings.

Prospective students should contact the Research Group Leader in the first instance to discuss potential graduate research opportunities.

Clinical Neurosciences Research Group

The Clinical Neurosciences group sustains a large research focus principally centred on epilepsy modelling, clinical and animal studies of epilepsy and other neurological disorders, epidemiological studies of epilepsy and other neurological disorders.

Graeme Clarke Institute

The Graeme Clark Institute for Biomedical Engineering promotes and coordinates the extensive bioengineering activities that exist across The University of Melbourne, drawing on emerging scientific and engineering approaches to drive transformative clinical solutions.

The Graeme Clark Institute is located in the Melbourne Biomedical Precinct which has established itself as a major global research and teaching powerhouse, with over 25 collaborators from health services, research and academic partners. The Graeme Clark Institute is at the centre of this precinct, and has unparalleled access to the clinical and research opportunities available across the entire network of partners. The strength of these partners, the relationships and existing collaborations, together with the proximity of the facilities provides unique opportunities to develop transformative health technologies.

By creating a community of engineers, scientists and clinicians in the healthcare system, relevant clinical problems will be identified and strategies for new approaches will be enabled and developed in partnership with industry.

More information about projects affiliated with the institute can be found here:

- https://biomedical.eng.unimelb.edu.au/research/projects/
- https://www.cmit.arc.edu.au/projects-university-of-melbourne

Diabetes Technology Research Group (University of Melbourne Dept. of Medicine at St Vincent's Hospital)

TOWARDS AN ADVANCED ARTIFICIAL PANCREAS AIMED AT OPTIMISING METABOLIC CONTROL IN PEOPLE LIVING WITH TYPE 1 DIABETES

Suitable for Honours or Masters

Group Leader: Prof David N. O'Neal

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Those living with type I diabetes (T1D) are faced with the daily challenge of matching insulin dosing with rapidly changing insulin requirements. Mismatch can result in high glucose levels which damage vital organs or low glucose levels which may lead to coma and seizures. An artificial pancreas (AP) automatically adjusts insulin delivery every five minutes in response to changes in blood glucose levels. However, even current AP systems remain challenged by unpredictable changes in insulin requirements associated with meals and exercise. Our research group have studies profiling counter-regulatory hormone levels during exercise of differing intensities in people with T1D. This will help us understand factors influencing insulin requirements during exercise and inform future AP systems using signals in addition to glucose (eg. lactate, ketones, fit-bit data, and heart-rate).

In 2020 we aim to implement exercise study protocols in healthy non-diabetic individuals that are identical to those we are implementing in people with T1D to benchmark our observations regarding the physiology

of exercise in those with T1D and provide a gold standard against which AP systems can be referenced when challenged with exercise. Other projects planned for 2020 include first-in-human studies examining advanced glucose sensors (surgically implanted and part of multianalyte sensing platforms), and AP systems with more advanced glucose control algorithms. The ultimate goal of these technologies is optimising metabolic control while minimising the burden on people living with T1D.

Diabetic Retinopathy and Health Informatics Collaboratory

Group Leader: Dr Laima Brazionis

Email: laimab@unimelb.edu.au

The Diabetic Retinopathy and Health Informatics Collaboratory is a group of academic, clinical and technical staff brought together to address the multidisciplinary challenges associated with chronic disease diagnosis and management. The group comprises medical and information scientists from the fields of endocrinology, epidemiology, eye care, nutrition, data modelling and software development with research nodes at The University of Melbourne, University of Sydney and La Trobe University.

There is growing evidence of multiple associations between chronic diseases and behavioural, biomedical and dietary risk factors across academic disciplines. Increased quantities and granularity of data and improved communication technologies represent a paradigm shift in patient information management and knowledge sharing.

As holistic approaches and technology become more integral to health service delivery, it is critical that we apply the same rigour and evidence-based assessment to these new interventions that we do to traditional practices

We conduct clinician-initiated research to produce evidence-based research development, implementation processes and tools to assist the health sector in the areas of:

- Diabetic Retinopathy Assessment
- eHealth Interoperability
- Nutritional Epidemiology (inc. dietary interventions)
- Health literacy, education & lifestyle assessment

With a focus on regional/remote communities and Indigenous Health.

The Diabetic Retinopathy & Health Informatics Collaboratory is the Health Informatics Core of the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Diabetic Retinopathy administered by the NHMRC Clinical Trials Centre, University of Sydney.

Prospective students should contact the Research Group Leader in the first instance to discuss potential graduate research opportunities.

Innate Immunity and Infectious Diseases Laboratory

Group Leader: Prof Kumar Visvanathan

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The Innate Immunity and Infectious Diseases group seeks to understand the role of the innate immune system in a variety of infectious diseases, including viral hepatitis, septic shock and mycobacterial infections; so that we can better dissect the complex interactions between the host and the innate immune system. More recently we have become increasingly involved in collaborations examining the role of the immune system in cancer, specifically in colorectal and Hepatocellular carcinoma where we have developed organoids that can be used to assay the potential success of immunotherapeutic medications in individual patient cancers.

Our ultimate goal is to generate a body of research that will clearly define the role of the innate immune system in these diseases so that we can develop new therapeutics and biomarkers.

Prospective students should contact the Research Group Leader in the first instance to discuss potential graduate research opportunities.

Neural Engineering and Brain Dynamics Research Group

A FRAMEWORK FOR CREATING SUBJECT-SPECIFIC MATHEMATICAL BRAIN MODELS

Suitable for Honours, Masters or PhD

Department: Medicine and Radiology **Location: St Vincent's Hospital**

Supervisors: Dr Dean Freestone, Prof Mark Cook, Prof David Grayden (Department of Electrical and Electronic Engineering)

Email: deanrf@unimelb.edu.au

This project aims to develop a framework for bridging the microscopic and macroscopic scales of neural dynamics. Methods will be developed to tailor macroscopic mean-field models to microscopic scale experimental data. The approach will be validated by comparing predictions of mean-field models to experimental data collected from calcium imaging and multi electrode arrays, which provide a ground truth. The creation of subject-specific models from data is important, as there is a large variability in neural circuits between individuals, despite seemingly similar network activity. The intended outcome is new insights into the processes that govern brain function and methods for improving interfacing to the brain. This project will enable inference of microscopic aspects of neural circuits from macroscopic data.

Currently, most microscopic aspects of neural circuits cannot be measured in humans without major damage. The framework will enable the creation of subject-specific neural circuit diagrams, providing deep insights into brain function. The outcomes will eventually be applied to better understand and treat brain diseases that currently have no cure, and to develop new and improved medical bionics.

EPILEPTIC SEIZURE FORECASTING

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Supervisors: **Dr Dean Freestone, Prof Mark Cook, Prof David Grayden (Department of Electrical and Electronic Engineering)**

For enquiries about current projects please contact:

Dr Freestone E: deanrf@unimelb.edu.au	Prof Cook E: markcook@unimelb.edu.au

Seizures appear unpredictable and greatly affect the quality of all aspects of life for patients with epilepsy and their carers. New advances in complex systems theory suggest that transitions from normal brain activity to seizures are preceded by measurable changes in the brain's responses to stimuli, known as critical slowing. Measurement of critical slowing will enable prediction of seizures, providing a warning system, and possibly an opportunity to deliver preventative therapies.

We will investigate if critical slowing can be used as a biomarker of seizure susceptibility in epilepsy. Critical slowing refers to the lengthening of a time period a system takes to recover to the normal state after perturbation when it is close to a tipping point or critical transition.

In many natural systems, critical slowing is the most promising way to measure the susceptibility of a catastrophic change in behaviour. We believe that critical slowing is also a property of the mammalian brain and can be used to track epilepsy-related changes. For example, we have preliminary data showing that electrically-evoked potentials can be used to track epilepsy-related critical slowing in rats, canines, and humans. We will investigate critical slowing in order to establish how it can be used to better predict transitions to seizures.

Critical slowing can be measured using electrophysiological measurements following perturbations. Perturbations may take the form of applied external electrical stimuli, sensory evoked potentials, or interictal epileptic spike-wave discharges (SWDs). We will study SWDs in a one-of-a-kind, long-term continuous dataset that was collected from 15 patients for up to three years. This data represents to first and only opportunity to address this important problem. We will also study responses to electrical stimuli in data collected from humans, canines and rats.

We have already shown very strong preliminary evidence that critical slowing occurs in a state of high seizure susceptibility, and that it can be manipulated by anti-epileptic drugs. We have also shown patterns in critical slowing vary with the sleep-wake cycle, and that the sleep-wake cycle is strongly linked to seizure occurrences. However, further investigation is required to validate critical slowing as a robust biomarker of seizure susceptibility. If our hypotheses are validated, this project will lead to new opportunities to develop interventions to prevent seizures.

CONTROL OF PROSTHETIC LIMBS FROM DECODED BRAIN SIGNALS

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Dean Freestone**
Email: deanrf@unimelb.edu.au

This research will restore mobility to patients who suffer from paralysis. We aim to create a device, known as a brain-machine interface, which is an artificial communication path from the brain that bypasses an injury, such as a damaged spinal cord or stroke. The interface will decode a user's intent and act upon it. Decoders will use physiological principals and state-of-the-art machine learning methods. We will test a user's ability to control an artificial limb using decoded brain activity.

This project will demonstrate proof of concept of the clinical viability of a device that will restore mobility to the millions of people worldwide. The device, known a brain-machine interface, will serve as an artificial communication channel from the brain that bypasses damaged tissue, such lesions caused by stroke or spinal cord injury. This interface will enable computer control by decoding the electrical activity of the brain, allowing communication with robotic prostheses, enabling people to reconnect with the physical world.

Despite the striking demonstrations of brain-machine interfaces for driving prosthetic devices, this technology has not been translated to the clinic. The major reason for this is that the electrode systems that capture the neural signals are unreliable. Consequently, the lifespan of these devices is limited.

We have recently solved the reliability problem and published two approaches for the successful decoding of the local field potentials, which are more stable than standard approaches. We have established methods that are based physiological principals and state-of-the-art machine learning approaches that solve complexity issues of local field potential decoders. Furthermore, we also have unequivocal evidence that local field potentials are reliable for long-term continuous recording.

In this project, we will directly test our brain-machine interface designs in humans who have subdural electrodes placed on the surface of their brains for epilepsy surgery purposes. We will assess the ability of these subjects to control a robotic arm in real time using decoded intracranial EEG signals. There is a strong need for brain-machine interfaces to restore mobility to people living with paralysis. We have a wonderful opportunity to provide freedom to millions, to advance medical technology in Australia, and to push the boundaries of science and advance our knowledge of the human brain.

SINGLE PULSE ELECTRICAL STIMULATION FOR EPILEPSY MONITORING AND TUNING OF DBS THERAPY

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Dean Freestone**
Email: deanrf@unimelb.edu.au

The project is a collaboration with Medtronic (MN, USA), where we will conduct a first-in-man feasibility study of a novel deep brain stimulator for the treatment of epilepsy seizures. The device is a brain implant that can stimulate brain regions and simultaneous record the neural responses. We will use a systematic combination of stimulating and recording to track epileptic activity and regulate abnormal brain activity. The technology will form the basis of a new therapy for epilepsy.

TOWARDS A PATIENT-SPECIFIC EXAMINATION OF EPILEPTOGENESIS

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Mark Cook**
Co-supervisor: **Dr Andre Peterson**

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Brain diseases in particular are highly patient specific, as we are all wired differently. How can we quantify and model these differences in brain network structures in order to personalise diagnosis and treatment in complex patient-specific diseases such as epilepsy? One direction towards this ultimate goal is to use graph theory and dynamical systems in combination with connectome data to convert brain network structures into matrices. We can then analyse the mathematical structure of these matrices using techniques from random matrix theory, pseudo-spectra and May-Wigner stability to understand why some networks are more pathological (unstable) than others.

This project is quite multi-disciplinary and is suitable for students from maths/physics/engineering interested in neuroscience and neurology.

EEG/ MEG NETWORK MEASURES AS A BIOMARKER IN PRE-SURGICAL PLANNING FOR EPILEPSY PATIENTS

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Alan Lai**
Co-supervisor: **Dr Andre Peterson**

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In both neuroscience and neurology, there is a plethora of data that has not been quantitatively analysed. One interesting way of analysing this `big data' is to convert it into a functional network that is spatially sampled at different points. This not only reduces the order of the data, but also provides a way of examining the internal structure of the data. Using various network measures, this project aims to find a functional biomarker that indicates cortical hyper-excitability. We can then use this to systematically analyse brain networks for pre-surgical planning for resective surgery in epilepsy patients.

The aim of this project will be to increase the success rate of surgeries, optimise the amount of cortical tissue resected from patients, and be able to successfully evaluate more complex cases that normally would not be eligible for surgery.

This project involves multiple fields such as epileptology, neuroimaging, neuroscience, network science and data analysis. Candidates from neuroscience, computer science, maths/physics/engineering are all suitable.

NEURAL MODELING OF EPILEPTIC DYNAMICS

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Andre Peterson**

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This project aims to understand the links between the average single neuron behavior with the behaviour of a network of neurons. In particular, we would like to understand how the electrical behaviour becomes unstable, for example, when there is a transition to a seizure-like state from a normal or resting state. We will use neurophysiology and neuroanatomy on multiple scales in combination with some mathematics to constrain the problem. This would involve some mathematical/ statistical analysis and computational simulations that are strongly grounded in neuroscience.

Students with an interest in brain modelling and some background in either neuroscience/ computerscience/ engineering/ physics/ mathematics, particularly Matlab programming are encouraged to apply. Mathematical/ theoretical skills would be appreciated but are not as important as being

interested/ motivated/ curious in a multi-disciplinary project. The project can be tailored to suit the student's background appropriately.

INVESTIGATING THE ELECTROPHYSIOLOGY OF NEURONAL NETWORK DYNAMICS

Suitable for Honours, Masters or PhD, this project is in collaboration with The Florey Institute

Department: Medicine and Radiology **Location: St Vincent's Hospital**

Primary Supervisor: Dr Andre Peterson
Co-supervisors: Prof Steve Petrou. A/Prof Chris Reid

For enquiries about current projects please contact:

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One of the current difficulties of treating neurological disease is that it is highly patient-specific, both diagnosis and treatment as everyone's brain is wired differently. The aim of this project is to understand the relationship between brain structure and brain activity. Specifically, the aim is to uncover the relationship between the structure of in vitro and in vivo neuronal networks and their behaviour, specifically their synaptic connectivity and patterns of neuronal firing. Of particular interest is the pathological case of Epileptic networks that produce abnormal electrical activity. Although it is known how various channelopathies can give rise to abnormal neuronal firing, their effect on network dynamics is unclear as it is difficult to take into account the network connectivity. This project uses and develops advanced electrophysiological methods to measure and quantify the relationship between synaptic connectivity and neuronal network activity. Uncovering this relationship has the potential to lead to novel patient-specific treatments of neurological diseases such as Epilepsy that will drive the practice of 21st century Precision Medicine.

VCCC Palliative Medicine Research Group

Palliative care is a unique medical speciality that focuses on achieving the best possible quality of life for people with serious illness. As an emerging field, palliative care is accruing an evidence base to ensure the best care underpinned by the best research is available to people who have no time to waste.

Our team brings together clinicians, researchers and allied health professionals, under the leadership of the VCCC Chair of Palliative Medicine. We seek to effect positive and systemic change in palliative care practice and accelerate the translation of research-generated knowledge into improved patient care nationally and internationally. Our team is clinically embedded within St Vincent's Hospital Melbourne and other partners of the Victorian Comprehensive Cancer Centre (VCCC).

Our Research

Our mission is to lead a program of robust, ethical and high-quality research that specifically focuses on improving:

- 'Systems of care' - the ways in which palliative care is provided

- 'Engagement with palliative care' - how we best talk about and come to shared decisions about treatment and care
- 'The evidence for best clinical care' - how we best support the patient and their family

Our team both leads and collaborates on a number of important studies which support our vision to effect positive and systemic change in palliative care practice.

A SYSTEMATIC REVIEW OF END OF LIFE QUALITY OF CARE INDICATORS

Suitable for PhD, Masters by Research, Master of Biomedical Science

Department: Medicine and Radiology **Location: St Vincent's Hospital**

Primary Supervisor: Prof Jennifer Philip
Co-supervisor: Dr Anna Collins

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Increasingly services around the world are seeking to benchmark the quality of the care that is provided to patients receiving palliative care. A series of indices have been developed to seek to enable assessment between and within services of the quality of palliative care delivered. However, different indices are used in different settings and such indices cross domains including health service use indicators, and patient and family reported outcomes. A systematic understanding of the indices available and their strengths and limitations is required in order to take this important field of work forward.

A SYSTEMATIC REVIEW OF THE MANAGEMENT OF ANXIETY IN PALLIATIVE CANCER PATIENTS

Suitable for Master of Biomedical Science

Department: Medicine and Radiology **Location: St Vincent's Hospital**

Primary Supervisor: Prof Jennifer Philip
Co-supervisor: Dr Anna Collins

For enquiries about current projects please contact:

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Dr Collins
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Anxiety is a common experience for people with cancer and particularly for those with advanced disease. On occasion, anxiety can be overwhelming and requires professional management including pharmacological, psychological and behavioural approaches. In advanced cancer, there is limited evidence to guide pharmacological best management. This project will establish the foundational tenets of a developing clinical trial program in the management of this symptom.

A SYSTEMATIC REVIEW OF THE MANAGEMENT OF SLEEP IN PALLIATIVE CARE CANCER PATIENTS

Suitable for Masters by Research, Master of Biomedical Science

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Jennifer Philip**
Co-supervisor: **Dr Anna Collins**

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Dr Collins
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Sleep disturbance is very common in a cancer illness, resulting from symptoms from the cancer itself, symptoms related to cancer treatment and the psychological effects of having a cancer diagnosis. This problem frequently escalates in patients with advanced disease. The management of sleep in this setting is currently the subject of a developing program of clinical trials using pharmacological agents. This systematic review would provide the foundational tenets for this program of work.

A SYSTEMATIC REVIEW OF THE MANAGEMENT OF NAUSEA UNRELATED TO CANCER TREATMENT

Suitable for Master of Biomedical Science

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Jennifer Philip**
Co-supervisor: **Dr Anna Collins**

For enquiries about current projects please contact:

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Dr Collins
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Nausea is a common symptom in advanced cancer and while there are extensive literature detailing best management of chemotherapy and radiotherapy induced nausea, the management of nausea unrelated to cancer treatments is less well established. As part of a clinical trial program which addresses nausea management in this setting, an up to date systematic review of the problem would provide useful foundational information.

AN EXPLORATION OF THE EXPERIENCE OF CARE AT THE END OF LIFE FOR PATIENTS WITH A HISTORY OF ILLICIT DRUG USE: A QUALITATIVE MEDICAL RECORD REVIEW

Suitable for PhD, Masters by Research, Master of Biomedical Science

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Jennifer Philip**
Co-supervisor: **Dr Anna Collins**

For enquiries about current projects please contact:

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Dr Collins
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People with a current or past history of illicit drug use who are receiving palliative and end of life care have unique and significant care needs, including managing symptoms, particularly pain, finding an appropriate setting for healthcare delivery, managing concurrent physical and psychological comorbidity, which can be concealed by ongoing drug use, and navigating complex psycho-social circumstances. We have a program of work examining the end of life care of this patient cohort, with mixed methods data collection from patients and health care professionals. We are seeking to add a qualitative medical record review to provide an additional dimension to facilitate understanding and improve care.

UNDERSTANDING THE MOST EFFECTIVE METHODS FOR TRANSLATING EVIDENCE INTO PRACTICE IN PALLIATIVE CARE

Suitable for PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Jennifer Philip**
Co-supervisor: **Dr Anna Collins**

For enquiries about current projects please contact:

Prof Philip
E: jphilip@unimelb.edu.au

Dr Collins
E: anna.collins@svha.org.au

The growing research capacity and vibrant clinical trials groups in Australia have created a rapidly expanding evidence base in palliative care. Yet the methods for translation of research findings into palliative care practice are not well established or tested including across the different sites of palliative care delivery – acute hospital, palliative care units and community care. This program of work will explore and empirically evaluate existing translational approaches and their application to palliative care as well as develop recommendations for study design to effective implementation into practice.

DEVELOPING A METHODOLOGY FOR BUILDING NEW CLINICAL TRIAL CAPABILITY

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Prof Jennifer Philip**
Co-supervisor: **A/Prof Brian Le**

For enquiries about current projects please contact:

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A/Prof Le
E: brian.le@mh.org.au

The opportunity to participate in clinical trials is valued by patients including at times of serious illness. It is well recognised that such opportunity and/or participation in trials has benefits for patients personally, results in improved clinical care, and also enhances evidence based practice for the services involved. Yet many patient cohorts including palliative care patients are not routinely offered such participation.

Recent investment by the Victorian Comprehensive Cancer Centre included a specific focus to build clinical trial capability in palliative care – an area which had not traditionally undertaken trials. An opportunity to undertake a detailed examination of the processes, requirements and outputs that facilitate the successful establishment of a clinical trials program in a 'trial-naïve' discipline is available. This mixed methods project will lead to the development of recommendations for other new trial groups with broad implications across multiple disciplines.

St Vincent's Hospital Departments Research Projects

St Vincent's is a major teaching, research and tertiary referral centre providing acute or chronic medical and surgical services, as well as clinical training.

Some of our active research departments/ unit include:

Endocrinology and Diabetes

Director: Prof Richard Macisaac

The Endocrinology and Diabetes unit comprises a multidisciplinary team of physicians, diabetes educators, dietitians and podiatrists.

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

Gastroenterology

Director: Prof Alexander Thompson

The Department of Gastroenterology strives to provide quality care for our patients through a focus on patient satisfaction, ongoing research, and the education and development of department faculty, research fellows and junior doctors. The Department of Gastroenterology at St Vincent's Hospital provides a comprehensive range of consultative and diagnostic procedures in gastroenterology. It has a particular interest in chronic viral hepatitis and other liver diseases, inflammatory bowel disease, therapeutic endoscopy and oesophageal disorders.

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

HEPATITIS C TREATMENT AMONG PEOPLE IN PRISON IN VICTORIA

Suitable for Honours

Primary Supervisor: Prof Alexander Thompson
Co-supervisors: Prof Mark Stoove, Dr Rebecca Winter

For enquiries about current projects please contact:

Prof Thompson E: alexander.thompson@svha.org.au	Prof Stoove E: mark.stoove@burnet.edu.au	Dr Winter E: rebecca.winter@burnet.edu.au

Imprisonment provides an opportunity to engage high risk individuals in hepatitis C virus testing and treatment with the goal of reducing prevalence, improving health, and preventing transmission. The identification and treatment of hepatitis C infection among people in prison is a crucial element of achieving WHO hepatitis C elimination goals. In 2016, a nurse-led state-wide hepatitis program was

implemented across the State of Victoria, Australia to assess and treat people in prison living with chronic viral hepatitis. The program is run by St Vincent's Hospital, Melbourne in partnership with the Justice Health Unit at the Victorian Department of Justice.

All persons entering prison are offered screening for viral hepatitis by prison health staff, as well as when moving between prison sites. People testing positive for hepatitis C are referred for assessment by a specialist nurse consultant via in-reach. The nurse consultants conduct clinical assessments and triage for consultation by supervising hepatologists via telemedicine or face-to-face.

This study provides the opportunity for the analysis of routinely collected clinical data to assess an aspect of the HCV treatment program, depending on the student's interest. Examples include HCV assessment, treatment initiation, pathways, outcomes, or program implementation. Univariate descriptive and prospective analyses examining the predictors of chosen outcomes of interest could be undertaken to help inform policy and practice in the prison health system.

Haematology

Director: Prof Constantine Tam

Research in the Department of Haematology focuses on general haematological disorders including lymphomas, chronic leukaemia, multiple myeloma, anaemia, and thrombotic and general bleeding disorders.

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

Immunology Research Centre

Director: Prof Peter Cowan
Email: peter.cowan@svha.org.au

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

Neurology

Director: Prof Mark Cook

Research in the Department of Haematology focuses on the following conditions: epilepsy, movement disorders, dizziness and migraines.

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

Oncology

Director: A/Prof Sue-Anne McLachlan

The Department of Oncology works collaboratively with Palliative Care, Psychosocial Cancer Care and other allied health professionals. The Department also have an active clinical trial portfolio and collaborate with Australian and international trial groups.

Prospective students should contact the Graduate Research Programs Coordinator at easternhill-gr@unimelb.edu.au in the first instance to discuss potential graduate research opportunities.

Surgery Research Projects

The Department of Surgery at St Vincent's Hospital constantly strives to provide the highest level of complex and innovative surgical care, comprehensive surgical training for tomorrow's leaders as well as ground-breaking basic science and clinical research. We undertake a wide range of research spanning from basic to clinical research.

Our approach to new discoveries is to apply a multidisciplinary research framework engaging orthopaedic surgeons, clinicians, biomedical engineers and basic biologists to address problems such as:

- Development and progression of cancer as typified by primary and secondary cancers of bone, breast, prostate and lung;
- Disease progression and drug interventions in musculoskeletal tissues;
- Repair of bone and joint defects using tissue engineering and regenerative technology;
- Clinical assessment of outcomes following joint replacement surgery and the prognostic indicators and determinants of outcome;
- Evaluation of risk and progression of musculoskeletal conditions affecting lower and upper body joints, using innovative motion sensors and custom developed software.

Advanced Limb Reconstruction Research Programme

Musculoskeletal disease, the second highest cause of disability globally, underpins research within the Department of Surgery at St. Vincent's. The Advanced Limb Reconstruction Research Programme (Director - Prof. Peter Choong) addresses a spectrum of conditions including degeneration, tumour, trauma and infection, and is divided into clinical (Arthritis Surgery, Musculoskeletal Oncology), tissue engineering (Cartilage, Muscle, Nerve Regeneration), bioengineering (3D printing, Advanced biofabrication, Medical devices), and robotics (Neural Prosthetic Interface, Limb Bionics, Robotic Surgery) streams.

MINDFULNESS, COGNITIVE PROCESSES AND COPING IN CHRONIC ILLNESS: INSIGHTS FROM A STUDY OF JOINT REPLACEMENT SURGERY

Group Leader: Prof Peter Choong
Supervisors: Prof Peter Choong, Prof David Castle, A/Prof Mike Salzberg, A/Prof Michelle Dowsey, Dr Elizabeth Nelson

Email: pchoong@unimelb.edu.au

This study uses a mindfulness-based psychological intervention to enhance outcomes in people undergoing total joint replacement (TJA) and, in so doing, test hypotheses about coping with chronic illness in an aged population.

This study is important because:

- The number of TJAs undertaken in Australia has doubled over the last decade (80,000 in 2010);

- The incidence of pre-operative psychological distress in TJA patients is reported between 30 and 60%; and
- Pre-operative psychological distress is associated with poorer pain and outcomes after TJA.

This study is the first of its kind and will provide a greater understanding of the role of a mental health enhancement program on the physical recovery of TJA patients.

EVALUATING THE IMPACT OF OBESITY ON KNEE LOAD OVER TIME IN THOSE WHO HAVE UNDERGONE OPTIMAL SURGICAL RE-ALIGNMENT AFTER TOTAL KNEE REPLACEMENT

Group Leader: Prof Peter Choong
Supervisors: Prof Peter Choong, Prof Kim Bennell, Mr Tim Wrigley, Prof Rana Hinman, A/Prof Michelle Dowsey, Ms Jane Kennan

Email: pchoong@unimelb.edu.au

The study examines the impact of obesity on knee joint loading over time in those who have undergone optimal surgical re-alignment in total knee replacement (TKR). This study is important because (i) the number of TKR's undertaken in Australia has doubled over the last decade with 40,000 procedures performed in 2010, (ii) obesity is emerging as an important risk factor which is over-represented (60%) in patients presenting for TKR, and (iii) 15-30% of patients express dissatisfaction or suboptimal improvement following TKR. Working with DePuy this study is the first of its kind, and will provide a greater understanding of the biomechanics of knee load during walking after TKR, the influence of obesity and how this affects TKR outcomes.

THE MARKA STUDY: MAXIMUM ACCEPTABLE RISK OF COMPLICATION IN TOTAL KNEE ARTHROPLASTY

Group Leader: Prof Peter Choong
Supervisors: A/Prof Michelle Dowsey, Prof Peter Choong, Prof Anthony Scott, A/Prof Vijaya Sundararajan, Dr Mandana Nikpour, Dr Elizabeth Nelson

Email: mmdowsey@unimelb.edu.au

The MARKA study represents an innovative clinical research project that brings together a multidisciplinary team recognised for their expertise in clinical, health services and health economics research to examine "riskbenefit" preferences in patients and surgeons considering TKA as a treatment option for end-stage osteoarthritis (OA).

OA is one of the most disabling diseases in developed countries and is responsible for significant disability in over 43 million people worldwide, 27 million of whom are 60 years of age or older. TKA is the mainstay of treatment for people with end-stage knee OA. The number of TKA's being performed each year has risen markedly over the past decade and on average has doubled in most OECD countries. In Australia, more than 46,000 people underwent TKA in 2012 at an estimated cost exceeding $1billion. While the beneficial impact of TKA on pain, disability and quality of life have been confirmed, many reports suggest 20-40% of patients express dissatisfaction post-operatively despite TKA procedures being technically and radiologically satisfactory. Patient expectation is the strongest predictor of satisfaction following TKA.

Unrealistic patient expectations and uninformed perceptions of potential benefits, risks and limitations of surgery lead to dissatisfaction following TKA.

The MARKA Study will use discreet choice experiments to i) estimate the maximum acceptable risk (MAR) of complications that patients with end-stage OA consenting to undergo TKA are willing to tolerate in exchange for improvement in pain and disability and ii) compare benefit and risk preferences of patients with end-stage OA undergoing TKA with surgeon preferences. Understanding how patients and clinicians balance the benefits and risks of undergoing TKA is critical for improving patient satisfaction and reducing the burden of poor outcomes of TKA that require ongoing care that is an imposition on an already overburdened health system.

THE ARTHROPLASTY AND BARIATRIC SURGERY (ABS) STUDY: A RANDOMISED CONTROLLED TRIAL OF LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING PRIOR TO TOTAL KNEE ARTHROPLASTY

Group Leader: Prof Peter Choong
Supervisors: Prof Peter Choong, A/Prof Michelle Dowsey, Ms Angela Cochrane, Prof Wendy Brown (Monash), Prof Danny Liew, Prof Paul O'Brien (Monash)

Email: mmdowsey@unimelb.edu.au

Obesity is risk factor for orthopaedic surgery and also correlates with poorer early and longer term outcomes. TKA is a common orthopaedic procedure that carries a significantly higher risk of complication when performed on obese patients. This is important because the number of knee replacements undertaken in Australia has doubled over the last decade with 40,000 procedures performed in 2010. Australia is one of the leading nations in terms of obesity. 70% of patients presenting for TKA at our institution are obese and 1/3 are severely obese. Together these trends suggest that a significant cohort of patients in Australia are at risk of poor outcomes following TKA because of their body weight. As such there is compelling health and economic reasons to focus on weight reduction in severely obese patients prior to TKA. However, current lifestyle interventions do not result in sufficient sustained weight loss for severely obese patients with knee OA.

Laparascopic adjustable gastric banding (LAGB) is a relatively safe, procedure that has been proven to be an effective form of inducing significant and sustained weight loss in the general obese population. To date, no research has evaluated whether LAGB will provide significant weight loss in severely obese patients with end stage osteoarthritis (OA) awaiting total knee arthroplasty (TKA) and whether this results in improved outcomes following surgery.

We are undertaking a 4 year multi-institutional RCT in severely obese patients with end stage OA. We plan to measure weight loss and outcomes as well as the cost effectiveness of a strategy that combines TKA+LAGB, compared to TKA alone. This study is the first of its kind, and will provide valuable clinical and procedural information for developing strategies for treating severely obese patients undergoing TKA and may have an additional impact on other high volume elective procedures.

BioFab3D@ACMD

BioFab3D@ACMD, located at St Vincent's Hospital, Melbourne, is Australia's first hospital-based biofabrication, robotics and biomedical engineering research centre. Here, researchers, clinicians, engineers and industry partners are working to build biological structures such as cartilage, muscle, bone, nerves and organs: almost anything that requires repair through disease and physical trauma.

The Cartilage Regeneration Program

Cartilage defects and diseases remain major clinical issues in orthopedics. The most common cartilage disease is osteoarthritis (OA), a degenerative joint disease that results from an imbalance in cartilage matrix remodeling marked by gradual loss of cartilage on the joint surface.

The cartilage regeneration project aims at preventing the onset of osteoarthritis by regenerating cartilage using unique 3D bioprinting technologies. Our group has developed a revolutionary device, called the Biopen, which allows surgeons to literally "draw" an implant composed of hydrogel material and stem cells, directly into a defect in the patient's knee. Preliminary results of both in vitro and in vivo studies for the Biopen-generated bioscaffolds are very promising.

The Biopen is often cited as one of the most exciting biomedical research programs in Australia. The project has already garnered significant national and international media attention, (e.g. Daily Mail, UK; Gizmodo US,; Forbes Magazine US, The Project on Channel 10, Australia), has been listed (twice) on the Timeline of Key Australian Medical Technology Inventions, has been nominated for the Eureka Prize, and is on track for commercialization via an Australian engineering firm.

Figure 1: The Biopen is a handheld device for surgical bioprinting.

CARTILAGE REGENERATION FOR IN SURGICAL 3D BIOPRINTING

Suitable for Honours, Masters or PhD

Department: **Surgery** **Location:** **St Vincent's Hospital**

Group Leader: Dr Claudia di Bella
Primary Supervisors: Dr Carmine Onofrillo, Dr Serena Duchi
Co-supervisor: Prof Peter Choong

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Dr Duchi
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The goal of our research is to prevent the onset of Osteoarthritis by regenerating cartilage using a unique 3D printing technology, that requires multiple iteration steps to select the optimal combination of a biocompatible material and stem cells, to efficiently regenerate cartilage.

With this project we aim to characterize in vitro and in human ex vivo models the characteristics of newly regenerated cartilage starting from 3D bioprinted stem cells once induced towards chondrogenic differentiation. In vitro and ex vivo models for evaluating cartilage repair/regeneration are of great value for transferring various culture systems into clinically relevant situations.

From this project the candidate will acquire skills and experience in stem cells culturing, 3D biopriting, perfusion bioreactors, molecular and immunostaining analyses, microCT imaging.

This project will provide opportunity for the student to take part in discovery and development process for future application of cartilage repair strategies in clinical settings.

CASE: CARTILAGE ANALYTIC SCREENING ENVIRONMENT

Suitable for PhD or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Group Leader: Dr Claudia di Bella
Primary Supervisors: Dr Carmine Onofrillo, Dr Serena Duchi
Co-supervisor: Prof Peter Choong

For enquiries about current projects please contact:

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Dr Duchi
E: serena.duchi@unimelb.edu.au

The goal of our research is to prevent the onset of Osteoarthritis by regenerating cartilage using a unique 3D printing technology, that requires multiple iteration steps to select the optimal combination of a biocompatible material and stem cells, to efficiently regenerate cartilage.

The aim of this project is to generate a novel bio-physical tool to simultaneously monitor the biodegradation of a hydrogel material and the production of Collagen II matrix from stem cells. The tool will be used to discover novel materials for cartilage repair strategies.

This project will train the candidate in stem cells culturing, chondrogenic differentiation, DNA amplification and transfection, CRISPR/CAS9 technology, molecular and immunostaining analysis and fluorescence microscopy, 3D bioprinting, material science.

This project will provide an opportunity for a Master/PhD student to take part in a discovery project embedded in a multidisciplinary team based at the 3DBioFab@ACMD, St Vincent's Hospital, Melbourne.

BIOFABRICATION OF AN IN VITRO 3D OSTEOSARCOMA MODEL

Suitable for Honours, Masters or PhD

Department: Surgery **Location: St Vincent's Hospital**

Group Leader: Dr Claudia di Bella
Primary Supervisors: Dr Carmine Onofrillo, Dr Serena Duchi
Co-supervisor: Prof Peter Choong

For enquiries about current projects please contact:

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Dr Duchi
E: serena.duchi@unimelb.edu.au

Osteosarcoma (OS) is a rare and highly aggressive bone cancer, with poor prognosis. Unfortunately, current *in vitro* preclinical models such as monolayer cell culture, fail to recapitulate the Tumour MicroEnvironment (TME) and thus accurate neoplastic behaviour, ultimately hindering therapeutic discovery. The employment of Three-Dimensional OS cell culture Models (3D-OSM) has the potential to better recreate the spatial, mechanical, and biological complexity of the TME, key elements crucial for understanding tumour prognosis and treatment effectiveness.

The goal of this project is to generate a 3D in vitro model of osteosarcoma using primary tumour cells and 3D bioprinting technologies. This project will train the candidate in tumour cells culturing, molecular and immunostaining analysis, 3D bioprinting, material science, fluorescence microscopy, microCT imaging.

This project is suited for an Honors/Master/PhD research project. The experimental work for this project will be conducted at the 3DBioFab@ACMD, St.Vincent's Hospital, Melbourne.

DEVELOPMENT OF MECHANICAL TESTING PROTOCOLS FOR VERY SOFT TISSUES

Suitable for Honours, Masters or PhD

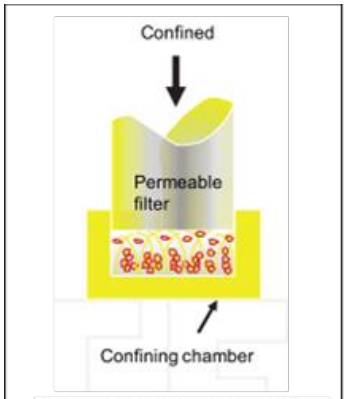
Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Cathal O'Connell**
Email: oconnell.c@unimelb.edu.au

In vitro cartilage tissue growth in hydrogels creates complex heterogeneous structures that are challenging to mechanically characterize.

Currently, unconfined compression is used to assess the compression modulus of the regenerated cartilage in hydrogel matrix.

Due to the inhomogeneities and their interaction with the fluid phase of the hydrated hydrogels, and to the viscoelastic properties of hydrogels, new techniques need to be investigated in order to obtain accurate measurement of the compressive stiffness modulus.



Confined compression set-up (reproduced from Korhonen and Saarakkala, Biomechanics and Modeling of Skeletal Soft Tissues, Theoretical Biomechanics, Dr Vaclav Klika (Ed.))

Two new techniques will be investigated:

- Confined compression: the aim of the project will be to design a porous indenter and a testing stage as illustrated in the frame; and
- Dynamic compression: the aim of this project will be to investigate the benefit of testing these soft materials using dynamic compression, to derive reproducible measurement of elastic and viscoelastic moduli.

This project would suit students with an interest in engineering, with prior experience or strong interest in learning Computer Aided Design, manufacturing techniques, and scientific programming software such as Matlab.

This project will provide an opportunity for the student to take part in discovery projects embedded in a multidisciplinary team based at the 3DBioFab@ACMD, St Vincent's Hospital, Melbourne.

DESIGN OF TENSILE STRENGTH TESTS FOR VERY SOFT MATERIALS

Suitable for PhD or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Cathal O'Connell**
Email: oconnell.c@unimelb.edu.au

The field of tissue engineering offers new therapeutic avenues by using 3D printed materials and patient's stem cells. Applications of these techniques at St Vincent's are cartilage, muscle, or neuronal tissues engineering.

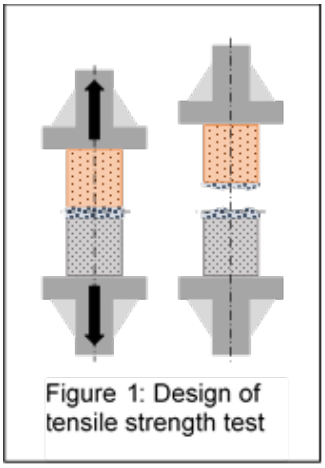


Figure 1: Design of tensile strength test

Currently, the mechanical properties of these hydrogels are tested in uniaxial compression for the compression modulus and rheology.for the storage modulus. However strength is a very important properties to investigate for the different applications. Tensile testing is the most acknowledged method to test material strength. Although this technique has been successfully developed for hard materials and rubbers, the development of such tests for very soft materials remains challenging.

This project would look at the design of a common tensile strength testing protocol for different applications such as cartilage or muscle regeneration, and would suit students with an interest in engineering, with prior experience in Computer Aided Design and good understanding of manufacturing techniques.

This project will provide an opportunity for the student to take part in discovery projects embedded in a multidisciplinary team based at the 3DBioFab@ACMD, St Vincent's Hospital, Melbourne.

DIFFUSION PROPERTIES IN HYDROGEL MATERIALS

Suitable for PhD or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Cathal O'Connell**
Email: oconnell.c@unimelb.edu.au

Growth of regenerated tissue in vitro is very sensitive to the diffusive properties of the nutrients and oxygen into the host material. This project proposes to develop a computational model of diffusion of molecules into hydrogels. The anticipated outcomes are 2D diffusion maps within the hydrogel material for different time points simulating the penetration of the growth factors. Depending on the length of the project, experimental validation can be added to the computational part.

This project would suit students with an interest in computer engineering and mathematical modelling, with prior experience in scientific programming such as Matlab and Python.

PROBING THE COMPLEXITY OF CARTILAGE USING THE ATOMIC FORCE MICROSCOPE

Suitable for Honours or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Cathal O'Connell**
Email: oconnell.c@unimelb.edu.au

The articular cartilage of the knee exhibits complex mechanical properties, including steep stiffness gradients, sensational lubrication, and dynamic viscoelasticity. However, studying and reproducing these properties has been a challenge, since they are exhibited at micro-scales.

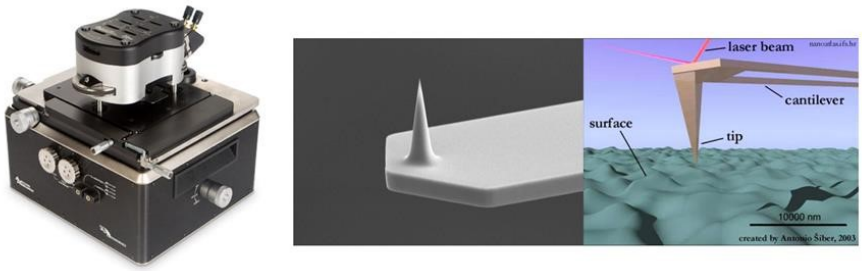


Figure 3: The MFP3D Origin Atomic Force Microscope

Atomic force microscopy (AFM) is a nanoscience technique which uses a tiny, super-sharp tip to 'feel' a surface. As versatile mechanical probe, AFM allows a unique insight into the mechanical microenvironment of materials and tissues. In this project you will use an AFM based at BioFab3D to study both natural and artificial cartilage at cell-relevant scales. Your measurements, including (i) mapping of elastic modulus, (ii) adhesion at the osteo-chondral interface, and (iii) friction/wear at the articulating surface, will provide a significant contribution towards efforts to regenerate natural hyaline cartilage.

Suited to students with a background in physics, engineering, materials science or similar.

BIOINK DEVELOPMENT FOR CARTILAGE TISSUE ENGINEERING

Suitable for Honours or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Dr Cathal O'Connell**
Email: oconnell.c@unimelb.edu.au

A critical aspect of any bioprinting strategy is the 'bioink' used to carry the cells through the bioprinter. During or after the printing process, the bioink is typically crosslinked to form a bioscaffold which holds its structure and encourages 3D cell growth.

In this project, you will develop novel hydrogel formulations tailored to the bioprinting of stem cells for cartilage regeneration. This project will pay particular attention to the rheological (i.e. flow) performance of the hydrogels, the formation of core-shell structures, and in-situ monitoring of the crosslinking reaction.

Study of stem cell development within printed structures may also be required, and so cell culture experience will be looked on favourably.

Suited to students with a background in biomedical engineering, biomedical science or similar.

BIOFABRICATION OF THE OSTEO-CHONDRAL INTERFACE USING MULTIMODAL 3D BIOPRINTING

Suitable for Honours or Masters

Department: **Surgery** **Location:** **St Vincent's Hospital**

Primary Supervisor: **Professor Peter Choong**
Co-supervisor: **Dr Cathal O'Connell**

For enquiries about current projects please contact:

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Prof Choong
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Figure 5: The GeSIM BioScaffolder allows 3D printing of multiple materials incorporating living cells

The osteochondral (OC) interface is not only the interface between two tissues, but also the evolution of hard and stiff bone tissue to the softer and viscoelastic articular cartilage covering the joint surface.[1]

Reproducing the distributed mechanical of the knee joint has so far remained an insuperable challenge. Now, with the advent of 3D bioprinting, we now have a method to recapitulate the complexity of human tissues for the first time. In this project, you will use state-of-the-art 3D bioprinters to create complex structures composed of multiple materials, and embedded with human stem cells. In particular, you will explore the layer-by-layer formation of the osteo-chondral interface.

Suited to students with a background in biomedical engineering, materials science, cell biology or similar.

REFERENCES:

1. Di Luca et al., "The osteochondral interface as a gradient tissue: From development to the fabrication of gradient scaffolds for regenerative medicine." Birth Defects Research Part C: Embryo Today: Reviews 105.1 (2015): 34-52.

**There may be options for a PhD project if the student can obtain a University Research Training Program scholarship.*

Centre for Research Excellence in Total Joint Replacement – OPUS

Is surgery appropriate for me? Is it worth it? What other options do I have?

Total joint replacement is a revolutionary treatment for people with severe osteoarthritis (OA), but operative costs, increasing demand and post-operation dissatisfaction is unsustainable within Australia. Our health system needs to appropriately balance the needs of patients with those of the health care economy.

OPUS is a Centre for Research Excellence that uses evidence-based research to revolutionise osteoarthritis care for better patient outcomes. We want to help people with OA ask the right questions and open a dialogue with health professionals to understand the best care that is right for them.

OPUS is working towards its mission by focusing on five streams that have been designed to improve and streamline the OA journey. This is a more personalised approach to produce better patient outcomes rather than a 'one size fits all' management program for all people with OA.

The aims of the five OPUS streams are:

1. Developing a tool to identify the most appropriate OA patients for TJR.
2. Identifying patient and surgeon perceptions of risk and decision-making.
3. Developing non-surgical alternatives for OA patients.
4. Redesigning a recovery program for TJR.
5. Identifying cost efficiencies and eliminating waste in the patient OA journey.

For more information about OPUS: http://www.opus-tjr.org.au/

Otolaryngology Research Projects

Otolaryngology which is co-located at The Royal Victorian Eye and Ear Hospital is a world leader in the treatment of hearing loss and ear (otological) surgery. The Department remains at the fore-front of research into cochlear implantation, and the preservation of hearing and balance function while operating on the inner ear. The direct interface that we have between lab-based or clinical research, and direct otolaryngology patient care leads to highly productive translational research outcomes.

Laboratory research seeks to understand the biological response of the inner ear to surgery and other types of stress, and applies drug delivery, gene therapy and regenerative strategies to the protection of restoration of hearing and vestibular function. We have a strong track record in developing new therapies in the laboratories and bringing them to clinical trials.

The Department is a leader in the application of Virtual Reality to surgical simulation, working closely with engineers and psychologists at the University, together with commercial partners to create sophisticated 3D rendered simulations that provide force feedback, and real-time training.

Otolaryngology has an interest in ear infection (otitis media) amongst Indigenous Australians, as this leads to early childhood hearing loss and contributes to disadvantage amongst these children. Our focus is upon large scale clinical trials.

Hearing Regeneration and Protection

IMPEDANCE TRIGGERED THERAPEUTIC INTERVENTION AFTER COCHLEAR IMPLANTATION

Suitable for PhD

Department: Surgery Location: Surgery, Otolaryngology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Christofer Bester
Co-supervisors: Prof Stephen O'Leary, Aaron Collins

Dr Bester	Prof O'Leary	Aaron Collins
E: christofer.bester@unimelb.edu.au	E: sjoleary@unimelb.edu.au	E: aaron.collins@unimelb.edu.au

A goal of modern cochlear implantation is to protect any natural, residual hearing the patient may have. Despite advances in electrode design and "soft surgery" techniques, up to 70% of implant recipients lose this hearing. We are pioneering the use of intra-operative monitoring of hearing function during cochlear implantation to actively preserve this function in theatre. However, even after an atraumatic surgery, many patients lose their residual hearing function in the following weeks. The loss of this hearing is often accompanied by a sudden, drastic increase in the electrical impedance of the implant. The purpose of this project is to test whether the monitoring of electrical impedances can be used to trigger a therapeutic intervention to prevent subsequent hearing loss. The project aims for the translation of research conducted in the department into improving clinical outcomes, during which you will be working closely with cochlear implant recipients as well as our industry partner (Cochlear Ltd).

HOW DO WE PROTECT HEARING WITH ADVANCED COCHLEAR IMPLANT ELECTRODE ARRAYS?

Suitable for Honours or Master of Biomedical Science

Department: Surgery Location: Surgery, Otolaryngology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Christofer Bester
Co-supervisors: Prof Stephen O'Leary, Aaron Collins, Dr J Jean-Marc Gérard

Email: christofer.bester@unimelb.edu.au

We are pioneering the use of intra-operative monitoring of hearing function during cochlear implantation to actively preserve this function in theatre. As part of this monitoring, the surgeon may adjust the electrode's trajectory actively during implantation to preserve hearing. With newer pre-curved electrode designs that are advanced out of sheaths, it is unclear how these manipulations affect the tip of the electrode array.

UNDERSTANDING THE HEARING LOSS CAUSED BY COCHLEAR IMPLANTATION

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Otolaryngology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Christofer Bester
Co-supervisors: Prof Stephen O'Leary, Dr Hayden Eastwood

Dr Bester	Prof O'Leary	Hayden Eastwood
E: christofer.bester@unimelb.edu.au	E: sjoleary@unimelb.edu.au	E: haydente@unimelb.edu.au

We are pioneering the use of intra-operative monitoring of hearing function during cochlear implantation to actively preserve this function in theatre. As part of this monitoring, we often see a sudden drop in cochlear output, which we hypothesize is due to a trauma occurring to the inner-ear. We have demonstrated that drops of a certain size are correlated with greater losses of hearing post-operatively. These drops can occur rapidly or slowly at multiple parts during the insertion. The purpose of this project is to investigate whether the timing, size, or slope of these drops affects the severity of post-operative hearing loss.

THE ROLE OF ENDOLYMPHATIC HYDROPS AFTER COCHLEAR IMPLANTATION

Suitable for Honours

Department: Surgery Location: Surgery, Otolaryngology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Hayden Eastwood
Email: haydente@unimelb.edu.au

Protection of the residual hearing after cochlear implantation is one of the main goals of modern implant surgery. Loss of hearing is often the result of the surgical trauma and associated inflammatory reactions. Endolymphatic hydrops (EH) is a little understood cochlear response to trauma, which has been associated

with hearing loss in other inner ear conditions. Previously EH has been difficult to study but our group have recently developed new histological and electrophysiological techniques for identifying EH after cochlear implantation. The goal of this project is to identify the extent and variation in EH after cochlear implantation and to examine any correlation between this variation to differences in residual hearing.

Indigenous Ear Health

OTITIS MEDIA (EAR INFECTION) IN INDIGENOUS AUSTRALIANS

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Otolaryngology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Prof Stephen O'Leary
Co-supervisor: Dr Katie Ozdowska

Prof O'Leary
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Dr Ozdowska
E: katie.ozdowska@unimelb.edu.au

Otitis media is exceedingly prevalent in Australian Aboriginal children, and causes a hearing loss that lasts throughout childhood and often into adult life. Recurrent infections and associated hearing loss hinders learning and educational opportunities, and may have life-long impacts. We are committed to reducing the burden of ear infection amongst Indigenous children, through clinical and experimental research. In the laboratory we are investigating disease burden by defining the microbiology of chronic otitis media and the immunological impact this has on Indigenous children.

Our group also leads a large-scale NHMRC supported clinical trial to determine the best surgical treatment for otitis media. Through several partnerships we also conduct clinical audits to improve clinical outcomes and guide future policy to improve detection, prevention, management and follow up of Aboriginal and Torres Strait Islander people diagnosed with ear disease and other ENT dysfunction.

Our team welcomes honours students with an interest in Indigenous Health, microbiology, audiology, medicine and surgery to assist with the goal of reducing the impact of ear disease upon Indigenous children.

Department of Medical Bionics/ Bionics Institute Research Projects

The Bionics Institute is a world leading centre of medical bionics. Our mission is to research, innovate and deliver technologies that improve human health.

For more than thirty years, we have been building on our experience and technological expertise in cochlear implants to pioneer new technologies that address otherwise untreatable, poorly treated or drug-resistant medical conditions.

The Institute creates, designs, evaluates, and improves bionic devices that interface with the human body to restore impaired sensory or other nervous system and bodily functions. Our bionic technologies seek to address the symptoms and impacts of living with hearing loss, vision loss, epilepsy, Parkinson's disease, and inflammatory bowel disease. We also develop novel clinical tools to objectively assess treatment effectiveness and improve clinical management of these conditions. This work is underpinned by fundamental research aimed at understanding the nervous system's response to electrical stimulation.

Our goal is to translate our research and innovation, using engineering and science, to address unmet clinical problems by delivering innovative implantable technologies to patients. To achieve this goal, we work closely with clinicians from Melbourne's major hospitals to ensure that all of our research programs are driven by a clearly identified health need.

Honours and Masters projects are offered through either the Department of Otolaryngology or Medicine.

PhD projects are offered through the Department of Medical Bionics.

Please note the Bionics Institute is not restricted to the specific projects detailed below and generally welcomes project ideas from students provided they are compatible with our overall research themes.

MULTISENSORY PROCESSES IN PATIENTS WITH HEARING LOSS AND/OR DEMENTIA

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: Prof Gérard Loquet

Email: gloquet@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

There is growing evidence of an association between hearing loss and cognitive decline in the elderly. However, the nature of this association (causal or common-factor) is yet to be established. Since both hearing impairment and dementia have heterogeneous underlying pathologies, the task of understanding the mechanisms of their association poses significant challenges that would require longitudinal studies of large cohorts to provide unequivocal evidence. Instead, in the project we chose to focus on one perceptual ability - multisensory integration – that has been studied in both hearing impaired populations and in those with cognitive decline or dementia. Former studies have generally not adequately controlled for hearing impairment in the dementia studies or vice versa.

Our aim is to investigate common or separate patterns of the effects of multisensory integration in the two populations, by studying multisensory integration in people with amnestic mild cognitive impairment with and without hearing loss, and in people with hearing impairment with and without amnestic mild cognitive impairment. The expected outcome (hypothesis) is to obtain an early biomarker for dementia in hearing impaired people or, if multisensory integration is comparable between the two groups, to identify a common underlying pathological process.

General methods to be used in the project:

In this project, we will use McGurk-type speech stimuli to test behavioral deficits of multisensory integration in the hearing impaired and the mild cognitive impaired group. Those studies will be further assisted by brain neuroimaging studies (high-density electroencephalography and functional near-infrared spectroscopy) to investigate whether the connectivity between regions of interest related to multisensory integration (i.e. superior temporal gyrus and sensory cortices) is reduced in the patient groups.

Suitable background of students:

This PhD project will suit a student with a background in Audiology, Neuroscience, Biomedical or Medical Sciences.

SIGNAL PROCESSING APPLIED TO NEUROIMAGING TECHNIQUES IN HEARING IMPAIRED PATIENTS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Prof Gérard Loquet**

Email: gloquet@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

In Australia, it is estimated that 3.6 million people suffer from hearing loss. Speech perception in background noise is one of the most often reported cognitive difficulties. So far, assistive hearing devices are not matching up to users' expectations and because there is a considerable variability across listeners, the optimal fine-tuning of hearing-aids is often unlikely. Recent advances in non-invasive neuroimaging methods such as high-density electroencephalography (hdEEG) and functional near-infrared spectroscopy (fNIRS) elucidate connectivity and whole brain dynamics at a subsecond temporal scale. Therefore, these objective measures are ideal to study temporal aspects of auditory processing in the cortex as well as the advantage of being less expensive and easier to implement than structural MRI, PET or SPECT, for example.

In line with current hearing-aid fitting procedures, which essentially relies on the pure-tone audiogram, we would like to bring neuroimaging techniques as part of the evaluation of hearing-impaired patients in order that specific compensation needs can be better addressed in the future. As a start, the present study will focus on recording hdEEG & fNIRS in bilateral hearing-impaired patients prior to any treatment to

reveal saptiotemporal dynamics of auditory information flows across widespread cortical regions. Results will be associated with audiological data to work around the hypothesis that hearing-impaired listeners can be categorized according to a cerebral “hearing profile”. The mid-term goal is to use this knowledge to better fit hearing-aids.

General methods to be used in the project:

Combined fNIRS/hdEEG session will be carried out in patients receiving hearing aids. Signal analysis will be performed to seek putative generators in the brain and reconstruct temporal hierarchy representations. The resulting brain topographical maps combined with audiological data will then be used to build “hearing profiles” and establish a link with the fitting of the hearing-aid.

Suitable background of students:

This PhD project will suit a student with a background in Audiology, Neuroscience, Biomedical or Electrical Engineering.

DRUG DELIVERY TO TREAT HEARING LOSS

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: A/Prof Andrew Wise

Email: AWISE@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Recent discoveries have shown that the synaptic connections between sensory hair cells and neurons in the inner ear are susceptible to damage from ageing and noise exposure. This type of damage leads to hearing impairment with particular problems of understanding speech in noisy environments, tinnitus and/or hyperacusis. There are currently no approved drug treatments that can prevent or repair hearing loss once it has occurred. This project will focus on developing a treatment for hearing loss. We have recently made significant progress in the development of a nanoparticle-based drug delivery system that overcomes some of the barriers for drug delivery to the inner ear. The project will involve in vivo deafness models to characterise the drug delivery system, and to test its safety and efficacy in repairing hearing loss. The project involves a multidisciplinary team of researchers with skills in biomedical and chemical engineering, molecular biology, systems physiology, and clinical research.

General methods to be used in the project:

The project will use a diverse range of experimental techniques including drug pharmacokinetics, behavioral, electrophysiological and histological techniques.

Suitable background of students:

This PhD project will suit a student with a background in physiology, cell or molecular biology, biomedical science, or neuroscience.

USING BRAIN IMAGING TO EXPLORE LANGUAGE DEVELOPMENT IN INFANTS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Prof Colette McKay**

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Functional near-infrared spectroscopy (fNIRS) is a child-friendly brain imaging technique that uses light to detect brain activity. It uses a cap containing light emitters and detectors that the person being imaged wears while doing tasks of interest. In this project, working directly with young normal hearing and hearing impaired infants and children, the student will first obtain normative fNIRS data about the development of important language areas in the brain in normal hearing children. They will then explore the effect of deafness and early intervention on this brain development in individual hearing impaired children.

General methods to be used in the project:

fNIRS imaging, language assessments, signal processing

Suitable background of students:

This PhD project has capacity for several students. It would suit graduates with qualifications in audiology or speech pathology with motivation to become familiar with fNIRS technical techniques and analyses methods. Experience working with young deaf children and their families is desirable.

Graduates with backgrounds in neuroscience, engineering or related disciplines are also welcome to apply. These applicants should have strong data analysis or signal processing skills including use of MatLab and have the interpersonal skills to work with young children and their families.

EXPLORING THE EFFECT OF NEURAL DEAD REGIONS IN THE COCHLEA ON HEARING WITH A COCHLEAR IMPLANT

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Prof Colette McKay**

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Neural dead regions in the cochlea are regions of the cochlea in a deaf person where there is poor survival of auditory nerve cells. Such regions are not suitable for electrical stimulation with a cochlear implant, but are difficult to identify. The presence of these regions is one main reason that some cochlear implant users do not understand speech well. This project, undertaken with cochlear implant users, will develop an objective method for identifying these dead regions in individuals. Currently we have psychophysical methods that provide clues to the presence of dead regions, but these methods are not suitable for clinical

use, or in young children. The project will use electrophysiological methods combined with psychophysical methods to both develop the objective diagnostic tool and to understand more fully what the impact of dead regions are on hearing ability with a cochlear implant.

This project will support potentially lead to new clinical procedures to optimize the programming of cochlear implants for individual people.

General methods to be used in the project:

psychophysics, electrophysiology, speech understanding

Suitable background of students:

This PhD project would suit a graduate with qualifications in audiology, neuroscience, engineering, experimental psychology, or related disciplines. Experience with EEG would be an advantage and strong skills in data analysis. Strong interpersonal skills are required as the student will be working directly with deaf individuals with a cochlear implant.

IMPROVING SPEECH UNDERSTANDING OF COCHLEAR IMPLANT USERS WITH NEURAL DEAD REGIONS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Prof Colette McKay**

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Many cochlear implant users do not understand speech very well. One reason for this is the presence of neural 'dead regions' in the cochlea. These dead regions affect speech understanding by making it difficult for each component frequency in a speech signal to be independently heard. Thus, implant users experience a 'scrambled' speech signal. In this project, conducted with adult cochlear implant users, we will use a psychophysical method to determine which parts of the cochlear contain neural dead regions in each individual. Then we will construct an individualised program for each individual that avoids using intra-cochlear electrodes that are near those dead regions. We will then evaluate whether this new individualised program improves their speech understanding. This project is a major opportunity to actually improve the quality of life of cochlear implantees and contribute to novel clinical management techniques. This project will potentially lead to new clinical procedures to optimize the programming of cochlear implants for individual people.

General methods to be used in the project:

Psychophysics, electrophysiology, cochlear implant programming

Suitable background of students:

This PhD project would suit a graduate with qualifications in audiology, neuroscience, engineering, experimental psychology, or related disciplines. Strong interpersonal skills are required as the student will be working directly with deaf individuals with a cochlear implant.

UNDERSTANDING DIFFERENCES IN OUTCOMES OF COCHLEAR IMPLANTS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Prof Colette McKay**

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Deafness has a detrimental effect on the structure and function of the auditory system, from loss and demyelination of neurons in the auditory nerve, to plastic changes in the brainstem and cortical areas. These changes can have detrimental effects on a person's ability to understand speech using a cochlear implant. Understanding the mechanisms of these changes, and how they impact on hearing, will lead to ways to optimise the cochlear implant function for each individual. This research will involve planning and conducting psychoacoustic and electrophysiological experiments designed to understand the individual characteristics that limit or enhance outcomes for those who receive a cochlear implant. This project will focus on testing a recent hypothesis for a mechanism to explain poor speech understanding: that the response of the auditory neural system in such cases is inconsistent, that is, it varies over time, and this will make it difficult to detect and use the important amplitude modulations in the speech signal and to relearn how to categorise speech sounds after implantation. This hypothesis will be tested by analysing electrophysiological measurements and correlating the findings with behavioural measurements of hearing. This project will potentially lead to new clinical procedures to optimize the programming of cochlear implants for individual people.

General methods to be used in the project:

psychophysics, electrophysiology, cochlear implant programming

Suitable background of students:

This PhD project will suit a student with a background in audiology, experimental psychology, engineering, neuroscience or a related disciple. Strong computing and statistical skills (Matlab, R or related) will be an advantage.

HEARING BUT NOT LISTENING: USING BEHAVIOURAL TRAINING IN PRE-CLINICAL STUDIES TO TEST THE ABILITY TO LISTEN TO COMPLEX SOUNDS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **A/Prof James Fallon**

Email: JFALLON@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Behavioural training of animals allows the testing of perception of complex sounds. When applied to animals with cochlear implants or treated with hearing therapeutics, this provides important information

on the performance of the intervention. This can provide more clinically relevant information than is obtained with traditional functional measurements or from histology. This added information is important, as many treatments or stimulation techniques look promising in pre-clinical models but fail in the clinic. Using behavioural training, we aim to reduce the gap between pre-clinical and clinical studies.

This project will develop new techniques for behavioural training of animals and test responses to complex stimuli. Results will be compared against traditional electrophysiological recordings and histology.

General methods to be used in the project:

behavioural training, signal processing, electrical engineering, electrophysiology.

Suitable background of students:

This PhD project would suit a student with a background in science (e.g. biomedical) or engineering (biomedical, electrical).

UNDERSTANDING HOW THE BRAIN PROCESSES COMBINED ELECTRICAL AND ACOUSTIC STIMULATION

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: A/Prof James Fallon

Email: JFALLON@bionicsinstitute.org
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The expansion of criteria for cochlear implantation to include patients with substantial residual hearing has focused interest on the benefits of combined electro-acoustic stimulation (EAS). Although such stimulation via a hybrid cochlear implant (CI) and hearing aid in the same ear has been shown to improve speech understanding, particularly in noise, and to increase the aesthetic quality of sound, almost nothing is known about the physiological mechanisms underlying these benefits. A number of animal studies have been performed, but they have used normal hearing animals and used simple acoustic and electrical stimulation that are not representative of complex electrical and acoustic information that represent speech and have limited clinical relevance.

This project will address this deficiency by investigating EAS in an appropriate animal model with clinically relevant acoustic and electrical stimuli.

General methods to be used in the project:

Electrophysiology, behavioural training, electrical stimulation

Suitable background of students:

This PhD project would suit a student with a background in science (e.g. biomedical) or engineering (biomedical, electrical).

REVERSIBLE SILENCING OF THE COCHLEA

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **A/Prof Rachael Richardson**

Email: RRICHARDSON@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Neural activity from the periphery has been shown to be critically important to the normal development and maintenance of neural processing in the brain. The auditory system has long been studied as an example of neural plasticity, with functional changes to neural processing resulting from deafness or severe hearing loss. Cochlear implants can provide peripheral input and partially reverse these changes from deafness. However, it is unknown if this incomplete reversal is due to the crude input from a cochlear implant or if it is a fundamental limit to plasticity of the mammalian auditory system.

Recently, optogenetic techniques have been developed to provide local inhibition of neural activity using light with high spatial and temporal precision. This project will make use of these advances and our existing skills with cochlear implants to reversibly silence parts of the cochlea over long time periods. This will answer questions for understanding the limits of brain plasticity. Knowledge from this project will feed into further developments of cochlear implants and hearing therapeutics.

General methods to be used in the project:

Electrophysiology, behavioural training, optogenetics, optics, histology

Suitable background of students:

This PhD project would suit a student with a background in science (e.g. biomedical) or engineering (biomedical, electrical).

DEVELOPING A DRUG THERAPY FOR HEARING LOSS

Suitable for PhD, Honours or Masters in Biomedical Science

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Supervisors: **Dr Niki Gunewardene, A/Prof Andrew Wise**

Email: NGunewardene@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Hair cells, the receptor cells for sound, are a highly susceptible part of the auditory system. Hair cell loss is the leading cause of deafness, occurring in almost half a billion people worldwide. Despite the prevalence, there are no biological treatments available for deafness. The current standards of care are restricted to palliative devices including hearing aids or cochlear implants that provide only partial hearing restoration for a limited patient population. As such, there is a significant demand for the development of a pharmacological treatment for hearing loss.

Manipulating specific cell developmental pathways in cochlear stem cells is a potential approach to activate hair cell regeneration and reverse hearing loss. This project aims to test small molecules or drugs that regulate pathways required for hair cell development for the treatment of hearing loss. The available projects fall into two categories and can be modified to suit individual background/strengths.

(i) In vitro: Developing a drug screening platform to test the efficacy of small molecules or drugs in promoting hair cell differentiation

(ii) In vivo: Investigating the potential of specific drug treatments in promoting hair cell regeneration and restoring hearing function in animal deafness models

General methods to be used in the project:

The project will involve the application of cell culture, next-generation sequencing, standard molecular biology, surgery, histology and hearing physiology techniques to assess the efficacy of drug treatments in animal deafness models.

Suitable background of students:

This PhD project will suit students with a background in cell or molecular biology, physiology, biomedical, genetics or neuroscience.

OPTOGENETICS FOR PRECISE NEURAL STIMULATION

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: A/Prof Rachael Richardson

Email: RRICHARDSON@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

The aim of this project is to develop the next generation of neural stimulation devices that use optical stimulation or combined optical/electrical stimulation in order to improve the precision of neural activation. The project will use cutting edge optogenetic techniques to express a light sensitive ion channel in neurons so that they can be activated with low-powered blue micro-LEDs. Electrophysiological recordings will be used to examine whether optical stimulation strategies can improve the spatial precision of neural activation. A significant advantage of improved precision of stimulation of the auditory nerve, for example, would be the ability to stimulate independent channels that would greatly enrich the auditory percept from a cochlear implant, such as the ability to perceive music.

General methods to be used in the project:

Electrophysiology, viral gene therapy, surgical device implantation, optical/electrical stimulation, optical modelling, cell culture, histology, immunohistochemistry, behavioural testing.

Suitable background of students:

This PhD project will suit a student with background in any of the following disciplines: neuroscience, physiology, biomedical engineering, or similar degrees. Electrophysiology and cell culture skills are desirable.

UNDERSTANDING CHANGES IN AUDITORY PROCESSING FROM NOISE INDUCED HEARING LOSS

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: A/Prof Andrew Wise

Email: AWISE@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Exposure to damaging environmental noise can lead to hearing impairment due to damage to the inner ear sensory cells (the cochlear hair cells and auditory neurons) or their synaptic connections. Recent evidence suggests that the cochlear synapses are the most sensitive to damage. It is thought that loss of the cochlear synapses can result in a reduction in the fidelity of the temporal encoding of sounds that is crucial for understanding speech, particularly in challenging hearing situations such as a noisy restaurant. This project will investigate the effects of hearing impairment brought about by the exposure to noise. The project will use behavioural experiments, acute electrophysiological experiments and anatomical studies to improve our understanding of noise-induced hearing impairment and to enable the development of therapeutic interventions to treat hearing impairment.

General methods to be used in the project:

Electrophysiology, behavioural training, histology

Suitable background of students:

This PhD project would suit a student with a background in science (e.g. biomedical) or engineering (biomedical, electrical).

TESTING NANOENGINEERED DRUG DELIVERY SYSTEMS TO TREAT HEARING LOSS

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: Dr Niki Gunewardene

Email: NGunewardene@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

It has long been established that hair cells in the inner ear are susceptible to damage. Recent evidence has revealed that the synapses between hair cells and neurons are the first to degenerate in the ageing or noise-exposed inner ear. Loss of the synaptic connections between hair cells and auditory neurons can

impair our ability to understand speech in noisy environments and may be associated with the generation of tinnitus and/or hyperacusis.

This project will focus on developing a treatment strategy to repair the synaptic connections in the damaged inner ear. We have recently made significant progress in the development of a nanoparticle-based drug delivery system. Here, we are interested in further interrogating the elution profile and bioactivity of the nanoparticle released drugs. The project will involve developing an in vitro model that mimics the loss of cochlear synapses to test the efficacy of nanoparticle-delivered drugs in promoting synaptic regeneration. In addition, this model will be used to investigate the molecular mechanisms underlying synaptopath.

General methods to be used in the project:

The study will involve micro-dissection, cell culture, and standard molecular biology and immunostaining techniques.

Suitable background of students:

This PhD project will suit a student with a background in cell or molecular biology, biomedical, genetics or neuroscience.

BRAIN CONNECTIVITY IN COCHLEAR IMPLANT USERS

Suitable for PhD

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: Prof Colette McKay

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

This project will develop and apply new fNIRS imaging signal processing methods to investigate connectivity in cortical language networks in both cochlear implant candidates (for prognosis) and new cochlear implant users (for diagnosis). The PhD extends the current work in developing new individualised diagnosis and clinical management to address the poor outcomes of up to a third of new adult cochlear implant recipients. It is hypothesised that the plastic changes of interest that affect outcomes are related to connectivity between different multisensory language areas. This PhD will develop signal processing techniques that can be also applied to other fNIRS applications in the Bionics Institute.

General methods to be used in the project:

fNIRS imaging, signal processing, data collection with cochlear implant users, speech understanding assessments

Suitable background of students:

This PhD project would suit an Engineer graduate or data scientist with high-level signal processing skills and who is interested in applying their skills to address important clinical needs.

IMPROVING OBJECTIVITY AND ACCURACY OF NEUROIMAGING ANALYSIS FOR DEEP BRAIN STIMULATION

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Dr Thushara Perera**

Email: TPerera@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

DBS entails the surgical implantation of miniature electrode arrays deep within the brain. These electrodes are connected to a pacemaker-like neurostimulator implanted under the skin in the chest. Similar to the way a pacemaker jolts the heart to keep rhythm, the neurostimulator provides pulses of electricity to the brain to suppress abnormal activity. This therapy has been used for over two decades and has resulted in remarkable outcomes for patients. One of the most important aspects of DBS surgery is the accurate placement of the electrodes. The neurosurgeon must carefully guide the electrode array (1.3mm diameter) to a target deep within the brain which is about 5mm in length – the size of a pea. Being just a millimetre off-target reduces treatment efficacy and leads to unwanted side-effects (such as slurred speech). Consequently, poorly positioned electrodes are often removed and (if possible) re-positioned during a second surgery. Neurosurgery is not without risk, and a second revision surgery is avoided at all costs.

This project will develop signal processing algorithms that aim to address current difficulties of DBS surgery to improve the safety and outcomes.

General methods to be used in the project:

Algorithm development, Data science (Python or equivalent), Digital signal processing (particularly image processing: co-registration and normalisation techniques), Mathematics (Matrices, Transformations, Vector operations), Statistics and machine learning, Data visualisation (2D/3D), Clinical trial execution and management

Suitable background of students:

This PhD project would suit electronics or biomedical engineer with a background in programming, data science, and mathematics. Previous experience with image processing and neuroimaging analysis will be highly regarded. Strong communication skills (verbal and written) must be demonstrated and a willingness to work in a flexible environment with a multidisciplinary team is crucial.

SMART PHONE CONTROL OF AN IMPLANTABLE MEDICAL DEVICE

Suitable for Honours or Masters in Biomedical Science

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: Dr David Nagayam

Email: Dnayagam@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

For some implantable devices we provide the patient with external hardware to communicate with the implanted device, to query the device status or simply to turn it on and off. With advances in mobile phone technology, it is now possible to collect meaningful data on device usage and provide it to the clinician for review. This function can provide prompt alerts of changes in device status or state of the recipient. Students in this project will develop a smart phone app to adjust device parameters and log daily usage patterns of an implanted medical device. Where feasible, there may also be hardware development using the USB capabilities of a smart phone.

Suitable background of students:

This Honors or Masters project would suit students with some knowledge of software development.

CLOSED-LOOP BIOELECTRICAL NEUROMODULATION CONTROL OVER BLADDER FUNCTION

Suitable for Honours or Masters

Department: Medical Bionics Department **Location: Bionics Institute**

Primary Supervisor: Dr Sophie Payne
Co-supervisor: A/Prof James Fallon

Dr Payne
E: spayne@bionicsinstitute.org

A/Prof Fallon
E: jfallon@bionicsinstitute.org

Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

The urinary bladder stores urine produced by the kidneys and voids it from the body at behaviourally appropriate times (micturition). However, following prostectomy or colorectal resections, the nerves that control the process of urination are often damaged, leading to urinary incontinence or retention. Although not life threatening, this condition is socially debilitating and often leads to depression, anxiety and increased rates of suicide. Controlling urination with a bionic device implanted onto nerves that innervate the bladder is a novel technique for the treatment of bladder incontinence/retention. An electrode array can be used to activate or inhibit neural signals in order to trigger or prevent urination. However, for this technology to be useful, precise timing of the application of electrical neuromodulation is essential. Therefore, developing a recording feedback system that detects neural signals in order to allow accurate and timely delivery of the stimulation (i.e. closed loop) is highly advantageous. Ultimately, this technology will detect when a bladder is nearly full, and will send electrical signals to the bladder nerve to stimulate urination at an appropriate time. This project will use the rodent urogenital system to develop neural

recording technology to be able to distinguish between different neural fibre types so that this technology can be utilized to develop closed-loop control over bladder function.

Suitable background of students:

This project would suit honors or master students that have experience in the following disciplines: neuroscience; bioengineering; physiology; biomedical science.

DISEASE DETECTION AND QUANTIFICATION WITH INERTIAL SENSORS

Suitable for PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Dr Thushara Perera**

Email: TPERERA@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

People with movement disorders (e.g. Parkinson's disease and dystonia) find it challenging to perform activities of daily living (such as getting dressed, eating, and drinking) that most take for granted. Fine motor skills are stifled by tremors, movement becomes strenuous due to increased muscle stiffness, and postural instability leads to falls. Evaluating these symptoms is crucial to managing therapy, seeking new interventions via clinical trials and understanding mechanism of disease through research. Existing assessment techniques rely on subjective methods such as surveys, patient diaries, and observation-based rating scales. This project will develop a medical device that allows us to overcome several limitations associated with subjective techniques: 1) inter- and intra-rater variability, 2) bias, 3) floor and ceiling effects, 4) limited resolution on ordinal scales, and 5) intermittent measurements at single time points. The student will design and manufacture prototype wearable devices, perform benchtop evaluation, and assist with clinical trials.

General methods to be used in the project:

Digital signal processing, rapid prototyping (3D printing, PCB layout and manufacture, etc.), software/firmware development, test and verification, human clinical trials, data science.

Suitable background of students:

This PhD project would ideally suit an electronics or biomedical engineer with an interest in medical device development. Previous experience with hardware design, software/firmware development, and rapid prototyping will be highly regarded. Strong communication skills are crucial as well as a willingness to work in a multidisciplinary team in a flexible environment.

VISUALISING ELECTRODE ACTIVITY FOR THE BIONIC EYE

Suitable for Masters of Biomedical Science

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Dr Matt Petoe**

Email: MPetoe@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

Electrode activity data has been routinely logged for our bionic eye clinical trial patients. However, there is not (as yet) suitable software to collate and visualise this data. The student will be responsible for writing C#, C++, Java, Python, or Matlab code to produce electrograms and draw comparisons of stimulus activity against recorded behavioural responses.

Suitable background of students:

This project is suitable for a student doing Masters in Biomedical Science, who is confident in code writing in one or more of the software types mentioned.

A NEW TEST OF LISTENING EFFORT

Suitable for Honours or Masters of Biomedical Science

Supervisors: **Prof Colette McKay**

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Email: CMcKAY@bionicsinstitute.org
Please cc enquiry to the student coordinator: student.enquiries@bionicsinstitute.org

When we listen in non-ideal environments, an increased effort is needed to understand speech. This problem affects the quality of life of hearing impaired people. Being able to measure listening effort can lead to better ways to evaluate the benefit of different hearing aid parameters, for example. This project will develop and evaluate in normal hearing listeners a new dual-task behavioural test for listening effort.

Suitable background of students:

This Masters in Biomedical Science or Honours project would suit a science student who is comfortable working with volunteer participants.

IMPROVING STROKE OUTCOME THROUGH BRAIN MONITORING AND ELECTRICAL STIMULATION

Suitable for Honours, Masters or PhD

Department: **Medical Bionics Department** **Location:** **Bionics Institute**

Primary Supervisor: **Dr Carli Roulston**
Co-supervisors: **A/Professor Chris Williams, Dr Matt Petoe**

Email: carlir@unimelb.edu.au / carli.roulston@florey.edu.au

Stroke affects ~60,000 Australians each year and is the second most common cause of death in Australia. Most strokes result in vary degrees of permanent brain injury due to a failure of neurons to re-grow at the injury site. This limitation in brain repair is often due to critical events such as inflammation that results in toxic signalling and formation of scar tissue that together create a major obstacle to brain repair and remodelling. Treatments that overcome these barriers may have greater success for recovery.

Our laboratory is focused on investigating new treatments that promote recovery after stroke using pre-clinical animal models. In this project we will assess functional and anatomical responses to electrical brain stimulation and record changes in electrical brain activity after stroke, with/without stimulation, for correlation with treatment effects, to establish brain monitoring as a biomarker for treatment success. We will also determine how stimulation works and who is most likely to benefit. Knowledge from this project will directly inform future clinical trial design using our device for stroke, as well as provide useful information for treating other forms of brain injury.

https://www.florey.edu.au/science-research/research-teams/pre-clinical-stroke-research

St Vincent's Institute Research Projects

Affiliated with the University of Melbourne and St Vincent's Hospital, St Vincent's Institute is an independent medical research institute conducting medical research into the cause, prevention and treatment of diseases that are common and have serious effects on health. Diseases studied at SVI include Type 1 and 2 Diabetes, obesity and heart disease, arthritis and osteoporosis, cancer, infectious diseases, and Alzheimer's and other neurological disorders. Students are enrolled either through Medicine or Surgery.

Bone Cell Biology and Disease Unit

Bone remains one of the most poorly understood parts of the body, and treatments for skeletal disorders including osteoporosis, osteogenesis imperfecta, non-union fractures, osteoarthritis and heterotopic ossifications are limited by this lack of understanding.

Like the skin, the skeleton continually replaces itself by the co-ordinated actions of two main cell types: osteoclasts that remove bone, and osteoblasts that replace it. Within the bone matrix itself is an intricate network of cells called osteocytes that co-ordinate this process and regulate the level of mineralisation of the bone matrix. Our research group, lead by Prof Natalie Sims and Prof TJ Martin, is internationally recognized for our work on inter- and intra-cellular signaling pathways in bone and cartilage, and to understanding their contributions to bone and joint disease. We focus on studying the cells of bone in culture and in genetically modified mice by a range of highly specialized methods including undecalcified histology and histomorphometry, micro-computed tomography, synchrotronbased FTIR, as well as more generally applicable techniques such as quantitative PCR, Western blotting, and cell culture. Since our work is so specialized, we do not expect new lab members to be proficient in these methods, and you will be trained during the course of your project.

A range of projects are available. One example is listed below; you are encouraged to contact us directly to discuss further.

HOW DOES THE PERIOSTEUM CONTROL BONE WIDTH?

Suitable for Honours

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Prof Natalie Sims
Co-supervisor: Dr Natalie Wee

For enquiries about current projects please contact:

Prof Sims
E: nsims@svi.edu.au

Dr Wee
E: nwee@svi.edu.au

Skeletal health is determined by the strength of our bones and how well they can resist breaking. Current treatments for osteoporosis (fragile bones) preserve bone strength by increasing bone formation and inhibiting bone destruction. While these therapies are good for the spine, they are not effective at other

bone sites (i.e. femur, hip, wrist). Strikingly, the femur, hip, and wrist are strong because they are rich in cortical bone, the hard-outer shell. If we can find a way to increase cortical bone width specifically, this will improve bone strength at the femur, hip and wrist – the sites that need strength the most when someone falls.

We will study the cells that are located within the periosteum (exterior surface of bone). Using lineage tracing, we will be able to identify and track cell populations within the periosteum. We will also examine how these cells respond to a known anabolic therapy leading to the development of wider bones, which leads to improved bone strength. By studying the cells and molecular mechanisms involved, we may identify novel targets and pathways that may be used in the future to improve bone strength.

This project will involve lineage tracing using mouse models, cryosectioning, immunofluorescence, flow cytometry, RNAseq and cell culture to characterise the periosteal cell populations and identify the molecular determinants of bone width.

WHAT CONTROLS THE DEVELOPMENT OF STRONG CORTICAL BONE?

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Prof Natalie A Sims**
Email: nsims@svi.edu.au

Studying cortical bone development has always been difficult because cortical bone develops at the same time as the rapid increase in bone size. We have developed a mouse model that has defective cortical bone formation, including defective skull formation, which provides an opportunity to understand those signalling pathways that contribute to the formation of the layers of the skull. Using in vivo micro-computed tomography and histology on archived samples, this project will map the process of cortical bone formation in the skull, and how it is modified in two different mutant mouse models.

Even though we know many signalling pathways that control closure of skull sutures after birth, the processes involved in forming the characteristic thickened cortical bone of the skull are poorly described.

We have developed a range of mouse models that will allow us to study the processes by which the thickened bone of the skull forms, and consolidates into two separate layers. These mice include strains with normal, porous, or thickened calvarial structures. In this project, you will carry out 3 dimensional micro-computed tomographic analysis to identify how skull formation changes in these mice over time, and will use histology to identify the cells and signalling pathways responsible.

This project will use small animal techniques, histology and histomorphometry, micro-computed tomography, immunohistochemistry, and possibly molecular biology, quantitative PCR, Western blot, and bone cell culture techniques.

This project is conducted in St Vincent's Institute of Medical Research, Bone Cell Biology and Disease Unit.

HOW ARE AUTOPHAGIC PROCESSES INVOLVED IN BONE MINERALISATION?

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Prof Natalie A Sims**
Email: nsims@svi.edu.au

Bone formation is made up of two different processes: first, osteoblasts produce collagen-containing osteoid, and then mineral crystals (hydroxyapatite) accumulate within the osteoid to make the hard mineralized bone substance. The mechanisms that control the balance between these two processes are not known, but if they are defective, it leads to brittle bones that break easily. Some examples of this are osteogenesis imperfecta, and osteoporosis. Understanding how these processes are controlled could lead to new ways to strengthen weak bones.

Our recent discoveries indicate that intracellular vesicles, including autophagy (intracellular recycling), are involved in mineral secretion by osteoblasts and osteocytes. We have carried out RNA-sequencing in bones from mice with brittle bones, and found changes in a range of autophagic genes. This provides new information about the way that cells in the skeleton control bone composition.

This project will use cell culture techniques, gene knockdown studies, and cell-based assays such as confocal immunofluorescence, molecular biology, reporter assays, and quantitative PCR techniques to determine the function of these autophagic genes in osteocytes and osteoblasts.

Cancer and RNA Biology Laboratory

We are interested in understanding human cancers. We have developed a number of models of human cancer in the mouse and are using these to develop a better understanding of the cancers, to identify new therapeutic targets and as preclinical testing platforms. We are interested in the role of RNA splicing mutations in myelodysplastic syndrome (MDS) and RNA editing by ADAR proteins. If you are interested in these topics please contact A/Prof Walkley to discuss possibilities.

Techniques: Models of human cancer; RNA-sequencing; Genome sequencing; Genome-wide screening; pre-clinical testing; target validation; experimental hematology; computational biology.

THE ROLE OF RNA EDITING ENZYME ADAR1 IN LIVER HOMEOSTASIS AND METABOLISM

Suitable for PhD, Masters by Research, Honours

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Carl Walkley**
Co-supervisors: **Dr Jacki Heraud-Farlow**

A/Prof Walkley
E: cwalkley@svi.edu.au

Dr Heraud-Farlow
E: jhfarlow@svi.edu.au

The gene ADAR1 is essential to perform a highly prevalent form of RNA modification termed A-to-I editing. Editing occurs primarily within repetitive elements in endogenous RNA that can fold to form immunogenic double-stranded RNA. When edited, this double-stranded RNA does not activate innate immune sensors. Mutation of ADAR1 however, leads to a profound upregulation of type I interferon in mice and humans and causes the severe auto-immune disease Aicardi-Goutieres syndrome. Recently, however, a novel function of Adar1 protein has been identified that is independent of its role in RNA editing. Preliminary results suggest a function in the liver to maintain normal metabolism.

This project seeks to further investigate this function using mouse genetics, cell culture, RNA sequencing and biochemical techniques.

NOVEL GENETIC INTERACTIONS WITH THE DOUBLE-STRANDED RNA-INDUCED AUTOIMMUNITY PATHWAYS

Suitable for Honours, Masters by Research, Master of Biomedical Science

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Carl Walkley**
Co-supervisors: **Dr Alistair Chalk, Dr Jacki Heraud-Farlow**

A/Prof Walkley	Dr Chalk	Dr Heraud-Farlow
E: cwalkley@svi.edu.au	E: achalk@svi.edu.au	E: jhfarlow@svi.edu.au

This project aims to dissect genetic interactions with a form of RNA modification termed, Adenosine-to-Inosine (A-to-I) editing. A-to-I editing results in a change to the encoded RNA sequence and its misregulation can have diverse consequences such as the development of the severe autoimmune disease, Aicardi-Goutieres syndrome, where the editing enzyme ADAR1 is mutated. Changes in RNA editing have also been implicated in cancer progression, and several neurological conditions such as autism, schizophrenia and epilepsy. The primary function of ADAR1 is do edit self double-stranded RNA (dsRNA) and mask it from our own immune system. We use mouse models, cell culture and molecular and biochemical techniques to model loss of editing by ADAR1 to better understand how cells deal with their own dsRNA. This project would characterize new players in this pathway identified in a genome-wide CRISPR/Cas9 screen.

Techniques: RNA biology, mouse genetics, cell culture assays, molecular biology/biochem, CRISPR/Cas9, bioinformatics

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Genome Stability Unit

Mutations to DNA cause many different types of human disease, including all cancers. DNA repair mechanisms have evolved to protect cells from mutation, and DNA repair genes are therefore important tumour suppressors.

The Genome Stability Unit at St Vincent's Institute researches the mechanisms by which DNA repair is controlled, or could be targeted in therapy. The group currently has a high researcher: student ratio meaning plenty of expert advice is available to students. $5,000 PhD top ups and honours scholarships

are available to outstanding candidates. Several BSc or BMedSci Honours or PhD projects will be offered in the area of DNA repair in 2017.

Read more about their research: **https://www.svi.edu.au/research_themes/genome_stability**

A THERAPEUTIC STRATEGY FOR KILLING CANCER CELLS BY DNA REPAIR INHIBITION

Suitable for PhD, Masters by Research, Honours, Master of Biomedical Science

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof Andrew Deans
Email: adeans@svi.edu.au

DNA damage drives cancer formation. BLM helicase is an enzyme that acts as a quality control factor during the repair of DNA damage. As such, BLM is a critical tumour suppressor protein in normal cells. However, inactivation of BLM in cancer cells leads to a big increase in sensitivity to death by chemotherapy. In some cells, BLM inhibition can even kill in the absence of additional DNA damage, by a process known as "synthetic lethality". In this project, you will investigate new strategies cells to inhibit the activity of BLM helicase in cells. The findings of your project will drive the development of new small molecule-based strategies for cancer treatment.

Our lab studies the mechanism of DNA repair by the BLM protein using cell-based and cutting-edge protein chemistry-based approaches, as well as structural biology. Using these approaches, we have identified critical weakness points in BLM protein that could be targeted. You will work on development of peptide-based inhibitors of BLM, using biochemical reconstitution, and genetic inhibitors of BLM using normal and cancer-derived human cells. This project will also investigate the mechanism of DNA repair by the BLM protein using cell-based and protein chemistry-based approaches. A combination of approaches will be used such as cell culture with patient cell lines, studies on chemotherapy toxicity, protein interaction and expression studies and analysis of recombinant human BLM using state-of-the-art protein expression systems. This project is part of a larger NHMRC-funded study into the role of DNA repair in cancer initiation and chemotherapy.

APPLICATION OF CRISPR-CAS9 GENE EDITING TO TREAT CHILDHOOD SYNDROMES

Suitable for PhD, Masters by Research, Honours, Master of Biomedical Science

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof Andrew Deans
Co-supervisor: Dr Astrid Glaser

A/Prof Deans
E: adeans@svi.edu.au

Dr Glaser
E: aglaser@svi.edu.au

CRISPR-Cas9 is a powerful sequence specific DNA cutting enzyme that can be used to correct genetic mutations. However, Cas9 breaks are repaired by one of two major pathways in cells: Non-homologous end joining (NHEJ) and homology-directed repair (HDR). Disruptive NHEJ can occur at any stage

throughout the cell cycle in the absence of homologous DNA. In contrast, introduction of specific mutations via HDR is restricted to the S and G2 phases and depends upon the availability of a suitable DNA template. Thus, HDR-based genome editing approaches are often restricted by unwanted NHEJ events, particularly in clinically relevant systems. Overcoming this limitation would greatly increase the therapeutic potential of genome editing.

The student will utilise the Genome Stability Unit's expertise in DNA repair and know-how in gene editing technology to force HDR and suppress NHEJ during CRISPR-Cas9 gene correction. You will use our EGFP to BFP conversion assay (Glaser A., et al Mol Ther Nucleic Acids 2016 doi: http://doi.org/10.1038/mtna.2016.48) to investigate DNA repair pathway choice, and to identify novel strategies that bias CRISPR/Cas9-mediated genome editing towards HDR. This will be achieved through the fusion of protein domains lending HDR-promoting qualities to Cas9. Fusions that promote HDR will then be tested in model gene editing systems, for eventual translation into human use – the project here allows some flexibility based on student interest or expertise as to the exact disease to be modelled. This is an exciting project, that has direct translational potential for application in near-future use of gene editing in treatment of human disease.

FUNCTION AND CRYO-EM STRUCTURE OF THE BREAST CANCER PREDISPOSITION GENE BRCA1

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Andrew Deans**
Co-supervisor: **Dr Rohan Bythell-Douglas**

Email: adeans@svi.edu.au

The Genome Stability Unit at St Vincent's Institute seek an honours or PhD student to join their multidisciplinary team, to uncover the molecular level details of the BRCA1 protein. BRCA1 contributes to the majority of known familial breast cancer risk in women by promoting DNA repair, a process critical to suppression of aging and cancer.

Disease states can arise from mutations that result in a change of just a few atoms within a protein comprised of tens of thousands of atoms. Our lab is interested in uncovering the molecular level details of important DNA repair pathways to understand the biology of healthy cells and how their dysfunction can lead to cancer. This information is the essential bedrock for developing preventative or chemotherapeutic therapies.

The project involves state of the art electron microscopy to visualise molecular level details of BRCA1 and its interaction partner protein BARD1. A model of BRCA1 bound to BARD1 is of significant scientific and therapeutic interest for the understanding of these proteins' role in breast cancer predisposition, and how different mutations cause different levels of risk. Our lab is also equipped to perform follow-up biochemical experiments based on information obtained through generation of the model. We have already established methods for producing other proteins involved in the DNA repair pathway and for interrogating their activity in the laboratory using both biochemical and cell-based assays. The Genome

Stability also works closely with other teams based in familial cancer clinics and breast cancer treatment centres.

The ideal candidate would be self-motivated, keen to learn numerous biochemical and cell-based techniques, and above all want to contribute to our knowledge of proteins involved in breast cancer predisposition and DNA repair.

THE ROLE OF FANCM GENE IN INHERITED BREAST CANCER

Suitable for Honours or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof Andrew Deans
Co-supervisor: Dr Elyse Dunn

Email: adeans@svi.edu.au

1 in 10 breast cancers are due to inheritance of a predisposing gene. In half of these cases, the inherited gene mutation is in the well characterised BRCA1 or BRCA2 genes. The normal function of BRCA1 and BRCA2 is in DNA repair, to suppress cancer by removing the damage to DNA that is caused by carcinogens. Over the last few years, many other DNA repair genes have been linked with familial breast cancer, including the FANCM gene.

Our lab studies the mechanism of DNA repair by the FANCM protein using cell-based and protein chemistry-based approaches. This project will test the breast-cancer associated FANCM mutations identified in a screen of 11,000 women with a history of breast cancer, in a set of assays so that we may determine why they might predispose to breast cancer. A combination of approaches will be used such as studies on chemotherapy toxicity, generation of CRISPR knockout cell lines, and purification and functional testing of recombinant human FANCM using state-of-the-art protein expression systems. There will also be the opportunity to work with patient samples and clinical implementation of findings. This project will be part of a larger Cancer Australia-funded study into the role of DNA repair in cancer initiation and chemotherapy.

THE ROLE OF RECQL4 GENE IN CANCER PREDISPOSITION

Suitable for Honours or Masters

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof Andrew Deans
Email: adeans@svi.edu.au

Mutations in the RecQL4 gene have been linked with cancer predisposition and three rare genetic disorders: *Rothmund-Thomson syndrome, Baller-Gerold syndrome* and *RAPADILINO syndrome.* Each have distinct phenotypes but all 3 syndromes eventually develop cancer at a young age. The current hypothesis to explain this high cancer incidence is that the RecQL4 gene is critical for 2 major cellular processes: DNA

replication and DNA repair. In many other inherited or spontaneous forms of cancer, defects in DNA replication or DNA repair lead to acceleration of cancer development.

Our lab studies the mechanisms of the RecQL4 protein using protein chemistry and cell-based approaches. This project will test RecQL4 mutations associated with *Rothmund-Thomson syndrome* in a set of assays so that we may determine how the mutations directly impair DNA replication and/or repair. The student will utilize a state-of-the-art protein expression system to produce the RecQL4 proteins, and test their biochemical function compared to wild-type protein. Mouse models of Rothmund-Thomson syndrome are also available to test the findings from the in vitro work, at the cellular and whole organism level.

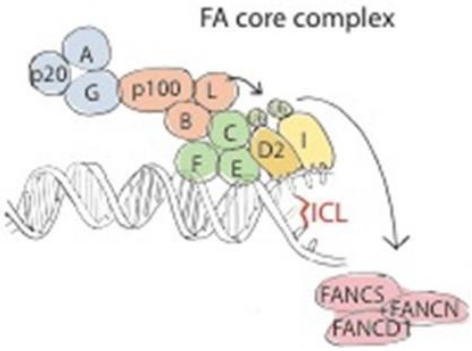
This project is conducted in St Vincent's Institute of Medical Research, Genome Stability Unit.

CANCER DRUG DISCOVERY BY INHIBITION OF A DNA REPAIR PATHWAY WITH CRISPR/ CAS9 GENE EDITING AND BIOCHEMISTRY

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Wayne Crismani**
Email: wcrismani@svi.edu.au



Want to cure cancer? We do too. Join our dynamic young team of experts, in the identification and characterisation of new potential cancer therapeutics. In this project, you would learn about DNA repair, genetic diseases like familial breast cancer, and a variety of laboratory-based techniques (CRISPR/Cas9 gene-editing in breast cancer cell lines, AlphaScreen drug discovery assays, recombinant DNA technology, drug discovery, cell-based chemotherapy response assays, pharmacokinetics, protein purification and in vitro enzyme assays).

A new mechanism being used to kill cancers is synthetic lethality – a combination of deficiencies in the expression of two or more genes leads to cell death, whereas a deficiency in only one of these genes does not (see Kais et al below). Our team is working towards identifying new targeted breast and ovarian cancer treatments, which exploits synthetic lethality. The team has made major breakthroughs in reconstituting the necessary DNA repair reactions in vitro, allowing new approaches to design DNA repair-inhibiting drugs. We already have many candidate drugs and gene-editing projects waiting for a motivated candidate.

Our team has a high Post Doc-to-student ratio so there will be plenty of research expertise and support for your project in the laboratory. By joining us you will gain exposure to basic and translational research that is at the forefront internationally. You will receive training in a molecular biology laboratory with a focus on biochemistry and cell biology, increase your understanding of cancer biology and treatment, and increase your employability particularly in the science sector.

$5,000 PhD top ups and Honours scholarships are available to a limited number of outstanding candidates. Scholarships are awarded on a competitive basis and at the discretion of St Vincent's Institute of Medical Research.

Background reading:

1. Van Twest et al 2017. Mechanism of Ubiquitination and Deubiquitination in the Fanconi Anemia Pathway. Molecular Cell
2. Kais et al 2016. FANCD2 Maintains Fork Stability in BRCA1/2-Deficient Tumors and Promotes Alternative End-Joining DNA Repair. Cell Reports

SPERMTYPING – SINGLE CELL ANALYSIS OF THE GENERATION OF GENETIC DIVERSITY VIA DNA REPAIR PATHWAYS

Suitable for Honours or Masters

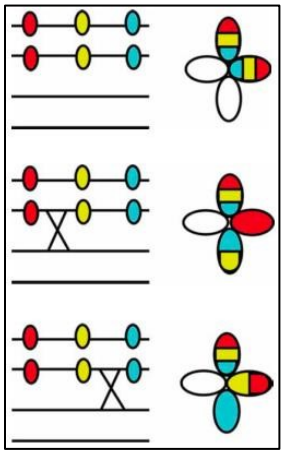
Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Supervisors: Dr Wayne Crismani and Dr Davis McCarthy

Email: wcrismani@svi.edu.au

Are you different from your brothers and sisters but have the same parents? Why is it that two parents can create children that are genetically unique? The answer is meiosis. We are seeking an enthusiastic bioinformatician or scientist with an interest in genetics and evolution, to uncover how DNA repair pathways regulate generation of diversity during meiosis.

In our bodies, DNA double-strand breaks are incredibly dangerous and must be repaired. Nonetheless, there are natural processes that actively generate DNA double strand breaks in their hundreds during meiosis, to allow genetic recombination, or the reshuffling of genetic material between related chromosomes. This process is tightly regulated by mechanisms that are widely conserved in eukaryotes. We previously showed that mutants of the gene FANCM cause a huge increase in meiotic recombination in plants (eg Crismani et al, Science 2012). A related gene has the same effect in yeast.



We have now generated FANCM-deficient mice to determine if the same process governs genetic diversity in mammals. This research has potential implications for our understanding and treatment of infertility in humans.

Your project will take place in a dynamic young team of experts skilled in genetics and single-cell genomics. You will learn and use a diverse set of bioinformatics techniques, which span; single cell sequencing, next generation bulk sequence analysis, haplotype analysis, analysis of recombination frequencies, mouse genetics and general analysis of meiosis. This project will see you develop significant computational novelty. The project will work towards uncovering how the generation of genetic diversity is regulated, and potentially affected in human disease such as certain types of infertility.

The project may be adapted to include some wet-lab experiments if there is a strong desire to do so.

Requirements: a degree in bioinformatics
Preferable: an understanding of molecular biology, particularly genetics.

$5,000 Honours and Masters scholarships are available to a limited number of outstanding candidates. Scholarships are awarded on a competitive basis and at the discretion of SVI.

Background reading:

1. Crismani et al 2012. FANCM limits meiotic crossovers. *Science*
2. Kasak et al 2018. Bi-allelic Recessive Loss-of-Function Variants in FANCM Cause Non-obstructive Azoospermia. *American Journal of Human Genetics*

Genomics and Immunology Laboratory

T cells constitute part of adaptive immune system. The differentiation of these cells is tightly controlled in order to produce cells that can effectively combat foreign pathogens without causing autoimmunity.

T cells come in a wide variety of functional subsets, each playing a different role under different immunological settings. We are interested in understanding the molecular mechanisms that control the differentiation of these cells.

Our lab is also interested in the biogenesis and function of non-coding RNAs. Other than a few notable examples, RNA was for a long time simply thought of as an intermediary between DNA (genes) and proteins, i.e., a transmitter of information. However, it is now clear that there are many classes of RNAs with functions in their own right, rather than coding for proteins. We are particularly interested in understanding the biogenesis of microRNAs, but also of other non-coding RNAs.

The following is a list of projects areas on offer. However, students are also encouraged to propose their own ideas. Projects within the general areas of Genomics, RNA biology and/or T cell biology are always a possibility, and can be adapted for PhD, Masters or Honours students.

Read more about their research: www.svi.edu.au/research_themes/genomics_and_immunology

TRANSGENERATIONAL INFLUENCE OF DIET ON AUTOIMMUNE SUSCEPTIBILITY

Suitable for PhD

Primary Supervisor: A/Prof Mark Chong
Email: mchong@svi.edu.au

The development of autoimmune diseases such as Type 1 Diabetes (T1D) and Systemic Lupus Erythematosus (SLE) is highly dependent on the genetic susceptibility alleles that are inherited. However, it is clear that environmental factors also play critical roles. Exposure to cues, such as diet, can influence the development of autoimmunity in at-risk individuals. Dietary factors can have direct effects on the immune cells of the body, or indirectly via influences on the microorganisms in the gut. While it is not difficult to envisage how an environmental factor can have a direct effect on at-risk individuals,

evidence suggest that such cues may also influence autoimmune susceptibility at transgenerational level. That is, the exposure of parent to an environmental factor then affects the susceptibility of their offspring. The goal of this project is to determine whether diet does indeed have a transgenerational impact in mouse models of T1D and SLE. In particular, this project will focuse on the impact of the diet of male parents. This is because diet is thought affect the small regulatory RNAs that are loaded into maturing sperm. These molecules have the potential to be transmitted upon fertilization of the ovum, where they may influence the gene regulatory landscape of the early embryo.

Human T-Cell Laboratory

Research in the Mannering laboratory focuses on defining the antigen specificity and function of human T cells that cause type 1 diabetes (T1D). Recently we pioneered techniques for isolating T cells from the pancreatic islets of deceased organ donors who suffered from type 1 diabetes. These cells give us an unprecedented opportunity to study human T cells from the site of autoimmune mediated beta cell destruction that causes T1D.

WHAT ARE ANTIGENS/EPITOPES ARE RECOGNIZED IN BY ISLET-INFILTRATING CD8$^+$ T CELLS IN PEOPLE WITH TYPE 1 DIABETES?

Suitable for PhD or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Stuart Mannering**
Co-supervisors: **Dr Colleen Elso, Prof Helen Thomas**

For enquiries about current projects please contact:

A/Prof Mannering	Dr Elso	Prof Thomas
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Type 1 diabetes is an autoimmune disease caused by the combined actions of CD4+ and CD8+ T-cell against the insulin-secreting beta cells found in the islets of Langerhans in the pancreas. While CD4+ T cells are the principal regulators of the (auto)immune response, CD8+ T cells are believed to be the primary 'killers' of beta cells in type 1 diabetes. However, the antigens/epitopes that are 'seen' by pathogenic CD8+ T cells are not defined. This is an important question because knowledge of the targets of CD8+ T cells is essential for the development of new therapies to prevent type 1 diabetes. In addition, this is a major gap in our understanding of human autoimmunity in type 1 diabetes.

We pioneered techniques for isolating and characterising human islet-infiltrating T cells (Pathiraja et al. Diabetes 2015), We now have a large panel of CD8+ T cells, or TCR sequences, from the residual pancreatic islet of seven deceased organ donors who suffered from T1D. This gives us a unique panel of CD8+ T-cell clones strongly implicated in the pathogenesis of human T1D to study.

We have established techniques for screening large of human TCRs for responses to numbers of beta cell antigens. This project will reveal the epitopes seen by human CD8+ T cells strongly implicated in the immune pathogenesis of type 1 diabetes. The student will learn state-of-the-art human T-cell

immunology, retroviral transduction and molecular biology techniques in a stimulating and supportive environment.

WHAT ARE THE FUNCTIONAL PROPERTIES OF HUMAN CD4+ T CELLS, FROM PEOPLE WITH TYPE 1 DIABETES, THAT RESPOND TO PROINSULIN C-PEPTIDE?

Suitable for PhD or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Stuart Mannering**
Co-supervisors: **Dr Colleen Elso, Prof Helen Thomas**

For enquiries about current projects please contact:

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Type 1 diabetes (T1D) is an autoimmune disease caused by the CD4+ and CD8+ T-cell response against the insulin-secreting beta cells found in the islets of Langerhans in the pancreas (referred to as islets). Genome wide association studies have shown that the HLA alleles HLA-DQ8 and DQ2 are strongly associated with risk of developing type 1 diabetes. Since the only known function of these HLA alleles is to present peptide antigens to CD4+ T cells, this strongly implicates CD4+ T cells in the immune pathogenesis of human type 1 diabetes. Following our discovery that many human islet-infiltrating CD4+ T cells recognize epitopes derived from proinsulin C-peptide (Pathiraja et al. Diabetes 2015 & Delong et al. Science, 2016). Proinsulin is insulin's precursor, C-peptide is produced during the processing of proinsulin to insulin. More recently we found that full-length C-peptide is an important antigen in people with type 1 diabetes (So et al *PNAS* 2018).

The aim of this project is to use 10X Genomics single-cell sequencing to analyse the TCR usage and epitope specificity of human CD4+ T cells that respond to C-peptide. In addition, the genes expressed by CD4+ T cells specific for C-peptide, an autoantigen, will be compared to genes expressed by CD4+ T cells, from the same donor, who respond to the microbial antigens, influenza matrix protein and/or tetanus toxoid. This work will give unprecedented new insights into the function, and TCR diversity, human CD4+ T cells specific for microbial an autoantigens. This work will lay the foundations for developing T-cell assays to monitor human beta cell antigen specific T cell responses in type 1 diabetes.

HOW TO DETECT A T CELL'S RESPONSE TO AUTOANTIGEN?

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Stuart Mannering**
Co-supervisors: **Dr Colleen Elso, Dr Pushpak Bhattacharjee**

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The goal of the research undertaken in the Mannering Lab is to identify the antigens recognized by human T cells implicated in the immune pathogenesis of type 1 diabetes. We take a functional approach to identifying antigens this means that we identify antigens based on a T cell's response. Traditionally this has been done using primary T-cell clones. These are T cells isolated from the blood, or more recently the pancreatic islets, which are grown and characterized in vitro. Unfortunately, primary T cells cannot be grown indefinitely in vitro. To circumvent this problem we have developed T-cell avatars, where the T-cell receptor from a primary T cell is cloned and transduced into a cell line. These avatars, which can be grown indefinitely are then used to analyse the TCR's specificity. However, we need robust and sensitive reporters that can indicate when a TCR has recognized an antigen.

The aim of this project is to develop a panel of promoter constructs that faithfully report on T-cell activation in a TCR transduced cell line. The student working on this project will develop high level skills in molecular biology, retroviral transduction and T-cell immunology.

Immunology and Diabetes Unit

Our research is focused on preventing pancreatic beta cell destruction to preserve beta cell mass in diabetes. We have identified pathways of beta cell death in type 1 and 2 diabetes. We aim to understand how different effector mechanisms participate in diabetes development, and how they can be prevented. The pathogenesis of type 1 and 2 diabetes is complex, with immune abnormalities in type 1 and insulin resistance in type 2 diabetes.

Read more about their research: https://www.svi.edu.au/research_themes/islet_biology

USING THE JAK1/JAK2 INHIBITOR BARICITINIB TO TREAT NEW-ONSET TYPE 1 DIABETES

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Prof Helen Thomas**
Co-supervisor: **Prof Tom Kay**

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Our goal is to prevent the immune-mediated destruction of insulin-producing pancreatic beta cells that leads to type 1 diabetes. The JAK-STAT signalling pathway is critical for immune-mediated pancreatic beta cell destruction. We have shown that inhibitors of JAK1/JAK2 prevent diabetes and also reverse newly diagnosed diabetes in the non-obese diabetic (NOD) mouse model of type 1 diabetes. The goal of this project is to investigate whether the JAK inhibitor baricitinib dampens autoimmunity and preserves beta cell function in human type 1 diabetes.

We plan to conduct a placebo-controlled trial to investigate the safety and efficacy of baricitinib in 83 individuals aged 12-30 years with recent-onset type 1 diabetes. The primary objective is to determine if baricitinib can reduce the loss of meal-stimulated C-peptide, a measure of beta-cell function. As

exploratory objectives, we plan to evaluate the impact of baricitinib on type 1 diabetes-associated immune responses. To achieve this, we will use two complementary approaches, single-cell proteomics and single-cell transcriptomics. We hypothesise that baricitinib will induce intra-individual and inter-individual changes in immune cells. Single-cell RNA-seq will capture the biological pathways altered by baricitinib while mass cytometry will be used to capture the phenotypical and functional differences between cells.

INHIBITING HYPOXIA AND INFLAMMATION-INDUCED DAMAGE TO IMPROVE THE OUTCOMES OF ISLET TRANSPLANTATION

Suitable for Honours or Masters

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Michaela Waibel**
Co-supervisor: **Prof Tom Kay**

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Islet transplantation is used clinically for replacement of insulin-producing pancreatic beta cells in a subset of patients with type 1 diabetes. During isolation, culture and transport of human islets for transplantation the islets are subjected to a number of stresses that may influence their survival, engraftment and function after transplantation. Analysis of transcriptional changes occurring during islet isolation and culture has provided valuable insights into the stress response of islets initiated by pancreatic islet processing. This has revealed changes in the RNA levels of markers of stress-activated pathways including hypoxia and inflammation.

Aim: We will test methods to reduce the stress response of islets before and during transplantation and determine if these promote islet survival in vivo. Mouse and human islets will be cultured in hypoxic conditions, together with small molecule inhibitors of inflammatory pathways, then transplanted under the kidney capsule of diabetic recipient mice. The minimal mass required for reversal of diabetes will be determined. Stress response gene expression will be measured in the islets and grafts. This work has the potential to be applied to clinical islet transplantation in the future.

FACTORS THAT DETERMINE ISLET ANTIGEN-SPECIFIC T CELL EXPANSION BEFORE THE ONSET OF TYPE 1 DIABETES

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Prof Helen Thomas**
Co-supervisor: **Dr Bala Krishnamurthy**

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Our goal is to prevent the cytotoxic $CD8^+$ T cell-mediated destruction of insulin-producing pancreatic beta cells that leads to type 1 diabetes. Islet-specific $CD8^+$ T cells appear in cycles in the blood reflecting waves of clonal proliferation, they expand just before diagnosis of diabetes and their quantity in the islets reflects the extent of pathology. These data are consistent with progression to diabetes being determined by islet-specific T cell number. However, how T-cell proliferation is regulated during spontaneous progression to type 1 diabetes is poorly understood. Insight into this and the ability to measure it, or the factors that regulate it, would provide valuable prognostic information in individuals at risk of developing type 1 diabetes.

We have recently observed that islet-specific $CD8^+$ T cells are dramatically increased in number in interferon-γ receptor mutant NOD mice. This explains why diabetes occurs in these mice in which other hallmarks of type 1 diabetes are suppressed and is a strong indication that the number of $CD8^+$ T cells may be an informative marker of disease progression.

Our hypothesis is that antigen-specific $CD8^+$ T cell expansion determines the rate of progression of diabetes and that this expansion is associated with a change in T-cell phenotype and increased cytotoxic function. We aim to identify mechanisms that regulate proliferation of antigen-specific $CD8^+$ T cells.

UNDERSTANDING HOW TYPE 17 IMMUNITY AND IL-17 CYTOKINES REGULATE TYPE 1 DIABETES

Suitable for Honours, Masters or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Andrew Sutherland**
Email: asutherland@svi.edu.au

Type 1 diabetes (T1D) is a human autoimmune disease involving the progressive destruction of the insulin producing β-cells in the pancreatic islets. A clearer understanding of the autoimmune processes will provide new opportunities for therapeutic intervention in human T1D patients. **Our primary goal is to cure T1D by developing novel immune therapies**.

Recent findings in our laboratory and others indicate that type 17 immune responses and IL-17 cytokines control the development of T1D in animal models. This project is focussed on identifying the underlying immune mechanisms and testing the therapeutics effects of immune inhibitors targeted against these

pathways in T1D. The project will make use both mouse and human systems including newly developed gene knockout NOD mice, novel immune inhibitors, CRISPR/Cas9 gene editing, cellular and molecular immunology techniques, pancreatic islet isolation, RNA-seq, and flow cytometry.

SVI provides $5000 Honours/PhD top-up awards for a limited number of outstanding students.

Molecular Genetics Unit

Keeping our genomic DNA intact and turning our genes on and off at the correct time is crucial for normal human development and the prevention of cancer. The laboratory is interested in molecular mechanisms involved in the regulation of the cellular response to DNA damage and the regulation of gene expression. We are studying these processes using a wide range of biochemical, cell biological, molecular biology, structural and genetic approaches in mice, yeast and human cells.

Read more about their research: https://www.svi.edu.au/research_themes/molecular_genetics

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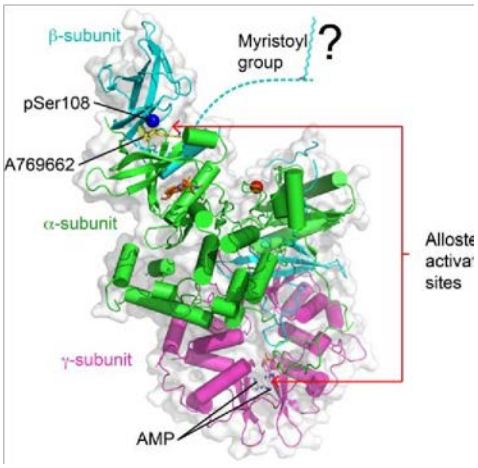
Protein Chemistry and Metabolism Unit



Our research is concerned with the control of the body's energy metabolism via an enzyme called AMPactivated protein kinase (AMPK). This enzyme acts as the body's fuel gauge, determining its energy level and is at the hub of metabolic control in response to diet and exercise.

Read more about their research:
https://www.svi.edu.au/research_themes/protein_chemistry_and_metabolism

Supervisors: Prof Bruce Kemp, Dr Sandra Galic, Dr John Scott, Dr Jon Oakhill, Dr Kim Loh, Dr Christopher Langendorf, Dr Kevin Ngoei

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qTRAP mass spectrometer

Many diseases have a metabolic dimension including type 2 diabetes, obesity, cancer and cardiovascular disease. These place enormous financial and medical burdens on the Australian economy. An important regulator of metabolism is the AMP-activated protein kinase (AMPK), an αβγ heterotrimer that functions as both a cellular fuel gauge and co-ordinator of wholebody metabolism. AMPK is indirectly activated by AMPelevating drugs such as metformin, the most widely used drug treatment for Type 2 diabetes. We offer both Honours and PhD projects that will produce innovative research into novel

mechanisms that control AMPK. These discoveries will greatly increase our understanding of AMPK regulation by cellular processes and aid design Crystal structure of AMPK of more effective AMPK drugs.

Our laboratory offers training in a wide area of biochemistry, structural biology, cell biology and mouse models. Typical methodologies we routinely use include molecular biology, protein expression and purification (E.coli and insect cells system), in vitro phosphorylation assays (kinase and phosphatase assays), crystallography, proteomics (mass spectrometry TOF and qTRAP), mammalian cell culture (transfection, RNAi, lentiviral system) as well as conditional mouse models (Cre-Lox recombination system, CRISPR knock-in mouse models, physiology and behavioral studies). These techniques are integrative across all projects and prospective students will receive appropriate training from experts in the field.

REGULATION OF GHRELIN SIGNALLING BY AMPK

Suitable for Honours or Masters of Biomedical Science

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Sandra Galic
Co-supervisor: Prof Bruce Kemp

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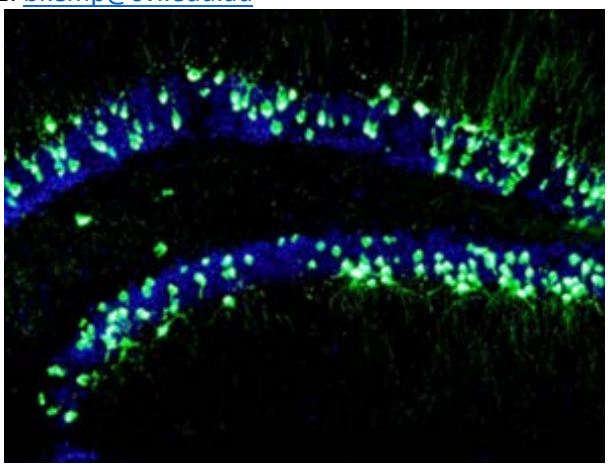

Ghrelin is a hormone that is produced by the stomach and acts in the brain to stimulate appetite, food-related reward behaviour and lipid storage in adipose tissue. Importantly, ghrelin is known to mediate the body weight regain that often follows diet-induced weight loss. We have shown that regulation of lipid metabolism in the hypothalamus by the energy sensing enzyme AMP-activated protein kinase (AMPK) is required for increases in appetite in response to low energy conditions, such as fasting or cold exposure. Furthermore, we have evidence that this process is mediated by ghrelin and that disrupting AMPK signalling suppresses ghrelin-induced body weight gain. This project will use genetically modified mice to determine whether deletion of AMPK from ghrelin-sensitive cells can suppress appetite during low-calorie feeding and whether specific targeting of ghrelin-AMPK signalling is an effective strategy to prevent rebound weight gain after dieting. This study will involve comprehensive metabolic analyses in mice including measurements of body composition, energy expenditure, physical activity, metabolic flexibility, food intake behaviour and glucose tolerance. In addition the project will offer training in a range of biochemical and histological techniques, such as analyses of fatty acid synthesis and oxidation, kinase activity, gene expression, immunoblotting, immunohistochemistry and ELISA.

INHIBITION OF MICROGLIA INFLAMMATION BY AMPK FOR OBESITY TREATMENT

Suitable for PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Sandra Galic
Co-supervisor: Prof Bruce Kemp

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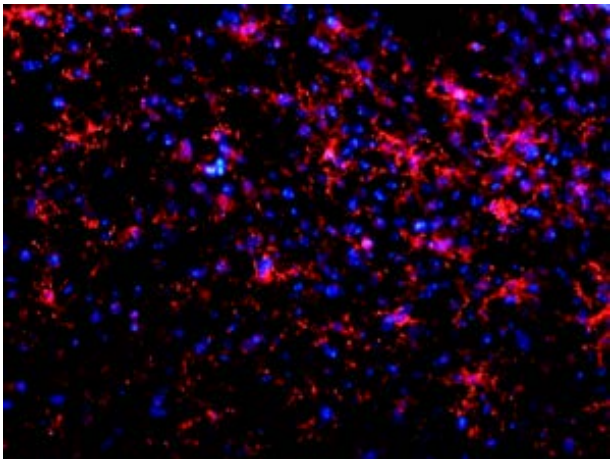

Consumption of high-calorie diets is associated with the onset of inflammation in the hypothalamus, the main brain area involved in the regulation of appetite, energy expenditure and glucose homeostasis. This overnutrition-induced inflammation is mediated by microglia, which are macrophage-like cells that normally protect the brain from pathogens and help with clearance of cell debris. However, when chronically activated in response to dietary fatty acids, microglia generate an inflammatory environment within the hypothalamus that is toxic for neighbouring neurons and damages neuronal circuits that normally control energy homeostasis and hepatic glucose production. We have previously shown that the AMP-activated protein kinase (AMPK) has anti-inflammatory effects in bone marrow derived macrophages and inhibits adipose tissue inflammation associated with a high-fat diet. This project will investigate whether AMPK activation in microglia can suppress hypothalamic inflammation and damage of appetite-regulating neurons resulting in reduced body weight gain with high-fat feeding. The study will involve the isolation and culture of primary microglia and handling of knockout and transgenic mice to investigate hormone signalling pathways, gene expression, whole-body energy homeostasis and hepatic glucose production. Commonly used techniques will include brain immunohistochemistry, confocal microscopy, immunoblotting, Real-time PCR, ELISA, flow cytometry, calorimetry and body composition analyses by NMR.

THE ROLE OF AMP-ACTIVATED KINASE IN SUPPRESSING ATHEROSCLEROSIS

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Kim Loh**
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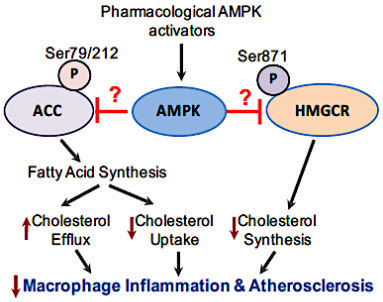

Fig. 1: Will activation of the AMPK pathway suppress atherosclerosis by decreasing cholesterol synthesis and uptake and increasing cholesterol efflux?

Stemming from dyslipidemia and maladaptive inflammatory responses, atherosclerosis precedes and predicts the development of cardiovascular complications including stroke and myocardial infarction, which account for more than 30% of all deaths worldwide. AMP-activated kinase (AMPK) is a key regulator of whole body energy metabolism, including lipid metabolism, glucose uptake and mitochondrial biogenesis. It has been shown that the suppression of AMPK activity under conditions of chronic over-nutrition may contribute to the development of metabolic diseases. We have recently shown that activation of the regulatory enzyme AMPK reduces cholesterol production in a way similar to statin therapy (Loh et.al 2019 Hepatology Communications). The main objective of this project is to study how AMPK controls cholesterol production in the liver and macrophages. AMPK's activation in response to exercise is thought to be part of the protective mechanism against the development of heart disease. We aim to investigate whether by changing the activity of AMPK, using drugs that currently in clinical trial, we can augment the body's natural control mechanisms and significantly reduce the development of atherosclerosis. Since reduction of AMPK activity was found in response to hyperglycemia, the project also aims to shed light on whether impairment of AMPK signaling responsible toward the pathology of diabetes-associated atherosclerosis. We hypothesize that pharmacological activation of the signaling cascade which culminates in AMPK activation may serve as an alternative cholesterol lowering therapy and reducing atherosclerosis development.

INVESTIGATING A NOVEL MECHANISM FOR IMPROVING BETA-CELL FUNCTION IN TYPE 2 DIABETES

Suitable for Honours or PhD

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Kim Loh**
Email: kloh@svi.edu.au

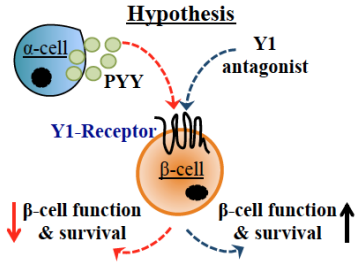

Fig. 1: The role of Y1 ligand, peptide YY (PYY) and Y1 antagonist in the regulation of β-cell function and survival.

Current efforts to enhance β-cell function focus mostly on the pathways that stimulate insulin release, very little is known about the inhibitory mechanisms that terminate insulin secretion. Improving β-cell function by inhibiting the counter-regulatory pathway that suppresses the release of insulin remains largely unexplored as a therapeutic option. Peptide YY has been shown to activate neuropeptide Y1 receptor to attenuate insulin secretion in mouse pancreatic islets. We have

identified that the neuropeptide Y1 receptor is also expressed in the β-cells in humans. Our recent published studies (Loh et.al 2017 Nature Communications) have shown that pharmacological inhibition of this receptor using a Y1 receptor specific antagonist, BIBO3304, significantly enhanced β-cell function in human islets. Despite this, the beneficial effects of Y1 inhibition in improving β-cell function and glycemic control in type 2 diabetes remain to be examined. We will now extend our published work with a detailed exploration of Y1 receptor inhibition in type 2 diabetes models. We aim to investigate whether pharmacological inhibition of Y1 receptor signalling will enhance β-cell function and improve glucose homeostasis in type 2 diabetes.

DRUG DEVELOPMENT FOR METABOLIC DISEASES

Suitable for Honours or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof. Jon Oakhill
Co-supervisors: Prof Bruce Kemp, Dr Chris Langendorf

For enquiries about current honours and PhD projects please contact:

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AMP-activated protein kinase (AMPK) is a central regulator of cellular energy metabolism that phosphorylates multiple protein targets to adapt cellular metabolism to energy and nutrient availability. AMPK dysregulation is associated with a range of prevalent metabolic diseases (e.g. type 2 diabetes, cancer and cardiovascular disease), thus huge efforts are being made to develop AMPK-targetting drugs.

AMPK is a heterotrimer complex composed of catalytic a (isoforms a1/2) and regulatory b (b1/2) and g (g1/2/3) subunits. A major problem with current pan AMPK-targetting drugs is they activate AMPK throughout the body, causing off-target effects such as cardiac hypertrophy. Intriguingly, AMPK b2-isoform is found almost exclusively in metabolically-active tissues e.g. liver, adipose and skeletal muscle, the latter of which is a validated target tissue for improved glucose control in response to pan-AMPK activators (Merck, Pfizer). Our aim is to develop b2-specific AMPK activators to trigger AMPK signalling in these tissues without complications associated with off-target effects.

As part of our team of 5 postdoctoral scientists, you will receive training from experts in biochemistry, cell biology, x-ray crystallography and mass spectrometry. The team adopts a collaborative approach with studies regularly published in high impact journals.

THE CELLULAR FUEL GAUGE: NOVEL MECHANISMS OF METABOLIC CONTROL

Suitable for Honours or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: A/Prof Jon Oakhill
Co-supervisor: Dr John Scott

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All living organisms have a critical need to couple energy and nutrient supply with growth. A major sensor of the nutrient status of a cell's environment is the evolutionarily conserved AMP-activated protein kinase (AMPK). AMPK acts as the cell's fuel gauge by directly sensing energy state (AMP, ADP and ATP), and orchestrating multiple branches of metabolism by phosphorylating and regulating key rate-limiting enzymes in these pathways.

AMPK is a heterotrimer complex composed of catalytic α (isoforms α1/2) and regulatory β (β1/2) and γ (γ1/2/3) subunits. While the majority of research effort has targeted downstream effects of AMPK signalling, relatively little is known about how AMPK itself is regulated. For example, ~150 phosphosites have been identified on AMPK, yet only a handful of upstream kinases have been characterised. Our research goal is to bridge this knowledge gap by hunting for regulatory AMPK kinases and metabolite ligands.

As part of our laboratory, you will receive multi-disciplinary training from experts in biochemistry, cell biology, x-ray crystallography and mass spectrometry. The team adopts a highly collaborative approach, with studies regularly published in high impact journals.

Structural Biology Unit

The focus of our research is to visualise the three-dimensional structures of medically important proteins using X-ray crystallography. A particular focus is proteins that play a role in infection (bacterial, parasitic or viral), cancer (particularly leukaemia, breast and prostate) and neurological diseases (e.g. Alzheimer's, Parkinsons). The structures provide a detailed understanding of how each protein works and how it contributes to disease. Most importantly, the structures can be used to discover drugs using computational and biophysical approaches.

Our work is supported by labs that specialise in protein expression, purification and electrophysiology.

The Unit includes the ACRF Rational Drug Discovery Centre funded by a $2M grant from the Australian Cancer Research Foundation that has equipment for protein production of large amounts of proteins and biophysical tools for measuring protein small molecule interactions. Structural biology projects involve regular experiments at the Australian Synchrotron which is only 20 minutes' drive from the laboratory.

Example projects in each of the disease areas follow.

Read more about their research: https://www.svi.edu.au/research_themes/structural_biology

TARGETING MICROGLIA IN NEURODEGENERATIVE DISEASES

Suitable for PhD, Honours

Department: **Medicine and Radiology** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: Prof Michael Parker
Co-supervisor: Dr Jon Gooi

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Dementias, such as Alzheimer's and Parkinson's diseases, are the fourth biggest killer in developed countries. A growing body of literature implicates microglial activation as a key point in the pathogenesis of a variety of neurodegenerative disorders including dementias and a potential avenue for the development of novel therapeutic agents. Microglial cells are innate immune cells of the central nervous system (CNS) and act as the first and main form of active immune defence. Upon detection of pathogens or damage, microglia adopt an activated state resulting in an inflammatory response. The activated microglia respond to alterations in brain tissue homeostasis by changing their gene expression profile, leading to the release of a host of neuroactive signalling molecules, such as neuroinflammatory cytokines, that can contribute to the pathophysiology of a wide range of neurodegenerative diseases and psychiatric disorders. Microglial cells can eliminate toxins generated in these diseases in a process called phagocytosis which involves engulfing the toxins followed by internalisation, destruction and elimination from CNS. However, in neurodegenerative diseases the microglia can be overwhelmed by the amount of toxic species present.

We have been focusing our work on microglial cell surface receptors that can be potentially modulated by small molecule ligands to increase phagocytosis whilst decreasing production of neuroinflammatory cytokines. Our pipeline for drug discovery starts by expressing and purifying target protein receptors, crystallising the proteins and determining their 3D atomic structures by X-ray crystallography at the Australian Synchrotron. We then use these structures to identify small molecules that will bind to the proteins by docking millions of molecules (virtual screening), one at a time, into cavities (druggable pockets) on the protein surface. We then purchase the most promising molecules and test whether they bind to the protein using direct binding assays. The tightest binding ligands are then tested in microglial assays to assess phagocytosis activity and cytokine production. Active molecules are then transformed into drug-like molecules using medicinal chemistry guided by the crystal structure. An example of our recent work in the area can be found in reference 1.

1. Miles LA, Hermans SJ, Crespi GAN, Gooi JH, Doughty L, Nero TL, Markulić J, Ebneth A, Wroblowski B, Oehlrich D, Trabanco AA, Rives M, Royaux I, Hancock NC, Parker MW. Small Molecule Binding to Alzheimer Risk Factor CD33 Promotes Aβ Phagocytosis. *iScience*. 2019 Sep 27; 19: 110–118.

STRUCTURAL BIOLOGY OF PROTEINS INVOLVED IN CANCER

Suitable for Honours, Masters or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Craig Morton
Co-supervisor: Prof Michael Parker

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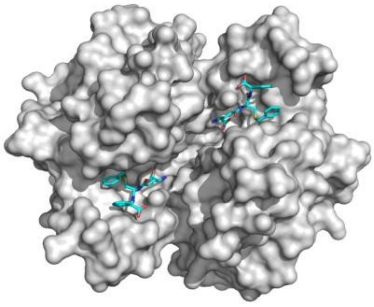
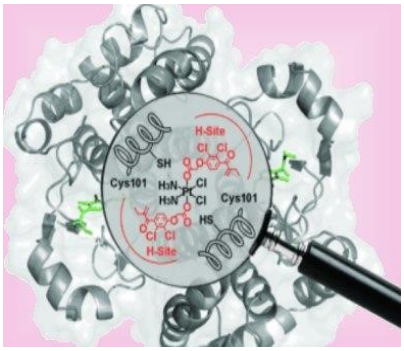




We are investigating, though structural and biochemical means, how a range of ruthenium, arsenic and osmium-based drugs and drug-like compounds interact with Glutathione S-Transferase (GST) family of proteins.

Conventional cancer chemotherapy kills rapidly growing cells indiscriminately, causing significant side-effects and can lead to disease re-occurrence and resistance to the drugs. One of our interests is the Glutathione S-Transferase (GST) family of proteins that function by recognising foreign small molecule toxins in the body, causing them to be eliminated from the cell. Unfortunately, commonly used anti-cancer drugs are also recognised as toxic by GST, which is often overexpressed in cancer tissues and is associated with transformation to malignancy and the adaptive resistance to anti-cancer drugs. There is thus an urgent need for the design of new anti-cancer drugs that circumvent the development of GST-mediated resistance to treatment. Very recently, there has been an increasing interest in the development of metal-based drugs as effective and potent protein targeted chemotherapies. We are investigating, though structural and biochemical means, how a range of ruthenium, arsenic and osmium-based drugs and drug-like compounds interact with GSTs. Students will investigate how these compounds work, as well as any drug-like molecules we develop, using X-ray crystallography and a range of biophysical techniques.

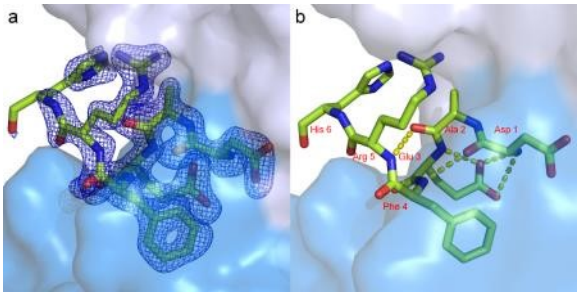
This project is conducted in St Vincent's Institute of Medical Research, Structural Biology Unit.

STRUCTURAL BIOLOGY OF PROTEINS INVOLVED IN MENTAL ILLNESSES

Suitable for Honours, Masters or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Prof Michael Parker
Email: mparker@svi.edu.au



Alzheimer's disease (AD) is the fourth biggest killer in developed countries. Amyloid precursor protein (APP) plays a central role in the development of AD, through generation of the toxic Abeta peptide by proteolytic breakdown of APP. Here we will use X-ray crystallography at the Australian Synchrotron to determine the 3D atomic structures of Abeta bound to therapeutic antibodies currently in clinical trials in order to understand how these molecules recognise Abeta. We have also developed novel diabodies which can target Abeta for elimination. Structural biology will guide engineering of more potent antibodies and diabodies as treatments for AD.

STRUCTURAL BIOLOGY OF PROTEINS INVOLVED IN INFECTION

Suitable for Honours, Masters or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Craig Morton
Co-supervisor: Prof Michael Parker

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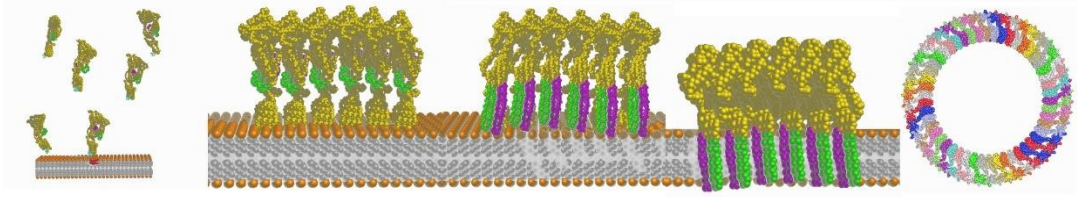

The b-barrel pore-forming toxins constitute the largest group of functionally related toxins/proteins and are expressed in many species in the prokaryotic and eukaryotic kingdoms and also include the membrane attack complex/perforin (MACPF) family of mammalian immune defence proteins. Despite their widespread occurrence and role in bacterial pathogenesis and immune defence, the detailed mechanism by which they form pores remains an enigma. The overall aim here is to visualise the 3D structures of family members as a basis for functional studies to reveal the molecular details of how these toxins insert into membranes to form b-barrel pores and how the process is regulated. The structures will shed light on one of the most fundamental biological events (namely, protein insertion into cell membranes) and

also provide the basis for the design of novel tools with various biotechnology applications and the design of novel antibiotics.

This project is conducted in St Vincent's Institute of Medical Research, Structural Biology Unit.

STRUCTURAL BIOLOGY OF PROTEINS INVOLVED IN BONE DISEASES

Suitable for Honours, Masters or PhD

Department: Medicine and Radiology **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Brett Bennetts
Co-supervisor: Prof Michael Parker

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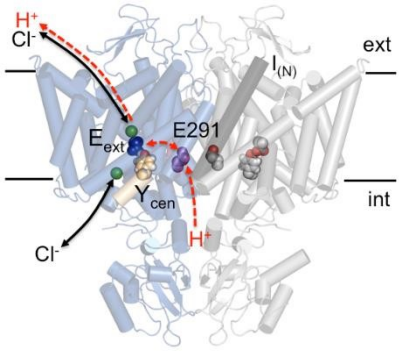

Figure: Understanding a rare disease to develop treatment for common bone diseases

Remodelling of bone is critical for normal physiological function and becomes dysfunctional in diseases such as Osteoporosis (bone thinning and fragility) and Osteosarcoma (bone cancer), where a paucity of bone material causes debilitating illness that is currently irreversible. Alternatively, mutation of a specific membrane protein, ClC-7, causes a rare inherited disease (Osteopetrosis) in which too much bone material is deposited leading to abnormally increased bone mass. Our preliminary studies have suggested a molecular basis for aberrant function of ClC-7 mutants in Osteopetrosis. The aim of this project is to fully characterise the mechanism of ClC-7 mutations that cause Osteopetrosis in order to develop drugs that mimic the phenotype of these mutations. Uniquely, these drugs would be able to reverse the damage done by a number of debilitating bone diseases. The project will involve a diverse range of experimental approaches, from X-ray crystallography and *in silico* computational studies to binding studies and functional measurements using advanced electrophysiological techniques and optical assays.

This project is conducted in St Vincent's Institute of Medical Research, Structural Biology Unit.

O'Brien Institute Research Projects (Department of St Vincent's Institute)

TISSUE ENGINEERING OF 3D SOFT TISSUES AND ORGANS FROM STEM CELLS

Note: This is not a specific project being offered, but it is an introductory overview of the Tissue Engineering Programs at the O'Brien Institute. Specific projects are listed after this. Students are generally enrolled through the Department of Surgery.

Tissue engineering is the creation of new body parts from the building blocks of cells, a matrix and a blood supply. The cells may be autologous or foreign and they may be differentiated to stem cells. These may be adult, embryonic or sourced from cord blood. The exciting new field of iPS cells offers the hope of individualized tissue without rejection.

- Matrix – the matrix environment influences cell behaviour. These matrices may be synthetic or biologically derived, rigid, biodegradable or hydro gels.
- Blood supply – we have developed a chamber model of in vivo tissue engineering where the blood supply is created by microsurgical means (AV loop) and when inserted into a closed chamber induces intense angiogenesis. In this environment, cells are attracted to the chamber and the fibrin matrix and a fibrous tissue organoid develops spontaneously.
- Cell manipulation – we can influence the specific tissue type that forms by seeding the chamber with cells, which can survive, and differentiate according to the environment created within the chamber. Using this technique we have been able to create skeletal muscle, fat and bone, as well as heart, pancreas, thymus, liver and growth hormone secreting organs.

By implanting a vascularized pedicle, containing a small amount of fat in the chamber, spontaneous growth of the fat occurs to fill the chamber space. In rats, rabbits and pigs we have tested this phenomenon and have been able to fill an 80mm chamber. This offers the potential to grow tissue for breast reconstruction.

Why does tissue grow within the chamber? We believe one of the critical factors in the growth observed is the creation of a space, which influences the forces transmitted through the cells. In general, tension results in cell proliferation and migration, while relaxation results in cell growth arrest, differentiation or apoptosis. Most recently, we have grown beating cardiac tissue in rat chambers from implanted cardiomyocytes and this tissue responds to cardiogenic drugs and to pacing.

This exciting field offers the possibility for a number of projects related to tissue engineering including microsurgery, angiogenesis, lymphangiogenesis, stem cell biology, mechanotransduction, cytoprotection and biomaterials (collaboration with The University of Melbourne Department of Bioengineering).

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2. Tanaka Y, Morrison WA et al, Generation of an Autologous Tissue Matrix Flap by Combining and AV Shunt Loop with Artificial Skin in Rats, Br J Plast Surg 2000 Jan; 53 : 51-7.
3. Lepore, D. et al, Survivial and differentiation of pituitary colony-forming cells in vivo, Stem Cells, 2007 Jul:25(7): 1730-6.

Cardiac Regeneration Group

INVESTIGATING CARDIOVASCULAR DISEASE IN FRIEDREICH'S ATAXIA USING HUMAN INDUCED PLURIPOTENT STEM CELLS

Suitable for Honours, Masters or PhD

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Shiang (Max) Lim**
Co-supervisor: **Dr Jarmon Lees**

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This project aims to generate patient-specific cardiovascular cells from induced pluripotent stem cells to establish novel human Friedreich's Ataxia disease models for disease modelling and drug discovery.

Friedreich's ataxia (FRDA) is an autosomal recessive disease characterized by degeneration of neurons and heart disease. Reduced frataxin (FXN) protein due to GAA repeat expansions within the first intron of the FXN gene results in mitochondrial dysfunction and iron accumulation leading to increased oxidative stress and cell death in the nervous system and heart. There is currently no treatment to effectively cure, halt or even slow the progression of FRDA. This project aims to generate patient-specific cardiovascular cells from induced pluripotent stem cells to establish novel human FRDA disease models for disease modelling and drug discovery.

The knowledge and skills involved in this project are suitable for students who are interested in stem cell biology, cardiovascular disease, and mitochondrial biology. A student working on this project will have the opportunity to learn various experimental skills, including; cell culture, protein and gene analysis, histology and mitochondrial assays.

MODELLING DIABETIC-INDUCED CARDIOMYOPATHY USING HUMAN CARDIAC ORGANOIDS

Suitable for Masters of Biomedical Science or PhD

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Shiang (Max) Lim**
Co-supervisor: **Dr Jarmon Lees**

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For people with diabetes the risk of heart disease is 2-4 times higher than in adults without diabetes. In particular, people with diabetes are significantly more prone to cardiac arrhythmias, an irregular heartbeat that can be fatal. The cardiac autonomic nervous system (the nerves that innervate the heart) plays an important role in arrhythmias and contribute to heart failure. However, current pre-clinical

human heart disease models completely lack this pivotal cell type. Our lab has recently established a novel proprietary cardiac organoid model that contains heart cells, blood vessels and autonomic neurons completely derived from human induced pluripotent stem cells. This project aims to use this new pre-clinical human model to study the pathophysiology of diabetic heart disease and arrhythmias.

The knowledge and skills involved in this project are suitable for students who are interested in stem cell biology, organoid research, cardiovascular disease and diabetes. A student working on this project will have the opportunity to learn various experimental skills, including; cell culture, protein and gene analysis, histology, electrophysiology and tissue engineering.

Lympathic and Regenerative Surgery Group

UNDERSTANDING THE ROLE OF CXCR7 IN LYMPHODEMA FOLLOWING RADIATION INJURY

Suitable for Honours, Masters or PhD

Department: Surgery **Location: St Vincent's Institute of Medical Research**

Primary Supervisor: Dr Ramin Shayan
Co-supervisor: Dr Tara Karnezis

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The range of cancers for which radiotherapy is being used is ever expanding with unavoidable dose exposure that occurs in surrounding normal cells. This radiation exposure does not have the effect of simply killing normal cells; but elicits a permanent damage or injury profile that not only persists, but continues to evolve throughout the life of the patient. These changes result in ongoing tissue contracture, pain, lymphodema, and tissue breakdown; in turn leading to significant disability, impairment of quality of life, infection, and potentially life-threatening exposure of vital structures. We have performed a raft of functional bioassays to specifically interrogate the key functions of lymphatic endothelial cells during the course of radiation induced lymphodema and have developed genomic, proteomic and metabolic platforms to understand the key signalling and communication pathways between lymphatic endothelial cells and their microenvironment critical for disease evolution. CXCR7, a chemokine receptor was one such gene shown to be differentially expressed during radiation injury. We would like to understand the role of this orphan receptor in radiation injury in animal models of radiation-induced lymphodema. The project will develop skills in cell biology, cell purification, FACs, bioinformatics and genetic mouse models.

This project is conducted in St Vincent's Institute of Medical Research, Lympathic and Regenerative Surgery Group, (O'Brien Institute Department of SVI).

GENE SIGNATURES OF THE 'LYMPHATICOME'

Suitable for Honours, Masters or PhD

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Ramin Shayan**
Co-supervisor: **Dr Tara Karnezis**

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The lymphatic system is a hierarchical system- comprised of lymphatic endothelial cells-that is integral to fluid homeostasis, absorption of dietary fat and immune cell surveillance. The lymphatic system can be hijacked during cancer to promote metastasis to distant organ sites and a dysfunctional lymphatic system can lead to debilitating a disease such as Lymphodema, the swelling of soft tissue often in the extremities. Lymphatic vessels are present in most organ tissues such as skin, liver, kidney, pancreas, heart, digestive tract, lymphoid organs and more recently, discovered in the brain. The nature and morphology of lymphatics would therefore reflect their function within a given organ system. We would like to gain an understanding of the genetic signatures of the "lymphaticome". This information will allow for a greater understanding of the lymphatic system and diseases relating to it and provide an avenue to develop organ specific therapeutics. The project will develop skills in cell purification and cell biology, FACs, microarray, bioinformatics and animal models of disease.

This project is conducted in St Vincent's Institute of Medical Research, Lympathic and Regenerative Surgery Group, (O'Brien Institute Department of SVI).

UNDERSTANDING THE MICROENVIRONMENT OF LYMPHODEMA

Suitable for Honours, Masters or PhD

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Ramin Shayan**
Co-supervisor: **Dr Tara Karnezis**

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Dr Karnezis
E: tkarnezis@svi.edu.au

Lymphodema is a debilitating disease caused by an impairment of the lymphatic system characterised by soft tissue swelling, fat accumulation, pain and recurring infection. Approximately 20% of cancer patients undergoing radiotherapy and/or surgical resection of lymph nodes will develop Lymphodema. Communication between cells is a fundamental process during disease progression. One of the key features of lymphodema is the accumulation of fat within the surrounding tissue, fibrosis, poor immunity and extreme pain. We would like to understand how adipocytes, nerve cells, fibroblasts and immune cells communicate with lymphatic endothelial cells during the course of lymphodema. The project will involve

development of genetic animal models, cell biology and cell imaging and bioinformatics to understand the communication between different cell types in affected tissue.

This project is conducted in St Vincent's Institute of Medical Research, Lympathic and Regenerative Surgery Group, (O'Brien Institute Department of SVI).

UNDERSTANDING THE GENETIC BASIS OF LIPIDEMA

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **Dr Ramin Shayan**
Co-supervisor: **Dr Tara Karnezis**

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Lipidema is a debilitating disease caused by excessive accumulation of fat in arms and lower extremities, affecting women at the onset of puberty. There is no known cure. Often, there is a lymphodema component associated with this disease but the precise role of lymphatics in disease pathology is unclear. This project will initiate a genetic screen of affected individuals and their families in order to identify genes that may be affected in these patients. This project will utilise microarray platforms, immunohistochemistry of human specimens, metabolomics, bioinformatics and the generation of animal models using CRISPR technology to determine whether there is a mutation within a specific gene of affected individuals that leads to Lipidema.

This project is conducted in St Vincent's Institute of Medical Research, Lympathic and Regenerative Surgery Group, (O'Brien Institute Department of SVI).

Vascular Biology Group

ENGINEERING A TISSUE FLAP

Suitable for PhD, Honours

Department: **Surgery** **Location:** **St Vincent's Institute of Medical Research**

Primary Supervisor: **A/Prof Geraldine Mitchell**
Co-supervisor: **Dr Anne Kong**

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Dr Kong
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Tissue flaps are used routinely in reconstructive surgery for coverage of acute or chronic wounds caused by trauma, cancer resection, and diabetes. Flaps consist of a large artery and vein (vascular pedicle) connected to a capillary network within a block of skin/fat/muscle. Flaps are harvested from one area of the body to cover defects at another site. However tissue flaps have limited availability, are morbid and

involve complex, costly surgery with high complication rates. A bioengineered alternative would be a major advance in the field of reconstructive surgery.

Providing a functional capillary network connected to the blood circulation is a major hurdle in engineering of tissues and organs. This project seeks to develop an engineered human tissue flap in vitro, focussing on the major blood vessels connected to a capillary network.

We have assembled in vitro interconnected human capillary networks from human induced pluripotent stem cell-derived endothelial cells (iPSC ECs) seeded in a porous scaffold. When transplanted into a wound the human capillaries survive and connect to the host circulation.

This project aims to connect the hiPSC derived capillaries to a 3D printed branched vascular pedicle seeded with hiPSC ECs, and hiPSC derived vascular smooth muscle cells (vSMC), thus forming a human tissue flap in vitro. The 3D printed pedicle will be constructed under the co-supervision of Dr Cathal O'Connell (RMIT) a biomaterials and multi-component 3D printing expert.

The project involves assembly of hiPSC-derived capillary networks, 3D printing a vascular pedicle and seeding with hiPSC ECs and vSMCs and connection of capillaries and pedicle in culture. In vivo testing of the tissues developed will occur post-optimization of the bio-engineered flap, but may not form part of an Honours project. The project will largely involve 3-dimensional cell culture, 3D printing, vascular perfusion, immunohistochemistry and immunofluorescence, and imaging techniques.

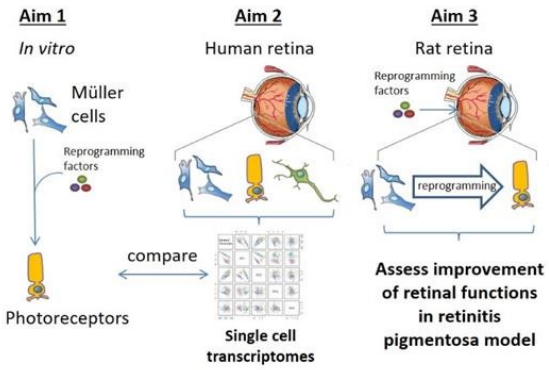
Ophthalmology, Department of Surgery/ Centre for Eye Research Australia (CERA) Research Projects

Ophthalmology research at the Centre for Eye Research Australia (CERA) has a strong reputation for its clinical and translational focus. Ranked amongst the top five ophthalmology research groups globally, its ultimate goal is to find solutions for the three major blinding eye diseases that affect Australians – macular degeneration; glaucoma and diabetic eye disease and to pioneer vision regeneration programs to give hope to people who have lost their sight.

Cellular Reprogramming Unit

Group Leader: Dr Raymond Wong

The Cellular Reprogramming unit aims to harness the medical potential of cellular reprogramming and stem cells to study and treat ocular diseases. Our research focuses on developing novel cellular reprogramming technologies to regenerate retinal cells, as well as stem cell technology to generate retinal cells. Our research utilises cutting-edge techniques that includes direct reprogramming/ induced pluripotent stem (iPS) cell technology, single cell transcriptomic analysis and the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) systems.



DEVELOPMENT OF REGENERATIVE THERAPY FOR PHOTORECEPTOR LOSSES USING CELLULAR REPROGRAMMING TECHNOLOGY

Suitable for Honours, Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Raymond Wong
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Photoreceptors are light-sensing cells that form the basis of our vision by converting light into electrical signals that can be decoded by the brain. The loss of photoreceptors is a key hallmark of many blinding diseases, such as retinitis pigmentosa, age-related macular degeneration, and diabetic retinopathy. These diseases affect millions of patients and cause a significant socio-economic burden on our healthcare system. Currently, there are no effective means to cure blindness once photoreceptors are lost. We must therefore find a new approach to help restore vision to these patients. Regenerative therapy to replace photoreceptors has the very real prospect of helping patients to restore vision.

Cell reprogramming could be the key to this critical issue. This innovative technology relies on converting one cell type into another by rewriting the transcriptome to alter the cell's identity. One of the most famous examples is the Nobel prize-winning discovery of induced pluripotent stem (iPS) cells, in which

the altered expression of four transcription factors converted adult fibroblasts into stem cells. Beyond iPS cells, direct reprogramming is now possible by converting one somatic cell type directly to another, such as fibroblasts to neurons, without passing through an intermediate stem cell state. this project aims to develop cell reprogramming technology to generate new photoreceptors, providing novel regenerative therapy approach to treat photoreceptor loss. Techniques involved in this project include cell reprogramming, CRISPR/Cas9, transcriptomic analysis, molecular cloning, fluorescent microscopy and virus generation.

Ophthalmic Genetics

Group Leader: Prof Alex Hewitt

The Ophthalmic Genetics group is interested in understanding the genetics and molecular mechanisms underlying inherited eye diseases. We utilise genetic tools such as whole exome/genome sequencing, genome-wide association studies and more recently CRISPR/Cas to decipher genes which may be responsible for causing disease. The ultimate aim of our research is to contribute to the development of future treatments and therapies for patients with the hope to prevent and/or cure blindness in these patients.

Prospective students should contact the Research Group Leader in the first instance to discuss potential graduate research opportunities.

Clinical Trials Research Centre

Group Leader: A/Prof Lyndell Lim

A/Prof Lyndell Lim, a Uveitis and Medical Retina Subspecialist, leads the Clinical Trials Research Centre at the Centre for Eye Research Australia. A/Prof Lim is largely involved in clinical studies, particularly in the field of uveitis and ocular immunology, and diabetic retinopathy. Her team runs both investigator initiated and sponsored clinical trials that aim to investigate new treatments in a variety of ophthalmic diseases.

Current projects include prospective randomised clinical trials in diabetic macular oedema, the major cause of visual loss in diabetic retinopathy, and chronic non-infectious uveitis, a form of blinding auto-immune disease of the eye.

THE EFFECT OF PREGNANCY ON DIABETIC RETINOPATHY

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: A/Prof Lyndell Lim
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The effect of pregnancy on diabetic retinopathy (DR) remains unclear due to conflicting findings from past studies that have varied significantly in their methodology, definitions and DR grading, thus making it almost impossible to pool their results.

In collaboration with UMEyecare, Royal Women's Hospital and Mercy Hospital for Women, we are currently conducting a prospective longitudinal cohort study to determine the effect of pregnancy and the post partum on the incidence and outcomes of DR in women with pre-existing diabetes. Unlike past studies, a significant proportion of our women are on continuous glucose monitoring (CGM), many of whom have closed loop systems.

The aim of this proposed project is to analyse risk factors for the incidence, prevalence and outcomes of DR during pregnancy and the post partum, particularly with regard to BSL control as measured by HbAic vs CGM parameters. Secondary outcomes for analysis will include neonatal outcomes, again in relation to presence/absence/severity of DR and glucose control parameters.

DEEP GENOME SEQUENCING OF HERPES SIMPLEX AND HERPES ZOSTER IN ACUTE RETINAL NECROSIS

Suitable for PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: A/Prof Lyndell Lim
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Acute Retinal Necrosis (ARN) is a rare but frequently blinding form of infectious posterior uveitis that is usually seen in those who are immunocompetent, unlike other forms of infectious viral retinitis that tends to occur in the immunosuppressive (e.g. CMV retinitis in AIDS).

Given that the vast majority of the population have been exposed to the herpes simplex and herpes zoster virus by adulthood, it is still unknown as to why a small minority of people develop ARN whilst the vast majority do not.

Recent studies in virology have suggested that complications of other forms of viral infections can be almost entirely predicted by the genome of the infecting virus after deep genome sequencing.

In a collaboration with the Sydney Eye Hospital and the University of Washington, Seattle, USA, we plan to examine 100+ Samples from cases of ARN, compared with samples from herpetic keratitis (a more common and less blinding form of herpetic eye disease) and sequence the causative virus through deep genome sequencing to determine whether the manifestation of ARN is indeed due to the virus, or the host.

Ophthalmic Neuroscience Unit

Group Leader: A/Prof Peter van Wijngaarden

The Ophthalmic Neuroscience Unit is focused on the discovery of novel imaging biomarkers of retinal and central nervous system diseases. The research combines state-of-the-art imaging with advanced image analysis methods including a range of artificial intelligence approaches.

SATELLITE IMAGING TECHNOLOGY TO DETECT THE EARLY SIGNS OF GLAUCOMA AND ALZHEIMER'S DISEASE IN THE RETINA

Suitable for PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: A/Prof Peter van Wijngaarden
Email: peterv@unimelb.edu.au

We aim to be the first group in the world to bring hyperspectral imaging, based on NASA satellite technology, to the clinic to improve the care of Australians with Alzheimer's disease, glaucoma and a range of retinal diseases. 400,000 Australians live with dementia and most have Alzheimer's disease. Abnormal proteins accumulate in the brain and retina for 10-20 years before memory impairment, providing an opportunity for early detection and treatment. There are no screening tests for the earliest stages of the disease. Similarly, glaucoma is a leading cause of vision loss affecting 300,000 Australians. Early treatment can save vision, but late diagnosis is typical. The deposition of abnormal proteins in the retina in Alzheimer's disease and structural changes in the nerve cells affected by glaucoma scatter light in characteristic ways which we can detect during the early stages of disease. This project combines clinical imaging with advanced image analysis methods, including deep learning approaches.

Glaucoma Research Laboratory

TAKING THE "GUESSWORK" OUT OF GLAUCOMA CLINICAL MANAGEMENT WITH NOVEL IMAGING

Suitable for PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Zhichao Wu
Email: wu.z@unimelb.edu.au

The clinical management of glaucoma seeks to prevent patients from experiencing visual disability from the progressive degeneration of retinal ganglion cells. This task is especially difficult by the lack of effective methods to detect and characterise disease progression accurately and meaningfully. Current

clinical tests are currently so variable that clinicians are often left with a great deal of "guesswork" in the clinical management of glaucoma. Optical coherence tomography is a modern clinical imaging technique that could accurately detect disease progression and predict long-term outcomes, given its ability to non-invasively visualise the retina three-dimensionally at near-cellular resolution. This powerful technology could be exploited to transform the clinical management of glaucoma patients.

This project will involve development of this imaging technique and analytical methods and understanding its relation to patient-reported measures of visual disability to understand the clinical relevance of its results.

EVIDENCE-BASED PRACTICE IN THE MANAGEMENT OF GLAUCOMA SUSPECTS

Suitable for PhD or MPhil

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisors: Dr Zhichao Wu, Dr Laura Downie

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Glaucoma is a leading cause of irreversible vision loss in Australia and worldwide, with half of those with this condition being undiagnosed. Approximately one in ten Australians over 50 years old would fit the criteria for being a glaucoma suspect, but there is limited evidence about how to identify those at high-risk of developing glaucoma and who prophylactic treatment is warranted for. The main evidence guiding the management of glaucoma suspects is based on two trials for those with ocular hypertension (i.e. raised intraocular pressure) from over 20 years ago, and individuals with ocular hypertension make up less than a half of those with suspected glaucoma.

This project will thus involve synthesising and critically appraising the evidence currently available, as well as obtaining prospective data on current practice patterns on the management of glaucoma suspects, so as to provide evidence-based guidance and identify key knowledge gaps that requires robust, prospective studies to address.

Macular Research Unit

Group Leader: Prof Robyn Guymer

The Macular Research Unit at the Centre for Eye Research Australia (CERA) is a leading research team focusing on the most common cause of vision impairment in people aged over 50 years in Australia – Age-related macular degeneration (AMD). The group is headed by Prof Robyn Guymer, an internationally renowned medical retinal ophthalmologist and clinician. Prof Guymer's research is focused on finding novel ways to assess, monitor and treat this devastating eye disease. She also collaborates to investigate underlying mechanisms involved in disease pathogenesis.

ENABLING TREATMENT TRIALS OF ATROPHIC AGE-RELATED MACULAR DEGENERATION

Suitable for PhD

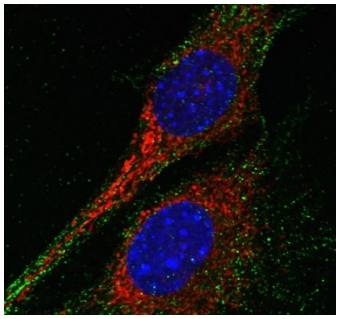
Primary Supervisor: Dr Zhichao Wu
Co-supervisors: Prof Robyn Guymer

Email: wu.z@unimelb.edu.au

Although treatments currently exist for the acute, neovascular complications of age-related macular degeneration (AMD), individuals that develop atrophic complications currently face an inevitable future of progressive central vision loss since no effective treatments are available to prevent or slow the unrelenting degeneration of the retina. Although many clinical trials are now underway for atrophic AMD, a significant barrier to their success is the lack of precise clinical measures to determine their efficacy. Furthermore, trials evaluating novel treatments for the atrophic complications of AMD may be evaluated in eyes where the disease is already too advanced.

This project will involve developing novel visual function techniques tailored for the specific stages of the atrophic disease process, especially for the early stages of the atrophic process where no outcome measures have yet been established. This will provide the necessary tools needed as a catalyst for the discovery of interventions for the debilitating complications of atrophic AMD.

Mitochondria and Neurodegeneration Unit



Group Leader: A/Prof Ian Trounce

Email: i.trounce@unimelb.edu.au

The Mitochondria and Neurodegeneration group investigates how mitochondrial dysfunction can lead to neurodegenerative processes, in particular glaucoma, Leber's hereditary optic neuropathy, Parkinson's and Alzheimer's disease, to identify novel therapeutic targets to prevent neuronal and vision loss.

Prospective students should contact the Research Group Leader in the first instance to discuss potential graduate research opportunities.

Mitochondrial Biology and Disease

Group Leader: **Dr Isabel Lopez Sanchez**

VALIDATION AND CHARACTERISATION OF BIOMARKERS IN MITOCHONDRIAL OPTIC NEUROPATHY

Suitable for Honours, Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: Dr Isabel Lopez Sanchez
Email: isabel.lopez@unimelb.edu.au

Leber hereditary optic neuropathy (LHON) is the most common mitochondrial disease and causes irreversible blindness primarily in young men. Using RNA sequencing we have identified potential protective and pathogenic biomarkers in this disease. This project aims to 1) Validate the biomarker potential of identified targets using clinical samples 2) Characterise the function of identified markers in cells and 3) Investigate the biological relevance of identified markers in other optic neuropathies

This project involves the use of a range of techniques and tools including cell culture, biochemistry, CRISPR-Cas 9, proteomics, immunocytochemistry and mitochondrial-specialised techniques.

DEVELOPING AN OPTIC ATROPHY GENETIC SCREENING PANEL FOR RESEARCH PURPOSES

Suitable for Honours

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: Dr Isabel Lopez Sanchez
Email: isabel.lopez@unimelb.edu.au

This project aims to improve the genetic diagnosis of optic atrophy, the most frequently inherited optic nerve disease, for further genotype-phenotype studies.

The techniques and tools used in this project include DNA extraction from clinical samples, molecular biology (PCR, restriction enzyme, gel electrophoresis), Sanger and whole exome sequencing.

Retinal Gene Therapy

Group Leader: **Dr Thomas Edwards**

The Retinal Gene Therapy group is pioneering an Australian centre for retinal gene therapy. The group aims to develop novel gene therapies to halt the progression and find a cure for inherited retinal diseases.

OCULAR GENE THERAPY: THE NEW ERA OF BLINDNESS PREVENTION

Suitable for Honours, Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Tom Edwards
Co-supervisors: Dr Lauren Ayton, Ms Jasleen Jolly (Nuffield Laboratory of Ophthalmology, Oxford University, UK)

Dr Edwards	Dr Ayton	Jasleen Jolly
E: thomas.edwards@unimelb.edu.au	E: layton@unimelb.edu.au	E: jasleen.jolly@eye.ox.ac.uk

In December 2017, the world's first direct-to-human gene therapy was approved for an inherited retinal disease called Leber Congenital Amaurosis. This disease normally onsets in early childhood and causes severe vision loss and blindness. Excitingly, the new gene therapy treatment was able to halt the progression of this disease, saving vision for the study participants. This has opened the doors for a new era of medicine – one where blindness may be able to be stopped in its tracks with the use of gene therapy. Our research group has international expertise in vision restoration (gene therapy, bionic eyes) and visual function assessment. We are developing new gene therapy treatments for patients with inherited retinal degenerations. We are also aiming to develop novel vision tests to determine which patients will do best with gene therapy treatments, and to then monitor their performance when they are in a clinical trial. We have a number of projects available, from laboratory work (developing and testing new gene therapies – primary supervisor Dr Tom Edwards) to clinical studies (vision testing – primary supervisor Dr Lauren Ayton). We welcome applications from scientists and clinicians of all backgrounds

Surgical Research Unit

Group Leader: Prof Mark Daniell

The Surgical Research Unit at CERA conducts two main streams of research: corneal disease research and surgical research into corneal transplantation and intra ocular lens implants.

The clear, protective layer at the front of the eye, called the cornea, can be damaged through disease, infection or injury that can block or distort vision. CERA's Surgical Research Unit carries out clinical research into new and more effective therapies for corneal diseases such as keratitis, keratoconus and ocular surface disorders. This includes projects with biochemical engineers and pharmacologists to produce an engineered corneal transplant from stem cells and an ideal biomaterial.

The Surgical Research Unit also includes clinical trials into the efficacy and safety of surgical therapies such as corneal transplants, cataract surgery and laser surgery. The ultimate aim of corneal transplantation

research is to develop an artificial cornea or grow corneal cells in the laboratory to prevent problems with rejection. The team is also looking at cellular responses to infection in the cornea.

The group is also interested in COVID-19 related pharmacological research and ApoE, IP and TP receptor mechanisms.

REPAIR OF THE CORNEA TO RESTORE VISION: TRANSLATION TO SURGICAL REPAIR DEVICE

Suitable for Honours, Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisors: Dr Karl Brown, Prof Greg Dusting and Prof Mark Daniell

Email: g.dusting@unimelb.edu.au

Severe burns and corneal disease leads to vascularisation and ulceration of the corneal surface, which is currently treated by corneal transplants and lifelong anti-rejection drugs. Many countries in the world do not have sufficient donors to meet the increasing demand for this procedure. At CERA we work closely with chemical engineers and veterinary scientists at the University of Melbourne to develop engineered constructs to replace the damaged corneal endothelium. Materials and procedures have been patented, and one is under commercial development.

The current project is to develop a source of corneal endothelium from human induced pluripotent stem cells (iPS cells) and grow these on patented hydrogel films to replace damaged endothelium. Alternatively, the reprogramming of appropriate cells from patient donors direct to corneal endothelium will be explored. Mechanisms of adhesion and proliferation of these cells will be examined, and preclinical transplantation studies will be carried out in sheep in the veterinary facility.

This project would be suitable for biomedical science students with an interest in cell biology, pharmacology or ophthalmology to work towards clinical application of this novel technique with an ophthalmologist, stem cell scientist, veterinary scientists and other cell biologists. It can be adapted for Honours, Masters or PhD students, working alongside scientists and clinicians.

GENOME-WIDE EXPRESSION PROFILING OF KERATOCONUS AND NON-KERATOCONUS CORNEAS

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Srujana Sahebjada
Co-supervisors: Prof Paul Baird and Prof Mark Daniell

Email: Srujana.sahebjada@unimelb.edu.au

Keratoconus is a potentially blinding eye disease of the cornea. Typically, it occurs in childhood and various intervention measures are currently used to slow its progression but there is no cure. While its aetiology is due to genes and environment, the involvement of these factors is still poorly understood. In this proposal we will greatly advance our understanding of disease through genetic analysis of this disease.

The project will involve undertaking RNA sequencing from the 3 different layers (epithelium, stroma and endothelium) of the cornea to assess what changes occur in gene expression from these corneal tissues collected from keratoconus cases compared to corneas from living (non-keratoconus) donors through enucleation as well as corneas collected through an EyeBank. Our preliminary analysis of RNASeq data have indicated that different analysis programs can lead to different outcomes in terms of which genes/pathways are identified and we would like to look further into this issue to determine the factors driving these outcomes. The student will be involved in analysis of RNASeq data and pathway analysis to better understand these findings.

Students with backgrounds in Bioinformatics, Genetics, Computer science and/or optometry and visual science are welcome to apply.

USING ARTIFICIAL INTELLIGENCE TO IMPROVE THE DIAGNOSTIC PREDICTIONS OF CORNEAL TOPOGRAPHY MACHINES FOR KERATOCONUS SUBJECTS

Suitable for Honours, Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Primary Supervisor: Dr Srujana Sahebjada
Co-supervisors: Prof Mark Daniell and Prof Paul Baird

Email: Srujana.sahebjada@unimelb.edu.au

Keratoconus is a common condition that affects the cornea and despite its increasing prevalence, the cause of keratoconus is largely unknown. There are many clinical gaps regarding keratoconus in terms of subclinical detection, clarifying its disease stage and identifying which features should be used to predict its progression. These gaps impact on a clinician's decision-making process for keratoconus disease management. The project aims at developing machine learning algorithms to identify features that define early subclinical keratoconus that are currently refractory as well as identify a series of features that are involved in a) disease staging, as well as b) risk of progression of Keratoconus. It provides an exciting opportunity to conduct big data analysis, generate AI model and manuscript writing.

Students with backgrounds in biomedical and computer science, statistics or optometry and visual science are welcome to apply.

Ocular Fibrosis Unit

Group Leader: Dr Jennifer Fan Gaskin

The Ocular Fibrosis Unit at CERA develops approaches to improve treatment and outcomes for patients with ocular diseases. The key area of research is to investigate ocular inflammation and fibrosis/ scarring after glaucoma surgery and chemical burn injuries in the eye. We are interested in translational approaches that include investigating the therapeutic potential of novel drugs and compounds using various preclinical models, molecular techniques, cell culture-based experimentation and analysing patient-derived materials.

A NON-CYTOTOXIC APPROACH TO REDUCE OCULAR FIBROSIS AFTER GLAUCOMA FILTRATION SURGERY

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisors: Dr Manisha Shah, Dr Elsa Chan, Dr Jennifer Fan Gaskin

For enquiries about current honours and PhD projects please contact:

Dr Shah	Dr Chan	Dr Jennifer Fan Gaskin
E: shah.m@unimelb.edu.au	E: elsa.chan@unimelb.edu.au	E: fan.j@unimelb.edu.au

Wound healing is a classical response to any tissue injury repair and this process often leads to scar-forming fibrotic lesions. Scarring response is a major problem and influences surgical outcomes in patients with eye diseases. The post-surgical scarring in the eye causes vision impairment and blindness. There are some non-selective cytotoxic drugs currently being used in clinic that exerts serious side-effects and leads to high recurrence rate of fibrosis and surgical failure. Hence there is an immediate need to investigate safer and more effective therapeutic alternatives.

We focus on investigating the post-operative ocular scar formation. By understanding the involvement of NADPH oxidase (Nox4 and Nox2)-associated pathways in reactive oxygen species (ROS) production in postsurgical ocular fibrosis, we aim to investigate how to improve long-term success of ocular surgery and prevent/treat post-operative ocular scar formation and vision loss in glaucoma patients. We use various molecular and cell culture techniques, cell signalling pathway analysis, histological analysis and preclinical mouse models of ocular fibrosis to study various aspects of this project.

NON-STEROIDAL THERAPY FOR THE MANAGEMENT OF CHEMICAL EYE INJURIES

Suitable for Honours or Masters

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisors: Dr Manisha Shah, Dr Elsa Chan

For enquiries about current honours and PhD projects please contact:

Dr Shah	Dr Chan
E: shah.m@unimelb.edu.au	E: elsa.chan@unimelb.edu.au

Chemical eye injuries are a condition of ophthalmic emergency that can produce extensive damage to the ocular surface and anterior segment of the eye and can lead to vision impairment. Early diagnosis and effective treatment can ensure best possible outcome for this potentially blinding condition. The existing first line of treatment comprises of antioxidant Vitamin C and topical steroid application to reduce inflammation and scarring. However, serious injuries often need longer treatment of these agents which can cause corneal thinning and perforation.

Our study will investigate, whether a new drug target NADPH oxidase 4 (Nox4) can prevent or reduce ocular inflammation and scarring after chemical burn injuries in the eye. Nox4 inhibitors may represent an alternative treatment or adjunct approach to reduce ocular scarring. We aim to conduct a systematic

investigation of the anti-scarring effects of a Nox4 inhibitor after ocular chemical burn injury using relevant preclinical animal models and various molecular and cell culture-based analysis.

Students will have an opportunity to explore molecular and cell culture-based experiments, Western blot, q-RT-PCR, immunohistochemical analysis, microscopy and imaging as well as some aspects of preclinical mouse model of ocular fibrosis. The student will be trained and expected to perform respective techniques and data analysis.

Ophthalmic Epidemiology

Group Leader: Prof Mingguang He

Prof. Mingguang He is a global expert in vision-related clinical and epidemiologic research. Prof He currently leads the Ophthalmic Epidemiology group at the University of Melbourne and Centre for Eye Research Australia and is the Director of WHO Collaborating Centre for Prevention of Blindness (Australia). The Ophthalmic Epidemiology group is comprised of eye disease researchers, public health specialists, epidemiologists, data scientists and Artificial Intelligence (AI) professionals. The team focusses on clinical and epidemiological research, randomised clinical trials, twin studies, imaging technology, AI and big data research. The studies explore integrating AI and eye disease screening in different area and clinical setting, which facilitates the application of new technology to improve healthcare efficiency and productivity.

IMPROVED EARLY DIAGNOSIS OF EYE DISEASES BY INTEGRATION OF RETINAL PHOTOGRAPHY AND ARTIFICIAL INTELLIGENCE TO BUILD AN OPPORTUNISTIC SCREENING SERVICE IN METRO, REGIONAL AND REMOTE PRIMARY CARE SETTINGS

Suitable for Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: Prof Mingguang He
Email: mingguang.he@unimelb.edu.au

This project will be based on Professor He's current AI-based fundus image diagnosis system, a do-it-yourself (DIY) screening system that is less dependent on technicians for image acquisition, and less dependent on eye care professionals in the interpretation of clinical images. The aim of the study is to understand the needs, develop the prototype and evaluate the usability of this DIY system, in real-world clinical setting of GP and endocrinology clinics and Aboriginal Medical Services. This DIY screening system is anticipated to allow non-eye professionals to perform eye disease screening that would improve acceptability, accuracy, accessibility and cost-efficiency of eye care delivery.

ARTIFICIAL INTELLIGENCE IN OPHTHALMOLOGY: FROM DATA TO ALGORITHM AND REAL-WORLD APPLICATION

Suitable for Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: Prof Mingguang He
Email: mingguang.he@unimelb.edu.au

This project aims to further evolve artificial intelligence technology to develop and validate a clinical decision system that can predict disease outcomes and prognosis, as well as help clinicians decide on treatment options, based on real-world multi-modality clinical data. In this project, a data linkage project will be conducted to establish a cohort of people with ocular imaging data by retrieving historic clinical records from eye care service providers and then link these people with Medicare claim and hospitalisation data through AIHW. This unique cohort will help develop algorithms using ocular imaging as biomarkers for systemic disease prediction. Using the latest AI technology, a Smart Clinical Query System will be developed as a tool to answer open questions that clinicians may ask in clinical practice. Initially, this system will take one disease domain, for example glaucoma, and will then be further expanded to other diseases using the same framework and strategies when validation is proven. The system will be validated in ophthalmology clinical practice settings to assess clinical accuracy, reproducibility against eye specialists, as well as the real-world impact and cost-effectiveness by comparing with conventional clinical management decisions.

ARTIFICIAL INTELLIGENCE SYSTEM TO DETECT EYE AND CARDIOVASCULAR DISEASES

Suitable for Masters or PhD

Department: Surgery Location: Surgery, Ophthalmology, Royal Victorian Eye and Ear Hospital

Supervisor: Prof Mingguang He
Email: mingguang.he@unimelb.edu.au

Retinal photography gives us the ability to visualise the retina, optic disc, macula and blood vessels. It is the most important, low-cost and non-invasive diagnostic tool for common eye diseases such as glaucoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD). The retinal microvasculature is a window to the body's overall microvascular health. Subtle retinal microvascular changes have been identified as effective biomarkers to predict the risk of cardiovascular disease (CVD), which accounts for 14% of Australia's total burden of disease. Currently, the interpretation of retinal imaging relies heavily on the subjective assessment of trained professionals.

Artificial intelligence (AI) offers the ability to revolutionise highly image driven medical specialities, including ophthalmology. Our research team has developed an AI system for the classification of the three aforementioned eye diseases and risk prediction for CVD. This technology has been validated and published in JAMA, Diabetes Care, Ophthalmology and JAMA Ophthalmology. Our AI system provides an opportunity to integrate AI technology with existing infrastructure to deliver an accurate, visually interpretable and user-friendly solution.

Using the advanced deep learning system that has been developed and validated by the team as a basis, this project brings together medical research institutes, technical developers, industry, consumer organisations, government policy and service providers to develop, translate and prove an all-in-one AI system (A-Eye) that aims to create innovative solutions for multiple health disciplines and needs, including an opportunistic screening model, diagnosis standardisation and a cross-disciplinary model of risk prediction for cardiovascular diseases. An “Eye and Systemic Disease AI Open Platform” will be created to enable resource sharing and workforce development to maximise the impact of AI on linking ocular imaging and systemic diseases.

Honours in Medicine

BIOM40001	Introduction to Biomedical Research (12.5 points) [2 week intensive course in February]
MEDI40005/ 13	Research Project in Biomedicine (75 points) [year long]
MEDI40006	Advanced Course Work (12.5 points) [Semester 1]

Prerequisites

Students are required to have a minimum Weighted Average Mark of 70%* across their undergraduate degree or an equivalent level of studies.

Acceptance is subject to the availability of suitable topics and supervisors, and placement is competitive.

Objectives

The Honours course is designed to:

- Provide advanced training in biomedical research in a multidisciplinary research environment.
- Develop the ability to critically analyse and independently interpret and evaluate experimental data.
- Develop oral and written communication skills to levels expected of a research scientist.

Departmental Assessment

Component	Due date
Literature Review (3,500 Words) [R]	April
Research Training Forum [CW]	March – June
Oral presentations [R]: Literature Review Final Oral Defense	 April October
Journal Paper Critical Review [CW]	TBA
Research Essay [CW]	TBA
Thesis (10,000 words) [R]	October
Supervisor / Laboratory Competence [R]	Ongoing

CW = Coursework
R = Research

Notes

You will receive a comprehensive Honours Handbook at your induction.

Successful completion of the Honours program requires an overall score greater than 65% with a pass in all components.

Honours in Hearing Sciences (Otolaryngology)

BIOM40001 Introduction to Biomedical Research (12.5 points) [2 week intensive course in February]
OTOL40001/3 Research Project (75 points) [year long]
OTOL40002 Advanced Course Work (12.5 points) [Semester 1]

Prerequisites

Students are required to have a minimum Weighted Average Mark (WAM) of 65% across their undergraduate degree or an equivalent level of studies.

Acceptance is subject to the availability of suitable topics and supervisors, and placement is competitive.

Objectives

The Honours program provides students with an introduction to the function of the auditory system and issues related to the treatment of hearing loss, and experience working in a research environment. On completion of the program, graduates will be able to:

- critically appraise scientific literature
- demonstrate detailed knowledge and understanding of their selected field of research
- display proficiency in various methodological techniques
- analyse and interpret research outcomes within the context of the scientific literature
- effectively communicate scientific ideas in both written and verbal formats

Departmental Assessment

Component	Due date
Literature [CW]	April
Research Seminars [NA]	Ongoing
Oral presentations: Literature Review [R] Journal Paper Critical Review [CW] Final Oral Defense [R]	 April May October
Thesis (10,000 words) [R]	October

NA = Not assessed
CW = Coursework
R = Research

Notes

You will receive a comprehensive Honours Handbook at your induction.

Successful completion of the Honours program requires an overall score greater than 65% with a pass in all components.

Graduate Research Degrees

Doctor of Philosophy (PhD)

A PhD at the University of Melbourne is awarded on the basis of a thesis of approximately 80,000 – 100, 000 words in which a candidate reports on an independent, sustained and academically supervised research project investigating a specialized topic.

The usual duration of PhD study is three years (full time), and all PhDs are assessed via external examination of the research thesis alone.

Master of Philosophy (MPhil)/ Masters by Research

An MPhil is designed to develop advanced skills in carrying out independent and sustained research and is awarded on the basis of a thesis of approximately 30,000 – 40,000 words.

The duration of MPhil study is 1.5 years (full time).

Other Graduate Research Degrees

Please do not hesitate to contact us to discuss your enrolment into other research higher degree programs (e.g. Doctor of Medical Science, Master of Medicine, or Master of Surgery) offered by the University.

Graduate Research Entry Requirements

Academic Entry Requirements

Applicants are normally required to have completed at least a four-year Australian honours degree or equivalent (e.g. an Australian medical degree) and achieved an overall average of greater than 80% in the relevant degree.

Applicants are also normally required to have completed a research project/ component that accounts for at least for 25% of the year's work at 4th year undergraduate or master's level.

Medical graduates from overseas universities will need to have achieved an overall average of greater than 80% in their degree.

International students must also meet the University's English Language entry requirements prior to commencement.

Further information on the University's academic and language entry requirements can be found here: http://futurestudents.unimelb.edu.au/

Funding and Scholarships

Scholarships Available for Local Students

Local* students enrolled in a graduate research degree program at the Eastern Hill Campus precinct are eligible to apply for the following University scholarships:

Research Training Program Scholarships (RTPs)

Established by the Australian Commonwealth Government, this scholarship is available to high achieving domestic students undertaking a Master by research degree or Doctoral by research degree. Benefits of an RTP include a living allowance, a relocation grant for interstate students, a thesis binding allowance and paid sick, maternity and parenting leave.

Selection is based on academic merit. Students must achieve a minimum overall average of 87 to be competitive for an APA.

Faculty Trust-Funded Scholarships

As a result of generous bequests, the University offers a number of prestigious scholarships to students with an outstanding academic record and excellent research potential.

** Local students are Australian citizens and permanent residents, and New Zealand citizens.*

Scholarships Available for International Students

International students enrolled in an RHD program at Eastern Hill are eligible to apply for the following University scholarships:

International Postgraduate Research Scholarships (IPRS)

IPRSs are funded by the Australian Government. Benefits of an IPRS include a waiver of tuition fees, a living allowance (APA-International), a thesis binding allowance and paid sick, maternity and parenting leave.

Selection is based on academic merit. Students must achieve a minimum overall average of 90 to be competitive for an IPRS.

Research Training Program Stipend and Fee Offset Scholarships (RTP)

Fee remission scholarships offered by the University covers full tuition costs but not overseas health cover. MIRSs provide students with a living stipend but do not cover tuition costs. International students are generally awarded both the fee remission and stipend scholarships.

Selection is based on academic merit. Students must achieve a minimum overall average of 85 to be competitive for an RTP.

Further information on the full list of University of Melbourne scholarships can be found here: http://services.unimelb.edu.au/scholarships

Apply now — Honours and Graduate Research

Honours

http://mdhs-study.unimelb.edu.au/degrees/honours/overview

Masters & PhD Programs

http://mdhs-study.unimelb.edu.au/degrees
Follow the link and select the disciple/program you wish to apply for.

Useful Resources and Links

Future Students: Admissions and Applications – Graduate Research Degrees

http://futurestudents.unimelb.edu.au/admissions/applications/research

Scholarships and Bursaries

http://services.unimelb.edu.au/scholarships

Contact Us

easternhill-gr@unimelb.edu.au