

Honours in the Discipline of Physiology

2020 Project List

Bachelor of Medical Science: BMedSc(Hons)
Bachelor of Science: BSc(Hons)

HONOURS PROJECTS – 2020

A list of projects available to Honours candidates in 2020 is provided below.

Dr Dan Johnstone is the Honours coordinator and should be contacted for general information at daniel.johnstone@sydney.edu.au

Potential supervisors within the Discipline of Physiology, or external supervisors (e.g. at Heart Research Institute, Kolling Institute, Brain and Mind Centre) affiliated with the Discipline of Physiology, should be contacted directly to discuss specific opportunities.

INTERNAL PROJECTS

Anderson Stuart Building, Charles Perkins Centre or Medical Foundation Building

MOLECULAR NEUROSCIENCE LAB

A/PROF BILL PHILLIPS

Email: william.phillips@sydney.edu.au

Phone: 9351 4598

Location: Room N348, Anderson Stuart Building

Lab overview

We study the molecular mechanisms of synapse development and adaptation, focusing on the mammalian neuromuscular synapse. Muscle specific kinase (MuSK) is a receptor tyrosine kinase that coordinates the embryonic development of the neuromuscular synapse. We have a particular interest in learning how synaptic signalling systems such as the MuSK system maintain healthy synapses and how they might be targeted in new ways of treating neuromuscular diseases.

Projects

Muscle Specific Kinase signalling and Duchenne muscular dystrophy

In Duchenne muscular dystrophy (DMD), deficiency of the muscle membrane protein, dystrophin, makes the muscle fibre vulnerable to damage with repeated rounds of fibre degeneration and regeneration leading to muscle atrophy. Recently we have found that increasing the expression or function of the muscle specific kinase (MuSK) using an adeno-associated viral vector protected dystrophic muscles from damage, in the mdx mouse model of DMD. This project will investigate, previously unknown functions of MuSK and the potential of the MuSK system to protect dystrophic muscles from degeneration. The project will involve analysing mRNA and immunolabelling to assess the impact of AAV-MuSK in muscle fibres.

LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY

A/PROF CATHERINE LEAMEY

Email: catherine.leamey@sydney.edu.au

Phone: 9351 4352

Location: Room N105, Anderson Stuart Building

Lab overview

Neural connections underlie every aspect of our perception, behaviour and cognition and are a product of both genetic factors and environment/experience. The visual pathway is particularly useful for investigating the relative roles of specific proteins and experience in the assembly and function of neural circuits. We have recently discovered that a family of molecules, known as the Ten-ms or Teneurins, play important roles in wiring up binocular visual pathways. The miswiring present in the knockout strains leads to behaviorally measureable visual deficits.

Projects

The capacity for Environmental Enrichment to restore function in Ten-m3 Kos

The misalignment of projections present in Ten-m3 KO mice leads to a form of functional blindness. Recent data suggests that enhancing the animals experience via environmental enrichment can lead to a recovery of vision. A number of projects exploring this important research avenue, including assessment of the degree of recovery following enrichment at different ages, investigation of underlying mechanisms and mimicking enrichment by addition of pharmacological agents are available.

Impact of increased ipsilateral projections on binocular vision

Our preliminary data demonstrates that Ten-m4 KO mice have additional ipsilateral projections from dorsal retina. The chief aim of this study is to determine how these extra projections affect the visual ability of the mice using a new behavioural paradigm developed in the lab.

Cellular substrates of binocular vision

How does an environmental stimulus lead to a behavioural response? Recent work has demonstrated that ethologically-relevant visual stimuli trigger robust behavioural responses in mice. The circuits underlying these responses are not known, but provide enormous potential for understanding how visual input is processed and transformed to trigger an appropriate behaviour. The visual deficits present in Ten-m KO mice present additional windows into the function of specific cell types. Projects addressing these issues using multi-photon imaging, neural tracing and electrophysiological recording are available.

Some of these are offered as collaborative projects in association with Dr Atomu Sawatari and Dr Dario Protti's laboratories. Other projects may also be available on request.

VISION LABORATORY

DR DARIO PROTTI

Email: dario.protti@sydney.edu.au

Phone: 9351 3928

Location: Room N659, Anderson Stuart Building

Lab overview

Our research work focuses on the function of the retina. Specific neuronal circuits provide ganglion cells, the output neurons of the retina, with excitatory and inhibitory inputs whose relative magnitude and timing determine the spatial and temporal properties of the electrical signals sent to higher visual centres in the brain. The relative impact of excitation and inhibition on ganglion cells output, however, is not well understood.

We are currently investigating the effect of cannabinoids, derivative compounds of marijuana, on the physiological properties of different types of ganglion cells in the eye.

Projects

Cannabinoids effects on vision

We have recently shown that exogenous cannabinoids modulate the transmission of visual information in the retina. In addition, we showed that the endocannabinoid system is active in normal conditions. This project will investigate how and where cannabinoids act on the retina by studying the effects of drugs that target different components of the cannabinoid system. For these studies we use genetically modified animals that express the light-sensitive membrane protein *channelrhodopsin* and other animals in which membrane channels have been knocked out.

The yin and yang of excitation and inhibition in the retina

Ganglion cells integrate excitatory and inhibitory signals from bipolar and amacrine cells respectively. The strength and relative timing of these inputs determine the output properties of ganglion cells. This project investigates how the balance of excitatory and inhibitory inputs impact on ganglion cell responses. To gain insight into this, we inject to various combinations of excitatory and inhibitory currents into ganglion cells and record their responses. This link to our video article can give you a good idea of the experimental approach:

<http://www.jove.com/video/50400/implementing-dynamic-clamp-with-synaptic-artificialconductances>

This is a joint project between Dr Dario Protti and Dr Jin Huang (N659. 9351 9065, jin.huang@sydney.edu.au)

The techniques used in these projects are patch-clamp recordings, optogenetics, dynamic-clamp recordings, confocal microscopy and computer modelling. For more information please contact Dr. Dario Protti: dario.protti@sydney.edu.au

Other projects are offered in collaboration with Dr. Cathy Leamey and Dr. Atomu Sawatari.

SENSORY SYSTEMS AND INTEGRATION

DR AARON CAMP

Email: aaron.camp@sydney.edu.au

Phone: 9351 9140

Location: Medical Foundation Building

Projects

A Noisy Nervous system: The impact of synaptic noise on sensory neuron sensitivity

The output of individual sensory neurons is ultimately dependent on the combination of synaptic inputs and intrinsic neuronal properties. We have shown that even small fluctuations (ones that do not cause either excitation or inhibition) in the membrane potential of sensory relay neurons produce dramatic changes in their subsequent output. This “synaptic noise” represents the impact of the network activation state within which sensory neurons are embedded, and presumably plays an important role in sensory neural signaling.

Using patch-clamp electrophysiological techniques you will investigate the sensitivity of neurons in the central vestibular (balance) pathway. This pathway provides an ideal model since neurons in the vestibular nuclei display a diverse suite of discharge properties, and are known for their capacity to undergo both synaptic and intrinsic “plasticity”. Specifically, you will characterize the gain (sensitivity) of type A, B and C neurons in the Medial Vestibular Nucleus (MVN) to injections of current, and synaptic noise. This information is crucial to understand how individual sensory neurons code information about the outside world.

The impact of visual stimulation on the vestibulospinal reflex.

Vestibular-mediated reflexes and the circuits that underlie them are embedded within a complex network of neural structures including the cerebellum, thalamus, and forebrain structures. As such it is likely that the output of the vestibular system is modulated by these structures in a context dependent manner. A question raised in this project is whether the cVEMP (a measure of balance function) can be altered in response to visual stimulation- a condition that occurs naturally, and ultimately whether there are differences in the way our nervous system modulates peripheral vestibular reflex function.

Vestibular evoked myogenic potentials will be recorded from target muscles in response to loud sound stimuli delivered via in-ear headphones. Myogenic responses will be measured using the Delsys dEMG system and data acquired using custom software prepared in-house using Matlab.

SIGNAL PROCESSING IN THE VISUAL SYSTEM

DR ALAN FREEMAN

Email: alan.freeman@sydney.edu.au

Phone: 8627 8860

Location: Room 115, R.C. Mills Building

Lab overview

Response properties in the visual system undergo a remarkable change in the transition from eye to cortex: whereas signals from the eye are photograph-like, cortical neurons are selective for stimulus characteristics such as contour orientation and can therefore provide the foundation for object recognition. My research work studies the neuronal mechanisms underlying the transformation of subcortical to cortical signals.

Projects

I use three methodologies – computational modelling, the analysis of existing neuronal data, and psychophysics. The modelling uses large-scale spatiotemporal neural networks, the existing neuronal data comprises responses collected from mammalian primary visual cortex in a colleague's laboratory, and the psychophysics involves human subjects responding to carefully-designed stimuli on a computer screen. The aims of this work are to understand more about the visual system, and to provide the front end of a machine-based object recognition system. The most powerful system resides in the human brain, and it therefore makes sense to copy the biological version as closely as possible.

CLINICAL NEUROPHYSIOLOGY LABORATORY

DR SUSANNA PARK

Email: susanna.park@sydney.edu.au

Phone: 9351 0932

Location: Brain and Mind Centre

Lab overview

Our research focuses on developing novel outcome measures and neurophysiological assessments in the clinical setting and determining how these can be applied to improve diagnosis, treatment and management of human disease.

Projects

Grip-lift function in sensory and motor neuropathies

Sensory feedback is important in effective object manipulation, allowing appropriate scaling of grip and load forces during precision grip. These parameters may be altered in sensory neuropathies, and may further demonstrate links with sensory deficits and functional status. Further precision grip deficits characterise patients with motor neuropathies such as multifocal motor neuropathy, motor neuron disease and Kennedy's disease. Examination of the patterns of deficit development between sensory and motor neuropathies may provide insights into mechanisms of patient dysfunction and symptoms progression. An object grip-lift task using the thumb and index finger to grip an object with two 3D force transducers will enable examination of the scaling of fingertip forces and temporal coupling between grip and lift movement phases during precision grip. This will be compared with quantitative assessment of hand function and sensation, using a range of sensory assessment tools to assess touch sensitivity and spatial discrimination as well as motor performance and strength.

Chemotherapy-induced peripheral neuropathy: Functional deficits and patient reported outcomes

Nerve damage following chemotherapy treatment is a serious side effect of cancer treatment that significantly affects quality of life in cancer survivors. Chemotherapy-induced peripheral

neuropathy (CIPN) develops with some of the most commonly utilised chemotherapies and produces tingling and numbness in the extremities, leading to sensory loss, functional difficulties and significant disability. However, despite the prevalence and impact of CIPN, there remains a lack of quantitative tools to identify toxicity, no standardised measurement criteria and no effective prevention or treatment. We are collecting novel neurophysiological assessments and a range of functional, clinical and behavioural tests across multiple sites to provide a complete assessment of nerve and functional capacity in cancer survivors. Potential honours projects within this larger research project include:

- i) Assessment of patient-reported comorbidities such as fatigue or depression and comparison to patient report of neuropathy symptoms, with the aim of developing a model of general treatment related toxicity
- ii) Health-related quality of life in patients with severe toxicity
- iii) Assessment of balance deficits and comparison with metrics of sensation such as vibration sense in patients with CIPN

ANDROLOGY RESEARCH GROUP,

A/PROF STEVE ASSINDER

Email: stephen.assinder@sydney.edu.au

Phone: 9036 3614

Location: G46, Medical Foundation Building

Lab overview

Prostate disease is very common in the ageing male. Prostate cancer is the most commonly diagnosed cancer in men and second most frequent cause of cancer-related deaths. It is estimated that there is at least 1 death every 4 minutes worldwide attributed to prostate cancer. Benign prostatic hyperplasia (BPH) affects at least half of all men over the age of 60 years and presents a significant burden to health care costs. Evidence suggests that obesity is a risk factor for both BPH and prostate cancer.

Our research is focused on oxytocin, the hormone of love. Our recent work has indicated that oxytocin acts at the prostate to increase *de novo* steroidogenesis. It has also shown that this hormone might also affect tissues important in regulating energy balance.

Projects

How might the “hormone of love” mitigate obesity and type 2 diabetes?

Oxytocin is best known for its roles in maternal physiology. During childbirth this hormone is released from the mothers brain and acts on the uterus to induce and maintain contractions. Following birth oxytocin is important in stimulating the release of milk during breast-feeding. Since the description of these classical actions oxytocin has been shown to have key roles in modulating maternal behaviour as well as other social behaviours such as pair-bonding. Indeed, it is for these roles that oxytocin has been dubbed “the hormone of love” (reviewed in Tom and Assinder, 2010). More recent evidences suggest positive metabolic effects of oxytocin through improved glucose metabolism, circulating lipid profiles, and increased insulin sensitivity (reviewed in Elabd and Sabry, 2015; Altirriba *et al.*, 2015). Hence, oxytocin is suggested to have pharmacological efficacy in treating obesity and type 2 diabetes.

Possible projects would determine: 1) how oxytocin modulates adipose and adrenal secretion of hormones important to maintaining energy balance; 2) how oxytocin affects lipid metabolism in adipose tissue and the liver and; 3) whether it modulates liver glucose metabolism (these projects are in collaboration with Dr Andrew Hoy); 4) whether oxytocin affects mitochondrial activity (in collaboration with Dr Ryan Davis, Kolling Institute).

VITAMIN D, BONE AND SKIN LABORATORY

PROFESSOR REBECCA MASON

Email: rebecca.mason@sydney.edu.au

Phone: 9351 2561

Location: Room N543, Anderson Stuart Building

Lab overview

The group has a particular interest in vitamin D and calcium physiology and the role of skeletal muscle in the maintenance of vitamin D status is being investigated in the offered project.

Projects

The role of muscle in the maintenance of vitamin D status

Most vitamin D is made in skin as a result of a photochemical reaction between UVB light and 7-dehydrocholesterol. The vitamin D is then converted to 25-hydroxyvitamin D, the major circulating form of vitamin D, in the liver and then to the active hormone, 1,25dihydroxyvitamin D in the kidney and other tissues. The half-life of 25-hydroxyvitamin D in blood is inexplicably much longer than that of most steroids and much longer than its binding protein. Because of this and since there is relatively little vitamin D made in winter (not much UVB and not much skin exposed), there must be a mechanism that reduces the degradation of 25-hydroxyvitamin D, to allow for this long period in which 25-hydroxyvitamin D stays in blood without being degraded. How this happens has not been investigated. Several lines of indirect evidence are consistent with a proposal that muscle somehow contributes to the longer than expected half-life of 25-hydroxyvitamin D. The project, which includes whole animal and cell culture studies, will test this hypothesis.

Abboud MA*, Puglisi DA*, Davies BN*, Rybchyn M, Whitehead NP, Brock KE, Cole L, Gordon-Thomson C, Fraser DR, Mason RS. Evidence for a specific uptake and retention mechanism for 25-hydroxyvitamin D in skeletal muscle cells. *Endocrinology* 154(9):3022-3030, 2013. * These authors contributed equally to the work.

Abboud M, Rybchyn MS, Liu J, Ning Y, Gordon-Thomson C, Brennan Speranza TC, Cole L, Greenfield H, Fraser DR, Mason RS. The effect of parathyroid hormone on the uptake and retention of 25-hydroxyvitamin D in skeletal muscle cells. *J Steroid Biochem Mol Biol* 173:173-179, 2017.

LIPID METABOLISM LABORATORY

DR ANDREW HOY

Email: andrew.hoy@sydney.edu.au

@HoyLipidLab

Phone: 9351 2514

Location: Lab 3 West, The Hub, Charles Perkins Centre

Lab overview

The Lipid Metabolism Laboratory investigates the mechanisms linking perturbed lipid metabolism and a range of pathologies. Currently, our primary interests are in insulin resistance/type 2 diabetes/obesity and cancer including breast, pancreatic and prostate, particularly how these cancers behave differently in an obese patient vs a lean patient. The lab located in The Hub, Charles Perkins Centre where the following projects will be available.

Projects

Novel proteins involved in fatty liver and insulin resistance

Insulin resistance is a unifying feature of the metabolic syndrome. The liver is an early site of perturbed insulin action and a critical regulator of whole body glucose and lipid homeostasis. The lipid droplet is the major site for storage of lipids and the movement of stored lipids out of this reservoir is highly regulated. We have recently identified proteins that locate to the lipid droplet whose abundance is altered in fatty liver and insulin resistance using innovative mass spectrometry and bioinformatic approaches. In this project, these highly novel candidate targets will be characterised using techniques including cutting-edge microscopy, cell culture, biochemical and radiometric metabolic analysis, and genetic manipulation.

Lipid metabolism and breast and prostate cancer

Lipid accumulation in both breast and prostate cancer is a common observation, especially in aggressive cancers. The vast majority of lipid is stored as triacylglycerols in lipid droplets within these cells. These lipid droplets are closely located to mitochondria, to serve a readily available supply of energy for tumour progression. This project will target the enzymes that regulate lipid flux at the lipid droplet, and elucidate their function and potential for therapeutic targeting in cancer. The project is part of a Movember-funded international program and will employ techniques including cell culture, genetic manipulation, radiolabel metabolic analysis, mass spectrometry, cutting-edge microscopy and cancer cell progression including proliferation, migration and invasion.

Cancer cell metabolism

Targeting metabolism has emerged as a potentially effective therapeutic strategy for many cancer types, which are driven by genetic alterations that are not tractable drug targets. To date, glucose and amino acid metabolism have received most attention and are well characterised, with lipid metabolism being the poor cousin, despite the numerous interactions between the metabolic pathways of these substrates. This project will exploit the heterogeneous genotypes of a diverse panel of cancer cell lines to assess substrate (glucose, glutamine, fatty acids) utilisation. This project will use a range of techniques including cell culture, biochemical and radiometric metabolic analysis, and stable isotope labelling in combination with mass spectrometry.

(Co-supervisors: Dr Andrew Hoy and Dr Lake-Ee Quek)

A Key Metabolic Switch in Cardiometabolic Disease

Non-alcoholic fatty liver disease (NAFLD) is now the commonest form of liver disease in the Western world, affecting one in three people in the general population, 90% of obese patients with T2D, and 5.5 of 6 million Australians with liver disease – accounting for much of the \$51 billion annual cost to our healthcare system. Liver fat is increasingly considered a primary driver of T2D, although exact mechanisms remain unclear, and is an independent risk factor for atherosclerosis. Further - and most clinically challenging - it is unknown which patients with liver fat will progress to metabolic complications.

Our collaborator, Dr John O'Sullivan from the Heart Research Institute recently discovered a new plasma biomarker (dimethylguanidino valeric acid [DMGV]) of liver fat that independently predicted diabetes up to 12.8 years before diagnosis in three distinct human cohorts of different

ethnicity (O'Sullivan et al., J Clin Invest, 2017). He has subsequently shown that DMGV is elevated in a human cohort of hepatic insulin resistance, and that the gene producing DMGV is upregulated in fatty liver disease. Intriguingly, in dietary models of NAFLD, we found sucrose (fructose + glucose) caused the most dramatic dysregulation of this pathway, consistent with recent reports showing fructose to have dramatic effects on hepatic insulin resistance in humans and mice. Together, these data suggest this pathway is most activated in lipogenesis leading to hepatic insulin resistance. In collaboration with Dr O'Sullivan, this project will test our proposed hypothesis using dietary models and genetically modified murine models in addition to liver biopsy and plasma samples from carefully characterized human cohorts. *(Co-supervisors: Dr Andrew Hoy and Dr John O'Sullivan (RPAH/HRI))*

Examining the role of common genetic variants in short-chain acylcarnitine metabolism in NAFLD and Type 2 Diabetes.

Dr John O'Sullivan from the Heart Research Institute recently demonstrated that short-chain acylcarnitines are associated with hepatic insulin resistance in a human hyperinsulinaemic-euglycaemic clamp study. He subsequently revealed that these metabolites were associated with liver fat and insulin levels in a large human cohort, and discovered common genetic variants in the ACADs gene that control their levels. In collaboration with Dr O'Sullivan, this project will utilize human iPSCs carrying these variants in the ACADs gene and will be performed in the. These iPSCs will be differentiated to hepatocytes, and functional assays will be used to compare lipid and glucose biology in hepatocytes homozygous for the minor allele of these variants with hepatocytes homozygous for the major allele. *(Co-supervisors: Dr Andrew Hoy and Dr John O'Sullivan (RPAH/HRI))*

BLOOD CELL DEVELOPMENT LAB

A/PROF STUART FRASER

Email: stuart.fraser@sydney.edu.au

Location: Medical Foundation Building

Lab overview

The Laboratory of Blood Cell Development focuses on using stem cells (embryonic stem cells, iPS and haematopoietic stem cells) to explore the processes regulating blood, bone marrow and neural development in normal and pathological conditions.

Projects

Nanoparticles as novel molecular detection systems (in collaboration with Physics)

We have developed a novel system that aims at offering a completely different method for studying and detecting cell surface molecule expression. This system could revolutionise diagnostics and research. Methods would include cell culture, flow cytometry, confocal imaging.

Neural chips

In collaboration with colleagues in Physics, we have developed novel surfaces for culturing neurons from pluripotent stem cells. These surfaces allow for the structured differentiation of neural and glial populations under engineered conditions. Methods would include; cell culture, stem cell differentiation, imaging, calcium signalling and confocal microscopy.

Re-forming the niche

Some patients with haematological disorders experience bone marrow failure, where the marrow no longer supports blood cell production. We have previously compared effective bone marrow (femur) and non-functional marrow (mandible) and found specific regulators which we propose decide whether marrow is supportive or non-supportive. Methods would include; cell culture, flow cytometry, imaging, stem cell culture, progenitor assays. This study could lead to novel interventions for bone marrow failure.

Regulators of blood cell development in the embryo

The first sites of blood production are the yolk sac and the allantois (which becomes the umbilical cord). We have discovered a macrophage population uniquely located in the yolk sac. We have also performed the first analysis of the allantois at the transcriptome level and discovered new markers and regulators of embryonic blood cell production. This project would either characterise the newly discovered macrophage population or explore blood and vessel development in the allantois. Methods include; mouse embryo dissection, flow cytometry, transcriptomics, progenitor assays, imaging.

DEVELOPMENTAL PHYSIOLOGY LABORATORY

A/PROF MARGOT DAY

Email: margot.day@sydney.edu.au

Phone: 9036 3312

Location: Room 232, Medical Foundation Building

Lab overview

Roughly 3% of babies born in Australia result from assisted reproduction involving fertilization and then culture of the embryo in vitro. It is known that the embryo culture environment causes significant alterations in gene expression, epigenetics, metabolism and cell proliferation during preimplantation development and that these alterations may have effects on later life.

Our studies aim to help us to understand the impact of the culture environment on pre-implantation embryonic development in order to improve reproductive outcomes. We study the physiological processes involved in fertilization of the oocyte and proliferation of the cells in the preimplantation embryo.

To do this we use a range of techniques including in vitro fertilization, isolation and culture of preimplantation mouse embryos, gene expression, cell signalling, electrophysiology and live cell imaging.

Projects

- The mechanisms by which the amino acids improve blastocyst development in vitro.

EMBRYONIC STEM CELL LABORATORY

DR MICHAEL MORRIS

Email: m.morris@sydney.edu.au

Phone: 9036 3276

Location: Room 139, Medical Foundation Building

Lab Overview

How do mammalian, including human, embryos grow? And how can stem cells grown in the laboratory shed light on the highly complex mechanisms that control development? My lab focuses on understanding the complex molecular pathways and circuits that control early stages of development – from pluripotency to gastrulation to cells of the developing nervous system.

Projects

Modelling early embryo development and neurogenesis using embryonic stem cells

Embryonic stem (ES) cells have the potential to differentiate into any cell type of the developing embryo and adult. So, they are invaluable in understanding the molecular mechanisms that drive normal development and can provide a window into what happens during abnormal development. ES cells also have great potential in treating a large number of currently incurable or poorly treatable human diseases and injuries, including neuropathies, brain and spinal injuries, muscular diseases, and diabetes. We use ES cells as an *in vitro* model to understand the key molecular mechanisms underpinning critical developmental milestones forming the nervous system.

We also develop protocols to direct the differentiation of ES cells to specific cell types that can be used in animal models of human disease and injury. In addition, we apply the knowledge we have gained from stem-cell behaviour *in vitro* to determine if the development of embryos themselves is controlled by the same or similar mechanisms. Thus, these projects examine the processes of development from pluripotency to germ layer formation to early neurogenesis and on to mature neural cells such as neurons, glia and neural crest cells that make up the central and peripheral nervous system. Our focus is on the many interacting signaling pathways and metabolic events that drive this directed differentiation.

Techniques to be used in these projects include tissue culture, cell signalling analysis, gene expression analysis, immunohistochemistry and fluorescence microscopy, flow cytometry, and measurements of aerobic and anaerobic metabolism.

ENVIRONMENTAL CONTROL OF PHYSIOLOGY LABORATORY

A/PROF BRONWYN MCALLAN

Email: bronwyn.mcallan@sydney.edu.au

Phone: 9036 3615

Location: Room G44, Medical Foundation Building

Lab Overview

Animal models are frequently used to understand physiological mechanisms. Comparative Physiologists use the diverse information discovered from a wide variety of non-laboratory animals

to help formulate ideas about physiological processes. Our current research has focused on the environmental control of structure and function in mammals, especially marsupials. Research includes the seasonal physiological and endocrinological changes in mammals and their morphological implications. We use the small marsupials *Antechinus stuartii* (brown antechinus), *Sminthopsis macroura* (stripe-faced dunnart), and *S. crassicaudata* (fat-tailed dunnart) as animal models. Projects include collaborations with other research groups at USYD and the UNSW.

Projects

The regulation of reproduction and metabolism by photoperiod and temperature

Seasonal changes in reproduction and torpor use (measured by open flow respirometry) are important for the survival of many small mammals. By exposing the marsupials *Sminthopsis macroura* and *Sminthopsis crassicaudata* to different photoperiods and temperatures we can understand more about the survival responses of mammals to environmental change.

Understanding the common molecules needed for live birth in vertebrates (With Prof Chris Murphy (Anatomy) & Prof Michael Thompson (Biol Sci))

The evolution of complex placentae is a fundamentally interesting but rare event, because it requires development of new structures and processes. With 100+ origins of viviparity, reptiles and mammals provide outstanding models for studying the evolution of a common vertebrate characteristic, namely viviparity and complex placentation. The honours project will focus on molecules which are important in the plasma membrane transformation of the uterus in preparation for implantation and later placental development in a marsupial mammal, *Sminthopsis crassicaudata*.

DEVELOPMENTAL & CANCER BIOLOGY LABORATORY

A/PROF MATT NAYLOR

Email: matthew.naylor@sydney.edu.au

Phone: 9351 4267

Location: N401, Anderson Stuart Building

Lab Overview

Research in the Developmental & Cancer Biology Lab focuses on understanding how normal development and cell function is controlled, and then, how this regulation is perturbed to result in human disease such as cancer. Specifically, research in the lab has focused on transcriptional and cell-matrix 'master' regulators of cell fate (eg. whether or not a cell undergoes proliferation or differentiation) in breast and prostate development and cancer. Using whole genome transcript profiling and subsequent mouse and human cell based models, we have identified several novel regulators of normal breast and prostate development and shown that altering the function of these genes can either speed up or slow down cancer progression.

Projects

Investigate the role of Paxillin in breast cancer & metastasis

Breast cancer is the most common invasive cancer of women, with Australian women having a lifetime risk of 1 in 9 for developing the disease. Although prognosis for early or locally contained disease is good, patients diagnosed with metastasis have a long term survival rate of only 5-10%. We have previously shown that Integrins, which regulate the interaction between a cell and its local

environment, control normal breast development and cancer progression. The role of paxillin, an integrin adaptor protein in this process remains unknown, but its expression is correlated with aggressive disease and cancer cell migration. This project will explore the role of paxillin in breast cancer cell function, tumourigenesis and metastasis. Techniques employed will include a combination of in vitro based techniques such as cell culture, morphology, migration and proliferation assays, shRNA, and in vivo based approaches such as genetic mouse models and xenografts.

Exploring the role of Paxillin in prostate cancer

Prostate cancer is the most common cancer of men and kills as many men as breast cancer does women each year. Similar to the Paxillin Breast Cancer Project, we have also recently demonstrated a role for a number of integrin and integrin related molecules in the progression of prostate cancer. This project will continue to explore the role of integrin signaling in prostate development and prostate cancer progression by using newly generated Paxillin floxed genetic mouse models, transgenic prostate cancer mouse models and by determining the effects of paxillin in prostate cancer cell function using cell culture, morphology, migration and proliferation assays, shRNA viral approaches, and further in vivo based approaches such as xenografts.

Metabolism and breast cancer

There is a clear link between metabolic disorders and obesity within a variety of different cancer types, including breast cancer. In addition, a key component in the progression of cancer is said to be the ability of a cancer cell to rewire its metabolic pathways to cope with increased energetic and biosynthetic demands required during tumour progression. We have demonstrated a novel role for ACC1 in this process. Using novel inhibitors in cell culture studies along with proliferation assays and mouse based carcinogenesis models, this project will investigate the effects of inhibiting lipogenesis and determine the subsequent effects on breast cancer cell growth and tumourigenesis.

Transcriptional regulators of mammary gland development and breast cancer

Control of cell fate and normal cell function is critical during development and is often perturbed during carcinogenesis and tumour progression. We have identified and developed a number of new mouse and cell based models to investigate or continue to define a completely novel function for a number of transcription factors not previously implicated in both the regulation of normal breast development or breast cancer. This project will utilise similar approaches and techniques to the projects previously described to determine the role of these transcription factors in the breast.

DIABETES AND INSULIN SECRETION LABORATORY

PROF PETER THORN

Email: p.thorn@sydney.edu.au www.thornlab.com

Phone: 8627 4629

Location: Charles Perkins Centre

Lab Overview

Our group uses cutting-edge microscopy, transgenic and molecular approaches to understand how insulin secretion is regulated in health and disease. Our latest work suggests that insulin secretion from pancreatic beta cells is controlled through synaptic-like connections with the blood vessels of

the islet. Our lab is based in the Charles Perkins Centre and consists of post-docs and students who will train and support the Honours students in these projects.

Projects

Understanding how the pancreatic beta cell synapse controls insulin secretion.

Our discovery that beta cells secrete insulin via a synaptic-like connection with blood vessels in the islet challenges accepted models of insulin secretion. Ongoing work in the lab is showing the synapse changes in type 2 diabetes, suggesting it may be significant in disease. The next step in this work is to prove that functional interactions in the synapse have significance for the control of insulin secretion. To this end, in this project we will stain for the key proteins in the beta cell synapse and use super resolution microscopy to determine their relative position. This approach will be complemented by live-cell two-photon imaging of insulin secretion. The outcomes of the project will be significant for both understanding and treatment of diabetes.

Refining cell-based therapies to cure type 1 diabetes.

We are working to engineer induced pluripotent stem cells to make them secrete insulin. Our experiments are testing some of the factors we are finding to be important in the control of beta cells in the islet with an aim to enhance the control of insulin secretion. For diabetic patients, cell replacement therapies have the promise, one day, to provide a cure for disease.

ENERGY METABOLISM AND INSULIN ACTION LABORATORY

PROF GREGORY COONEY

Email: gregory.cooney@sydney.edu.au

Phone: 8627 4756

Location: Level 5 West, Charles Perkins Centre

DR AMANDA BRANDON

Email: amanda.brandon@sydney.edu.au

Phone: 8627 5104

Location: Level 3 West, Charles Perkins Centre

Lab Overview

The broad aim of our research is to understand how different aspects of genetic make-up, environment (temperature, nutrition) and behavior (exercise) contribute to altered energy balance and the development of obesity and metabolic disease.

Projects

Role of environment and nutrition in the development of obesity-induced insulin resistance.

The exact mechanisms responsible for obesity-related metabolic disease such as diabetes and cardiovascular disease are not completely understood but are associated with the development of insulin resistance in liver, muscle and adipose tissue. Over-nutrition (including the macronutrient content of the diet) and environmental conditions like ambient temperature and exercise can impact on body fat accumulation and alter normal metabolism. We have developed dietary models of obesity in mice housed at different temperatures that differ in the degree of impairment of insulin action. This project will comprehensively examine the differences in insulin action in tissues from these mouse models using metabolic flux measurements, assessment of insulin signalling pathways and lipidomic and proteomic analysis to tease out what aspects of obesity predispose animals to insulin resistance and whether dietary or environmental interventions can reduce obesity-related metabolic disease.

METABOLIC CYBERNETICS LABORATORY

PROF DAVID JAMES

Email: david.james@sydney.edu.au

Phone: 8627 1621

Location: Level 5 West, Charles Perkins Centre

Lab Overview

Metabolism plays a central role in all biological processes. It is coordinated by numerous homeostatic mechanisms across multiple organs and defining the rules that govern the control of this complex network is one of our major interests. To do so we work both at the systems level to measure processes as broad as protein phosphorylation on a global scale as well as at the molecular level to interrogate the role of specific pathways in whole body metabolism. Many of our studies are performed across different genetic backgrounds in mice and involve different environmental perturbations such as diet or exercise. Technologies span a range of areas including mass spectrometry, molecular biology, biochemistry, cell biology, live cell imaging and bioinformatics.

Projects

Mapping new functions of insulin and exercise

Insulin and exercise activate extensive signalling cascades to regulate an array of cellular processes. Identifying the composition of these signalling networks and the proteins responsible for eliciting specific functions of insulin and exercise is essential in understanding the defects that cause metabolic disease where insulin signalling is defective, and in harnessing the power of exercise to promote health. We have recently interrogated the insulin and exercise-regulated phosphoproteome, revealing the extent of these signalling networks and a number of new phosphorylation sites on proteins modified in response to these stimuli. This project aims to characterise the function of novel insulin or exercise-regulated phosphoproteins and to identify the upstream kinase.

The interaction between diet and the genome in flies and mice

We and others have acquired evidence that genes and diet interact in a complex manner to govern health outcomes. We postulate that this is a major reason that diets do not work at a population scale. To better understand this complex interaction, we are feeding either flies (*Drosophila melanogaster*) or mice of vastly different genetic backgrounds with a range of diets that mimic those seen across different human populations. By collecting large scale omics data combined with phenotypic outcomes we aim to better define the gene-environment interaction.

The mechanism of insulin resistance

Insulin resistance is a risk factor for the development of a number of diseases including type 2 diabetes, cardiovascular disease and some cancers. Our group has discovered several links between nutrient processing and insulin resistance. This project aims to investigate the molecular basis for how mitochondrial metabolism affects insulin responses.

Insulin regulation of lipolysis

One of the most important actions of insulin in mammals is to suppress lipolysis or fatty acid release in adipocytes. Indeed, an impairment in this process may play a major role in diseases including non-alcoholic fatty liver disease and steatohepatitis. We have recently discovered a novel regulator of lipolysis in fat cells. This project will explore how insulin regulates the function of this protein to coordinate the release of fatty acids from the lipid droplet.

Students will learn a wide range of techniques including molecular biology, cell culture, metabolic/biochemical assays, mitochondrial bioenergetics, microscopy, western blotting, mass spectrometry and statistical analyses.

NUTRITIONAL IMMUNOMETABOLISM TEAM

A/PROF LAURENCE MACIA

Email: laurence.macia@sydney.edu.au

Phone: 8627 6525

Location: Level 4 East, Charles Perkins Centre

Lab Overview

We are interested in understanding how gut bacteria affect host physiology with a particular focus on the immune system. Our aim is find optimal methods to manipulate gut microbiota to prevent disease development.

Projects

Identification of novel methods of communication between the gut microbiota and the host

The trillions of bacteria that inhabit our gut, also called gut microbiota, are known to impact on our health by triggering or preventing disease development. These bacteria can directly interact with their host or indirectly through the release of soluble products that in turn affect cell function. Whether the gut bacteria communicate with the host via other methods is not known.

The aim of this project is to understand the impact of bacterial extracellular vesicles (EV) on host physiology. EV are membrane-surrounded structures released from cells such as bacteria that cargo proteins, lipids and nucleic acids. EV are known to act as communication and signalling vesicles in various cellular processes.

In this Honours project the student will characterise EV released by the mouse gut microbiota and study their impact on gut epithelial and immune cell function.

The techniques that will be employed involves flow cytometry, nanoparticle tracking analysis, cell culture, PCR and ELISA.

COMPARATIVE CARDIOVASCULAR PHYSIOLOGY

DR MELISSA CAMERON

Email: melissa.cameron@sydney.edu.au

Phone: 9351 5228

Location: Anderson Stuart Building

Lab Overview

The regulation of blood pressure is tightly regulated in the resistance blood vessels within the body; therefore understanding how these vessels vasodilate and vasoconstrict is of considerable importance. My research studies the evolution of signalling pathways in the vasculature of

vertebrates. In particular, I focus on nitric oxide and endothelium-derived hyperpolarisation in non-mammalian vertebrates and how these systems have evolved comparatively to mammals.

Projects

Does endothelium-derived hyperpolarisation contribute to vascular tone in resistance blood vessels of non-mammalian species?

Endothelium-derived hyperpolarisation (EDH) has been shown in mammals to mediate vasodilation of resistance vessels. Currently, little is understood about the role of EDH in non-mammalian species. Recent findings from my laboratory have shown a link to EDH contributing to vasodilation in resistance blood vessels from amphibians; however, further exploration is necessary. This project will further the initial findings, with a possible expansion to other species such as fish, birds or reptiles. This project will use an integrative approach to the laboratory work, which include, but are not limited to, molecular biology techniques (gene/protein expression) and physiological techniques such as wire myography/organ bath experimentation.

APPLIED MATERIALS GROUP

DR STEVEN WISE

Email: steven.wise@sydney.edu.au [@docswise](#)

Phone: 8627 9458

Location: Lab 3 West, The Hub, Charles Perkins Centre

Lab overview

The Applied Materials Group is developing new materials and devices for tissue repair, particularly for cardiovascular applications. Working in multi-disciplinary research teams the group specialises in device and materials engineering, blood compatibility and interactions with endothelial and smooth muscle cells. A strength of his group is their comprehensive range of pre-clinical models for evaluation of new materials. The lab located in The Hub, Charles Perkins Centre where the following projects will be available.

Projects

Engineering a physiologically relevant blood vessel in vitro

The development of biocompatible materials for treatment of cardiovascular disease, will be improved by better *in vitro* models of the vascular system. However, the field is lacking sophisticated bioreactor technology that sufficiently recapitulates key physiological parameters. The primary outcome of this project will be the development of a high value product; an advanced perfusion bioreactor technology with an unparalleled ability to mimic biological environments in vitro. This project is a partnership with Codex Research who have designed a prototype bioreactor for use in vascular applications, bearing synthetic vascular grafts engineered in our lab. The bioreactor aims to generate physiological arterial pressure, flow and shear conditions and allow real-time monitoring of these parameters. The project will determine: 1) optimal synthetic graft parameters to support vascular cells, 2) validation of vascular cell functionality and 3) response to balloon injury, using synthetic conduits seeded with human vascular cells. (*Co-supervisors: Dr Steven Wise, Dr Joy Michael*)

Next Generation Immunomodulatory Cardiovascular Devices

Although it is well established that chronic inflammation is central to the progression of cardiovascular disease (CVD), immunotherapies are not routinely used for clinical management. Large clinical trials have shown that *systemically* delivered broad-spectrum immunotherapies can compromise patient immune function. Immunotherapy *localisation* to sites of disease may increase effectiveness and safety, revolutionising the treatment of CVD. This project will design and develop new bioactive vascular materials that modulate local inflammation, representing a promising new way to treat underlying pathology, thereby establishing safe, effective, and lasting immunotherapies. The project will include design and engineering of bioactive material surface coatings, evaluation in cell culture models, with the potential for evaluation of devices in established pre-clinical models. The focus will be to increase our understanding of how materials can be designed to reduce pathological inflammation. (*Co-supervisors: Dr Steven Wise, Dr Richard Tan*)

Carbon-based nanocarriers for emerging therapeutics

Nanomedicine is a rapidly emerging research field aimed at enhancing specific targeting, accumulation and controlled release of therapeutics, whilst minimising effects on healthy tissue. However, translation into clinical practice has been limited by the complexity and costs associated with development of safe and efficient nanomaterials. This project aims to further develop a new class of patented nanoparticles. Different project streams are available including: (a) optimised delivery of genetic materials (e.g. siRNA, miRNA, plasmids) co-delivered using the nanoparticle platform and (b) evaluation of the potential of combination therapies, comprising chemotherapeutic drugs (e.g. paclitaxel, docetaxel) to advance treatment options for metastatic breast cancer in partnership with collaborators at the Garvan Institute of Medical Research. (*Co-supervisors: Dr Steven Wise, Dr Miguel Santos, Dr Monica Lam*)

PHYSIOLOGY EDUCATION RESEARCH

DR SHARON HERKES

Email: sharon.herkes@sydney.edu.au

Phone: 9351 3910

Location: Room E216, Anderson Stuart Building

Overview

Physiology is considered a ‘hard’ content discipline. Our group is interested in the processes students use to learn physiology and how academic teaching and assessment practices can improve student engagement, learning, and performance outcomes with an emphasis on innovative teaching practices and technology-enhanced learning.

Projects

Strategic ‘connection’ opportunities in online platforms

Students value feeling connected to their cohort and their teachers. In the face-to-face setting, personal interactions and the physical environment help to create this connection, promote a sense of community and provide on-demand feedback opportunities for students. Building similar connections in the online space is more challenging. This project aims to compare and evaluate the connection and feedback opportunities afforded in online platforms and lessons, with a view to proposing strategic practices for development and evaluation.

Unpacking the Physiology Learning Process – Compare the Pair.

It is widely recognised that many students enrolled in physiology courses find it significantly challenging to learn the many concepts and principles of this integrated discipline. The aim of this project is to determine the techniques that lead to efficient and sustainable learning of physiology. The project will compare study techniques and resources used by students completing degrees with double majors where physiology is one of the majors.

EXTERNAL PROJECTS

Kolling Institute, Heart Research Institute, Brain and Mind Centre, other Disciplines

The Discipline of Physiology on occasion accepts into its Honours course students who are performing their research in laboratories outside the Discipline. The project must be closely allied to physiology and students undertaking projects off campus must attend the all formal timetabled sessions for Honours students, which occur weekly within the Discipline.

Supervisors and laboratories which have indicated their interest in taking such students are listed below. You should contact the supervisor of the project directly to discuss opportunities in the first instance.

NEUROGENETICS LABORATORY

DR RYAN DAVIS

Email: ryan.davis@sydney.edu.au

Phone: 9926 4868

Location: Kolling Institute

Lab Overview

The Neurogenetics Laboratory bridges basic and clinical research into mitochondrial diseases, with direct access to patient-derived cell lines and samples. The main research focus is on improving mitochondrial disease diagnosis, understanding the pathophysiological basis of disease and identifying potential treatments in order to improve patient care and health outcomes.

Projects

Light modulation of mitochondrial function in mitochondrial disease

Mitochondrial diseases are a large and diverse group of incurable, inherited disorders with the common feature of mitochondrial respiratory chain dysfunction. There are currently no effective treatments for mitochondrial diseases. Evidence has emerged to suggest LED light exposure (photobiomodulation) can enhance mitochondrial function and thus improve mitochondrial disease manifestations.

In this project, mitochondrial disease patient-derived cell lines will be exposed *in vitro* to different light regimes (wavelength, duration, pulse) using a custom-built LED light source. Mitochondrial function will then be assessed to determine any light-mediated improvements.

Potential methods to master during the project include cell culture, flow cytometry (general mitochondrial health assay), biochemical assays (e.g. cellular ATP synthesis rate), molecular

biology assays (e.g. nuclear vs mitochondrial DNA content) and cellular bioenergetic analysis, in addition to general laboratory and research skills.

This project will be co-supervised by A/Prof Stephen Assinder.

OXIDATIVE SIGNALLING GROUP

DR KRISTEN BUBB

Email: kristen.bubb@sydney.edu.au

Phone: 9926 4913

Location: Kolling Institute

Lab Overview

Our laboratory is interested in investigating novel therapies for cardiovascular diseases. We are particularly interested in oxidative modifications that contribute vascular dysfunction in the context of peripheral vascular disease and pulmonary hypertension. We are located in state-of-the art laboratories within the Kolling Institute of Medical Research, at the Northern Clinical School campus. You will be embedded in the culture of this institute and the vibrant laboratory group with 10+ other honours/ PhD students spread across the department.

Projects

Elucidation of substance P and neurokinin 1 signalling in the pulmonary circulation

Pulmonary hypertension (PH) is a chronic disease of small pulmonary vessels characterized by progressive remodelling of the pulmonary vasculature, resulting in increased pulmonary vascular resistance, right heart failure and death. Given that it often occurs at a young age, the diagnosis of PH is devastating for those affected and novel treatments are urgently needed. Substance P can act as either a vasoconstrictor or vasodilator, depending on the circumstances. It has been postulated that substance P dysfunction is an underlying cause of PH. Pre-clinical models of PH are associated with increased lung substance P and pulmonary pressure can be decreased by depleting or inhibiting substance P. Likewise, activation of the substance P receptor, neurokinin 1 (NK1-R) leads to increased pulmonary pressure. The *aim* of this project is to *elucidate the role of substance P and NK1-R signalling in normal and hypoxic / inflammatory conditions in the pulmonary circulation*.

Methods: This honours project will involve investigating this signalling pathway using a pharmacological strategy in both cultured cells and also in isolated blood vessels. Techniques you will learn and use include cell culture, immunoblotting, RNA expression analysis, biochemical analysis and histology. You may also have the opportunity to learn isolated vascular function experiments depending on your interests.

CARDIAC BIOLOGY AND HEART FAILURE GROUP

DR SCOTT LEVICK

Email: scott.levick@sydney.edu.au

Phone: 9926 4911

Location: Kolling Institute

Lab Overview

Our group uses an array of molecular, cellular, and whole animal techniques to identify mechanisms underlying adverse cardiac remodelling that leads to heart failure. Our recent work has identified a critical and complex role for neuropeptides in modulating cardiac structure and function in various disease states. We are particularly interested in how neuropeptides and inflammatory cells interact to influence adverse cardiac remodelling. Models of cardiac remodelling that we use include diabetes, hypertension, and myocardial infarction.

Projects

The Peptide Catestatin as an Anti-Fibrotic in Cardiac Disease

Catestatin is a peptide that is relatively understudied in the heart. Rodent studies have indicated that its administration can improve cardiac function following myocardial infarction. However, its ability to modulate cardiac fibrosis has not been examined. Cardiac fibrosis is critical because it underlies heart failure with preserved ejection fraction, which makes up approximately 50% of heart failure cases and for which there is currently no specific treatment. This project will use the angiotensin II mouse model of cardiac fibrosis to examine the ability of catestatin to protect against fibrosis. The project also includes measurement of cardiac function in vivo, as well as molecular approaches and isolated cardiac fibroblast experiments to identify key molecules being regulated in cardiac fibroblasts.

The Contribution of Neuropeptide Y to Promoting Cardiac Fibrosis

Cardiac fibrosis is a critical component of adverse cardiac remodelling because it underlies heart failure with preserved ejection fraction, which makes up approximately 50% of heart failure cases and for which there is currently no specific treatment. This project will use the angiotensin II mouse model of cardiac fibrosis to examine the contribution of neuropeptide Y (NPY) to cardiac fibrosis. Neuropeptide Y is co-released from sympathetic nerves with noradrenaline, which contributes to the development of heart failure. This project will use antagonists of the NPY receptors, together with NPY knockout mice, to identify the role of NPY and each receptor in fibrosis. Isolated cardiac fibroblasts will be used to test the effects of NPY on myofibroblast conversion, proliferation, and extracellular matrix synthesis. The molecular pathways initiated by NPY in fibroblasts will also be examined.

Is sacubitril effective in treating diabetic cardiomyopathy?

Sacubitril is the latest pharmacological approach approved for use in heart failure patients. It is a combination angiotensin receptor antagonist/neprilysin inhibitor that has been shown to be more effective than standard angiotensin converting enzyme inhibitor therapy in reducing risk of death and hospitalisation in heart failure patients. What is not known is the efficacy of sacubitril in diabetic cardiomyopathy, where enlargement of the heart occurs along with fibrosis due to high glucose levels. This project will use mice that develop diabetes as a result of a mutation in the leptin receptor, to test the efficacy of sacubitril in reversing cardiac hypertrophy and fibrosis. Functional assessment of the hearts of these mice will be achieved using echocardiography and pressure catheterisation of the heart. Molecular studies will use isolated cardiac fibroblasts cultured under high glucose conditions to examine the effect of sacubitril on gene expression and molecular signalling pathways.

PAIN MANAGEMENT CELLULAR RESEARCH GROUP

DR CHRIS VAUGHAN

Email: chris.vaughan@sydney.edu.au

Phone: 9926 4950

Location: Kolling Institute

DR BRYONY WINTERS

Email: bryony.winters@sydney.edu.au

Phone: 9926 4950

Location: Kolling Institute

Lab Overview

Our group is examining the mechanisms underlying acute and chronic pain, and identifying novel therapeutic approaches. This work is carried out by using *in vitro* patch clamp electrophysiology and *in vivo* animal models. We are particularly interested in the endogenous cannabinoid system as a pain therapeutic target.

Projects

Endocannabinoid modulation of descending inputs to the midbrain periaqueductal grey - using optogenetics and electrophysiology

The midbrain periaqueductal grey (PAG) forms part of a descending analgesic pathway which receives inputs from higher brain centres, such as the amygdala, and projects via the medulla to the spinal cord. Endogenously generated cannabinoids produce pain relief from within the PAG by inhibiting synaptic transmission onto neurons within this brain region. The origin of these cannabinoid sensitive inputs is unknown.

This project will examine how the amygdala communicates with the PAG, and how this is modulated by endogenous cannabinoids. This project will use a combination of:

- (1) patch clamp electrophysiology – to examine how endogenous cannabinoids regulate synaptic transmission in PAG slices.
- (2) optogenetics – microinjection of channelrhodopsins (ChR2) into amygdala - to optically stimulate specific inputs from amygdala to PAG in the experiments described in (1).

HUMAN REPRODUCTION UNIT

PROF CHRIS O'NEILL

Email: chris.oneill@sydney.edu.au

Phone: 9926 4870

Location: Kolling Institute

Lab Overview

The molecular regulation of gamete and embryo function, including the processes of fertilisation and cellular differentiation.

Detailed analysis of the dynamic reprogramming of chromatin structure and function that underlie the changes in gene expression patterns that are central to normal development.

Investigation of the causes and consequences for normal development of errors in this dynamic reprogramming of the genome.

Projects

Molecular regulation of normal embryo development

Fertilisation causes a switch in the organisation of the genetic material inherited from the egg and sperm so that it codes for totipotency. Totipotency is the unique state that allows a cell to differentiate into any, and all, of the many different cell types that form the body and placenta. A detailed molecular description of this process is essential for a clear understanding of the processes of normal embryo development but are also required for advances in cell based regenerative medicine.

This project examines the processes of chromatin reorganisation that is initiated by fertilisation and is responsible for the onset of normal patterns of gene expression within the early embryo that code for totipotency. The work uses mouse embryo models and will entail extensive embryo culture and manipulation, gene knock-down strategies, quantitative microscopic analysis and gene & protein expression analysis. An enthusiasm for understanding processes of cell signalling pathways and their interaction with the embryo's transcriptional machinery is an advantage. The effects of changes in embryo nutrition on these processes are examined.

VASCULAR COMPLICATIONS GROUP

DR MARY KAVURMA

Email: mary.kavurma@hri.org.au

Phone: 8908 8907

Location: Heart Research Institute

Lab Overview

Our research is aimed at understanding fundamental mechanisms in molecular and cellular biology leading to complications associated with vascular diseases.

Projects

Identify the role of FasL/Fas in endothelial cells and in atherosclerosis

Fas ligand (FasL) is a member of the tumour necrosis factor (TNF) ligand superfamily, known to induce apoptosis in cells expressing its receptor, Fas. Interestingly, FasL overexpression in endothelial cells has been shown to protect against atherosclerosis. In this study, we will interrogate the role of the FasL/Fas pathway in endothelial cells *in vitro*, and in atherosclerosis-prone mice *in vivo*. We will also assess plasma levels in patients with coronary artery disease. A range of techniques will be used in this study, including cell culture and molecular biology techniques (e.g. luciferase assays, chromatin immunoprecipitation), gene expression (PCR, Western blotting), ELISA, and *in vivo* models of atherosclerosis.

Generation of new blood vessels by DR5 in peripheral artery disease

This proposal extends on our published findings showing TNF-related apoptosis-inducing ligand (TRAIL) as a new molecule critical in generating stable blood vessels by stimulating new blood vessel development. Whether TRAIL promotes blood vessel development via its receptor, DR5 is unknown. In this project we will examine whether DR5 can promote blood vessel development *in vitro*, *ex vivo* and *in vivo*. A range of techniques will be used including proliferation, migration, and tubulogenesis assays, 3D angiogenic sprouting and *in vivo* models of angiogenesis involving ischaemic injury (hindlimb ischaemia). Additional techniques include Laser doppler perfusion, histology, gene expression (PCR, Western blotting) and ELISA.

Do TRAIL signals improve wound healing in diabetes?

This proposal extends on our published findings showing TNF-related apoptosis-inducing ligand (TRAIL) is critical for new blood vessel development. Whether TRAIL can improve wound healing by stimulating the generation of new blood vessels in diabetes is unknown. In this project we will examine whether TRAIL can promote blood vessel development in a diabetic environment *in vitro*, and in wound healing in diabetes *in vivo*. A range of techniques will be used in this study, including *in vitro* proliferation, migration, and tubulogenesis assays. The *in vivo* wound healing model will also be performed. Additional techniques include Laser doppler perfusion, histology, gene expression (PCR, Western blotting) and ELISA.

HAEMATOLOGY RESEARCH LAB HRI

DR FREDA PASSAM

Email: freda.passam@hri.org.au

Phone: 8627 7492

Location: Level 3 East, Charles Perkins Centre

Lab Overview

The Haematology Research Lab aims to discover novel pathways in blood clotting which can lead to the development of effective and safe drugs to treat thrombosis. Current projects focus on the role of integrins and thiol enzymes in the development of thrombotic disease.

Projects

Thiol isomerases as novel antithrombotic targets

An exciting discovery in the thrombosis field is that enzymes, named thiol isomerases, regulate the function of blood cell receptors and clotting proteins by reacting with their disulphide bonds. In this project we will dissect the role of a thiol isomerase, named ERp5, in clot formation by using mice with genetic deletion of ERp5 in their platelets. We will examine how ERp5 regulates the interaction of platelets with endothelial cells and neutrophils in the vasculature. We will explore the role of ERp5 in thrombosis and its potential as a novel antithrombotic target.

Techniques: These studies will employ platelet function tests, flow cytometry and confocal microscopy. This project will provide the opportunity to learn the method of intravital microscopy for real time study of clot formation in mice.

Biochips for the assessment of thrombotic tendency

Many patients with a thrombotic tendency go undetected by routine laboratory tests in part because the available assays do not reflect the conditions in the circulation. The Haematology Research Lab uses biochips in a microfluidic system that mimics the flow of blood in vessels. In this project you will study blood cell adhesion and thrombus formation in the microfluidic devices to assess for persisting thrombotic tendency in patients with a history of thrombosis, who have completed treatment. You will also compare the efficiency of antithrombotics in normalizing thrombus formation in the biochips.

Techniques: This project involves the design and assembly of the biochips, cell perfusion assays and confocal microscopy.

Redox biomarkers in thrombotic disease

The redox balance (balance of reduction and oxidation reactions in our blood) is essential for a healthy circulation. Redox imbalance causes alterations of protein function contributing to the development of thrombosis. The Haematology Research Lab has developed assays to study the redox modifications of the platelet integrin $\alpha 2\beta 3$ and plasma protein von Willebrand factor to identify patients at high risk of thrombosis who will most likely benefit from drugs which restore the normal redox balance.

Techniques: This project employs mass spectrometry to study the redox modifications of clotting proteins, platelet and plasma functional assays of redox activity.

THROMBOSIS RESEARCH GROUP

A/PROF SIMONE SCHOENWAEELDER

Email: simone.s@hri.org.au

Phone: 8627 4117

Location: Level 3, Charles Perkins Centre

Lab Overview

“Atherothrombosis is a major healthcare problem in Australia, affecting more than 50 per cent of the adult population. We’re hoping to develop innovative approaches to reduce the risk of blood clot in patients and ultimately save lives”

Research undertaken in our laboratory is focused on determining the mechanisms underlying clot formation in healthy individuals; using this knowledge to better understand the mechanisms leading to platelet hyperactivity and pathological blood clot formation; and ultimately development of safer and more effective therapies to treat cardiovascular diseases including heart attack, stroke, diabetes and the metabolic syndrome.

Projects

Crosstalk between dying platelets and neutrophils – an important role in microvascular dysfunction
(Co-supervisors – Prof Shaun Jackson and Dr Yuping Yuan)

Ischemia reperfusion (IR) injury commonly occurs in a wide range of human diseases, including acute myocardial infarction (AMI) and ischemic stroke. IR injury is characterised by poor blood flow (hypoperfusion) in the micro-vasculature despite the re-opening (recanalization) of originally blocked macro-arteries. Up to 30-40% of stroke or AMI patients exhibit microvascular hypoperfusion following recanalization of culprit arteries. However, there are currently no effective therapies to prevent microvascular obstruction and tissue hypoperfusion. Clinical and experimental studies have suggested that platelet activation and neutrophil plugging within the microvasculature are key events contributing to microvascular obstruction, although underlying mechanisms are not completely understood.

We have recently identified a new mechanism by which platelets and neutrophils cause microvascular obstruction¹. This previously unrecognised thrombotic mechanism is induced by the ‘ripping’ and ‘dragging’ of fragile membranes from dying platelets, mediated by neutrophils rolling over the surface, with membrane fragments acting as a glue to bridge adjacent neutrophils and facilitate neutrophil aggregation, leading to vessel occlusion. We have now discovered that platelets and neutrophils can interact and influence each other via bidirectional communication – wherein dying platelets can convert neutrophils to a hyperadhesive inflammatory state; and in turn,

neutrophils can induce platelet death via production of oxidants. This bidirectional communication operating between platelets and neutrophils may exacerbate microvasculature dysfunction and inflammation during IR injury. This project will involve the use of animal models of ischaemia reperfusion, confocal microscopy, gut and lung histology, and other *in vitro* cell biology and biochemical approaches, to investigate this unique communication mechanism and its contribution to disease.

¹Relevant publications from our group: Yuan ,et al, *Sci. Trans. Med*, 2017 Sep 27;9(409).

Solving a sticky clotting problem in Diabetes (*Co-supervisors – Prof Shaun Jackson, Dr Arnold Ju*)

Diabetes has become one of the major healthcare challenges of the 21st century and a leading cause of cardiovascular disease worldwide. Up to 70% of all diabetes-related deaths are due to cardiovascular disease, primarily related to atherothrombosis. Diabetes not only enhances the development of atherosclerotic plaques, increasing risk of heart attack, ischemic stroke and peripheral vascular disease, diabetic individuals also exhibit a prothrombotic phenotype, or increased propensity to form blood clots. In 2009, we discovered a new mechanism promoting thrombus formation – through biomechanical (rheology-dependent) platelet activation, which promotes clotting or aggregation of low activation state (discoid) platelets¹. We now have evidence that this novel mechanism is dysregulated in diabetes, leading to excessive clotting².

In this project, using animal model of diabetes and diabetic human cells, we will examine the impact of diabetes on the biomechanical adhesive function of the major platelet integrin adhesion receptor, and whether dysfunctional reactive oxygen species (ROS) (common in diabetes) can contribute to this increased clotting. Finally, we will examine whether inhibiting ROS pathways reduces platelet hyperactivity and thrombosis in diabetes.

Relevant publications from our group: ¹Nesbitt WS, et al. *Nature Med.* (Article) 15(6):665-673, 2009; ² Ju et al, *Nat Commun.* 2018 Mar 14;9(1):1087.

New approaches to the treatment of ischaemic stroke (*Co-supervisor – Prof Shaun Jackson*)

The development of a blood clot blocking blood flow to the brain (ischaemic stroke) is the third most common cause of death and the most common cause of adult disability globally. The central goal of therapy for stroke is the prompt reperfusion of occluded blood vessels to minimise tissue death. This is achieved through delivery of fibrinolytic agents modelled on tissue-type plasminogen activator (t-PA). These are the only clinically approved treatment for stroke sufferers, and are not without significant limitations, with lysis resistant blood clots, as well as hemorrhage presenting as major complications. Studies suggest that combining inhibitors of platelets or clotting together with fibrinolytic agents can enhance cerebral reperfusion and reduce reocclusion following thrombolysis. Unfortunately, the benefits of combined antiplatelet/thrombolytic therapy are partially offset by the increased risk of life-threatening intracerebral bleeding caused by currently approved anti-platelet agents, limiting the widespread use of this approach.

We have identified a new class of antiplatelet agents (inhibitors of PI 3-kinase p110 β)¹ that are highly effective at promoting and facilitating thrombus dissolution and complete vascular reperfusion, without markedly increasing bleeding. Preliminary studies have revealed that PI3K β inhibitors lead to localised regions of thrombus instability, that lead to the development of channels within the body of the thrombus. This project will use a newly established model of ischaemic stroke in mice to examine whether our novel anti-platelet agent can facilitate thrombus dissolution and complete vascular reperfusion of occluded vessels, protecting against end-organ damage to the brain. Studies involve the use of *in vivo* models of thrombosis and thrombolysis, genetic mouse models and state-of-the-art imaging systems (confocal microscopy, intravital microscopy).

These studies may lead to new approaches to regulate the size and stability of blood clots forming in the body, providing major clinical benefit in the delivery of thrombolytic therapy (blood clot removal).

CLINICAL RESEARCH

DR KEYVAN KARIMI & PROF SHAUN JACKSON

Email: keyvan.karimi@hri.org.au

Lab Overview

Our mission is to detect the earliest signs of heart and blood vessel damage with a view to preventing serious complications in later life. We have several research projects ongoing in our laboratory, including those which aim to identify changes that occur in pulmonary microvasculature in response to hypoxia, and in disease states such as pulmonary hypertension - a rare but deadly disease. In these instances, our focus is to establish new therapies that could be tested in the clinical setting.

Projects

Coronary microvasculature in health and disease.

In collaboration with Professor Jackson, we will use intravital microscopy to identify new pathways for microvascular regulation in physiology, and in disease processes - in particular in ischaemia and reperfusion injury in the heart.

ATHEROSCLEROSIS AND VASCULAR REMODELLING

DR ASHISH MISRA & PROF SHAUN JACKSON

Email: ashish.misra@hri.org.au

Lab Overview

Our main objective is to broaden understanding of the cellular and molecular mechanisms involved in blood vessel wall patterning, define the role of these pathways in vascular abnormalities and complications, and then link these insights to translational research to improve the prevention and treatment of human cardiovascular disease.

To this end, we employ a unique blending of lab models and cultured cells, as well as human samples, with the aim of unveiling the pathogenesis of cardiovascular diseases.

Our ultimate goal is to prevent and reverse vascular disease to prevent heart attack and stroke.

Projects

Impact of Diabetes of haematopoietic cells linked to atherosclerosis

Obesity and diabetes are major risk factors for a broad range of cardiovascular diseases. With three-times as many people in the world estimated to die from over-nutrition than from starvation or malnutrition in today's society, the health implications of this "diabesity" epidemic are enormous. Based on current trends, this scenario will get worse, leading to a tsunami of cardiovascular diseases that could overwhelm a healthcare system already struggling to deal with an ageing population. Thus, there is an urgent need to uncover the fundamental mechanisms underlying the

development of diabetes, including how cardiovascular risk factors affect atherosclerosis – in order to develop rationale strategies for minimizing the impact of these risk factors on our health and economy.

Bone-marrow derived stem cells (BMDSCs) and progenitor cells are integral to tissue homeostasis and repair and contribute to health through their ability to self-renew and commit to specialized effector cells. Importantly, defects in a variety of progenitor cell populations have been described in both preclinical and human diabetes. The general perception is that diabetes drives defects in bone marrow derived stem cells (BMDSCs) which accrue damage over time, disrupting tissue homeostasis and increasing risk of morbidity. However, the mechanisms by which defective BMDSCs can influence the pathology of individual plaque cells in atherosclerosis, and the subsequent impact this has on diabetes and obesity remains unknown.

In this study, we will be characterizing effects of these BMDSCs on atherosclerotic plaque burden using state-of-the-art of the art transgenic mouse models and cardiovascular genetics. We will be using Cre-LoxP system, genetic knockouts, lineage tracing, clonal analysis, *Single-cell RNA sequencing*, *bone marrow transplant and culturing BMDSCs*, *histology of mouse and human patient samples* and *general cell and molecular biology techniques*.

CARDIOVASCULAR NEUROSCIENCE GROUP

DR MELISSA FARNHAM

Email: melissa.farnham@hri.org.au

Phone: 8208 8992

Location: Heart Research Institute

Lab Overview

My lab is interested in the central control of blood pressure and breathing. For the last few years we have been focussing on a model of obstructive sleep apnoea and the role of a neuropeptide called PACAP. We are studying both the anatomical and functional brain changes that occur during OSA that result in the development of hypertension.

Projects

Sleep apnoea and hypertension: What goes wrong in the brain?

To investigate how sleep apnoea results in hypertension, we study anatomical and functional changes in the brain and spinal cord.

Cardiovascular disease is the principal cause of death in Australia and 10% of cardiovascular disease is now attributed to Obstructive Sleep Apnoea (OSA), a condition characterised by intermittent episodes of hypoxia during sleep and evident in over 10% of the population. The most plausible link between OSA and cardiovascular disease is that in OSA, intermittent activation of chemoreceptors leads to sympathoexcitation, in turn, leading to hypertension. Why OSA patients develop metabolic dysfunction, particularly hypertension, is unclear.

We use rodent models of OSA, both anaesthetised and conscious to measure blood pressure, heart rate and various sympathetic nerve activities following pharmacological manipulations of the central nervous system. The physiology experiments are combined with immunohistochemistry and molecular experiments to assess the signalling changes within the brain and spinal cord. We also study how OSA causes diabetes and are trying to identify the central pathways that lead to glucose handling dysfunction in OSA.

HUMAN MOVEMENT AND NEUROSCIENCE

DR JOANNA DIONG

Email: joanna.diong@sydney.edu.au

Phone: 8627 5491

Location: Room 108, R.C. Mills Building

Lab Overview

Our research aims to understand the mechanisms of normal human movement, impaired movement in people with stroke or other clinical conditions, and motor control during daily activities. We use transducers to measure force and angle (i.e. the study of kinematics and kinetics), and electromyography to measure muscle activity. We use scientific computing for biological and transducer signal analysis, and we are passionate about research reproducibility and good science.

Projects

What type of eccentric exercise is most effective at increasing joint range of motion?

Loss of passive joint range of motion (contracture) is common after stroke and other neurological conditions, causes physical disability and pain, and is difficult to treat. Eccentric exercise is known to increase lower limb flexibility (assessed by joint range of motion or muscle fascicle length). However it is not known what intensity of eccentric exercise is most effective at increasing joint range of motion. This study aims to examine different protocols of eccentric exercise training to determine an effective and safe eccentric stimulus intensity to increase joint range of motion. This is a laboratory-based experimental study: repeated measures design, sample size = 20. Outcomes: delayed onset muscle soreness (DOMS), maximal and submaximal ankle plantarflexion torque, passive ankle dorsiflexion torque and angle. Time effects of outcomes will be assessed, and comparisons performed using paired t-tests.

INTEGRATIVE NETWORKS AND NEUROIMAGING LABORATORY

DR JAMES M. SHINE

Email: mac.shine@sydney.edu.au

Phone: 0478 596 811

Location: Brain and Mind Centre

Lab Overview

I use multi-modal neuroimaging (such as fMRI and EEG) to understand the mechanistic fundamentals of cognition and attention, both in health and disease. I am particularly interested in understanding the pathophysiology of cognitive dysfunction in Parkinson's disease, and across a spectrum of dementia syndromes. Recent work in my lab has begun to explore how highly conserved neuromodulatory neurotransmitter systems impact the network structure of the brain to support cognitive processing, and how those systems might become impaired in Parkinson's disease.

Projects

Noradrenaline and Cognitive Function – Investigating the forgotten symptoms of Parkinson’s disease

Although Parkinson’s disease has been traditionally thought of as a disorder of movement, people with the disease also suffer from impairments in cognitive function. Unfortunately, the classical models that people have used to understand Parkinson’s disease (which predominantly implicate the neurotransmitter, dopamine) are unable to adequately explain how or why these “non-motor” impairments occur, making them difficult to detect and to treat. Recent work has shown that the cognitive impairments in Parkinson’s disease may relate to pathology within the autonomic ‘arousal’ systems of the brain. These systems rely on a different set of neurotransmitters, such as noradrenaline, which play a crucial role in coordinating normal cognitive function. Thus, impairments in these systems may account for the presence of cognitive impairment in Parkinson’s disease.

To test this hypothesis, we plan to measure the network signature of the brain while simultaneously tracking ongoing changes in the autonomic arousal system, using non-invasive measures such as pupillometry and blood pressure monitoring paired with functional MRI. A successful student would help to collect peripheral autonomic measures while people with Parkinson’s disease (along with others with different forms of dementia) perform challenging behavioral tasks during functional MRI scanning. We will then use this data to estimate the dynamic network signatures that underlie cognitive processing and relate to noradrenergic ascending arousal systems.

Overall, this project offers an excellent opportunity to learn functional neuroanatomy through novel investigations of the brain using advanced neuroimaging techniques. In addition, the project also represents a great chance to learn a range of clinical skills, to gain experience in the investigation of cognitive performance across multiple neurodegenerative disorders, to analyse physiological signals and to relate these changes to physiological autonomic signals in the brain.