



THE UNIVERSITY OF
MELBOURNE

Faculty of Dentistry, Medicine and Health Sciences
Melbourne Medical School

Department of Medicine & Radiology
@

Austin Health Heidelberg

Bachelor of Biomedicine (Hons)
&
Bachelor of Science (Biomedical & Health Sciences)
(Hons)

Honours Projects 2017



The Honours Program [BBiomed (Hons) and BSc (Hons)] offered through The Department of Medicine AH is a full-time one-year course that commences in February and concludes at the beginning of November after the student has completed their final assessment. Part-time enrolment or mid-year intake is not available.

Our course is made up of 3 subjects:

- Honours Research Project in Biomedicine;
- Introduction to Biomedical Research (coursework) and
- Advanced Studies in Biomedicine (coursework)

The contribution of marks from the Research Project and the Coursework components for Honours is 75% and 25% respectively.

Honours Research Project in Biomedicine subject (MEDI40014 & MEDI40015)

The student will conduct an original research project in a basic or clinical research laboratory under the supervision of a research scientist from the department during the period February to early November. This subject aims to provide opportunities for students to gain an understanding in, and extend the practice of biomedical research. The student will be introduced to current literature and techniques in specialised areas. The research project will form part of a larger project or the basis of an expanded project. In both cases the work may culminate in an original research publication.

Assessment:

- A written thesis (75%)
- A literature review in the area of the project under study (10%)
- An abstract and oral presentation of the research project (7.5%)
- An oral presentation of thesis results and response to questions (7.5%)

Introduction to Biomedical Research subject (BIOM40001)

This subject aims to extend the student's education and intellectual development in a field of biomedical science not pertaining to the subject of their research project.

Assessment:

Two written assignments (each not exceeding 3,000 words) submitted during the semester, each worth 50% (subject to change).

Advanced Studies in Biomedicine subject (MEDI40002)

This subject aims to extend the student's education and intellectual development in a field of biomedical science not pertaining to the subject of their research project.

Assessment:

- A written assignment (45%)
- An oral presentation including response to questions (45%), on a topic relating to a distinct area of advanced biomedical research which does not pertain to the student's research project
- Attendance and participation at Departmental Research in Progress and Continuing Education Seminars (10%)

How to apply for Honours

All projects advertised in this booklet are based at the Heidelberg campus and students are enrolled in the course offered by Department of Medicine (Austin Health).

Contact the supervisor

Contact the supervisor responsible for your preferred project and arrange to meet them in person - when you meet with them, take time to have a look at the laboratory and resources available and ask questions about the project and what is expected of you.

Apply for a project

When you have found a project that interests you **and** the supervisor has agreed they would be interested in supervising you, apply formally for admission to the course and lodge your project preference. If you have not met with the supervisor, you will not be offered a position with them.

Lodge your online application for admission between Friday 26 August and Friday 11 November 2016.

Lodge your project preference via HATS between Monday 12 September and Friday 25 November 2016.

Visit the faculty MDHS website for instructions on how to lodge your applications and preferences: <http://sc.mdhs.unimelb.edu.au/how-apply>

Closing date

Applications for admission close 11 November 2016 and project preferences must be lodged by 5pm on 25 November 2016.

2017 Round 1 offers will be issued from Monday 19 December 2016. Students who meet the minimum entry requirements but are not made a Round 1 offer may be considered for Round 2 in mid-January. Late applications may be considered on an individual basis.

For further information regarding the Honours course at Austin Health, Heidelberg contact:

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www.austinmedicine.unimelb.edu.au

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Bone Biology Research Laboratory

A/Prof Rachel Davey
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Laboratory/Group Location

Level 10, Lance Townsend Building, Austin Hospital, Heidelberg

What we do

The focus of our research is to investigate the cellular and molecular pathways through which hormones act, using the powerful combination of physiology and genetically modified mouse models. Knowledge gained from our research has potential for the development of improved therapies for the treatment of metabolic bone diseases such as osteoporosis, obesity and muscle wasting.

Honours projects available

Understanding how androgens act in bone to decrease fat mass

Supervisor: A/Prof Rachel Davey

Obesity has been deemed a pandemic by the WHO with approximately 60% of Australian adults being overweight or obese, with childhood obesity rates also on the rise. The current forms of treatment are manifestly inadequate and therefore novel approaches to therapy are required. Hypogonadism, or low serum levels of testosterone, in men, leads to increased fat accumulation. Conversely, treatment of hypogonadal males and female-to-male transgender patients with testosterone significantly decreases fat mass. The mechanism by which testosterone exerts its effects to decrease fat mass however, are poorly understood.

We, and others have shown, in mice, that deletion of the target for testosterone action, the androgen receptor (AR), results in a phenotype that mimics the three key clinical aspects of hypogonadism in human males, that is increased fat mass, and decreased bone and muscle mass. We have compelling new data showing that expression of the AR specifically in the progenitor cells (PCs) residing in the bone marrow of mice in the absence of the AR in all other tissues (PC-AR Gene Replacements), attenuates fat accumulation. Fat depots in PC-AR Gene Replacement mice are significantly lower than littermate controls.

The aim of this project is to determine the metabolic consequences of decreased fat mass in our PC-AR Gene Replacement mice in vivo. This will be achieved by extensively characterising the fat phenotype of the PC-AR Gene Replacement mice using a number of physiological and molecular biology approaches including measures of activity, glucose and insulin tolerance, energy expenditure, oxidation rates, in addition to histological, biochemical and molecular analyses. In addition, mice will be fed a high fat diet to test whether this model is resistant to weight gain.

Significance: The information gained from this study will be of great clinical significance as it will lead to the development of novel therapeutic agents designed to target these

specific actions of testosterone that decrease fat. The clinical utility of such a therapy for treating obesity will apply to large groups of patients who cannot be administered testosterone due to potential side-effects. This includes women, ageing men and prostate cancer patients undergoing androgen deprivation therapy.

Techniques: Quantitative Real Time PCR (Q-PCR), metabolic studies, immunohistochemistry, biochemical assays, fat tissue and bone marrow histology.

Discovering new gene pathways to improve muscle function

Supervisors: A/Prof Rachel Davey and A/Prof Mathis Grossmann

Aim: To validate and characterise a novel “pre-clinical” genetically modified mouse model in which the expression of Actc1 specifically in skeletal muscle can be induced by treatment with tetracycline (iSkM-Actc1 mice).

Sarcopaenia is a major adverse effect of androgen deprivation therapy (ADT) given to men with prostate cancer counterbalancing the cancer-specific benefits of this treatment. Using state-of-the-art RNA sequencing, we have identified that androgen deprivation leads to an increase in expression of the actin alpha cardiac muscle 1 (ACTC1) gene in human skeletal muscle, which we have also confirmed in a rodent model of androgen deprivation. We hypothesise that overexpression of Actc1 in skeletal muscle of adult mice will mitigate androgen-deprivation-associated sarcopaenia. To test this hypothesis we will generate a novel “pre-clinical” mouse model in which the expression of Actc1 specifically in skeletal muscle can be induced by treatment with tetracycline (iSkM-Actc1 mice).

The first, but crucial step in this project is the initial characterisation of the iSkM-Actc1 mouse line for its responsiveness to doxycycline treatment to induce the overexpression of Actc1 in skeletal muscle and the tissue specificity and level of this overexpression. As such, this project will involve working with genetically modified mice and molecular biology techniques.

Significance: Characterisation of Actc1 in this genetically modified mouse model may provide a target to counteract sarcopaenia, whether due to ADT or due to the age-associated decline in testosterone.

While the main focus of your work will be laboratory based, there is opportunity for exposure to complimentary clinical data collection and attendance of specialty clinics. The beauty of this project is that it provides the full scope of benchtop to bedside research.

Cardiovascular Research Group

Professor Louise Burrell

Dr Sheila Patel

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Dr Elena Velkoska

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Laboratory/Group Location

Level 7, Lance Townsend Building, Austin Hospital, Heidelberg

What we do

Cardiovascular (CV) disease remains the leading cause of morbidity and mortality in our society. Our group has a strong focus on translational research with studies encompassing both clinical and basic research in coronary artery disease (CAD), hypertension, diabetes and kidney disease, and their contribution to CV disease. A major investigative focus of our group is to study novel biomarkers (circulating, genetic and imaging) involved in the pathophysiology of CV disease.

Honours projects available

The Kruppel-like factor 15 gene and its role in the development of cardiac hypertrophy

Supervisor: Dr Sheila Patel

Left ventricular hypertrophy (LVH) is a heritable trait associated with adverse cardiovascular (CV) outcomes including heart failure. More detailed understanding of the molecular mechanisms that contribute to LVH is needed. With regards to the latter, the Kruppel-like factors (KLF) are members of the zinc-finger class of DNA-binding transcriptional factors, and have emerged as important regulators of cell growth and differentiation. To date, 18 family members have been identified including KLF15, which is highly expressed in cardiac myocytes and acts as a repressor of pathological cardiac hypertrophy. This project will investigate the role of KLF15 in the development of cardiac hypertrophy. An opportunity exists for an Honours Student to characterise the KLF15 gene in our experimental models of cardiac hypertrophy.

Techniques: This project will use a range of approaches including tissue processing, RNA isolation, gene expression studies, immunohistochemistry and biochemical analysis.

Characterisation of novel components of the RAS in cardio-renal disease

Supervisor: Dr Elena Velkoska

Kidney disease is a major clinical problem, and patients with kidney disease are at increased risk of CV disease. Activation of the RAS plays a major role in the progression of cardiac and kidney disease. Novel strategies are under investigation that target recently discovered components of the RAS, namely ACE2 and angiotensin 1-7. These components play an important role in the pathogenesis of disease, however they are yet to be fully characterised in the context of kidney disease development and progression.

You will be part of an exciting project that will use various laboratory techniques to characterise the changes of RAS components in the heart and kidney of experimental models at different stages of kidney disease. This will provide important information to aid in future development of novel therapeutic targets and biomarkers of disease.

Techniques: The long-term animal studies have been completed and cardiac and renal function data shows promising and exciting results thus far. You will be involved in completing the laboratory-based analysis for this project, which will examine changes in various RAS components at the gene and protein level in tissue and in plasma and urine. This includes tissue processing, immunohistochemistry for protein levels and localisation, real-time PCR for gene expression, autoradiography for tissue binding and various assays for peptide and enzyme analysis. All of these techniques are established in our laboratory.

Cardiovascular and Tumourovascular Research Laboratory

Professor David Hare

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Laboratory/Group Location

Level 10, Lance Townsend Building, Austin Hospital, Heidelberg

Honours projects available

An anti-calcitonin receptor (CTR) antibody for the detection of programmed cell death: the role of CTR in a novel adaptive response in a pre-apoptotic mechanism

Supervisors: Dr Peter Wookey and Professor David Hare

Programmed cell death (PCD) is an essential process in life. The sequelae of events resulting in capitulation and PCD, include changes in mitochondrial membrane potential, shunting of phosphatidylserine to the cell surface, activation of caspases, chromatin condensation and DNA fragmentation, amongst other key molecular events. Less well established in cells under duress from cytotoxins is an adaptive response which includes increasing metabolism and concomitant expression of CTR. The role of glycosylated and unglycosylated forms of CTR, intracellular processing of CTR + ligand, the route of intracellular endosomes and effects on cell metabolism, will be examined in this study. A novel anti-CTR antibody developed in house will be used to monitor this previously undescribed event in PCD.

Techniques to be used: Cell culture, FACS analysis, immunoblots, immunohistochemistry, including multi-labelling with antibodies and confocal microscopy. No animal contact.

The expression of GLP-1 receptor in mouse tissues using a unique anti-GLP-1 receptor antibody developed in house

Supervisors: Dr Peter Wookey and Professor David Hare

Glucagon-like peptide 1 and its cognate receptor GLP-1 Receptor (GLP-1R) are important components that have led to the treatment with incretins of type 2 diabetes. This peptide/G protein-coupled receptor system is also important in heart disease and potentially important for novel treatments of hypertension and obesity.

Based on the key structural features in the extracellular domain (ECD) of GPCRs, an anti-human GLP-1R antibody was developed here. This antibody will be validated using CHO cell lines that express GLP-1R and negative controls, and compared to other anti-GLP-1R antibodies available commercially.

The initial aim is to validate this antibody and to characterize the positive cell types in control mouse tissues (GLP-1R+ve) relative to KO tissues (GLP-1R-ve). In particular heart tissues, pancreas, brain and gut are all of considerable interest. These cell types lay the basis for responses to administration of incretins and help us further understand the basis for the putative increased incidence of pancreatic cancer with incretin treatment.

Techniques to be used: Immunoblots, FACS analysis, cell culture, immunohistochemistry and confocal microscopy. No animal contact.

The expression and functional significance of heme oxygenase and heme transporter in the brain tumour glioblastoma and high grade glioma cell lines

Supervisors: Dr Peter Wookey and Professor David Hare

The deadly brain tumour glioblastoma (GBM) exhibits many characteristics rarely featured in normal tissues including altered pathways for generation of cellular energy indicating an atypical metabolism. These events are accompanied by expression of key proteins such as the stress marker heme oxygenase-1 (HO-1, hsp 32) and a transporter of heme, originally characterized as feline leukaemia virus C receptor-2 (FLVCR 2). Other than functioning in the release of iron (III) from heme, an important metabolite for rapid growth, these components (HO-1 and FLVCR2) play some role in survival of differentiated cells. Such survival has advantages for expansion of GBM tumours including maintaining the array of cellular phenotypes which share the same often bizarre genotype. Preliminary studies with anti-FLVCR2 antibodies have defined a role for FLVCR2 in the survival of differentiated sub-populations of these tumour stem cells.

Techniques to be used: Cell culture to determine the actions of antibodies on growth and differentiation of the brain tumour stem cells, immunohistochemistry, including multi-labelling with antibodies and confocal microscopy. No animal contact.

Islet Biology & Metabolism and Molecular Obesity Group

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Dr Barbara Fam
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Lab/Group Location

Level 7, Lance Townsend Building, Austin Hospital, Heidelberg

What we do

Type 2 diabetes is characterised by hyperglycaemia which is caused by a defect in insulin sensitivity and insulin secretion. It is evident that the defect in insulin secretion is necessary for hyperglycaemia to ensue in diabetes. Furthermore, it is clear that obesity/high energy intake is closely associated with the increased prevalence of diabetes, contributing to both insulin resistance and reduced insulin secretion. The focus of our group is to understand genetic and biochemical mechanisms that contribute to reduced insulin secretion by using pre-clinical models including transgenic and knockout mice with islet beta cell dysfunction. The group aims to understand genetic and epigenetic mechanisms that contribute to weight gain and obesity.

The primary focus of the Molecular Obesity Laboratory is to investigate the genetic, epigenetic and biochemical mechanisms that are involved in body weight regulation through the use of various rodent models of obesity. This will allow our group to delineate why obesity occurs and be able to provide better therapeutic targets to curb this ever growing epidemic.

Honours Projects Available

Genetic Analysis of Impaired beta Cell Function and Loss in Type 2 Diabetes

Supervisor: A/Prof Sof Andrikopoulos

The aim of this study is to identify the pancreatic islet gene(s) responsible for the increased diabetes susceptibility of a model of diabetes when challenged with a hyperglycaemic environment. Once identified, the equivalent genes will be searched for in the human genome.

Investigation of the role of Seps1, a novel glucose-regulated selenoprotein with anti-oxidant activity

Supervisor: A/Prof Sof Andrikopoulos

The aim of this study is to investigate the possibility that the hyperglycaemia of diabetes results in suppression of Seps1 in β -cells, leading to progressive β -cell damage.

Techniques: This project involves analysis of transgenic and knockout mice of pancreatic β -cell

Assessment of mitochondrial function in a mouse model of obesity and type 2 diabetes

Supervisor: A/Prof Sof Andrikopoulos

The aim of this study is to investigate the contribution of mitochondrial dysfunction to the type 2 diabetes phenotype of the New Zealand Obese (NZO) mouse.

Techniques: Assessment of mitochondrial oxidative capacity and ROS production in muscle, liver and pancreatic β -cells from NZO mice.

Using the 'Gene Mine' to identify novel genes that influence the incretin effect

Supervisor: A/Prof Sof Andrikopoulos

Incretins are hormones that are released from the gut in response to nutrient ingestion and act on pancreatic β cells to enhance insulin secretion. In type 2 diabetes, a reduction in the incretin effect contributes to a progressive decline in insulin secretion. The aim of this study is to utilise the 'Gene Mine' to identify novel genes that influence the incretin effect.

Techniques: Glucose tolerance in the presence or absence of incretins will be assessed in several genetically distinct mouse strains that have arisen from the Collaborative Cross. A genetic linkage analysis will then be used to identify genes that influence incretin action

Does Epigenetics play a role in the current obesity epidemic?

Supervisor: Dr Barbara Fam

The aim of this project is to identify the genetic and epigenetic causes underlying common obesity using a rat model of diet-induced obesity that mimics the current human situation. Identification of these genes and epigenetic markers will provide us with the tools necessary to develop novel drugs/diets to combat the current obesity epidemic.

Techniques: Energy balance studies (body weight, food intake, energy expenditure) in animals, feeding/dietary interventions in animals, gut hormone analysis, gene expression using Real Time PCR, Western Blotting for protein analysis, collaborations with epigenetic techniques.

Liver & Gastroenterology Research Group

Professor Peter Angus

Dr Chandana Herath

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Laboratory/Group Location

Level 7, Lance Townsend Building, Austin Hospital, Heidelberg

What we do

Our group was the first to describe the upregulation of the Renin Angiotensin System (RAS) in both animal models and human cirrhosis. A major research focus is on the role of the RAS in liver fibrosis/cirrhosis in both animals and humans. In this context, we are currently studying the effects of newly discovered components of the RAS in experimental liver fibrosis. In particular, we are investigating the therapeutic potential of RAS components, and also targeting RAS components using drugs currently available in clinical practice to improve experimental hepatic fibrosis and portal hypertension in animal models of liver disease.

Honours projects available

ACE2 gene therapy - Mechanism(s) by which angiotensin converting enzyme 2 (ACE2) improve hepatic fibrosis

Supervisors: Dr Chandana Herath and Professor Peter Angus

We have strong data to suggest that ACE2 treatment ameliorates liver fibrosis in various models of mice with liver disease. This led us to investigate the mechanisms by which ACE2 improves liver fibrosis. The current project is an in vitro project, and therefore you will use liver cells isolated from mice and rats with and without liver disease and from mice already receiving ACE2 gene therapy. The primary cells that are isolated will include parenchymal cells such as hepatocytes and non-parenchymal cells such as hepatic stellate cells and Kupffer cells. Whilst parenchymal cells are responsible for metabolic activity of the liver, non-parenchymal cells are involved in the maintenance of the hepatic architecture, wound healing response and defence against invasive pathogens. The isolated cells are cultured in vitro and maintained under standard conditions. Once the cells are adhered to the bottom of the plate, they will be infected with a non-harmful virus carrying the ACE2 gene. At different time points you will harvest the supernatant and the cells for measurement of various parameters including gene and protein expression and cytokine production. Moreover, in order to investigate the molecular mechanisms by which ACE2 renders beneficial effects in liver fibrosis, the viral infected cells will be subjected to a number of interventions in which various intracellular signalling pathways, including p38 MAPK, JNKs, ERK1/2 MAPK, NF-KB and NADPH oxidase, will be blocked using compounds that are readily available to us.

Techniques: This project requires you to work with laboratory animals. Techniques include isolation of mouse and rat liver cells, cell culture quantitative real time PCR and Western blotting.

Role of the RAS in regional blood flow in cirrhosis

Supervisors: Dr Chandana Herath and Professor Peter Angus

The mesenteric vasodilatation in cirrhotic patients plays a key role in the development of portal hypertension, an increased pressure in the portal vein feeding the liver with blood draining from the gut. Portal hypertension leads to formation of varices and variceal bleeding and therefore, it is a major complication of cirrhosis with increased morbidity and mortality. We are therefore interested in studying the role of Renin Angiotensin System (RAS) antagonists and agonists on hemodynamic changes that occur in cirrhosis. You will use a number of compounds including receptor blockers in anaesthetised rats. Drug infusion will be performed via cannulated vessels (eg. femoral vein), and blood pressure and portal pressure will be measured via catheters placed in the arteries (eg. femoral artery or carotid artery) and portal vein, respectively. In addition, coloured microspheres will be injected into systemic and portal circulation to investigate cardiac output and regional blood flow measurements in the presence or absence of various RAS agonists and antagonists.

Techniques: The student will be required to do some animal (mouse and rat) work. Techniques include blood vessel cannulation in anaesthetised rats and mice, and drug injection and blood withdrawal, pressure recording using a comprehensive computer based system.

Metastasis Research Group

Professor Albert Frauman

Dr Sujitra (Billie) Detchokul
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Laboratory/Group Location

Level 5, Lance Townsend Building, Austin Hospital, Heidelberg

What we do

Prostate cancer is one of the commonest cancers worldwide. Our research is looking at mechanisms of prostate cancer progression and of treatment resistance, using molecular biology, structural biology and bioinformatics approaches in biomarker discovery as a means of identifying new diagnostic and drug targets. We have taken 2 approaches. Firstly, we have tested novel inhibitors of prostate cancer invasion/metastasis and secondly, we have undertaken a time-course, whole genome analysis of an in vitro model of evolving androgen resistance. These strategies should lead to new diagnostic, prognostic and therapeutic approaches to this common malignancy.

Honours projects available

Anti-CD151 inhibition in prostate cancer progression

Supervisors: Dr Sujitra Detchokul and Professor Albert Frauman

Prostate cancer is the most commonly diagnosed cancer in developed countries. The tetraspanin CD151 is a prognostic marker which promotes cell motility in prostate cancer. The tetraspanins are a superfamily of four transmembrane domain cell surface proteins expressed in a wide variety of cell types and, of relevance to cancer progression, are involved in cellular adhesion, cell motility and tumour suppression or activation. The tetraspanins are thought to regulate their activities via the organisation of a cell surface membrane microdomain which facilitates their interaction with a range of other proteins such as integrins, immunoreceptors and signalling molecules.

We have identified potential anti-CD151 compounds, which inhibit prostate cancer progression. The aim of this Honours project is to confirm anti-metastatic potential of these compounds in in vivo mouse models of primary human tumour xenotransplants. In addition, investigation of potential mechanisms of action of these compounds in angiogenesis will be carried out using in vitro tube formation assay.

Time-related genetic changes during the transition to androgen insensitivity in prostate cancer

Supervisors: Dr Sujitra Detchokul and Professor Albert Frauman

The development of castrate-resistant prostate cancer (CRPC) after androgen-deprivation therapy is common and hinders effective treatment and management of this disease. We have evidence to suggest that androgen-sensitive prostate cancer cell lines undergo phenotypic changes after prolonged androgen-deprivation. Moreover, prolonged androgen-deprivation increases proliferation, motility and invasion of prostate cancer cells. The aim of this project is to investigate the changes in prostate androgen-regulated genes

and pathways as cell lines progress to CRPC phenotypes. RNA sequencing data have already been generated in our lab.

Techniques: The experimental approach involves analysis and identification of the androgen-regulated genes from differentially expressed gene profiles of prostate cancer cells as a result of prolonged exposure to anti-androgen treatments in a time course manner. Validation of gene expression will be performed in wet-lab experiments ie. quantitative real time PCR, immunohistochemistry and Western blotting.

Post-stroke Musculoskeletal Systems Collaboration Group

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A/Prof Rachel Davey
Musculoskeletal and Molecular Endocrinology Research Group, Department of Medicine,
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Laboratory/Group Location

Melbourne Brain Centre & Lance Townsend Building, Austin Hospital, Heidelberg

What we do

Our group, comprising basic scientists and clinical researchers, investigates the effects of stroke on bone and muscle.

Honours projects available

Post-stroke changes to bone microarchitecture in a rat model of transient middle cerebral artery ischemia

Supervisors: Dr Karen Borschmann, Dr Rachel Davey

This project will extend work that has been previously undertaken by our group. We undertook a randomised, controlled study of rats that underwent middle cerebral artery occlusion (MCAo) or sham surgery. Animals in the stroke group experienced left sided stroke impairments. All animals had physical activity measures recorded for 4 weeks after surgery. Long bones were collected then scanned by microcomputed tomography (CT) at 2 damage, and a sub-set of animals underwent MRI and CT scans for analysis of muscle and fat content of hind limbs.

An honours project is available to undertake a detailed assessment of micro-CT images to determine whether stroke affects the microarchitecture (and therefore the strength) of femoral bones. A sub-study will involve calculation of muscle and fat volumes from the MRI and CT images, and there is the potential to undertake analyses of stored bloods. There is no contact with animals required in this study. Results of this project will help us to understand the mechanisms of increased bone fracture risk after stroke and relationship with physical activity, to guide the development of interventions to improve outcomes for people with stroke.

Translational Neurogenetics Group

Professor Samuel Berkovic

Dr Michael Hildebrand

michael.hildebrand@unimelb.edu.au, Tel: (03) 9035 7143, <http://www.epilepsyresearch.org.au/>

Laboratory/Group Location

Epilepsy Research Centre, Melbourne Brain Centre, Department of Medicine, Austin Hospital, Heidelberg

What we do

Genetic epilepsies are common affecting ~ 2% of Australian children. The Epilepsy Research Centre includes basic and clinical researchers at the Melbourne Brain Centre, Austin Hospital, Walter & Eliza Hall Institute, all affiliated with The University of Melbourne. Together with collaborators we are the leaders in the genetics of epilepsy field in Australia. The scope of the Translational Neurogenetics Laboratory at the Melbourne Brain Centre, Austin, Hospital, is principally gene discovery and characterisation in simple Mendelian and complex epilepsies using current and emerging molecular genetics techniques including next generation sequencing.

Honours projects available

Detection of Somatic Mutations in Sporadic Epilepsies

Supervisors: Dr Michael Hildebrand and Prof Samuel Berkovic

We have recently posited that, in addition to obvious inherited epilepsies, and those shown to be due to de novo mutagenesis in parental gametes, there may be a sizeable 'hidden genetics' component of epilepsy due to somatic mutation. This occurs post-zygotically, is largely confined to the brain and is difficult or impossible to detect by conventional sequence analysis of peripheral blood. This has been supported by discovery of somatic mutations restricted to certain brain malformations where brain tissue is available, and very recently by analysis of post-mortem tissue in autism. Here we wish to push the boundaries and establish techniques to detect somatic mutations in brain using a minimally invasive approach. This approach would then be applicable to epilepsies and other brain disorders to maximise gene discovery and, eventually, for translation of Precision Therapies to the clinic. At present, the route to discovery of somatic mutations in brain is via the privileged situation of having brain tissue from surgical or autopsy specimens; this is not generally applicable to common epilepsies. Here we propose investigating the feasibility and yield of a strategy to detect somatic mosaicism via a minimally invasive lumbar puncture. Our hypothesis is that analysis of cell-free DNA from cerebrospinal fluid will allow detection of 'high load' somatic mosaicism

Techniques to be used: This exciting and data rich project takes advantage of genetic material from patients and comprehensive clinical information analysed over many years. We use the latest techniques in molecular genetics, including cell-free DNA extraction, molecular inversion probe gene capture, next generation sequencing, pyrosequencing and bioinformatics. This project will also involve standard molecular genetics techniques (e.g. PCR, DNA sequencing)

Translational Breast Cancer Program

Olivia Newton John Cancer Research Institute

<http://www.onjcri.org.au/#home-2>

Professor Robin Anderson

robin.anderson@onjcri.org.au, Tel: (03) 9496 9669

Laboratory/Group Location

Level 5 ONJ Centre, Austin Hospital, Heidelberg

What we do

Our research will help us to achieve our goal of reducing deaths from breast cancer. We have developed pre-clinical models to identify genes, both in the tumour cells and in the tumour cells and in the microenvironment that regulate the spread of cancer to specific organs such as the liver, lungs and brain.

Honours projects available

The relevance of SMAD4 expression in regulation of breast cancer metastasis

Supervisors: Professor Robin Anderson, Dr Allan Burrows

Metastatic breast cancer is the second most common cause of cancer-related death in women worldwide, and around 20% of women with breast cancer will die due to the development of metastatic disease, the onset of which may take up to 20 years to manifest. Previously, our group discovered that bone morphogenetic protein 4 (BMP4) is a powerful suppressor of metastasis in preclinical breast cancer models and a good prognostic factor in patients with breast cancer.

The aim of this project is to determine the consequences of canonical or non-canonical signalling through SMAD4 for metastasis suppression. SMAD4, a well-known tumour suppressor, is required for canonical BMP4 signalling and, in its absence, BMP4 can signal through MAPK and NFκB pathways, possibly leading to promotion of metastasis.

The 4T1.2 mammary tumour line is highly metastatic when grown as tumours in mice. Expression of BMP4 in the tumour cells or treatment with recombinant BMP4 inhibits metastasis. In this project, we will generate cells with stable knockdown or CRISPR/Cas9 mediated deletion of SMAD4 to determine the consequences of loss of SMAD4 on BMP4 mediated inhibition of metastasis. In addition, the human breast cancer line, MDA-MB-468 has a mutation resulting in no SMAD4 expression. We will determine the consequences on tumour growth and metastasis of restoring SMAD4 expression in these cells.

This project will involve tissue culture, genetic engineering of cells to change the level of SMAD4 expression, western blotting to measure changes in canonical and non-canonical BMP4 signalling and tumour growth in mice.

Florey Department of Neuroscience and Mental Health

<http://www.florey.edu.au>

Laboratory Location

The Florey Institute of Neuroscience & Mental Health, Melbourne Brain Centre Austin campus, Austin Hospital, Heidelberg

Some of the projects offered by The Florey Institute of Neuroscience & Mental Health are based at the Heidelberg campus and students will be enrolled via the Department of Medicine, Austin Health. For further details on projects, please refer to the Florey Student Projects 2017 available on their website.