School of Human Sciences

Student Research Projects

Honours & Masters

Anatomy, Human Biology, Physiology & Neuroscience
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Supervisor and Topic

Supervision
The role of the supervisor is to advise, guide and provide constructive feedback to the student through the processes of choosing a realistic topic, designing a project, doing the research, and interpreting the findings and writing the dissertation.

Things to do before deciding on a supervisor:
- Talk with a few prospective supervisors about their research interests and prospective topics, as well as their styles of supervision and what they expect of their students; and
- Talk with your prospective supervisors’ current and former Honours and postgraduate students about their experiences.
- Things to discuss and negotiate with your supervisor very early in the program:
  - The regularity, timing and format of your meetings;
  - The type and level of assistance that you would like, and your supervisor is prepared to give, with respect to choosing a topic and setting goals; finding appropriate literature; collecting the data and information; analysing and interpreting your findings; planning the dissertation; and writing and reviewing the dissertation.

Choosing a Topic
Before deciding on a topic, it is usually a good idea to first identify one or more prospective supervisors according to the criteria above. Then, in consultation with your prospective supervisor/s, identify some possible topics and projects according to the following criteria:
- Choose an area that is sufficiently interesting to you to maintain your enthusiasm for a year-long project;
- Choose a topic in which you can identify questions to be answered or gaps to be filled in the current knowledge; and
- Find a project that is realistic for you to complete within the time allocated for your research and dissertation.
Information for Honours Applicants

In an Honours year, the learning emphasis is on completing an original research project. Projects are guided by academic staff who are internationally recognised in their specific fields of research. Students acquire the specialized skills required to complete their particular research project, and also develop generic research skills such as analytical and problem-solving abilities, and a variety of communication skills. These are not only vital for future success in research but stand graduates in good stead whatever career they may subsequently pursue. Throughout the year, students also work in close collaboration with a like-minded peer group and professional university staff.

Honours are available in the following discipline:

- Anatomy and Human Biology
- Physiology
- Neuroscience

General information about Honours in Anatomy, Physiology and Human Biology can be found at http://www.aphb.uwa.edu.au/courses/honours.

Entry to Honours requires at least a 65% average in 24 points of level 3 units that are relevant to the honours discipline you wish to study. Enrolment must be full time and students enter the course in February.

As a starting point, applicants should talk to potential supervisors. Research areas and associated staff can be found at http://www.aphb.uwa.edu.au/research.

Suggested projects are posted on our honours website: http://www.aphb.uwa.edu.au/research/student-projects

If students wish to nominate and pursue topics of their own devising, they can discuss this with a supervisor.

Students can apply for a prestigious Dr Margaret Loman-Hall Honours Scholarships to support their studies. Further information is available at: https://www.student.uwa.edu.au/faculties/faculty-of-science/school-of-human-sciences/Anatomy-Physiology-and-Human-Biology-students/courses/honours/loman-hall

In addition you may want to contact the School’s Honours Convenors, Associate Professor Jeremy Smith and Associate Professor Tony Bakker. For Neuroscience queries please contact Dr Alex Tang. Biomedical Science may also be accommodated.

Other useful websites include the School’s home page (http://www.aphb.uwa.edu.au/), and http://www.student.uwa.edu.au/learning/studysmarter/getsmart/honours-and-masters-hub
### Brief Overview of Honours Units (2022)

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<th>Unit</th>
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<th>Tasks</th>
<th>Unit Mark %</th>
<th>Final Mark %</th>
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<td>Scientific Communication Part 1</td>
<td>Research Proposal</td>
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<td>APHB4002</td>
<td>6 points</td>
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<td>Proposal Seminar</td>
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<td>APHB5515</td>
<td>Honours Dissertation Part 1 &amp; 2</td>
<td>Dissertation (AC Assessment Continuing)</td>
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<tr>
<td>APHB4003</td>
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Students who complete this Honours degree will be eligible for up to 24 points credit if they then go on to study the Master of Biomedical Sciences or other Masters degrees. Students who have competed Honours will therefore have completed the units APHB5514, 5515, 5516, 5517 which form the Dissertation part of the Coursework and Dissertation pathway of a Masters degree. Note that no credit will be offered to students who take the Master of Clinical Audiology.

* continuing assessment between APHB4001 and APHB4008, Scientific Communication Parts 1&2 = 25% of final Honours grade.

# continuing assessment between APHB4002 and APHB4003, Research Design & Analysis Parts 1&2 = 25% of final Honours grade.
Deafness and other hearing disorders such as tinnitus are among the most common forms of sensory impairment with profound consequences for the individual and society. Normal hearing depends on the proper function of the many components of the inner ear and the brain pathways to which it is connected. Our laboratory seeks an integrated understanding of the normal operation of this sense organ and its associated neural pathways and to describe the mechanisms underlying various hearing pathologies.

**Project: Stress system and tinnitus**  
*With Assoc/Prof Jenny Rodger and Jack Zimdahl*

Phantom sensations are a curiously perplexing group of disorders. Tinnitus is a phantom sensation arising in the auditory system. Tinnitus is thought to be the result of abnormal neural activity in the auditory pathway. Interestingly, prevalence of tinnitus in higher in groups that experience high stress. It has been proposed that the limbic system may exert an inhibitory gating effect on the abnormal neural activity in the auditory pathway and stress may interrupt these mechanisms.

In this study we explore whether animals with high stress levels (induced by neonatal dexamethasone injections) are more likely to develop tinnitus after hearing loss. The project involves animal handling (rats), behavioural testing (elevated plus maze, morris water maze, gap induced inhibition of acoustic startle) and some histology.

**Project is suitable for:** Honours, Masters, PhD  
**Supervisor:** Assoc/Prof Helmy Mulders

**Essential qualifications**  
*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Each project will take place in the Cancer Epigenetics Laboratory at the Harry Perkins institute of Medical Research.

**Project 1. Engineering the cancer epigenome and targeting metastatic behaviour using epigenetic editing tools.**

With Dr. Charlene Waryah

Cancer is one of the major causes of death in Australia. For decades, the origin of cancer was attributed to genetic mutations, deletions and copy number amplifications. Recent advances have illuminated the aberrant epigenetic landscape which not only contributes but in some cases, drives cancer development and progression. Epigenetic marks are heritable covalent modifications in the DNA or associated proteins. Epigenetic modifications provide the mechanisms by which a cell “knows” and “remembers” which genetic information to read and which to ignore. Epigenetic modifications include DNA methylation and modifications in the proteins that the DNA is wrapped around. Unlike genetic mutations, epigenetic modifications are reversible and this can be used to restore the normal state of gene expression in the cancer. Our laboratory develops novel epigenome-targeted therapies to reverse the abnormal epigenetic modifications frequently observed in cancer. In this proposal, we aim to reverse the epigenetic modifications of key cancer drivers using the CRISPR/dCas9 system. We propose the development novel and more selective technologies able to stably suppress the genes that cause cancer spread.

Project is suitable for Honours, Masters, PhD

**Supervisor:** A/Prof Pilar Blancafort

**Essential qualifications**

For Honours: An appropriate undergraduate degree with a biological science, cell biology and basic molecular biology emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree with a biological, cellular and basic molecular biology science emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.

**Desirable Skills/Experience**

Knowledge of statistics, cell biology, basic biochemistry and cell biology

**Project 2. Development of a novel strategy using engineered peptides to selectively sensitise metastatic breast cancers to chemotherapy agents.**

With Dr. Edina Wang

The goal of this study is to develop innovative targeted treatments for triple negative breast cancers (TNBCs). TNBCs are responsible for the majority of breast cancer deaths in Australia and throughout the world. These cancers do not express oestrogen receptor alpha, progesterone receptor and epidermal growth factor receptor 2, which are common targets exploited in the clinic. They belong to the basal-like subtype breast cancer, which accounts for 15% of all breast cancers. In the metastatic
setting, they are highly resistant to chemotherapy. DNA-damaging agents used in chemotherapy that lack target specificity, cause wide range adverse effects. Thus, there is an urgent need to develop novel, more specific and targeted molecular approaches to treating this lethal disease.

As a cutting-edge therapy for TNBCs, we propose the generation of interference peptides (iPeps), which are synthetic peptides engineered from oncogenic transcription factors overexpressed in these breast cancers. The iPeps carry cell penetration and nuclear localization sequences that allow the peptide to be rapidly internalized across the cell and nuclear membranes. In addition, the iPeps are designed with residues essential for protein-protein interactions and DNA-binding derived from the endogenous oncogenic transcription factor. The iPeps then compete with the endogenous transcription factor by sequestering the binding partners necessary for transcriptional and DNA-binding activities.

Furthermore, we will use this highly innovative approach to physically link the i Pep with small molecules like Doxorubicin and pro-drugs like platinum IV, to localize them specifically in the nucleus of the cancer cells. We hypothesize that the iPeps will serve as “guides” for the chemotherapeutic drugs, directing them precisely into the nucleus to induce DNA damage. These iPeps will increase the selectivity and the kinetics of the small molecule’s uptake, as well as decrease the dose of the small molecule required for anti-cancer efficacy, thus lowering chemotherapy toxicity. This strategy will be employed in both TNBC cell lines and several aggressive breast cancer animal models, and eventually be adapted to patients to help eliminate the mortality associated with metastatic breast cancer, particularly for these triple negative breast cancers.

Project is suitable for Honours, Masters, PhD

Supervisor: A/Prof Pilar Blancafort

Essential qualifications

For Honours: An appropriate undergraduate degree with a biological science, cell biology and basic molecular biology emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree with a biological, cellular and basic molecular biology science emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.

Desirable Skills/Experience

Knowledge of statistics, cell biology, basic biochemistry and cell biology
Gene regulation in development and disease  
Associate Professor Archa Fox  
E: archa.fox@uwa.edu.au  
T: +61 8 6488 3297

Project 1. Paraspeckles as stress-responsive biomarkers in sheep

It is well known that many different stressors influence gestational outcome, and that stress experienced in the womb may also influence development throughout life. Therefore there is an urgent need to better understand how stress is modulated within the uterine environment. Paraspeckles are subnuclear bodies that regulate gene expression in many cellular contexts, but particularly in response to cellular stress. Paraspeckles are a cellular structure that is built on a long noncoding RNA molecule, called NEAT1 (nuclear paraspeckle assembly transcript 1). This project will examine a role for paraspeckles in altering gene regulation in response to stress in pregnancy.

What is the evidence for a role for paraspeckles in placental response to stress?

(1) NEAT1 was originally named TncRNA, or trophoblast noncoding RNA, and trophoblasts are the cell type that form the placenta, but this has never been examined in terms of paraspeckles, (2) the NEAT1 knockout mouse has defects in female reproduction, and (3) paraspeckles are most prevalent in tissues that are highly plastic in their differentiation status, as well as highly secretory, both of which are typical to the placenta.

You will use RT-qPCR to measure NEAT1 RNA levels in murine placental tissue isolated from placentas of control and stress treated pups, as well as tissue staining methods to label paraspeckles in placental tissue. You will culture the BEWO trophoblast cell line, use microscopy to examine paraspeckle abundance in normal and stress conditions. Should time permit you will measure changes in abundance of paraspeckle target genes under stress conditions, as well as ablating paraspeckles by transfecting BEWO cells with siRNA targeting NEAT1 to characterise the effect of loss of paraspeckles in trophoblasts.

Project is suitable for Honours, Masters, PhD

Supervisors: Assoc/Prof Archa Fox and Dr Caitlin Wyrwoll

Project 2. Studying the molecular glue that holds paraspeckles together

Paraspeckles are subnuclear RNA-protein granules that regulate gene expression in many contexts, particularly under stress conditions. We are interested in studying the underlying properties of the forces that hold paraspeckles together. They are interesting structures, as they are not enclosed in a membrane – so how do molecules get targeted there, and how are these molecules held there? It is important to understand these processes as many of the molecules found within paraspeckles are also found in pathological toxic aggregates in neurodegenerative disorders, such as motor neuron disease. We need to understand the way these molecules functionally aggregate into structures such as paraspeckles, in order to figure out why they pathologically aggregate in neurodegeneration.

In this project you will use different molecular biology techniques to create mutations in key amino acids within different paraspeckle proteins, and then transfect fluorescent protein fusions of these constructs into cultured cells to examine their paraspeckle localisation. You will use fluorescent in situ hybridisation against the paraspeckle marker NEAT1 to detect paraspeckles. You will also work in vitro to study the biophysical properties of these proteins, in collaboration with Professor Charlie Bond.
This project will yield important insights into the nature of the functional aggregation of MND-associated proteins into paraspeckles.

**Project is suitable for** Honours, Masters, PhD

**Supervisors:** Assoc/Prof Archa Fox and Prof Charles Bond

**Project 3. How changing paraspeckles influences cell health and response to stress**

Most human cells have the potential to build paraspeckles in their nuclei, however generally they have small/less abundant paraspeckles under normal growth conditions. In contrast, when cells are stressed through a variety of signals such as serum starvation, oxidative stress, pH imbalance, mitochondrial stress, heat shock and proteotoxicity, cells increase transcription of NEAT1 and thereby increase the abundance of paraspeckles. One challenge in studying the downstream roles of paraspeckles in response to these stressors has been separating the effects of the stressor from the effects of paraspeckles. To overcome this, we have developed a method of transiently increasing paraspeckle abundance without stressing the cell first: through delivery of antisense oligonucleotides that bind the nascent NEAT1 transcript.

In this project you will characterise this new tool to boost paraspeckles in a variety of cell and disease models. You will culture cells, deliver the antisense oligos and then track cell health and characteristics in a variety of assays. You will also experiment with ways of labelling the cells that have taken up the oligos.

*This project would suit someone with an interest in cell biology, cell culture and cellular models of disease*

References


**Project 4: A biomarker for physiological stress in large animals**

It is well known that many different stressors influence cellular responses and physiological outcome. Paraspeckles are subnuclear bodies that regulate gene expression in many cellular contexts, and particularly in response to cellular stress. Paraspeckles are a cellular structure that is built on a long noncoding RNA molecule, called NEAT1 (nuclear paraspeckle assembly transcript 1).

Loss of NEAT1 in mice results in an inadequate reaction to physiological stress manifested as hyperlocomotion and panic escape response. Our preliminary work has shown NEAT1 is expressed in sheep peripheral tissues and blood samples. However, the physiological role of NEAT1 and paraspeckles in the central nervous system in response to physiological stresses is still poorly understood. In this project we will use a variety of samples from large animals (sheep and pigs) that have been subject to different stressful scenarios. We will use these samples to investigate the role of NEAT1 and paraspeckles in different physiological settings. In addition, we also hope to develop a novel biomarker in blood samples with real-time, quantitative measures of animal brain function that can inform a lifetime index of animal welfare and stress state.

**Supervisors:** Archa Fox, Song Zhang, Dominique Blache

**Essential qualifications**

For Honours: An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Currently, cardiovascular disease accounts for 32% of all deaths in Australia. This is a staggering proportion and continues to exceed death from all cancers combined (30%) and from road deaths (4%). A number of the deaths in the cardiovascular group are due to arrhythmia or disturbances in the electrical activity in the heart.

The normal electrical activity in the heart is controlled by the movement of ions through specialised channels in the membranes of cardiac cells. The autonomic nervous system plays an essential role in regulating cardiac function and many of its effects are mediated via sympathetic neurotransmitters that regulate the activity of these ion channels.

Certain pathophysiological conditions contribute to arrhythmias such as hypoxia and oxidative stress. Under these conditions there is a reduction in blood flow to the muscle in the heart resulting in a reduction in available oxygen and reactive oxygen species production. This is then followed by an increase in generation of reactive oxygen species. There is increased sympathetic drive and the heart has a greater vulnerability to sudden cardiac death. Understanding how cardiac ion channels are regulated under these conditions is crucial to understanding the ionic mechanisms involved in the triggering of ischemic arrhythmias. In addition an increase in reactive oxygen species can contribute to the development of cardiac hypertrophy (enlarged heart) and cardiac failure. We have good evidence that an early mechanism involves increased calcium influx through the L-type calcium channel.

The laboratory uses molecular biology techniques for expression and purification of ion channel protein and biochemical techniques for assay of generation of reactive oxygen species and cell viability. The method that will be used to study membrane currents is the patch-clamp technique. This technique is an extremely powerful method for studying the electrophysiological properties of biological membranes and its contribution to the advancement of research was justly recognised with the awarding of the Nobel Prize in Physiology or Medicine in 1991 to its developers Erwin Neher and Bert Sakmann. The technique can be used to study ion channels either at a whole-cell level or at the level of a single channel. In addition, since the intracellular composition of the cell can be controlled, this can be exploited to determine any second messengers involved. Patch-clamp technique is also used in the laboratory in conjunction with fluorescent dyes to record changes in intracellular calcium, reactive oxygen species generation and mitochondrial function.

Project 1. How does the L-type calcium channel regulate mitochondrial function in pathology where actin filaments are disrupted?

(Collaboration with Prof Christine Seidman, Harvard University and Prof Chris Semsarian, Sydney University)

Mitochondrial respiration is abnormal in hearts where actin or cytoskeletal proteins are disrupted and it is not understood why. This project follows from data generated by previous students in the lab. We have evidence that the L-type calcium channel can regulate mitochondrial function via the actin
cytoskeleton. The project involves the use of patch clamp technique to study L-type calcium channel currents in mouse myocytes isolated from hearts of mice with disease involving disruption in cytoskeletal proteins and fluorescent detection of changes in mitochondrial membrane potential, NADH and superoxide production after activation of the channel.

Alterations in expression of proteins in mdx mouse hearts that co-immunoprecipitate with the channel (assessed by Mass Spec) will be identified using immunoblot analysis.

**Project 2. How does oxidative stress alter the sensitivity of the L-type calcium channel to isoproterenol? What effect does this have on the action potential?**

*(Collaboration with Professor Yoram Rudy, University of Washington, St Louis, Missouri, USA)*

This question seeks to understand how arrhythmias occur during ischemia/reperfusion in the heart (after a heart attack). Isoproterenol is a beta-adrenergic agonist (and mimics the effects of catecholamines such as adrenaline in the heart). This project will use patch clamp technique to study the effect of oxidative stress and isoproterenol on L-type calcium channel currents in addition to K and Na channel currents and record changes in action potentials. Information gained from patch-clamp studies are incorporated into the Rudy-Luo model. Changes in action potential configuration are modelled and the relative risk of arrhythmia is determined.

**Supervisor:** Professor Livia Hool

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
High-resolution analysis of the human immune response to HIV: implications for cure research and vaccine design

Summary:
More than 35 million people worldwide are infected with HIV including >22,000 Australians. Anti-HIV therapy can reduce mortality associated with infection but treatment does not provide a cure, is life-long and remains a substantial financial burden in Australia and worldwide. The main impediment to cure is the enormous diversity of HIV. A significant proportion of this variation is due to mutations in the HIV genome that allow the virus to escape from our immune response (viral adaptation). In this study, we will utilize our unique ability to analyze the host’s immune response at the single cell level to examine viral adaptation during the critical acute phase of infection. Understanding viral adaptation will aid in the rational design of vaccine candidates for either preventative or therapeutic strategies.

Scientific Background and Rationale:
The prototypic anti-viral immune response requires the actions of an array of naïve CD4+ and CD8+ T cells which, upon antigen-stimulation, differentiate into a highly specific population of “best-fit” clonotypes with an optimal T cell receptor (TCR) repertoire for clearance of virally infected targets and anti-viral memory. In the case of highly mutable viruses such as HIV, this process is subverted prominently by an extreme capacity for viral escape from CD8+ T cells. The extent of CD8+ escape, or more broadly adaptation, to immune responses, in founder/transmitting viruses or vaccine immunogens influences the subsequent quality of immunological control (1).

However, this mechanism alone is not sufficient to explain immune failure in HIV infection. It has been established that effective CD4+ T cell responses are necessary for quality CD8+ T cell responses (2, 3). We have characterised mutations in HIV sequences, which suggest that HIV can actually adapt to CD4+ T cell responses. This is a novel form of adaptation, which may operate in early infection, and have critical long-lasting effects on subsequent antibody and CD8+ T cell responses. Furthermore, while functional studies have shown examples of viral mutations causing disruption of antigen presentation leading to loss of antigen recognition, these ‘classical’ mechanisms represent only one strategy of adaptation. We have previously shown that the adapted viral strain can still be recognised by the host’s T cells in many instances (4, 5) and these T cells can exhibit greater functional avidity to the cognate peptide than T cells that target the non-adapted form (6).

We hypothesise that viral adaptation to T cell pressure, rather than leading to ‘classical’ escape, may result in the selection of a narrow, high avidity, TCR repertoire that ultimately is less effective at viral control, perhaps because of viral exhaustion. We can now address this issue using our established single cell analysis approach. Understanding how the TCR diversity of a maturing immune response can be altered or exploited by a pathogen is a fundamental question for many acute and chronic
pathogens for which natural, vaccine or cell therapy-based immunity is not currently effective or available. The link between TCR repertoire changes and effector functions at the single clonotype and global response levels is also a fundamental question for anti-viral immunity.

**Significance:**

The mechanisms of viral adaptation to T cell responses are fundamental concepts for host-pathogen interaction, and have important clinical implications. The cumulative burden of providing immediate and life-long anti-retroviral therapy (ART) to all individuals with HIV infection is significant, and the HIV incidence and prevalence continues to increase in Australia every year since 1999 despite good ART coverage (7). Harnessing immunological clearance as an alternative to ‘drugs for life’ could reduce this health and economic burden, as well as advance the global research efforts for HIV eradication. Improved therapeutic vaccines could ideally be combined with anti-latency strategies as a potential synergy in Australian research, with resulting benefits for global health.

Current immunogen design approaches do not solve the problem of viral adaptation nor do they consider how to overcome viral adaptation to CD4+ T cell responses in ensuring sustained CD8+ and antibody responses for vaccine memory.

**References:**


**Project is suitable for** Honours, Masters, PhD

**Supervisor:** Dr Silvana Gaudieri

**Essential qualifications**

For Honours: An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Comparative Physiology of Adaptation
Professor Shane Maloney
E: shane.maloney@uwa.edu.au
T: +61 8 6488 3394

Our group is interested in the physiological mechanisms whereby animal species (including humans) adapt to environmental stressors. We focus mainly on thermal and osmotic stress, but exercise, inanition (starvation), and infection are also studied, and recently the operation of circadian clocks and their role in physiological function (with Dr Peter Mark). Most experimental work is at systems level, but organ and molecular levels are also studied. Our long-term aim is to identify specific adaptations that allow animals to survive and reproduce in challenging environments, and to identify how “homeostasis” handles the trade-offs when simultaneous challenges are presented to an organism. Prospective Honours students with a background in General Systems Physiology, Exercise Physiology, Applied Animal Physiology, or Comparative Physiology are encouraged to apply. Depending on the project chosen a background in Cell Physiology could be an advantage.

Students will be exposed to a range of approaches and techniques including (in non-human animals) recovery anesthesia and surgery, implantation of physiological recording equipment, blood sampling for hormone measurement, and husbandry techniques for various species. In human research we use state of the art equipment to record physiological parameters in ambulatory subjects, including core and skin temperature transmitters, ambulatory blood pressure recording equipment, laser Doppler skin blood flow techniques, and infra-red thermography for surface temperature measurement.

Project 1: Biomarkers of positive animal welfare state
The viability of the animal production industries is dependent on their ability to demonstrate to the broader community that the welfare of production animals is being rigorously assessed using indicators that reflect the animals’ positive experience. New methods for the assessment of animal welfare are needed to match the new and future standards for welfare. Over the last 5-10 years, the definition of animal welfare has included the concept that animals should experience a “life worth of living” and therefore the next generation of biomarkers for animal welfare need to reflect a positive welfare state and a positive mental status. The project aims to screen biomarkers that have been linked to positive emotion, or positive perception of a situation, by humans and other laboratory animals.

The candidate will run animal experiments using sheep exposed to known positive, neutral, and negative situations. The emotional state of the animal will be measured at different time points using established behavioural tests. Biological samples, primarily blood and also less invasive samples such as saliva, will be collected to measure a suite of potential novel markers of positive experiential state. The tools to measure these new biomarkers will be developed and further validated under field conditions on farm.

Supervisors: Dr Dominique Blache (SAgE), Prof Shane Maloney, Prof Alan Tilbrook (Uni of Queensland)

Project 2. The role of episodic ultradian events of temperature in preparedness in humans
Biological rhythms are characterized as infradian (> 24 hours), circadian (~24 hours), or ultradian (~4 hours). Ultradian rhythms are often dismissed as noise within the circadian rhythm, but growing evidence suggests that ultradian events may be centrally regulated, like circadian rhythms. Spikes in
brain temperature precede locomotive and foraging activity, and ultradian rhythms in core body temperature have been hypothesized to play a role in mental alertness. Evolutionarily speaking, ultradian rhythms may underlie the preparedness of an organism to respond to external stimuli, such as during hunting or predation. The aim of this project is to establish the nature of the relationship between mental alertness and ultradian rhythms of core body temperature in humans. You will record and analyze motor data in response to transcranial magnetic stimuli that are given at various stages of naturally occurring ultradian events characterised using telemetric (real-time) measures of body temperature.

**Supervisors:** Dr Dominique Blache (SAgE), Prof Shane Maloney, Ass/Prof Jennifer Rodger (SHS)

**Project 3. Relative importance of different Zeitgebers in the control of rhythmicity and survival in the Drosophila**

Circadian rhythms refer to endogenous biological processes that fluctuate over a 24-hour period, allowing organisms to anticipate predictable physiological challenges that occur during the day/night cycle. Research in chronobiology increasingly indicates that robust circadian rhythms (i.e., rhythms with large amplitudes) are linked to improved metabolic health and longevity. Zeitgebers refer to resetting cues that synchronize and set the timing of circadian rhythms. Temperature appears to be a potent zeitgeber for circadian rhythms and may directly drive clock gene expression; therefore, it is possible that an increased amplitude of clock gene expression, driven by an increased amplitude of temperature cycles, could have a positive effect on longevity. In laboratory mammals, it is a challenge to demonstrate a direct relationship because of the difficulties of manipulating their body temperature. However, we can drive circadian gene expression in *Drosophila melanogaster*, a well-established model organism for genetics and circadian biology, by manipulating ambient temperature, which is impossible to do in mammals. Recently, we demonstrated that flies exposed to cycling ambient temperatures live significantly longer compared to flies housed at constant temperature. The project aims to investigate the effect of constant or cycling ambient temperatures on circadian gene expression and lifespan. Sub-projects may include investigations into the interaction of temperature with various other known zeitgebers, including light, noise, and diet, and investigate their effects on clock gene expression, lifespan, activity, feeding/mating behaviour, and physiology. Results from this project may shed light onto the role of circadian rhythms and various zeitgebers on the process of ageing.

**Supervisors:** Prof Shane Maloney, Dr Dominique Blache (SAgE), Ms Grace Goh

**Project 4. Nerve conduction velocity, ion pump activity, and the cardiac pacemaker during cooling in the cane toad (Rhinella marina)**

In Australia, cane toads (*Rhinella marina*) are classified as pests. Since their introduction into Queensland in 1930, their numbers have reached around 200 million. To try to limit the population, many thousands of toads are killed annually using a variety of methods. Toads are also killed for university teaching and research. Gradual cooling then freezing has been a common method for humane killing, but is now deemed unacceptable by some authorities. The aim of the project is to measure the activity of various components of the nociceptive pathway at different temperatures. You will make measures using a PowerLab, similar to the practicals you did in PHYL2002, to elucidate the Q10 for nervous activity in toads. Your results will help to determine whether cane toads have the necessary physiology to detect pain when they are frozen.

**Supervisors:** Prof Shane Maloney, Dr Dominique Blache (SAgE)
Project 5. Impact of ultradian patterns of body temperature on lifespan and reproduction in *Drosophila*

Metabolic processes control the flow of energy and protein in the body, helping to maintain biological function. One function central to metabolism in mammals and birds is the regulation of body temperature. Research in chronobiology increasingly indicates that robust circadian rhythms (i.e., rhythms with large amplitudes) are linked to improved metabolic health and longevity. In addition to the circadian rhythm of body temperature, there exist very short episodic increases in temperature (also called episodic ultradian events). An inverse relationship between the amplitude of circadian rhythm and the number of episodic ultradian events has been described in a number of all homeotherm species. The role and the mechanism controlling the interaction between circadian and ultradian rhythms has never been studied simply because, in homeotherm, it is impossible to dissociate or manipulate them independently. Drosophila is a perfect model to investigate the role of body temperature on biological function. However, the body temperature of *Drosophila melanogaster*, a small body size heterotherm, can be easily manipulated with changing ambient temperatures.

The project aims to investigate the relative role of both the circadian and the ultradian rhythm of body temperature on lifespan reproductive function and associated gene expression.

**Supervisors:** Dr Dominique Blache (SAgE), Dr Kelsey Pool (SAgE), Prof Shane Maloney

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Project 6. Orbital tissue relationships to intraocular and intracranial pressure.

The orbit represents the contents of the bony orbit in mammals and all vertebrates. The eye sits within the orbit, insulated by loose fat and fibrous tissue which performs a delicate and complex role. This role is necessary to insulate the eye from sudden movements, shockwaves and to form a steady base to allow rotational eye movements without translation of the eye in any particular direction (in order to keep ones visual world stable). Several diseases can affect the orbit and they do this principally by adding tissue either through tumour growth or inflammatory tissues which have a bulk or mass effect upon the orbital tissue compressing the optic nerve or muscles or distorting the eyeball itself.

Our work will mimic tumour growth by implanting balloon catheters within the orbits of pigs whilst we measure the intraocular, intraorbital and intracranial (cerebrospinal fluid pressure) pressures.

The technical setup is complex but one will learn a great deal about ocular and orbital pressure physiology through this work. One core hypothesis will be that the orbital tissue pressure is evenly distributed with relatively little tissue buffering within the orbit.

The orbital pressure is likely to impinge directly upon the cerebrospinal fluid compartment that exists around the optic nerve right up to the eyeball itself and hence have a direct effect upon that pressure compartment. New methods to directly measure the cerebrospinal fluid pressure around the optic nerve will be used. We will also be apply photoplethysmographic techniques to develop methods to non-invasively measure the pressure in orbital tissue. Depending upon your interests, some of these core aims can be built into a prospective PhD.

**Supervisors:** Prof Shane Maloney, Prof Bill Morgan [Lion’s Eye Institute]

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Most of our attention in relation to blood vessel physiology concerns blood flow, pressure differentials, and resistance in classical physical terms. However, there is recent, exciting new understanding of how pulse waves are transmitted along blood vessels and how pulse wave transmission can be influenced by vascular compliance and resistance in particular. The translation of an intravascular pressure pulse wave to blood vessel wall pulsation involves local compliance and
vascular stiffness. All of these factors are involved in significant blinding diseases such as glaucoma, diabetic retinopathy, retinal vascular diseases, and also raised intracranial hypertension. We have developed a photoplethysmographic technique that maps the retinal vascular pulsation characteristics (amplitudes and timing). We have only just begun tapping into how this technique can be applied to diseases as well as using it to understand basic physiology of the retinal vessels. How the retinal vessel (in particular vein) wall pulse wave attenuates (the rate of pulse amplitude reduction with distance along vessel) is thought to change with alterations in vessel compliance and resistance. Several diseases are key exemplars causing change in those parameters, namely diabetes with diabetic retinopathy, long standing systemic hypertension and retinal vein occlusion. Diabetic retinopathy and vein occlusion cause approximately 12% of blindness which is clearly a devastating problem.

There is a great need to identify patients at risk of going blind with these diseases and this technology shows great potential. It requires much deeper physiological understanding for its application.

This project would be for someone interested in characterising normal pulse wave attenuation characteristics and in the diseases mentioned, along with exploring the role of timing characteristics including pulse wave transmission in normality and disease. It is most likely that much deeper understanding of vascular physiology including pulse wave transmission characteristics will be derived through this work which will have as yet unknown applications and ramifications. It is almost certain that some of the applications will be very relevant to the monitoring and treatment of the diseases mentioned.

**Supervisors:** Prof Shane Maloney, Prof Bill Morgan [Lion’s Eye Institute]

**Project 8: Is there a clock in the sheep stomach? Or chronobiology and rumen function**

Circadian rhythms refer to endogenous biological processes that fluctuate over a 24-hour period, allowing organisms to anticipate predictable physiological challenges that occur during the day/night cycle. Research in chronobiology increasingly indicates that robust circadian rhythms (i.e., rhythms with large amplitudes) are linked to improved metabolic health and longevity. Zeitgebers refer to resetting cues that synchronize and set the timing of circadian rhythms. Temperature appears to be a potent zeitgeber for circadian rhythms and may directly drive clock gene expression; therefore, it is possible that an increased amplitude of clock gene expression, driven by an increased amplitude of temperature cycles, could have a positive effect on longevity. The microbial population that is present in the rumen is crucial for digestion of a forage diet, and that population is naturally exposed to the circadian rhythms of temperature of the sheep. Amazingly, so far all experiments done using either artificial rumen or culture of rumen fluid in-vitro have been done at constant temperature.

This project aims to explore the role of circadian rhythms of temperature in the rumen on the activity and survival of the microbial population.

**Supervisors:** Dr Dominique Blache [SAgE], Prof Phil Vercoe [SAgE], Prof Shane Maloney [SHS]

**All projects are suitable for:** Honours, Masters, PhD

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Project One: Primate behavioural ecology research:

- Comparative study on aspects of primate socioecology (using literature data)
- Observational research on primate behaviour/cognition at the Perth Zoo

Project Two: Human behavioural ecology

Example: Questionnaire-based, experimental, and observational research on social behaviour/organisation, mate choice and cooperation in humans

Project is suitable for: Honours/ Masters

Supervisor: Senior Lecturer Cyril C. Grueter

Desirable Skills/Experience

Basic knowledge of statistics (especially regression analyses) would be desirable.
The projects, which all have the same set of conditions, are:

- For **highly motivated** students there is potential to undertake field studies of family well-being in East Timor involving questions of family structure, ecology, social networks and child growth. Some language study before commencing will be required and only students with records of high achievement in appropriate units will be considered.
- Intergenerational relationships in terms of help provided to adult offspring by mothers and fathers
- Family composition effects on development and reproductive strategies (survey work in Australia or work in Timor-Leste).
- Database development and statistical analyses of patterns of ecology and life history traits across species
- Behavioural studies of captive mammals (especially primates) at the Perth Zoo
- Behavioural studies of sex differences in humans

If you have another idea in the area of evolutionary ecology, talk to me about it; I am open to new and interesting questions.

**Suitable for:** Honours, masters, PhD

**Supervisor:** Assoc/Professor Debra Judge

**Essential qualifications**

*For Honours:* An appropriate undergraduate major with a human biology, zoology or anthropology emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate honours degree with a human biology, zoology or anthropology emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.

**Desirable skills/experience**

Knowledge of basic statistical analyses is helpful but can be learned during the project. Ability to learn a further language is a requirement for some international research projects.
Our team includes about 30 graduate students and more than 200 collaborators across the globe. The core values of the research team are about making a just and equitable society. All students are fully supported during their studies and we have a near 100% record of peer review publication from students’ efforts (with the student being the lead author). Research with this team will make a difference to the world.

Please have a look at ircohe.net for lots more interesting info on who we are, what we do and the sorts of things you can do with our team.

All projects are designed to the individual’s passion. We ask you what you would like to do! We have projects for Honours, Masters, and Doctorate students and are keen to help you find a terrific, fun learning experience on a pathway to a great future life.

**To be part of the team only needs one thing. An interest in the world and making it a better place. We accept anyone with this passion.**

**International Communities**

We have a series of projects that address international community development. Below is a typical project but there are many others that are available to do – please if you have a passion in the area come and talk.

**Example Project:** Rebuilding dental services in countries after war?

Sri Lanka is a developing country about the size of Tasmania with the population of Australia with the history of 30 years long internal conflict which ended recently; leaving the people of Sri Lanka with many difficulties.

Many African counties face up-hill battles to provide health care. The team works on research and development project to design ways to enhance health access in these communities.

**Mapping the world**

We have a series of projects that look at building state-of-the-art digital maps to address issues of health access. This year one of our honours students has mapped the entire city of Sao Paulo in Brazil – all 20million people, all transport networks, everything. We have many projects that will give you a chance to learn some amazing leading edge mapping skills useful in all sorts of future roles from public health to NGO volunteering.

Today we are working on projects mapping health services and traffic density in COVID-19 environments with big data supplied by Google.
Marginalised Communities

We have a series of projects that address Australian marginalised communities and inequity. Below is a typical project but there are many others that are available to do – please if you have a passion in the area come and talk.

**Example Project:** Do having grommets link to poor oral health?

Many children suffer from ear infection and need to have grommets to treat the infections. The bacteria involved in these infections are similar to those that cause tooth decay. The proposed study will use Big Data techniques to test the hypothesis that there may be a linkage between these two conditions and that providing a dental surveillance program for patients attending for ear infections may reduce the emergency need for dental care for children and thus reduce health care costs and human suffering. The study will also include some health financing and cost-benefit analysis.
Neuroscience
Associate Professor Stuart Hodgetts

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T: +61 8 6488 8642

Cell and tissue transplantation, pharmacotherapy, gene therapy and the repair of central nervous tissue damaged after injury.

The research by the neuroscience groups in Anatomy, Physiology and Human Biology has a particular emphasis on cell and tissue transplantation, gene therapy, bioengineering, in vivo reprogramming, pharmacotherapy, photobiomodulation, and the repair of central nervous tissue damaged after injury. Ways are being tested for preventing nerve cells from dying after injury and promoting plasticity and the regenerative growth of damaged axons. The potential for replacing compromised cells with new healthy cells, including stem cells, is also under investigation. Studies are mostly carried out in the spinal cord.

Project is suitable for: Honours, Masters, PhD

Supervisor: Assoc/Prof. Stuart Hodgetts

Other supervisors: Emeritus Prof Alan Harvey

Essential qualifications:

For Honours: An appropriate undergraduate degree with a biological science emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.

Desirable skills/experience

Neuroscience emphasis. Cellular and molecular biology knowledge would be helpful.
Recent data from our laboratory demonstrate no effect of central kisspeptin treatment on accumulative food intake. Despite this, neuroanatomical links have been established between kisspeptin cells and appetite regulating neurons expressing neuropeptide Y (NPY) and Pro-opiomelanocortin (POMC). Moreover, kisspeptin results in the activation of NPY cells in the hypothalamus. Electrophysiological data also suggests kisspeptin regulates the activity of NPY, and also POMC neurons. Taken together, these data strongly suggest kisspeptin has effects on energy expenditure.

Experiments will be conducted to measure the effect of kisspeptin and the absence of kisspeptin signalling in mice on energy Expenditure. GPR54 (Kiss1r) knock-out mice or their wild-type littermates will be challenged with a high fat diet for 12 weeks. Mice will then be tested on indices of energy balance including:

- Measurement of whole body energy metabolism (using metabolic cages for indirect calorimetry)
- Assessment of whole body glucose metabolism (using intraperitoneal glucose and insulin tolerance tests)
- Assessment of body composition (Using dual energy X-ray absorptiometry DEXA)
- Assessment of neuropeptide systems involved in energy metabolism (using in situ hybridisation).

Results from these experiments will shed light on the known link between the reproductive system and metabolism and will, potentially, offer novel therapeutic alternatives for the treatment of obesity and related metabolic disorders.

**Project is suitable for:** Honours, Masters, PhD

**Supervisor:** Dr Jeremy Smith

**Essential qualifications:** none

**Desirable skills/experience:** A background in molecular biology is desirable but not essential.

**The role of kisspeptin in implantation and placentation**

Kisspeptin, the neuropeptide product of the Kiss1 gene, is synthesized by neurons within the hypothalamus and is critical for the release of gonadotrophin-releasing hormone (GnRH) and fertility. In humans, kisspeptin secretion into the peripheral circulation increases dramatically (approximately ten-thousand-fold) during pregnancy and declines precipitously at term, indicating a placental origin. The placenta is known to express KISS1 and kisspeptin receptor (KISS1R) mRNA and it appears to be localized to the trophoblast compartment. We aim to determine the expression of Kiss1 mRNA in the mouse placenta and examine the effect of reduced kisspeptin signaling (using a kisspeptin receptor knock-out mouse) on feto-placental growth.

Experiments will be conducted to measure feto-placental growth in an Kiss1r KO model.
Kiss1rKO mice or their wild-type littermates will be examined at day 14 and 18 of pregnancy.

We will examine:

- Fetal weight
- Placental weight and morphology
- Assessment of key placental genes (using RT-PCR)
- The effect of kisspeptin and the absence of kisspeptin signalling in mice on placental histology

Results from these experiments will shed light on the function of kisspeptin in the placenta and will, potentially, offer novel therapeutic alternatives for the treatment of placental insufficiency and/or pre-eclampsia.

**Project is suitable for** Honours, Masters, PhD

**Supervisors** Dr Jeremy Smith and Dr Caitlin Wyrwoll

**Desirable skills/experience**

A background in molecular biology is desirable but not essential.
Project 1: Innate Defence Regulator Peptides to Modulate Postnatal Inflammatory Response

Inflammation and infection are the key drivers of adverse neurodevelopmental outcomes and increased morbidity and mortality in preterm infants. New immunomodulatory therapies that target inflammation and infection may improve preterm infant outcomes. Innate defence regulators (IDR) are synthetic derivatives of host defence peptides, which have antimicrobial and immunomodulatory actions. IDR-1018 is a highly promising IDR with demonstrated immunomodulatory and neuroprotective efficacy in newborn mice, and antimicrobial activity against gram-positive and gram-negative bacteria. This project will involve preclinical evaluation of IDR-1018 and its systemic effects in a preterm lamb model in the Preclinical Intensive Care Research Unit. Newborn lambs were ventilated for 24 hours in 2019 prior to euthanasia and tissue collection. In 2021, we will evaluate short-term inflammatory responses to postnatal ventilation after intravenous and enteral IDR-1018, and the dose-response. Longer duration (2 month) studies conducted in 2021 will also commence on lambs that would provide samples for a PhD starting 2022 for an Honours student looking to progress and continue in research.

This project offers Honours or HDR students opportunities for investigating the impact of IDR-1018 on postnatal inflammatory responses in key organs, including the thymus, liver and immune system. Projects have a laboratory (molecular & cell biology) focus depending on the interests of the student and the time available for investigation. Postnatal lamb studies for this project were completed in 2021, and this project will focus on tissue processing and analysis. New studies are planned in 2022 that would extend the project to a PhD.

**Project is suitable for:** Honours/ Masters/PhD

**Principal Supervisor:** Professor Jane Pillow

Additional supervisors will be involved depending on the student interests and organ system to be studied.

**Essential qualifications:**

*For Honours:* An appropriate undergraduate degree with a biological/physiological science emphasis, and a minimum weighted average of 65 % in the level 3 subjects that comprise the relevant major from an approved institution. Evidence of successful teamwork and personal organizational skills. Applicants will be assessed on a case-by-case basis for suitability to the project.

*For Masters or PhD:* An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Evidence of successful teamwork and personal organizational skills. Applicants are assessed on a case-by-case basis.

**Desirable skills/experience**

Preparedness to work with large animals including surgery and post-mortem tissue collection

Strong work ethic, Commitment to excellence.
**Project 2: Creatine loading of the fetal lamb to protect against the antenatal pro-inflammatory stimulus**

Being born preterm predisposes infants to increased mortality and morbidity. One of the biggest risk factors for preterm delivery include chorioamnionitis; inflammation of the membranes surrounding the fetus. During chorioamnionitis, the fetus is exposed to pro-inflammatory stimuli and oxidative stress, which have adverse effects on the immature and developing organ systems with lifelong consequences. Therefore, evaluation of emerging therapies targeting inflammation and oxidative stress are critical in improving outcomes for preterm infants. Creatine supplementation is a promising treatment that has been trialled in small animal models but which requires further investigation is (Dickinson et al., 2014). Creatine has mild anti-inflammatory and anti-oxidant properties, which can be protective against tissue injury during the fetal inflammatory syndrome. A maternal diet high in creatine could load the fetus with creatine and protect from potential damage and growth delays, improving long term neurological and systemic outcomes.

**Potential honours projects:**

Investigate the effect of creatine in neuroinflammation, injury and altered structure of the brain, particularly in areas associated with neurodevelopmental impairments found in preterm birth. This would involve immunohistochemical and molecular analysis, such as qPCR.

Investigate the effect of creatine on hepatic inflammation and disturbed metabolism. This would involve morphologic, immunohistochemical and molecular analysis.

**References**


**Essential qualifications:**

*For Honours:* An appropriate undergraduate degree with a biological/physiological science emphasis, and a minimum weighted average of 65 % in the level 3 subjects that comprise the relevant major from an approved institution. Evidence of successful teamwork and personal organisational skills. Applicants will be assessed on a case-by-case basis for suitability to the project.

*For Masters or PhD:* An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Evidence of successful teamwork and personal organisational skills. Applicants are assessed on a case-by-case basis.

**Desirable skills/experience**

Preparedness to work with large animals including surgery and post-mortem tissue collection
Strong work ethic
Commitment to excellence

**Project 3: Effect of a cycled environment on clock gene expression and/or salivary melatonin and cortisol levels in premature infants.**

Circadian rhythms are vital to normal fetal development, but the fetus is dependent on maternal circadian rhythms until near-term. Preterm infants spend the first months of postnatal life in the disruptive setting of constant environmental light and noise, without maternal circadian inputs.
Disturbed circadian rhythms are associated with neonatal morbidity and prolonged initial hospitalisation, and in utero programming for late-onset metabolic syndrome. Importantly, circadian rhythm disruption compromises neurodevelopment in animals. We are leading a clinical trial that aims to establish if individual diurnal cycling of environmental light and noise levels improves cognitive outcomes of very preterm infants compared to more constant background lighting and noise. This project offers Honours students to be involved in substudy associated with this trial and to be involved clinical research within an established and highly functional clinical research team.

**Potential Projects**: Substudy to determine if exposing extremely preterm infants to a cycled environment results in a circadian rhythm via analysis of clock gene expression in buccal cheek swabs and melatonin/cortisol secretion in saliva.

**Project is suitable for**: Honours

**Supervisors**: Professor Jane Pillow, Professor Shane Maloney, Dr Peter Mark, Ms Natasha Sorensen

**Essential qualifications**:

*For Honours*: An appropriate undergraduate degree with a biological/physiological science emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Evidence of successful teamwork and personal organisational skills. Applicants will be assessed on a case-by-case basis for suitability to the project.

**Desirable skills/experience**

Preparedness to work with large animals including surgery and post-mortem tissue collection

Strong work ethic, commitment to excellence.

**Project 4: Developing a viable ovine model of extremely preterm birth**

Clinicians are increasingly aware of the effect that prematurity itself, as well as diseases of the lung and the gastrointestinal tract, can have on the development of the premature brain. Postnatal studies using the preterm lamb as a model of the preterm human infant are generally reported for the 125-128 d lamb equating to approximately 83-85% of full-term gestation. Whilst the direct equivalent of 83-85% gestation is 33-34 weeks gestation (moderately preterm), the lung is still relatively immature approximating the 28-30 w human preterm infant lung. In contrast, the brain of 128 d lambs are relatively mature and considered “near term”, compromising our ability to evaluate the effect of treatments for lung and gastrointestinal disease on brain development.

The successful development of an extremely preterm lamb model would increase the clinical translation relevance of our work. The feasibility of using more premature lambs needs to be determined before the commencement of a future planned protocol on circadian rhythm intervention in which the primary outcome will be focused on brain development. Hence, we propose an initial study using a stepped reduction in gestation and an intensified fetal lung maturation protocol to identify the fetal lung maturation protocol (glucocorticoids) and gestation most conducive to achieving our future objectives.

**Potential Projects**. Two projects will be available including 1) comparison of different corticosteroid protocols for postnatal management of the extreme preterm lamb and 2) effectiveness of an optimised fetal lung maturation protocol on short term postnatal respiratory function and gas exchange in preterm lambs delivered at 124 d (83%), 121 d (81%), 118 d (79%), and 115 d (76%) gestation to identify the most appropriate gestation for further model development.

**Project is suitable for**: Honours/ Masters Coursework Dissertation

**Principal Supervisor**: Professor Jane Pillow
Additional supervisors will be involved depending on the student interests and organ system to be studied.

**Essential qualifications:**

*For Honours*: An appropriate undergraduate degree with a biological/physiological science emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Evidence of successful teamwork and personal organisational skills. Applicants will be assessed on a case-by-case basis for suitability to the project.

*For Masters or PhD*: An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Evidence of successful teamwork and personal organisational skills. Applicants are assessed on a case-by-case basis.

**Desirable skills/experience**

Preparedness to work with large animals including surgery and post-mortem tissue collection

Strong work ethic

Commitment to excellence
Early life environment is a powerful determinant of adult health outcomes. Each year, Dr Wyrwoll offers a range of research projects that address this topic. Broadly, these environmental stressors encompass issues such as malnutrition, physiological stressors arising from climate change, drug use, and models of glucocorticoid exposure. Projects can range from working with animals models, to computer modelling, to cell based projects, to analysis of human health datasets. Please contact Caitlin directly for more information.

**Project is suitable for** Honours, Masters, PhD

**Supervisors:** Dr Caitlin Wyrwoll (SHS)

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.

**Desirable skills/experience**

A background in reproductive biology/ animal work/ molecular biology is desirable but not essential depending on the project.
Reproductive and Developmental Biology
Dr Peter Mark
E: peter.mark@uwa.edu.au
T: +61 8 6488 2609

The major interests of our group centre on the importance of circadian biology in relation to placental function, maternal adaptation to pregnancy, and developmental programming. Current studies are focussed on the impact of maternal obesity, omega-3 fatty acids and glucocorticoid excess on pregnancy outcome (from the perspective of both the mother and the developing fetus).

Project 1: Developmental origins of health and disease (DOHAD)

Studies in relation to DOHAD focus on the effects of fetal glucocorticoid excess on the adult phenotype, particularly in relation to programming of adult-onset diseases such as hypertension, diabetes and obesity. The capacity of postnatal diets to either exacerbate (e.g. by a high fat diet) or rescue (e.g. dietary fish oil) adverse outcomes is an important focus of this work.

Tissue banks have been collected from a large scale glucocorticoid programming study and these are available for analysis. Tissues including heart, kidney and adrenal gland have been collected at 6 months of age from control and programmed offspring raised on standard, high fat or high fat/high omega-3 diets. They have been collected at four time points across a 24 hour period, enabling circadian profiling of gene expression and tissue function to be layered into the analysis.

Supervisors: Dr Peter Mark (Chief), with W/Prof Brendan Waddell

Project 2: Circadian rhythms in the spiny mouse placenta

Circadian biology underpins all major metabolic processes to appropriately align physiology of the organism with behaviour. Altricial (immature at birth) organisms, such as the rat and mouse, have minimal circadian variation in placental function, possibly to supply the fetus with constant nutrition during the relatively brief period of fetal growth. Precocial (relatively mature at birth) organisms are often born with metabolic rhythmicity (e.g. in liver function) which may be driven by exposure to peaks and troughs in substrate supply from the placenta.

This project aims to determine whether placentas from the precocial spiny mouse exhibit distinct circadian rhythmicity in their function in association with fetal liver rhythmicity. Samples have been collected from pregnant spiny mice in collaboration with Dr Hayley Dickinson, The Ritchie Centre at The Hudson Institute, Victoria. Placental expression of clock genes and nutrient transporters will be determined at various stages throughout gestation to determine the timing of onset for placental rhythmicity.

Supervisors: Dr Peter Mark (Chief), with W/Prof Brendan Waddell and Dr Hayley Dickinson, Monash University

Project 3: Maternal circadian adaptation to pregnancy

Pregnancy is one of the greatest physiological and metabolic challenges the body is confronted with. Maternal metabolism exhibits a predominantly anabolic phase during the first half of gestation, to lay
down sufficient nutrients in maternal metabolic tissues (e.g., liver and adipose tissue) to meet the high energetic demands of the developing fetus later in gestation, via catabolism of the stored nutrients.

In addition, many metabolic pathways exhibit circadian rhythmicity in their activity, so they can optimise their performance to appropriate times of day e.g. food consumption during the day and fasting overnight.

Tissues have been collected at 4 hourly timepoints across 24 hours from non-pregnant mice and during mouse pregnancy (days 6, 10, 14 and 18 of pregnancy; term =19 days). Metabolic pathways and their circadian rhythmicity in these tissues will be interrogated through quantitative PCR and Western blot analysis to identify how liver and adipose tissue change during this metabolic adaptation to pregnancy.

**Supervisors:** Dr Peter Mark (Chief), with W/Prof Brendan Waddell

**Project 4: Maternal obesity disrupts circadian adaptation to pregnancy and fetal and placental development**

Obesity during pregnancy is associated with numerous adverse outcomes including preeclampsia, gestational diabetes, fetal overgrowth and somewhat counter-intuitively, some mothers exhibit fetal growth restriction. In obese pregnancies complicated by fetal growth restriction, placental dysfunction is considered a likely cause of the reduced fetal growth. This placental dysfunction may eventuate, in part, through maladaptation of maternal circadian rhythmicity in metabolic processes.

Female rats were fed cafeteria items (e.g., meat pies, biscuits, chocolate cake) for eight weeks prior to mating, and through pregnancy. By the time of mating, the CAF-fed rats were ~25% heavier than control rats, fed only normal chow. Maternal metabolic tissues (liver and adipose tissue), placental tissue and fetal liver were collected at 4 hourly intervals across days 15-16 and 21-22 of gestation (term = 23 days). These tissues show marked changes in circadian expression of clock genes following consumption of the CAF diet, with the amplitude of the rhythm frequently reduced. Further investigation in alterations in metabolic pathways will identify other genes that are dysregulated in maternal obesity.

**Supervisors:** Dr Peter Mark (Chief), with W/Prof Brendan Waddell

**Project 5: Pathways to infertility: mechanisms of action of phyto-oestrogens**

Background: *Trifolium subterraneum* clover has historically been used as a pasture throughout Western Australian sheep farms, due to its palatability to livestock and low maintenance requirements. However, in the 1930s and 40s, reproductive anomalies in flocks grazing *Trifolium subterraneum* clover were linked to the presence of phytoestrogens. Phytoestrogens are non-steroidal, naturally occurring phytochemicals produced in plants, partly in response to stress. Phytoestrogens are functionally and structurally similar to oestrogens, particularly 17β-oestradiol, found in mammals including sheep. Phytoestrogens act as a mixed agonist/antagonist of oestrogen action, suppressing the hypogonadal-pituitary axis and competing for oestrogen receptors, ERα and ERβ.

In sheep ingesting oestrogenic clover, the cervix loses the ability to respond to oestrogen, thus failing to produce the viscoelastic mucous necessary for fertilisation. However, some sheep are not affected by the ingestion of oestrogenic clover.

The molecular basis of the resistance to phyto-oestrogen exposure is not understood. This project aims to compare the expression of oestrogen receptors ERα and ERβ and related intracellular mechanisms in ewes exposed to phyto-oestrogens, that were either successful or unsuccessful in the production of a lamb.

**Supervisors:** Dr Peter Mark, Dr Dominique Blache, Dr Caitlin Wyrwoll

**Projects are suitable for** Honours, Masters by Research, PhD
Essential qualifications

For Honours or Masters: An appropriate undergraduate degree with a biological science emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters by Research or PhD: An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Lifestyle and psychosocial factors influencing human fecundity and fertility (database and survey studies)

- The impact and interaction of age, nutrition, and stress on male and female reproductive processes (database, survey and lab based projects possible).
- Issues surrounding the use of donated gametes and embryos in assisted reproductive technology (survey based and qualitative type projects possible).

For students interested in assisted reproductive technology (ART), opportunities exist for collaborative projects in the above areas with Dr Peter Burton at Concept Fertility Centre. Laboratory based projects focus on the impact of ART procedures on sperm biology and clinical outcomes.

Students are encouraged to contact Kathy Sanders to discuss any other topics on Reproductive Biology they may wish to pursue.

Project is suitable for: Honours, Masters, PhD

Supervisor: Assoc/Prof Kathy Sanders

Essential qualifications:

For Honours: An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
The respiratory group in the School of Anatomy, Physiology and Human Biology, in collaboration with scientists at Sir Charles Gairdner Hospital and Telethon Kids Institute, has a long-standing interest in the control and function of conducting bronchi. The trachea, bronchi and other airways conduct air into and out of the lung. During an asthma attack contraction of airway smooth muscle (ASM) narrows the conducting bronchi and obstructs airflow. Airway obstruction also occurs in several other respiratory diseases including Chronic Obstructive Pulmonary Disease (COPD), chronic bronchitis and emphysema. The broad focus of our research has been in understanding the detailed mechanisms involved in the control of airway diameter and airway obstruction.

**Project 1: The role of Kiss1r in obesity-asthma development**

Obesity is a preventable condition, yet worldwide prevalence has almost tripled within the last 45 years, with 67% of Australians considered overweight or obese in 2017-18. Of particular concern is the impact of obesity on existing disease. There is mounting evidence that delineates a strong association between obesity and asthma; severity of asthma is greater in obese individuals who are less responsive to current treatments. The mechanisms underlying the obesity-asthma relationship are unknown. We have recently examined the role of kisspeptin in energy balance by characterising the metabolic profile of Kiss1 receptor (Kiss1r) knock out (KO) mice. These mice developed an obese phenotype compared with wild type littermates. This project will therefore utilize Kiss1r KO mice to first elucidate the role of Kiss1r in normal respiratory physiology, and in the context of excessive weight gain.
Supervisors: Dr Kimberley Wang, A/Prof Peter Noble, Dr Jeremy Smith

Project 2: Intrauterine growth restriction and asthma development
Studies have shown that restricted fetal growth in the womb may be linked to the development of asthma in childhood and adulthood. The reason for this association is not clear but we believe that restricted growth may alter the normal development of airway and lung tissue leading to impaired function and symptoms of wheeze, chest tightness and cough. Using an established in utero growth restricted mouse model, this project aims to determine if growth restriction is accompanied by a change in airway smooth muscle contractile phenotype. This study will measure force production of tracheal airway smooth muscle in organ bath chambers using tissue obtained from normal and growth restricted mice.

Supervisors: Dr Kimberley Wang, Assoc/Prof Peter Noble

Project 3: Contractile properties of human airways from subjects with and without COPD
Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation which is not reversible. According to the World Health Organisation, COPD is predicted to be the third leading cause of death worldwide by 2030. The mechanisms producing airflow limitation in COPD are unclear but likely involve changes to the contractile properties of the airway smooth muscle layer. To study human airway smooth muscle, subjects undergoing lung resection surgery (to remove tumours) are recruited and permission obtained to use airway tissue in our in vitro organ bath studies. Contractile responses are measured in bronchial rings from subjects with and without COPD. Approval from the Human Ethics Committee has been obtained.

Supervisors: Assoc/Prof Peter Noble, Dr Peter McFawn, Prof Alan James and Mr John Elliot

Project 4: Airway wall development
Increased airway smooth muscle (ASM) cell size, number and absolute volume of extracellular matrix (ECM) all contribute to the increased thickness of the ASM layer in adult asthmatic patients and likely account for the excessive, reversible airway narrowing that characterizes asthma. The ASM layer is thickened early in life and even before doctor-diagnosis of asthma. An intriguing possibility is our overarching hypothesis that the ASM layer is thickened from birth and represents an independent risk factor for the development of asthma. This project strives to understand better how the ASM layer matures from late gestation to adulthood and what specific structural changes (i.e., ASM cell volume and number and ECM deposition) account for the increased thickness of the ASM layer in young asthmatics. An understanding of the mechanisms that produce the normal increase in the volume of the ASM layer from late gestation to adulthood, and how these are altered in asthma, will reveal maturational processes susceptible to disease at different stages of life. This project will utilise a unique human tissue bank of airways acquired from subjects with and without asthma over a range of ages spanning late gestation to adulthood. Histological techniques will be used to morphometrically track changes in wall structure during development and in disease.

Supervisors: Assoc/Prof Peter Noble, Prof Alan James, Mr John Elliot, Dr Kimberley Wang

Project 5: Characterising physiological properties of kangaroo airways
Comparative physiological studies using animal models provide an opportunity to better understand the relationship between airway structure and function. The present study will focus on the kangaroo airway. While in most mammals, thoracic expansion occurs as a result of respiratory muscle contraction, when hopping, air is drawn in and out of the kangaroo lung as a result of the inertia and subsequent forward momentum of abdominal masses. There is no present literature on the physiology of the kangaroo airway. This study will characterise contractile properties of kangaroo airways including maximal force production to contractile agents (acetylcholine and histamine) and length adaptation.
Supervisors: Assoc/Prof Peter Noble, Dr Kimberley Wang, Prof Shane Maloney

Project 6: Using anatomical optical coherence tomography to measure airway wall structure

Asthma and chronic obstructive pulmonary disease are characterised by thickening of the airway wall. Understanding the importance of airway wall thickness to abnormal lung function will aid in the development of new therapies such as bronchial thermoplasty, which reduces the volume of smooth muscle lining the airway wall. However, few technologies provide a reliable measurement of airway wall thickness. Optical Coherence Tomography (OCT) is an imaging technology that constructs surface and subsurface images from the reflection of light waves. While OCT is increasingly being recognised as a promising technology for the study of airway disease, further development is required. The present project will test the utility of polarisation sensitive OCT using airway samples from animals and humans.

Supervisors: Assoc/Prof Peter Noble, Prof Sampson, Dr Karol Karnowski, Prof Alan James

Project 7: Respiratory pattern in airway disease

Over the last decade a surprising finding in respiratory research is that breathing protects against airway obstruction in healthy subjects but not in subjects with asthma or chronic obstructive pulmonary disease (COPD). In a healthy person taking a deep breath greatly reduces bronchoconstriction and relaxes airway smooth muscle. Few studies have examined the pattern of breathing and how this differs between healthy subjects and those with respiratory disease. This project aims to measure the frequency and pattern of spontaneous deep breaths (i.e. sighs) in healthy subjects and patients with respiratory disease such as asthma. This project will use respiratory monitors to measure normal breathing pattern in human volunteers.

Supervisors: Dr Peter McFawn, Assoc/Prof Peter Noble, Prof Alan James

Project 8: Force adaptation

Over the last decade, work with isolated airway smooth muscle (ASM) has shown that ASM has a plastic length-tension curve, that is, given time the muscle will adapt to make its current length the optimum operating length (i.e., length adaptation). Two recent reports in the literature suggest a similar phenomenon can happen to muscle force production: when ASM is left partially contracted over an extended period of time, the maximum force that the muscle can produce is increased. This project will attempt to prove the phenomenon of force adaptation and test whether continuous partial contraction can cause excessive airway narrowing that is observed in diseases such as asthma. This project will use bronchial segments from large animal species (sheep and pigs) and also involve translational experiments on human airway tissue.

Supervisors: Dr Peter McFawn, Assoc/Prof Peter Noble

Project 9: Novel airway explants

Cell culture is an extremely useful technique but limited for studying integrated organ function like a bronchus. The tissue explant technique is an adaptation of tissue culture to larger structures like an intact blood vessel or airway tube. Explanting allows prolonged incubation of an isolated tissue under highly controlled conditions that is not possible in vivo or in classical organ bath methods. Our question is how do changes in the mechanical and chemical environment of the lung produce airway wall structural changes? Can incubation of tissues with cytokines present in asthma make an airway “asthmatic” or does prolonged exposure to high intraluminal pressure change airway contractility? The project will develop a method to explant bronchi from large animal species (pigs and sheep) under conditions were the luminal pressure can be controlled.

Supervisors: Assoc/Prof Peter Noble, Dr Donna Savigni, Dr Peter McFawn
**Project 10: Variable breathing and airway function**

Our laboratory has previously shown that simulated breathing movements in isolated bronchial tubes prevents airway collapse. It is theorised that a loss of the beneficial effects of breathing is a precursor to airway obstruction in asthma. However, while our prior studies have modelled breathing as a fixed sinusoidal rhythm, breathing is irregular in nature comprising both small and large breaths at a variable rate. There is now increasing evidence to suggest that this natural irregularity of breathing promotes normal airway function but this has yet to be tested. The present project will for the first time determine how a variable breathing rhythm impacts airway function and how this may be disrupted in disease leading to poor airway function. Techniques will include a newly developed and custom-designed organ bath system that provides a comprehensive assessment of mechanical airway wall properties and simulation of different human breathing rhythms.

**Supervisors:** Dr Peter McFawn, Assoc/Prof Peter Noble

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Skeletal muscle comprises up to 40% of a human’s body mass and is crucial for every day actions such as breathing, moving and swallowing. When skeletal muscles do not function properly they can cause severe diseases, such as muscular dystrophy and congenital myopathy. An emerging skeletal muscle disease associated with ageing is sarcopenia, which is tightly linked to osteoporosis and falls in the elderly.

Having the ability to study animal models is often crucial for medical researchers to better understand biology, and to then devise and evaluate potential therapies for disease. Even if certain experiments can be performed in tissue culture, ultimately studies require an animal model to be the test-bed to allow appropriate and thorough evaluation.

We have previously successfully studied the skeletal muscle physiology of a range of mouse models. We currently have a range of mouse lines that have skeletal muscles that are either impaired or superior in function. For those that are impaired, where mice have an inability to exercise normally, the aim is to understand why this impairment exists, and whether the application of possible treatments is efficacious. In those mouse lines with skeletal muscles that are performing better than expected (e.g. mice show an exceptionally high capacity to exercise), we would like to unravel the underlying mechanisms responsible. Once uncovered, activation of these mechanisms could be used in the future to prevent or treat skeletal muscle diseases such as muscular dystrophy.

In addition to skeletal muscle physiology techniques, students would have the opportunity to include other techniques used to phenotype mice in their tailored Honours project.

These include genetics and molecular biology, tissue biopsy and histology, immunostaining, various types of microscopy, protein and RNA extraction, voluntary running wheel analysis, and magnetic resonance imaging.

Please contact us to discuss the possible projects on offer if you are inspired to try to better understand skeletal muscle diseases and to develop therapies for them. If you choose such a project, you would use a range of exciting techniques with well-established, respected and friendly medical researchers at the School of Anatomy, Physiology and Human Biology, and at the Harry Perkins Institute of Medical Research.

**Project is suitable for** Honours, Masters, PhD

**Supervisor:** Assoc/Prof Tony Bakker

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Can blocking skeletal muscle stretch-activated Ca\textsuperscript{2+} channels prevent ventilation-induced diaphragm skeletal muscle damage.

Preterm babies are often unable to breathe on their own due to the immaturity of the respiratory system, and require an extended period of mechanical ventilation. While essential for survival, this intervention is thought to lead to damage of the developing respiratory muscles, which can significantly extended the requirement for ventilation and also contribute to respiratory failure.

We have recently shown that diaphragm muscle from preterm lambs is more susceptible to stretch-induced muscle damage than diaphragm muscle from lambs born after the normal gestation period. Skeletal muscle fibres contain specialised stretch-activated Ca\textsuperscript{2+} channels, which are thought to play a role in muscle development and growth. However when they are inappropriately or over activated, muscle damage can result through intracellular Ca\textsuperscript{2+} overload and activation of Ca\textsuperscript{2+}-activated proteases and the release of reactive oxygen species.

Stretch-activated Ca\textsuperscript{2+} channels can be blocked by the antibiotic streptomycin, and this drug has been used to prevent stretch-induced muscle damage in animal models of Duchenne muscular dystrophy (Zhang et al., 2012). We hypothesise that stretch of the diaphragm during artificial ventilation activates stretch-activated Ca\textsuperscript{2+} channels leading to muscle damage and dysfunction.

Aims of the study:

Aim 1. To compare the effects of passive stretch and lengthening (eccentric) contractions on force output in diaphragm preparations from young (3 weeks old) and mature mice (8 weeks) using a muscle test system. These experiments will determine whether young mice are more susceptible to stretch induced diaphragm damage.

Aim 2. To investigate the ability of streptomycin to prevent stretch-induced muscle damage in diaphragm preparations from young and mature mice.

Aim 3. To determine whether mechanical ventilation results in diaphragm muscle damage using a mouse artificial ventilation model.

Aim 4. To examine whether any ventilation-induced diaphragm damage can be prevented in mice by pre-exposure to streptomycin.

The results of this study could provide new strategies to prevent ventilator-induced diaphragm dysfunction in premature babies.


Project is suitable for Honours, Masters, PhD

Supervisor: Assoc/Prof Tony Bakker

Essential qualifications

For Honours: An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Skeletal muscles serve numerous functions that are essential for life. Not only do they provide the power required for movement and locomotion, but they also have vital roles in respiration, thermoregulation and metabolism. Not surprisingly, the loss of muscle mass and/or muscle function can be life threatening. Skeletal muscles of pre-term and neonatal babies, elderly people and of people suffering from muscle diseases such as Duchenne muscular dystrophy (DMD) are highly vulnerable to injury and are inherently weaker than healthy muscle. Importantly, skeletal muscle has the unique characteristic that it can adapt to the mechanical loads that it develops. This mechanotransduction process underlies the hypertrophic response to exercise and repair of muscle tissue following injury.

The goal of our research group is to understand the mechanisms of muscle damage and contractile dysfunction associated with ageing and disease, the molecular basis of skeletal muscle adaptation, and evaluation of potential therapeutic treatments for muscular dystrophies. The specific research areas that we focus on are outlined below.

1. **Factors that affect the functional development of the diaphragm and contribute to breathing problems in vulnerable populations.**

   The diaphragm is the major component of the respiratory muscle pump and is rhythmically active throughout life, from the moment of birth until our final breath. So the functional capacity of the diaphragm is critically important for achieving its life-sustaining role in ventilation. Appropriate in utero development of the diaphragm is essential for the establishment of spontaneous breathing at birth; respiratory capacity can be a limiting factor for exhaustive exercise; and respiratory muscle weakness is associated with increased morbidity and mortality in critically ill patients. Using an ovine model of preterm birth, and rodent models of diaphragm immaturity, we have identified unique activation properties of the neonatal diaphragm, characterized the rapid adaptation of the diaphragm immediately after birth, and established the impact of common, clinically relevant in utero exposures on the functional development of the diaphragm. We have also characterised the vulnerability of the diaphragm to contractile dysfunction in several animal models of human diseases including Duchenne muscular dystrophy, dysferlinopathy, and mucopolysaccharidosis. We have ongoing projects focused on the physiological investigation of diaphragm muscle function during development and rodent models of human diseases.

2. **Effects of oxidation on skeletal muscle stiffness and mechanotransduction.**

   Muscle contraction and shortening involves the cyclic interaction between myosin heads (crossbridges) on the thick filaments with binding sites on the thin (actin) filaments, a process that is driven by ATP hydrolysis. However, the force production during eccentric (lengthening) contractions arises from the strain of crossbridges as well as the strain of non-contractile proteins such as titin. The increased force produced during eccentric contractions can be damaging, but also trigger a strong
adaptation process resulting in muscle growth. The precise mechanisms of this mechanotransduction process are not well established but must be related to the transmission of force within the sarcomeres. We have recently shown that muscle stiffness increases when exposed to oxidants such as hypochlorous acid (HOCl), and others have shown that the titin filament is sensitive to oxidation. This project aims to determine the effects of oxidation on the active and passive stiffness of skeletal muscle and if this alters the mechanotransduction process. This research is focused on unravelling the complex molecular mechanisms of tension development during muscle activation and will provide valuable insight into the mechanisms of exercise induced muscle damage and adaptation in response to eccentric exercise.

3. Utility of heart rate variability and electro-dermal activity as objective measures of workload in a simulated future submarine control room.

Workload can be described as the relationship between task demands placed on and operator and the available mental capacity of the operator to meet those demands. If task demand exceeds operator capacity, task performance can be compromised. However, accurate evaluation of workload is challenging and there is often divergence between subjective and objective measures of operator workload. Subjective workload assessments are easy to administrate and interpret, but they may represent a distraction to the operator and data can only be collected at specific time points. Physiological measurements such as heart rate variability (HRV) and electrodermal activity (EDA) have the potential to provide continuous objective measures of workload but also display high individual variability and are sensitive to emotional and physiological stresses independent of workload. HRV is subject to complex regulation by the sympathetic and parasympathetic divisions of the autonomic nervous system, whereas EDA primarily reflects activity in the sympathetic nervous system. The aim of this project is to evaluate the efficacy of HRV and EDA as objective measures of operator workload during laboratory based experiments comparing different simulated future submarine human-machine interface (HMI) consoles.

Suitable for: Honours, Masters, PhD

Supervisor: Assoc/Prof Gavin Pinniger

Essential qualifications:

For Honours: An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major, from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Dystrophic and normal skeletal muscles

Professor Miranda Grounds
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The research of the Grounds laboratory is dedicated to all aspect of skeletal muscle biology, mainly using in vivo pre-clinical studies, with a major recent focus on loss of muscle mass during ageing, and on basic research and development of therapies for muscular dystrophies: specifically, the severe childhood disease Duchenne Muscular Dystrophy (current collaboration with Peter Arthur at UWA) and the adult onset Dysferlinopathy also known as Limb Girdle Muscular Dystrophy type 2B (due to dysferlin-deficiency). One defined Honours project for 2022 is indicated below, but several others may emerge later in 2021 (depending on new data and potential funding). We are happy to discuss projects with students related to their specific interests.

Project: Understanding the mechanisms behind immune-mediated changes in dysferlinopathy

The limb-girdle muscular dystrophies 2B/Miyoshi myopathy are human genetic diseases resulting from defects in dysferlin. Dysferlin is a membrane associated protein present in many cell types including muscles, but also in key immune cells such as macrophages. Dysferlinopathies manifest post growth and increase in severity with age, yet the precise mechanisms leading to muscle damage with severe loss of function is unknown. This research builds upon our investigations into the molecular basis for the dystropathology in dysferlinopathies (Grounds et al, 2014. PMID: 24685690), with recent papers also describing novel alteration in lipids in muscles of dysferlin-deficient BLAJ mice (Haynes et al, 2019. PMID: 31203232). This ongoing research involves many collaborators and new studies into altered immune responses in these mice, with dedicated Honours students in 2019 and 2020 (Jackaman et al, unpublished data). This research is currently funded by the JAIN foundation: see www with much information related to this disease https://www.jain-foundation.org/

Dysferlinopathy is characterised by excessive inflammation of muscles, with infiltration of immune cells, especially macrophages and T cells, from the periphery. Yet, the mechanisms behind immune-mediated dysferlinopathy pathology and associated cellular changes are not well understood. Therefore, this project aims to thoroughly investigate immune cell changes in dysferlin-deficient BLA/J, compared with control normal wild-type C57BL/6J, mice. A systematic approach will be employed to characterise tissue-specific immune cell changes within muscle and how this affects other tissues (e.g. heart, kidney, liver). The project will use advanced peptide homing, imaging and flow cytometry techniques to investigate properties of immune-related cells, and the impact of a candidate therapeutic drug, and will be based with collaborators across Curtin Health Innovation Research Institute and Harry Perkins Institute for Medical Research. Findings will help to form the basis for well-informed decisions for selecting appropriate candidate drugs for therapy, along with newly identified readouts of drug efficacy on dysferlinopathic changes.

Project is suitable for: Honours, PhD

Supervisors: Miranda D Grounds and Erin Lloyd (UWA), with Dr Connie Jackaman (Curtin University) and Dr Juliana Hamzah (Harry Perkins)

Essential qualifications:

For Honours: An appropriate undergraduate degree with a biological science emphasis, and a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

For Masters or PhD: An appropriate Honours degree with a biological science emphasis or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
My research focus is in controlling cell fate by providing different microenvironments. The fate of cells was thought to be primarily dictated by biochemical signals including cytokines and growth factors for decades, however, more recent data suggested cells also responded to their neighbouring cells and extracellular matrices (ECMs). Previously, I have shown that stem cells from fat (adipose-derived stem cells – ASCs) were able to feel/sense and respond (mechanosense) to matrices mimicked stiffness of brain, skeletal muscle, and bone and committed to differentiate into those tissue lineages, respectively. Intracellularly, stem cells transduce these biophysical/mechanical signals into biochemical signals from cell membrane to nucleus and this process is called mechanotransduction. Our group aims to study how mechanical cues (especially stiffness) control stem cells (and other cells e.g. cancer cells) by focusing on 3 areas: 1) investigating intracellular mechanism how (stem) cells respond to ECM mechanical cues, 2) developing bio-inspired ECM (2D and 3D biomaterials) as platforms to control (stem) cell fate, 3) programming (stem) cells to be used in (stem) cell therapy, tissue engineering and regenerative medicine.

Project 1. Mechanosensing-driven cancer cell screening on high-throughput stiffness gradient hydrogel
The stiffness (one of the mechanical properties of tissue) is known to be involved with epithelial to mesenchymal transition (EMT) which is the initial step for metastasis which is responsible for most of the deaths related to breast cancer in Australia and worldwide. However, our understandings how cells in breast tissue interact with their healthy vs. cancerous microenvironment are very limited. In this project, MCF10A (healthy epithelial cells) will be tested on stiffness linear gradient hydrogel ranging from 1 to 10kPa (covering healthy and cancerous stiffness) to screen the interaction between cells and their mechanical environment at single cell level. MCF7 (cancerous but not metastatic) and MDA231 (metastatic cancer) cells will also be studied on gradient platforms to study the effect of environmental stiffness on cancer migration/invasion. Findings from this project may open a new opportunities to treat cancer patient as ‘mechanotherapy’ in near future.

Project 2. Role of YAP/TAZ in stem cell mechanotransduction, differentiation, and migration in 3D
With Prof. Kun-Liang Guan and Dr. Henry Park at UCSD
There are several pathways and key signaling molecules suggested in mechanotransduction. Most of suggested pathways involve focal adhesion with extracellular binding of integrin to ECM protein as a starting point and intracellular interaction of beta unit of integrin to actin-myosin through focal adhesion kinase (FAK), talin, and vinculin binding. Intracellular forces generated by different matrix stiffness will decide localization (cytoplasmic vs. nucleic) of YAP/TAZ (transcriptional coactivator in Hippo pathway), which will control transcriptional level as a final step. Bone marrow-derived stem cells exhibited cytoplasmic localization of YAP/TAZ on soft hydrogel (fat-like stiffness) but YAP/TAZ was localized in nuclei on stiffer hydrogel (bone-like stiffness). Differentiations into fat and bone lineages were also observed and YAP/TAZ overexpression or knockdown cells altered mechanical induction (no bone differentiation on bone-like stiffness when YAP/TAZ knock-downed).
Most studies with YAP/TAZ assumed it as a downstream of mechanosensing but more recent results (YAP/TAZ changes integrin expression profile in cancer research) suggest that YAP/TAZ may have feedback effect to ‘feeling’ or YAP/TAZ act as upstream of ‘feeling’ as well.

In this project, we aim to investigate the effect of YAP/TAZ on mechanosensing (once considered as upstream of YAP/TAZ) in the context of intracellular force generation (direct response from extracellular stiffness), migration, and differentiation.

Project 3. Mechanotransduction driven cardiac differentiation of stem cells in 3D
With Associate Professor Adam Engler at University of California, San Diego (UCSD)

The human heart, a mechanically dynamic tissue, pumps out ~5L of blood/ minute. At tissue level, its mechanical function has been widely studied, but little is known at cellular level how cardiac muscle cells mechanically coordinate their beating with neighboring cells or how mechanical extracellular stimuli dictate cardiac muscle cell behavior. One cardiac muscle cell *in vivo* may make three principal connections with its surroundings (i) cell-ECM adhesion via integrin-mediated focal adhesion, (ii) cell-cell adhesion via N-cadherin, and (iii) cell-cell gap junction with ion channels including the calcium channel. In disease models in particular, not only biochemical signaling changes but also the mechanical environment alters the cell’s behavior via these 3 main connections. For example after myocardial infarction (MI), excessive deposition of collagen causes greater ECM stiffness, which may alter focal adhesion complex / actinin (i.e. the Z-band – an important structure bearing contractile forces) and disrupt cytoskeletal structure resulting in loss of contraction and alteration of cell-cell interaction via N-cadherin. This project aims to address how these 3 main connections (N-cadherin, focal adhesion, and gap junction) control the cardiomyocyte’s function in disease. Three specific aims address 1) the effects of ECM stiffness on cardiomyocyte function; cell-ECM mechanotransduction, 2) mechanosensitivity of cardiomyocyte via N-cadherin; cell-cell mechanotransduction, and 3) ion handling capacity, especially calcium which is the main driving force for cardiomyocyte contraction, examining different cell-cell / cell-ECM situations.

Project is suitable for Honours, Masters, PhD

**Supervisor:** Dr Yu Suk Choi

**Essential qualifications**

*For Honours:* An appropriate undergraduate degree with a minimum weighted average of 65% in the level 3 subjects that comprise the relevant major from an approved institution. Applicants will be assessed on a case-by-case basis.

*For Masters or PhD:* An appropriate Honours degree or equivalent research experience from an approved institution. Applicants will be assessed on a case-by-case basis.
Sports Science and Exercise Health
Professor Paul Fournier
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Short term deleterious effects of breakfast skipping
- Effect of breakfast skipping combined with exercise on cognitive function and driving performance on a driving simulator. Co-supervisor: Troy Visser, Brendan Lay
- Effect of ingesting protein to oppose the oxidative stress and the other ill effects associated with breakfast skipping. Co-supervisors: Peter Arthur
- Effect of dietary state and time of day on the oxidative stress that is caused by carbohydrate ingestion Co-supervisor: Peter Arthur

Appetite control and nausea physiology
- Bicarbonate loading as a means to oppose the appetite suppression and nausea that occur after sprinting. Co-supervisor: Robert Merrells
- Carbohydrate intake as a means to oppose the appetite suppression and nausea that occur after sprinting. Co-supervisor: Robert Merrells

Exercise and type 1 diabetes
- Effect of under-water cycling in cold water on blood glucose in people with type 1 diabetes. Co-supervisor: Shane Maloney
- Effect of high temperature and body hydration level on blood glucose response to exercise in people with type 1 diabetes. Co-supervisor: Shane Maloney
- Localised skin cooling as a means to prevent exercise-mediated hypoglycaemia in type 1 diabetes. Co-supervisor: Shane Maloney
- Effect of high blood glucose level on cognitive function and driving performance in type 1 diabetes. Co-supervisors: Brendan Lay
- Effect of simulated high altitude on the hyperglycaemia associated with high intensity exercise in type 1 diabetes. Co-supervisor: Shane Maloney

Sport performance research
- Effect of carbohydrate intake post-sprinting as a means to speed up recovery of sprint performance capacity