

Honours year in the Faculty of Science: Bachelor of Medical Science: BMedSc(Hons), Bachelor of Science: BSc(Hons)

After completing the requirements for award of a BMedSc or BSc, a good student who has **majored** in Physiology may be permitted to undertake a fourth, or 'Honours', year.

The Honours year consists mainly of a research project carried out in the laboratory of a member of the Academic Staff, who acts as the student's supervisor. Early in the course the student is required to write an extended essay based on the subject of their research project and throughout the year to participate in a weekly seminar. Examination is mainly by thesis, but also by the student's performance in the laboratory and in the end-of-year public seminar.

Opportunities exist to gain teaching experience by casual employment as a demonstrator in undergraduate practical classes. After the Honours year the student may be allowed to undertake a PhD or MSc. To qualify for entry into these honours courses you need to meet the minimum requirements of the Faculty of Science and the Discipline.

Application Process and Deadline

All students must apply to be admitted to an Honours year. Gaining entry into Honours is competitive - the standard you need to achieve must meet certain minimum requirements, but will also depend on the number and quality of other applicants in that year. **You are required to meet with the Hounours coordinator, Dr Assinder (stephen.assinder@sydney.edu.au), to discuss your intentions and lodge a completed expression of interest form with him prior to lodging an application form with the Faculty of Science.** An EoI can be downloaded from the Discipline website. A copy of a completed and signed EoI is the only documentation you should submit as proof of contact with the Discipline. **Only those applicants that have attached a completed EoI and that have met with Dr Assinder prior to lodging their application will be approved.**

An application process checklist is provided below.

Domestic students - internal (currently enrolled) and external

Domestic students please note: As deferment of honours is not possible, you must apply in the semester prior to commencement.

Students applying for Honours will need to use the resources on this page to follow these steps:

1. Download and read the [Honours Application Information](#)
2. Meet with potential supervisors.
3. Those students intending to undertake honours in Physiology need to agree a project with a supervisor and obtain their agreement by signing the expression of Interest form (available on the Physiology website: <http://sydney.edu.au/medicine/physiology/students/honours/index.php>).
4. Fulfil any requirements of the school or department prior to lodging an application at the Faculty. This might include matching projects and available supervisors with students.
5. Those students intending to undertake honours in Physiology need to meet with the honours coordinator, Dr Assinder **prior** to lodging your application online.
6. If you are applying for Honours in more than one area, then list your areas in order of preference on the application form. You will need to repeat step 2 for each area you are applying to. Please list the discipline area (eg. Biology, Cell Pathology) as appears on the [coordinator contact list](#), or your application may not be considered.
7. Submit a completed [online application form](#) including relevant [documentation](#) (A completed and signed EoI is required by Physiology, by the [due date](#) (you will need to find your honours course among the list of courses, then click "Apply Now").

Honours Application Deadlines

[Honours](#) application deadline
(for Honours commencement in Semester 1, 2015)

Sunday 30 November 2014

A step-by-step guide to the application process has been developed by the Faculty of Science and is available on the Physiology website under Honours.

Graduate Diploma in Science: GradDipSc

Students who do not qualify for the above Honours courses, may be admitted to a program essentially identical to that of the BMedSc(Hons)/BSc(Hons) and obtain the diploma upon successful completion of this one year program. However, the GradDipSc is a full fee course while the Honours courses incur a HECs payment.

Master of Philosophy(MPhil)

Another option for students who fall below the cut-off for honours. Medical and Science graduates may enrol for the degree of Master of Philosophy, by research and thesis. Candidature lasts from 1 to 2 years full-time; 2 to 4 years part-time. Enrolment for this degree is made through the Sydney Medical School. The candidate is expected to complete an appropriate research project and submit a thesis.

Scholarships

The Faculty of Science offers a full year and summer scholarships for Honours students. More information can be found: at http://sydney.edu.au/scholarships/current/honours_scholarships.shtml

The **Discipline of Physiology** offers a number of summer vacation scholarships for students who complete an 8 week (\$1000) or 4 week (\$500) period of research during the summer vacation and who subsequently enrol in Honours and who hold no other scholarships. Award of the scholarships are made solely at the discretion of the Discipline.

The **Faculty of Medicine** also offers Summer Research Scholarships to full-time students currently enrolled in Australian or New Zealand universities. This is a fabulous opportunity for students to try their hand at medical research.

For more information and to look at the wide range of projects available please go to the following website: <http://www.medfac.usyd.edu.au/research/srs/index.php>

Honours Projects - 2015

The projects listed below are available to "Honours" candidates in 2015. These one-year research programs are available in a number of themes that can accommodate a wide range of students. The Honours home page gives information on the current program and expectations.

Dr Stephen Assinder is the honours coordinator and should be contacted for general information at stephen.assinder@sydney.edu.au

Potential supervisors within the discipline should be contacted directly to discuss specific opportunities. The following research labs are associated with the discipline.

- Laboratory of Motor & Sensory Systems – Dr Haydn Allbutt
- Andrology Research Group - Dr Stephen Assinder
- Neurobiology Laboratory - Professor M.R. Bennett
- Auditory Neuroscience Laboratory - Associate Professor S. Carlile
- Epithelial Transport Laboratory – A/Prof Anuwat Dinudom & Professor D.I. Cook
- Developmental Physiology Laboratory - Dr M. Day
- Laboratory of Blood Cell Development – Dr Stuart Fraser
- Lipid Metabolism Laboratory – Dr Andrew Hoy
- Laboratory of Developmental Neurobiology - Dr C. Leamey
- VitaminD, Bone & Skin Cell Laboratory - Professor R.S. Mason
- Environmental Control of Physiology Laboratory - Dr Bronwyn McAllan
- Embryonic Stem Cell Laboratory - Dr Michael Morris
- Developmental & Cancer Biology Laboratory - Dr Matthew Naylor
- Molecular Neuroscience Laboratory - Dr W.D. Phillips
- Vision Laboratory - Dr D. Protti
- Molecular Physiology of Membrane Transport – Professor Phil Poronik
- Systems Neuroscience Laboratory - Dr Atomu Sawatari
- Retinal & Cerebral Neurobiology Laboratory - Professor Jonathon Stone
- Visual Neuroscience Research Group – Prof Paul Martin.
- High Blood Pressure research Group – Prof Paul Pilowsky.

OFFERED PROJECTS IN 2015

(listed by theme)

Nervous System, Senses and Movement:

AUDITORY NEUROSCIENCE LABORATORY

Anderson Stuart Bldg, Room N438, Telephone: +61 2 9351 3205

Associate Professor Simon CARLILE directs a multi-disciplinary research group aimed at understanding the mechanisms underlying our perceptions of auditory space. Research projects involve bioacoustics, neural coding, behavioural/psychophysical studies, computer simulations and digital signal processing. Areas of current research include the bioacoustics and psychophysics of our perception of spatial location including the influence of head movements and the integration of auditory and visual information.

Project Title: Auditory spatial perception and the cocktail party problem.

Much of our research focuses on the so-called "cocktail party" problem. That is, how are we able to hear out a talker of interest from a noisy backdrop of other sounds competing for our attention?

While this is a significant signal processing problem, it is not an effortful task for most people with

healthy hearing. However, even mild hearing loss severely impairs an individual's ability to do this effectively, and the most advanced hearing aids are unable to confer much perceptual benefit in these conditions.

We take a multidisciplinary approach to the issue, blending bioacoustic and psychophysical methods with computational modelling to identify the cues which the healthy auditory system uses to selectively focus attention in acoustically lively environments. This includes the examination of a number of basic perceptual questions that have implications for the manner in which much of this information is processed and integrated with other spatial senses (vision in particular). Furthermore, in a conversation between individuals, a listener has to constantly switch their attention from person to person to follow the conversation. We have recently shown that attention deficits have a profound effect on the ability to listen effectively in noisy environments, however, very little is currently known about the mechanism and costs of attention switching. Additionally, we are interested in the mechanisms by which the auditory system accommodates to changes in the inputs produced by age-related changes in ear shape and sensitivity. The outcomes of this research are informing the design of next generation hearing aids.

Project Title: Perception of auditory motion

Our sense of auditory motion can be induced either by the motion of our own bodies through an environment containing stationary sound sources, or by our ability to detect and track motion of the sound sources themselves. In most everyday environments, we encounter a complex mixture of both. ANL is currently conducting a range of bioacoustic and psychophysical studies that examine this little understood perceptual-motor capability. As this basic function is known to be degraded in individuals with certain neurological disorders, among them schizophrenia, this research also has implications for the development of a predictive clinical test for these illnesses. Our preliminary work has uncovered both surprising similarities to and differences with the way in which we perceive moving visual stimuli, thereby contributing to both integrated and differentiated models of spatial motion.

Project Title: Pitch, segregation, contour and melodic/prosodic perception

Pitch perception has proven to be a complex phenomenon that underlies not just the appreciation of music but our capacity to segregate different concurrent sounds and plays an important role in the perceptual organisation of auditory scenes. Pitch is very poorly rendered in cochlear prosthesis and consequently, cochlear implant users have little appreciation of music and little capacity to segregate concurrent talkers. We have a number of projects examining pitch coding and perception in the context of speech and music processing that combine classical psychophysics with advanced digital signal processing and computational modelling of this complex perceptual process.

RETINAL AND CEREBRAL NEUROBIOLOGY LABORATORY

Anderson Stuart Building, Room N551, Tel. 9351 4740
jonathan.stone@sydney.edu.au

Professor J Stone leads a research group whose work focuses on degenerative diseases of the central nervous system (the CNS, especially brain and retina). The work is pioneering in the field of neuroprotection, how to stabilise the ageing CNS in the face of stresses which cause dementia (Alzheimer's disease), Parkinsons disease (PD) and age-related macular degeneration (AMD). Areas of current research include 1) proving the neuroprotective effect of interventions, including photobiomodulation, dietary saffron and carefully devised protocols of peripheral ischaemia; 2) using a range of rodent (rat and mouse) models of these diseases; and 3) identifying the mechanisms which mediate the protection obtained.

Projects: Mechanisms of neuroprotection: the biology of tissue survival in the face of stress
Honours students will be allocated a focussed project within this general title. As an example: The time course and mechanism of neuroprotection induced in the brain by photobiomodulation in a rodent model of neural degeneration

Each student will be closely supervised while they begin their project; the project will have strong laboratory and intellectual infrastructure, with a well-defined focus on specific experiments. Once under way with his/her project, each student will have considerable independence and scope for originality.

MOLECULAR NEUROSCIENCE LAB

A/Prof Bill Phillips (william.phillips@sydney.edu.au)

The Molecular Neuroscience Lab studies the control of voluntary muscle via the neuromuscular junction. We study the molecular signalling systems that underlie the synaptic relationship between motor nerve and muscle fibres and how these systems can provide protection against disease-causing agents in myasthenia gravis, old age and in motor neuron disease.

Project 1: Can voluntary exercise help protect against autoimmune MuSK myasthenia gravis? Myasthenia gravis (MG) is an autoimmune disease that disrupts the neuromuscular junction (NMJ) leading to fatiguing muscle weakness. Autoimmune antibodies from a subset of MG patients targeting Muscle Specific Kinase (MuSK) were recently shown to be the cause of MG when injected into mice. Unfortunately the available treatment options for MuSK MG have problems. For example, immunosuppression can increase the risk of infection and cancer. Cholinesterase inhibitor therapies can exacerbate (rather than improve) MuSK MG. Mouse models of MuSK MG have shown that the autoantibodies interrupt tyrosine kinase signalling function of MuSK that is needed to stabilize acetylcholine receptors in the postsynaptic membrane of the NMJ, leading to muscle weakness. Earlier studies in rats suggest that muscle use (exercise) might provide an alternative way to stabilize acetylcholine receptors. This project will test the potential of voluntary wheel running exercise to stabilize postsynaptic acetylcholine receptors and inhibit the onset of muscle weakness in a mouse passive IgG transfer model of MuSK MG. The project will involve daily monitoring of mice, muscle dissections, histology, confocal immunofluorescence microscopy and image analysis methods.

Project 2: Influence of the MuSK-rapsyn system in a mouse model of Duchenne muscular dystrophy.

Duchenne muscular dystrophy (DMD) is a fatal inherited disease of boys involving the degeneration of muscle fibres. DMD is caused by mutation to the dystrophin gene that makes the muscle fibre membrane more vulnerable to damage during eccentric muscle stretch (such as when running down a hill). Muscle Specific Kinase (MuSK) is a receptor tyrosine kinase that stabilizes acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction (NMJ). A recent report indicates that in mice lacking dystrophin (*mdx* mice) the level of expression of MuSK is reduced. It suggested that inadequate MuSK might contribute to making the *mdx* muscle membrane vulnerable to damage. This project will inject recombinant adeno-associated viral vector to deliver extra MuSK into the muscles of *mdx* mice to see if this can protect muscles from the damage normally caused during downhill running exercise on a treadmill. The project will involve careful monitoring of mice, muscle dissections, histology, confocal immunofluorescence microscopy and image analysis methods.

VISUAL NEUROSCIENCE RESEARCH GROUP

Save Sight Institute, Sydney Eye Hospital, and Discipline of Physiology.

Prof Paul R. Martin

We study the connections of neurones in the retina and processing of visual signals in the brain. Our special interests are colour vision and interaction of visual signals with brain pathways controlling attention. Our laboratories are part of the ARC centre of excellence for integrative brain function (CIBF, cibf.edu.au). In 2015 qualifying students will be offered CIBF scholarships and join this strong research network involving collaborative projects with Australian and International laboratories.

PROJECTS :

1) Colour pathways in the thalamus.

You will join our team of electrophysiologists to measure single and multi-cell activity in primate brains. We have discovered that on part of the visual thalamus which transmits "blue" colour signals is also involved in brain pathways controlling slow-wave oscillations in sleep, anaesthesia and epilepsy. You will learn modern electrophysiological methods to record and understand how networks of nerve cells work to control brain rhythms.

2) Parallel pathways in human and non-human primate retinas.

You will help to expand and develop our new methods for identifying nerve cell connections in the fovea of human donor retinas and retinas of non-human primates. You will learn single-cell injection and immunochemical methods to help us identify new types of nerve cells and their connections in the retina.

for more information please contact Paul at prmartin@physiol.usyd.edu.au

LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY

Anderson Stuart Bldg, Room N663, Telephone: +61 2 9351 4352

Dr Catherine A. Leamey

Phone: 9351 4352

Email: cathy@physiol.usyd.edu.au

Neural connections underlie every aspect of our 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 measurable visual deficits.

Potential projects include:

- 1) **Downstream mediators of Ten-m function:** We have recently identified candidates for Ten-m function and obtained mice where these genes are mutated. Anatomical, physiological and behavioural analyses of these animals present provide excellent opportunities for Honours projects.
- 2) **Mechanisms underlying recovery of vision in Ten-m3 KOs:** The misalignment of projections present in Ten-m3 KOs 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, possible via reduced inhibition. Projects exploring this important research avenue, including mimicking enrichment by addition of pharmacological agents, also present very promising Honours projects.

- 3) **Ten-ms at synapses:** Ten-ms may be able to modify the growth of both pre-synaptic and post-synaptic structures, and may also modify synapses themselves. A good model for this is the neuromuscular junction. This project is offered in collaboration with Drs Phillips, Protti and Sawatari.
- 4) **Ten-m3 in the formation of thalamostriatal connections:** Recent data from our lab has shown a critical role for Ten-m3 in the formation of thalamostriatal projections. The relationship between the altered thalamic afferents and one of their main targets, the cholinergic interneurons is a topic of interest and will be explored in this Honours project by combining immunostaining with neuronal tracing experiments in knockout animals.

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

Direct enquiries can be made by email to: Dr Cathy Leamey - cathy@physiol.usyd.edu.au

VISION LABORATORY

Anderson Stuart Bldg, Room N659, Telephone: +61 2 9351 3928

Dario Protti

Dario Protti, dario.protti@sydney.edu.au, Anderson Stuart Bldg, Room N659, Telephone: +61 2 9351 3928

Our research work focuses on the function of the visual system and in particular on the retina. The retina is a light sensitive tissue located at the back of the eye. It consists of an intricate network of neurons, which are critical in the first stage of visual processing and consequently visual perception. The output neurons of the retina are the ganglion cells. Specific neuronal circuits provide ganglion cells 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, derivatives compounds of marijuana, on the physiological properties of different types of ganglion cells in the eye.

Project Title

1) Pharmacological modulation of ganglion cell responses by cannabinoids:

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.

2) Impact of the balance between excitation and inhibition on the properties of ganglion cells of the eye:

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)

3) Modelling of ganglion cell output using NEURON: our physiological experiments provide us with information about the excitatory and inhibitory synaptic inputs that determine the output of retinal ganglion cells. In this project you will use measurements of synaptic inputs made in our lab and manipulate their magnitude and temporal properties to establish the critical features that determine neuronal spiking. This project consists of computer simulations carried out in the modelling environment NEURON.

The techniques used in these projects are patch-clamp recordings, 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.

SYSTEMS NEUROSCIENCE LABORATORY

Anderson Stuart Building. N104 Anderson Stuart Building

Ph: 9036 7127

Email: atomu@medsci.usyd.edu.au

Dr Atomu Sawatari

We use a variety of anatomical, physiological, and behavioural methods to reveal the influence of environmental and genetic factors on the development and function of sensory and cognitive circuits.

Project 1: Revealing the Identity of Retinal Ganglion Cell Types that Contribute to Binocular Circuitry (A collaborative project with Dr. Dario Protti and Dr. Catherine Leamey)

A combination of anatomical (retrograde tracing) and physiological techniques (single cell recording and labelling as well as possibly multiphoton imaging) will be used to identify and characterize retinal ganglion cells (RGCs) that contribute to the binocular visual processing in the mouse. During the course of the project, the student will acquire skills in surgery, in vitro patch-clamp recording, anatomical tract tracing, tissue processing, and data analyses. If time permits, the same combination of methods will be used to examine the homologous population of RGCs in a transgenic animal (the Ten-m3 Knock Out mouse) that exhibits specific and consistent deficits in the binocular pathway.

Project 2: Can the Application of Trophic Factors Mimic the Effects of Environmental Enrichment on Developing Cognitive Neural Circuits? (A collaborative project with Dr. Catherine Leamey)

Environmental factors can dramatically influence the wiring and function of neural networks. Recent evidence has revealed that trophic factors can potentially mimic the effects of exposing animals to enriched environments. The extent to which systemic application of neurotrophins can influence the emerging functionality of cognitive brain regions is not well characterized. For this project, a combination of anatomical (retrograde tracing) and behavioural techniques will be used to reveal the manner in which a specific neurotrophin influences the development and function of one of a number of brain regions associated with perception, decision making, learning, and memory.

Cancer, Cell Biology, Reproduction and Development

ANDROLOGY RESEARCH GROUP,

Medical Foundation Building Room G46 Telephone: +61 2 90363614
stephen.assinder@sydney.edu.au

Dr Stephen Assinder

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. A common treatment option is the removal of androgens either by chemical or physical castration.

Unfortunately many tumors develop resistance to this therapy (androgen independent or castrate resistant prostate cancer), and ultimately the patient will die.

Our research is focused on:

1. Endocrine regulation of cancer cell proliferation. In particular we are interested in how various hormones and cytokines affect tumourigenesis.
2. Understanding how the loss of structural proteins involved in organization of the cell cytoskeleton contribute to the development of cancers.

Project 1: Oxytocin and cancer. Endocrine-related breast and prostate cancers are commonly treated by hormone ablation therapies. Unfortunately advanced cancers become resistant to treatment and inevitably result in death. Our work has led us to propose that analogues of the hormone oxytocin (OXT) might present an alternative treatment option. If proved so, they could rapidly be brought to approval for treating CRPC as OT analogues are already used in birth management. We have recently shown in prostate cancer cell lines that OXT likely affects de-novo steroidogenesis and synthesis of the common precursor of all steroids, cholesterol. This project will explore these findings further. This project will employ many techniques including cell culture, Affymetrix cDNA array technologies, RT-PCR, real time PCR, western blots, xymography.

Project 2: Targetting the copper transporters to improve prostate cancer treatment. Some of the most successful chemotherapeutic agents for use in oncology are platinum-based drugs such as cisplatin. Drugs with a central complexed platinum ion are delivered into cells by the copper transporters (Ctrs). The native ion for transport by the Ctrs is reduced copper however these receptors can also transport other divalent metal cations such platinum. Copper transporter-1 (Ctr1) is the predominant copper transporter whilst Ctr2 is less well understood. Both can transport platinum-based drugs. Prostate cancer is notoriously recalcitrant to conventional chemotherapies, and cisplatin is not useful for treatment of prostate cancer due to insensitivity. This project will:

1) Assess copper transporter expression and regulation in normal prostate tissue and prostate cancer cell lines.

2) Determine the signalling systems down-stream of copper transporters in prostate cancer cells.

This project will employ many techniques including cell culture, RT-PCR, real time PCR, siRNA knockdowns, western blots, flow cytometry, luminex protein array assays.

This project is in collaboration with Dr Stuart Fraser.

VITAMIN D, BONE AND SKIN LABORATORY

Anderson Stuart Bldg, Room N543, Telephone: +61 2 9351 2561 or +61 2 9351 4099

Professor Rebecca Mason and Dr Tara Brennan-Speranza.

The group studies the endocrine and local regulation of bone turnover, vitamin D physiology and the role of vitamin D compounds in protection from UV irradiation in skin.

Current projects in bone and mineral include studies on regulation of bone turnover by calcium and other agents, including potentially novel agents to treat osteoporosis.

The major study in vitamin D physiology is the role of muscle in the maintenance of vitamin D status. The area of vitamin D and skin research interest is mechanisms of skin cell protection from ultraviolet irradiation and ways of enhancing this.

Dr Tara Brennan-Speranza's laboratory investigates the role of the skeleton in whole macro nutrient metabolism, focusing on the proteins, receptors and pathways involved in this multi-system endocrine loop.

Studies also include investigations into possible therapeutic agents on the skeleton, with a focus on the actions of bone forming cells - the osteoblasts.

Project 1: Role of Vitamin D and other compounds in protection of skin cells from UV

Our group has shown that vitamin D compounds, which are well known to be made in skin, have an important physiological function in skin to protect skin cells from the damaging effects of UV radiation. We have also shown that several types of DNA damage is reduced in skin cells and animal and human skin after UV when active vitamin D-like compounds are given immediately after irradiation and that these compounds protect from UV induced skin cancers (eg Dixon et al. Cancer Prev Res 4: 1485-94, 2011). The project will examine some likely mechanisms of action of the vitamin D compounds and other agents which act like vitamin D. These agents could potentially be used in sunscreens and after-sun preparations to reduce UV damage.

Project 2: The role of osteocalcin in the modulation of whole body energy metabolism

Osteocalcin is a bone-specific protein but recent evidence indicates that it plays a previously unsuspected role in the control of glucose and fat (energy) metabolism (Brennan-Speranza et al. JCI, 122:4172-4189, 2012). The mechanism by which the body senses osteocalcin is still unclear although evidence points to a Class C G-protein coupled receptor (the GPRC6A) as the osteocalcin receptor. This project aims to uncover the controversies surrounding osteocalcin-sensing by the body as well as further understanding the pathways by which this little protein from the skeleton controls whole body energy metabolism using molecular and cell biology techniques and mouse models.

Project 3: The role of skeletal uptake of 25 hydroxyvitamin D in maintenance of vitamin D status.

Vitamin D status (measured as concentration of circulating 25 hydroxyvitamin D (25OHD) is determined by rates of intake and rates of degradation. Relatively little is known about the latter. 25OHD has a half-life in blood of 15-50days, far longer than most steroids and far longer than its binding protein, vitamin D binding protein. Work in our laboratory has recently identified a specific uptake and retention mechanism for 25OHD in skeletal muscle, which may act to sequester 25OHD and reduce its degradation in the liver and elsewhere (Abboud et al. Endocrinology 154(9):3022-3030, 2013). We have recently shown that the uptake of 25OHD is regulated, but have little information on the mechanism or how this process contributes to maintenance of vitamin D status, which is what the proposed project will investigate.

Project 4: Mechanisms of action of calcium-like agents to enhance bone mass and reduce risk of fracture

Strontium is effective in reducing fractures in older people, but its mechanism of action was unclear. Our group has shown that strontium and other calcium-like compounds, including a reduce the signals for bone resorption, stimulate bone cell anabolism and improve the ability of bone forming cells to withstand stress (Rybchyn et al. J Biol Chem 286:23771-23779, 2011). We have evidence that strontium acts, at least in part, through the receptor and cell signal pathway which mediates calcium responses in bone. There are other agents which could activate this pathway in slightly different ways and thus prove even more effective at adding bone and reducing fracture risk. The project will examine how these agents affect signaling and function in human bone cells.

Direct inquiries can be made by email to: tara.speranza@sydney.edu.au or rebeccam@physiol.usyd.edu.au

LIPID METABOLISM LABORATORY

Lab 3 West, The Hub, Charles Perkins Centre
Telephone: +61 2 9351 2514

Dr Andrew Hoy

The Lipid Metabolism Laboratory is concerned with the mechanisms linking perturbed lipid metabolism and a variety of pathologies. Currently, our primary interests are in insulin resistance/type 2 diabetes and cancer including breast, pancreatic and prostate. The lab recently moved into the Charles Perkins Centre where the following projects will be available.

Project Title: Ubiquitination of lipid droplet proteins and their role in insulin resistance

Insulin resistance is a unifying feature of the metabolic syndrome. The liver is an early site of perturbed insulin action and key 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. Evidence suggests a link between the process regulating the degradation of proteins, which involves ubiquitin, the lipid droplet and the proteins that coat the lipid droplet. In collaboration with colleagues at The Kinghorn Cancer Centre, Garvan Institute of Medical Research, this project centres on identifying ubiquitinated proteins that localise to the lipid droplet in liver and how this is altered in insulin resistance. Candidate targets will be identified and subsequently characterised. The project will employ techniques including mass spectrometry, cell culture, biochemical and radiometric metabolic analysis, genetic manipulation.

Project Title: Linking lipid droplet metabolism with breast and prostate cancer biology

Lipid accumulation in 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. Annexin A6 (AnxA6), a member of the annexin family, is a multifunctional scaffolding protein with tumour suppressor activity in breast cancer, reducing cell proliferation, migration and invasion. AnxA6 is known to inhibit oncogenic signalling events, but novel observations made in the laboratory of A/Prof Thomas Grewal in the Faculty of Pharmacy, now link the regulatory role of AnxA6 in cell signalling with its ability to control lipid uptake and content. In collaboration with A/Prof Grewal, this project will elucidate the role that Annexin A6 plays in regulating lipid homeostasis in both breast and prostate cancer and its function in cancer progression. The project will employ techniques including cell culture, genetic manipulation, radiometric metabolic analysis, cancer cell progression including proliferation, migration and invasion.

Direct enquiries can be made by email to: Dr Andrew Hoy – andrew.hoy@sydney.edu.au

DEVELOPMENTAL PHYSIOLOGY LABORATORY

Medical Foundation Building, Room 232, 92-94 Parramatta Rd Camperdown, Telephone: +61 2 9036 3312

Dr Margot Day

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.

Honours projects are available on the following topics:

- The mechanisms by which the amino acids improve blastocyst development in vitro.
- The role of cell cycle regulated K channels in proliferation of embryonic cells.
- The expression of scaffolding proteins during early embryo development (in collaboration with Prof. Phil Poronnik).

Direct enquiries can be made by email to: Dr Margot Day - margotd@physiol.usyd.edu.au

BLOOD CELL DEVELOPMENT LABORATORY

Medical Foundation Building, Room 233, 92-94 Parramatta Rd, Camperdown, Telephone: +61 2 9036 3313

Dr. Stuart FRASER

The Laboratory of Blood Cell Development has three main research focuses;

1. Understanding the processes regulating blood cell development in the embryo and adult mammal.
2. Using in vitro embryonic stem cell differentiation systems to model embryonic developmental processes.
3. Understanding the evolution, function and regulation of copper transport proteins.

Project 1: Copper, Macrophages and Mammalian Evolution.

Copper is essential for cell function and survival. Copper is brought into cells via the copper transporters CTR1 and CTR2. We have found that the genes encoding these proteins have a unique genomic organisation in mammals compared to non-mammalian species. We want to ask, what effect does this genomic organization have on being a mammal? The cell type thought to express CTR1 and CTR2 at highest levels is the activated macrophage, a critical component of the immune system. Are there copper-dependent aspects of the immune system that have helped mammals to evolve separately from non-mammalian species? What has driven this evolutionary step?

Methods to be employed include; cell culture, protein expression analysis, confocal imaging, flow cytometry, bioinformatics and comparative analysis with mammalian and non-mammalian model systems.

Project 2: Copper transport in the cell nucleus

We have made the surprising discovery that both transporters can be found within specific compartments of the nucleus. This is unexpected as copper is highly toxic and generally thought only to be required in the cytoplasm and mitochondria for energy production. This project will explore the localisation, expression and function of copper metabolism proteins in the nucleus. This has clinical significance as these transporters are used for transporting platinum-based chemotherapy transporters. Expression of these copper transporters in the nucleus could therefore be linked to the development of resistance to chemotherapy. This project will involve; cell culture, chemotherapy treatment of cells, confocal imaging, flow cytometry and protein analysis.

These projects are in collaboration with Dr Steve Assinder.

Project 3: Characterising a newly discovered cell type in the yolk sac.

The yolk sac is a thin membrane that surrounds the developing embryo supplying it with nutrients from the maternal side. The yolk sac is also the first site of blood cell production, an essential step in embryogenesis. To dissect the role of the yolk sac in development, we have developed a system to identify and separate all of the major cell type in this organ namely the blood cells, endothelial cells and mostly recent the outer layer of epithelial cells. Surprisingly, we have found a new cell type that expresses both epithelial and blood cell markers and which we believe may reside within the epithelial layer. This project will look at several important questions. 1) What is this cell type? 2) How does it develop as the embryo matures and 3) what is the function of this cell type during embryogenesis?

Methods to be used include; embryo dissection, flow cytometry, confocal imaging, transgenic reporter mouse analysis, gene expression analysis and cell culture.

Direct enquiries can be made by email to: Dr. Stuart Fraser- stuart.fraser@sydney.edu.au

ENVIRONMENTAL CONTROL OF PHYSIOLOGY LABORATORY

Medical Foundation Building (K25) Room G44; Telephone 9036 3615; Email: bmcallan@medsci.usyd.edu.au

Dr Bronwyn McAllan

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.

Project 1: 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.

Project 2: 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*.

MOLECULAR PHYSIOLOGY OF MEMBRANE TRANSPORT

Professor Philip Poronnik: philip.poronnik@sydney.edu.au

Our lab seeks to understand how the activity and regulation of membrane transporters and receptors are altered in disease states.

Project 1: Proteomic analysis of membrane proteins in diabetic nephropathy – To date we know a lot about the individual pathways that are responsible for the development of diabetic kidney disease. However, we know less about the nature of the changes in proteins at the cell surface. This project will involve treating cultured renal epithelial cells with conditions that mimic diabetes and harvesting the membrane proteins. The samples will then be subjected to 2D-gel mass spectrometry and proteins that show significant changes in expression will be further analysed and validated. This project is in collaboration with Prof Jens Coorssen at UWS.

Project 2: Probing the Ubiquitome – Our lab has a strong interest in ubiquitination as a mode of regulation of membrane function. We are currently collaborating with Dr Darren Saunders at the Garvan Institute on a very exciting series of projects using new proteomic methods to understand the kidney and brain ubiquitomes and how their profiles are altered in disease. This project involves sample preparation from tissues and cells in culture, mass spectrometry of the samples, data analysis and target validation.

EXOCRINE PHYSIOLOGY AND BIOPHYSICS LABORATORY

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Associate Professor Anuwat Dinudom

Research opportunities in research on epithelial transport

Investigates the cellular mechanisms that control ion and fluid transport in epithelium lining the kidney, gut, lung and exocrine glands. Current studies are focused on elucidating the mechanisms by which protein kinases regulate activity of the epithelial Na⁺ channel (ENaC) and elucidating the cellular mechanisms that underlie the disturbance of Na⁺ absorption and Cl⁻ secretion in the lung caused by H5N1 avian influenza virus and H1N1 human influenza virus.

Our laboratory (PC2 facility) is located on Level 2 of the Medical Foundation Building. A range of techniques and equipment, including molecular biology, electrophysiology (patch-clamp and Ussing chamber), cellular ion imaging and tissue culture are available in house.

In 2015 we offer two projects.

Project 1: Regulation of the epithelial Na⁺ channel by protein serine/threonine kinases.

The epithelial Na⁺ channel, ENaC, is a Na⁺ selective anion channel that is expressed in the kidney, collecting duct, distal colon, lungs and excretory ducts of salivary glands. ENaC plays a critical role in the maintenance of Na⁺ and fluid homeostasis and, consequently, the regulation of plasma volume and blood pressure. Activity of ENaC is tightly regulated by physiological factors such as hormones and growth factors via cellular mechanisms that involve protein kinases. Apoptosis signal-regulating kinase 1 (ASK1) is a MAP kinase kinase kinase that mediates the cellular signalling response to oxidative stress. ASK1 has been implicated in pathogenesis of cancer, diabetes, cardiovascular and neurodegenerative diseases. Preliminary data from our laboratory suggest that ASK1 is a negative regulator of ENaC by reducing total expression and suppressing proteolytic activation of the channel. This project will use molecularbiological and electrophysiological techniques to investigate cellular mechanisms by which ASK1 regulates epithelial Na⁺ transport via ENaC.

Project 2: Regulation of the epithelial Na⁺ channel by Zinc transporter, ZnT-1.

This project aims to investigate a novel regulation of the epithelial Na⁺ channel (ENaC) by ZnT-1. ZnT-(Slc30a1) is the only member of the putative zinc transporter family that is ubiquitously expressed and can be found in epithelial cells, including the colon, the kidney and the lungs, tissues where the activity of ENaC is crucial. Recent studies indicated that ZnT-1 is a modulator of the Raf/Ras/ERK MAP kinase signalling system. In cardiac myocytes, activity of ZnT-1 protects the cell against ischemia reperfusion by stimulating T type calcium channels by a mechanism that involves Ras/Raf/ERK signalling cascade. Little, however, is known about the role of ZnT-1 in epithelial ion transport. Data from our laboratory suggest that a number of ENaC's modulators regulate the channel via ERK1/2 signalling system and that H-Ras downregulates ENaC via the Raf/ERK1/2 signalling cascade. In this project, epithelial cells in culture will be used to elucidate the role of ZnT-1 in the ERK mediated modulation of ENaC. For that purpose the cells will be transfected with ZnT-1, or its fragments, and ENaC activity will be evaluated by measuring short-circuit current across the epithelium. Inhibitors, siRNA and dominant negative mutants will be applied to decipher the underlying molecular mechanism of ZnT-1's involvement in the regulation of ENaC.

DEVELOPMENTAL & CANCER BIOLOGY LABORATORY

Anderson Stuart Bldg, Room N401 Email: matthew.naylor@sydney.edu.au; Tel: +61 2 9351 4267

Dr Matt Naylor

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.

Project Descriptions:

1) **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, siRNA, and in vivo based approaches such as genetic mouse models and xenografts.

- 2) **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.
- 3) **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.
- 4) **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

EMBRYONIC STEM CELL LABORATORY

Medical Foundation Building

Dr Michael Morris

ph: 9036 3276; mob: 0432 972 361

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. We have discovered a number of simple molecules which, surprisingly, act like growth factors to promote embryo development at various stages.

Embryonic stem (ES) cells have the potential to differentiate into any cell type of the developing embryo and adult. For this reason they have proved invaluable in understanding the molecular mechanisms that drive normal development and can provide a window into what happens during abnormal development. In addition, ES cells 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.

Since ES cells recapitulate many of the complex processes that occur during mammalian embryogenesis, this provides enormous experimental advantages because it is possible to identify molecules, signaling pathways, metabolic and events that contribute to stemness and that direct the differentiation of stem cells to specific cell fates.

What we do

1. We use ES cells as an *in vitro* model to understand the key molecular mechanisms underpinning critical developmental milestones forming the nervous system.
2. 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.
3. 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. In particular, we focus on 3 key milestones in development that must be negotiated successfully: formation of the blastocyst, gastrulation, and neurogenesis.

Thus, these projects examine the processes of development from pluripotent cells to multipotent neural progenitor cells that ultimately can be driven to form neurons, glia and neural crest cells that make up the central and peripheral nervous system. Our focus is on the many interacting signalling 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.

You are welcome to direct your enquiries to Dr Michael Morris via email (michaelmorris@med.usyd.edu.au) or phone.

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Cardiovascular Physiology:

HIGH BLOOD PRESSURE RESEARCH GROUP

High Blood Pressure Research Group (affiliate to the Dept of physiology; University of Sydney)
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OUR RESEARCH

In the High Blood Pressure Group we investigate the way that different neurons, and neurotransmitters, in the brainstem and spinal cord control the heart, blood vessels and breathing. We also investigate the ways that these pathways learn and remember information (neuroplasticity).

From a disease perspective, we study how abnormalities of these critical neural pathways can lead to high blood pressure and other health problems.

Project 1: How the autonomic nervous system responds to experimental epilepsy.

Epilepsy is not simply a benign condition in which the person suffering the disorder loses consciousness for a short period. Epilepsy also affects the autonomic nervous system causing changes that can include abnormal rhythms in the heart. In some cases this abnormal rhythmicity leads to death. We hypothesise that seizure activity in the cortex propagates to the brainstem and hypothalamus, activating the sympathetic nervous system, and that as a result, abnormally high levels of sympathetic discharge cause hypertension and cardiac arrhythmias. In order to study the effects of epilepsy on sympathetic nervous system, we use approaches that include molecular biology, functional neuroanatomy and integrative neurophysiology in vivo. Specific techniques include immunofluorescence, blood pressure recording and nerve recording, amongst many others. The precise nature of the project, and the technical approaches used will be tailored to the background and interests of the individual student.

Project 2: How the autonomic nervous system responds to **intermittent hypoxia**.

At sea level, we breathe a mixture of approximately 20% oxygen and 80% nitrogen. If the concentration of oxygen falls below 20%, peripheral chemoreceptors become strongly activated, leading to an increase in sympathetic nerve activity, and ventilation. Short periods of hypoxia – breath holding – have no lasting effects. But intermittent hypoxia over long periods can lead to a marked activation of the sympathetic nervous system and hypertension. The main disorder in which intermittent hypoxia occurs is sleep apnoea, where decreases in blood oxygen level can be very severe, until the individual is roused from sleep. To study the effects of intermittent hypoxia on the sympathetic and respiratory systems, we use approaches that include molecular biology, functional neuroanatomy and integrative neurophysiology in vivo. Specific techniques include immunofluorescence, blood pressure recording and nerve recording, amongst many others. The precise nature of the project, and the technical approaches used will be tailored to the background and interests of the individual student.

For more information about our work, and recent publications see our website: pilowsky.org

External Honours Projects

The Discipline of Physiology on occasion accepts into its Honours Course students who are performing their research in laboratories outside the Department. The project must be closely allied to physiology and an internal supervisor who is familiar with the area must be prepared to act as the associate supervisor. The student should normally have undertaken at least one 3rd year course in Physiology and must attend the teaching 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 express your interest.

Heart Research Institute, Immunobiology Group. 7 Eliza Street, Newtown 2042.
Email: bursillc@hri.org.au. Web: www.hri.org.au. Telephone: 02 8208 8905

Labs/Investigators: Christina Bursill, Melissa Farnham, Paul Pilowsky and Stacy Robertson
The Immunobiology and High Blood Pressure Groups are concerned with identifying cell signalling pathways and cell types in the vasculature, and central nervous system that are important in the genesis of cardiovascular disease.

The role of inflammatory monocytes in the central nervous system in hypertension

Chemokines are small proteins that direct the migration of inflammatory cells, including monocytes and microglia, to sites of injury or repair. There is increasing evidence that activated monocytes, which express a specific set of chemokine receptors, are responsible for inflammation in regions of the brainstem responsible for regulating blood pressure. We aim to investigate the role of chemokines, which recruit circulating monocytes and activate microglia, in the development of hypertension.

To achieve this we will:

- Examine the translocation of circulating monocytes into the brainstem
- Determine if translocated monocytes can transform into microglia or activate microglia
- Determine the extent to which local microglia or transformed monocytes can cause a prolonged stimulation of brain nuclei that control the circulation resulting in changes in blood pressure.
- Determine the inflammatory status of circulating monocytes isolated from rats at different stages of hypertension and determine if chemokines are present in critical areas of the brainstem.

Technical approaches may include: quantitative RT-PCR, multiple label immunohistochemistry, flow cytometry and animal models of hypertension.

All methods/techniques are well established in our laboratory.

All training will be provided, and experiments conducted, in our modern facility in the heart of Newtown.

For more information please email Christina: bursillc@hri.org.au or Paul: pilowskyp@hri.org.au

Project 2 Dr Christina Bursill: The role of high-density lipoproteins in the regulation of

VEGFR2 and angiogenesis. Angiogenesis is the process by which new blood vessels are formed. It is critical for tissue repair following injury or in ischaemia, which occurs, for example, following a heart attack. Vascular endothelial growth factor (VEGF) receptor-2, is a key receptor that regulates angiogenesis. We have recently found that high-density lipoproteins (HDL), also known as

the 'good cholesterol' increase the expression of VEGFR2 in endothelial cells. In this project we will determine the mechanism by which HDL regulates VEGFR2 *in vitro* and also in an *in vivo* model of ischaemia-induced angiogenesis. This project will employ tissue culture, RT-PCR, Western blotting, flow cytometry and siRNA knock-down techniques as well as provide experience with an animal surgical model of angiogenesis. All methods/techniques are well established in our laboratory. All training will be provided in a modern facility in the heart of Newtown.

For more information please email Christina - bursillc@hri.org.au

Supervisors: Dr. Ben Rayner and Assoc. Prof. Clare Hawkins. Inflammation Group, Heart Research Institute. Contact email: ben.rayner@hri.org.au

The Inflammation Group's research is focused on understanding the role the body's inflammatory response plays in the oxidative damage and cell death evident during the development of atherosclerosis (hardening of the arteries). Understanding the molecular mechanisms invoked and the damage sustained within cells of the vasculature during atherosclerotic lesion progression is crucial to developing treatment options that may reverse or halt this process.

Project Title: Investigating the effects of myeloperoxidase-derived oxidants on macrophages.

Synopsis: There is epidemiological, clinical, and experimental evidence that cellular stress and excessive inflammation are causally linked to various pathological conditions including atherosclerosis. One of the hallmarks of atherosclerosis is the infiltration of macrophages within the vascular wall at sites of inflammation, contributing to atherosclerotic lesion formation. Excessive oxidant formation within this environment, generated as part of the inflammatory response to injury, results in oxidative stress, damage and ultimately death to all cells of the vasculature [1].

Monocytes and macrophages play an integral role in inflammation and the pathology of atherosclerosis. This project will focus on delineating the precise intracellular mechanisms and molecular pathways within macrophages that result from exposure to myeloperoxidase-derived oxidants, as human atherosclerotic lesions are enriched in myeloperoxidase, and this enzyme is a major risk factor for the development of atherosclerosis [2, 3]. The techniques that will be employed in this project include using human macrophage cell culture models, gene analysis by quantitative real-time PCR, protein expression analysis by Western blotting and ELISA, coupled with microscopy and flow cytometry to analyse cellular dysfunction and death.

References

- [1] Stocker, R.; Keaney, J. F., Jr. Role of oxidative modifications in atherosclerosis. *Physiol. Rev.* **84**: 1381-1478; 2004.
 - [2] Davies, M. J.; Hawkins, C. L.; Pattison, D. I.; Rees, M. D. Mammalian heme peroxidases: From molecular mechanisms to health implications. *Antioxid. Redox Signal.* **10**: 1199-1234; 2008.
 - [3] Rayner, B. S.; Love, D. T.; Hawkins, C. L. Comparative reactivity of myeloperoxidase-derived oxidants with mammalian cells. *Free Radic. Biol. Med.* **71**: 240-255; 2014.
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Neuro-Otology Laboratory

Brain & Mind Research Institute, Room 507, Telephone +61 2 93510748

Dr Daniel Brown is the head of the Neuro-Otology laboratory, whose primary aim is to investigate the physiology underlying hearing and balance disorders such as Meniere's Disease. Primarily, we are interested in fluid dynamics of the inner ear. Our research combines *in vivo* electrophysiological experiments in guinea pigs, novel techniques for post-mortem imaging and 3D reconstruction of the inner ear labyrinth, and measurements of physiological responses from humans.

Project Title: Functional Role of Valves in the Membranous Labyrinth in the Inner Ear

Meniere's Disease is a hearing and balance disorder that afflicts approximately 50,000 Australians. It is characterised by fluctuating hearing loss, tinnitus, fullness in the ear, and severe attacks of vertigo. The hallmark of Meniere's is a bloating of the fluid-filled membranous labyrinth in the ear, which houses the mechanically sensitive cochlear and vestibular hair cells. Our recent research has focused on the function of a tissue duct in the membranous labyrinth that separates the vestibular system from the cochlea. This duct appears to function as a fluid valve (it's called the 'Valve of Bast'), temporarily opening when cochlear pressure increases, squirting fluid into the vestibular system and causing a transient loss of balance sensitivity. To investigate the symptoms of Meniere's, and the function of the various inner ear valves, we perform a variety of physiological experiments such as injecting artificial endolymph with biomarkers into anaesthetised guinea pigs, whilst monitoring *in vivo* electrophysiological responses from the cochlea and vestibular system. We also image inner ears post-mortem and reconstruct in 3D using techniques such as Micro-CT or using our custom-built Light Sheet Fluorescent Microscope.

Project Title: Functional & Morphological changes resulting from Increased Blood-Labyrinth-Barrier Permeability

Like the Blood-Brain Barrier that limits fluid and molecule communication between cerebrospinal fluid and blood, the capillaries of the inner ear also have tight junctions that limit the communication between blood and inner ear fluid (perilymph) – the Blood-Labyrinth-Barrier (BLB). An immune response of the inner ear causes an increase in the BLB permeability, resulting in a moderate swelling of the membranous labyrinth and fluctuating hearing loss, and changes in the extracellular matrix proteins in the ear. This typically resolves within a week or so, and the inner ear recovers. It's thought that in some people, this transient immune flare-up in the ear can permanently alter the ears fluid dynamics, resulting in a chronic build-up of fluid in various compartments. Which parts of the ear become damaged resulting in this build-up of fluid is not yet clear, but is vital to our understanding of Meniere's Disease. Our laboratory is developing the tools and techniques, including *in vivo* electrophysiology and whole-mount post-mortem imaging, to investigate the long-lasting effects of immune challenges in the inner ear.