*Are you considering and looking for information on……..*

# Honours Degree in Physiology?

*Then proceed to the following sections in this guide;*



*Unsure if Honours and research is for you? Have you considered undertaking the Semester 1 or 2 undergraduate research program in ……*

# PHY3990 – Physiology Research in Action?

*Then proceed to the following sections of this guide;*



*Are you ready to undertake Honours or PHY3990?*

# Review Projects and Supervisor…..

*In the following sections of this guide;*

# Considering an Honours Degree in Physiology?

The Department of Physiology offers Honours programs for Bachelor of Science, Bachelor of Biomedical Science, and Bachelor of Medical Science students. As a Department we take enormous pride in the quality of our Honours program and our Honours students.
The Honours year is a highly challenging and equally rewarding one where you will take the first steps towards a career in scientific research. There are a few important steps you need to take to apply for Honours and this book is designed to take you through them.

*Probably the first question you need answered is……..*

# What is an Honours Degree in Physiology?

The objectives of an Honours degree in Physiology are to:

- Develop high-level skills in the design, implementation and analysis of rigorous scientific research, and problem solving strategies applicable to scientific method.
- Enhance acquisition of transferable skills in scientific communication (written and oral), critical thinking, independent organisation, time and resource management, and collaborative team work.
- Enhance the competitiveness of our graduates in their future chosen career pursuits.

*OK, I like the sound of that, but……..*

# What do I actually do in Honours?

The Physiology BSc Honours course comprises two units:
**BMH4100 (36 points):** The major focus of this unit is the research project that you will carry out under the guidance of your supervisor(s). The assessment tasks are a literature review, the thesis that you submit at the end of the year, two seminars that you will present during the year, and a final defence (interview) with your examiners and the honours convenors.
**BMH4200 (12 points):** The emphasis of this unit is to provide you with skills essential for good scientific practice, including critical thinking, scientific writing and presentation skills and statistical analysis. The assessment tasks include written critiques of seminars delivered by our doctoral/masters students or researchers, journal club workshops, workshops on scientific writing, workshops and prescribed reading on statistical methods and experimental design, a statistics assignment, and two exams which test your ability to critically evaluate scientific work.

Bachelor of Biomedical Science (BMS) Honours students do BMS4100 (which is identical to BMH4100) and BMS4200. BMS4200 is similar to BMH4200 but is administered through the School of Biomedical Sciences. For further information go to:
http://www.med.monash.edu.au/biomed/honours/index.html

*Mmmmmmm, sounds good but……..*

# Can anyone do Honours?

No. As the name implies the Honours degree is a prestigious course for students who have proven their capabilities by doing well in third year.
For entry to BSc Honours in Physiology you need to have completed a Bachelor of Science or equivalent (e.g. Bachelor of Biomedical Science) with at least a distinction grade (70%) average in 24 points (or equivalent) of level-three studies taught within the School of Biomedical Sciences (course codes PHY, BCH, DEV, MIC, PHA or IMM). Some other third year units might be considered relevant, at the discretion of the honours convenors and the Faculty of Science. There is no pre-requisite in terms of level 3 PHY units, but the Physiology Honours Convenors will need to be satisfied that you have the grounding in physiology to undertake your chosen project. For further information go to:
http://www.sci.monash.edu.au/undergrad/honours/

For entry to BMS Honours in Physiology you need to have completed the requirements for a Bachelor of Biomedical Science at Monash University, or a comparable qualification in biomedical science. You will need to have achieved an average of 70% or greater in at least 24 points at third-year level (including at least 12 points in biomedical science core units).
There is no pre-requisite in terms of level 3 PHY units, but the Physiology Honours Convenors will need to be satisfied that you have the grounding in physiology to undertake your chosen project. For further information go to:
http://www.monash.edu.au/study/coursefinder/course/3418/

*OK, I think I'm on target to achieve these scores and I'm still interested in doing Honours in Physiology……..*

# What do I do next?

You need to find a research project and supervisor to take you into their lab. At least one of your supervisors must be a member of staff or an adjunct member of staff of the Department of Physiology. That is, you must choose a project offered within this booklet. The Department of Physiology is a large research department covering all aspects of physiology from the level of the cell through to tissue and whole animal physiology, including human physiology and clinical research. Further we offer projects covering a large range of research fields. These research fields are listed on Pages 11 - 14 with a short explanation of the area. We suggest you read through these explanations first and pick the area(s) you are interested in. Then go to the section in the book that lists the projects on offer for that section.

Once you have found a few projects you like, contact the potential supervisors by email or phone and arrange a visit to find out more about the projects on offer, visit the lab and get an idea of the type of work you would be doing, and talk to other students and research staff from the lab that you would be working with. Remember this is an important year so make sure you are comfortable with all these aspects.

It is important to note that the ability of a supervisor to sign you on to a project will depend on that project still being available and the limited number of students a supervisor can take on. So start talking to potential supervisors now.

*Great, I've picked my project and supervisor……..*

# How do I apply to do Honours in Physiology?

1. **Formal Application to Faculty:**

**For BSc honours** you should apply online through the Faculty of Science:
https://www.monash.edu/science/current-students/science-honours

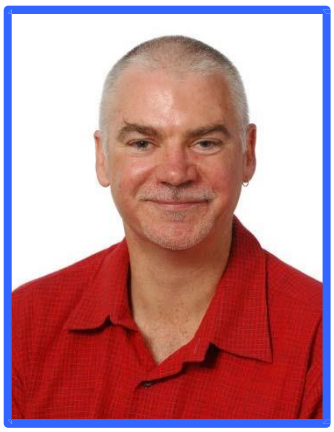
**For BMS honours** there is also an online application process:
http://www.med.monash.edu.au/biomed/honours/

It is mandatory that you should also complete the application process through the department regardless of whether you are applying for BSc or BMS honours (see below).

2. **Department Project Allocation:** This form will be available on the Moodle sites of all 3rd year Physiology units. This form must be completed and submitted, regardless of whether you are applying for BSc or BMS honours (or both). It should be filled in by both you and your potential supervisors and then signed by one of the Honours convenors. This form must be submitted to one of the honours convenors (Roger Evans, Siew Chai or Nicholas Price) by FRIDAY 16th NOVEMBER**.

*Sounds simple enough but……..*

# I have a few questions. Who should I ask?



## Professor Roger Evans

**Physiology Honours Chief Examiner & Co-convenor**

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26 Innovation Walk
Phone: 9905 1466
Email: Roger.Evans@monash.edu

## Associate Professor Siew Yeen Chai

**Physiology Honours Co-convenor**
**BMH4100 Convenor**

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Email: Siew.Chai@monash.edu

## Dr Nicholas Price

**Physiology Honours Co-convenor**
**BMH4200 Convenor**

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26 Innovation Walk
Phone: 9905 5131
Email: Nicholas.Price@monash.edu

# Are you an undergraduate student contemplating Honours but unsure if research is right for you? Undertake a unit of PHY3990 in semester 1 or 2 or over the summer before you commit to Honours in Physiology!

The Department of Physiology offers a Research in Action unit (PHY3990) commencing in both Semester 1 and 2 or over the summer which gives high achieving students an opportunity to work with an academic supervisor and complete a research project in Physiology in one semester. The Department of Physiology has an excellent array of research projects on offer, many of which can be adapted to PHY3990. We hope that you enjoy your initial research experience with us in PHY3990 and continue into Honours. Note, however, that you can still do Honours even if you have not done PHY3990 (i.e. it is not a pre-requisite for Honours).

*PHY3990 is a trial run to see if you enjoy research……*

## What is PHY3990?

For PHY3990, students will spend the equivalent of 12 hours per week undertaking research, in the laboratory conducting experiments, analysing results, reading existing literature as well as writing. All assessments for this unit are related to the research project and there are no exams! The objectives of PHY3990 are to:

- Develop an understanding of the technical and research skills required to undertake a research project.
- Develop basic skills in scientific communication, analytical thinking and time management.
- Provide a sample of the "Honours year experience".

For more information and links to unit guide please visit;

https://www.monash.edu.au/pubs/handbooks/units/PHY3990.html

*Wow! I would like to give a PHY3990 unit a go ……..but first……*

# Do you have the prerequisites for PHY3990?

You must have completed all first and second year level units in your approved major and have completed 12 points of study in the discipline area at 2nd year level as well as a distinction average over 24 points at second or third year level.

*You have the prerequisites? Great…… What next?*

# Find a project and supervisor…..

- Go through the projects in this handbook and choose a research project of interest.
- Next you need to make sure that the project is also offered to PHY3990 students and not just Honours. To do so, check under each specific project title and identify if the project is offered or can be adapted to PHY3990.
- If your project is offered as part of the PHY3990 unit then contact the appropriate supervisor(s) to discuss the project in more detail. This is a great opportunity to meet your supervisor, learn more about the project, and request additional reading material that you can read to help you decide if this project and laboratory is the best fit for you.

*You have identified a research project that you find exciting, it's available as a PHY3990 unit and both you and your supervisor are happy to proceed with your enrolment into the unit……next big question…..*

# How do you apply to PHY3990 Semester 1, 2 or Summer Unit?

*It is easy just follow the following check list and steps…..*

1. Make sure you meet prerequisites for enrolment into the unit.
2. Choose a project and supervisor.
3. Commit to undertake the unit with the consent of your supervisor.
4. Complete and submit **ALL** the following forms.

## *If you are Bachelor of Science Student- Form A and Form B;*

**Form A: Department of Physiology Application for PHY3990 Project S1,S2 or Summer**. Must be signed by Supervisor, PHY3990 Unit Convenor or Assistant Convenor and yourself and returned to Tomris Mustafa (26 Innovation Walk (Building 13F), Room 221) by **FRIDAY 16th NOVEMBER** for semester 1, 2019 (semester 2 and summer unit 2019 TBC).

**and**

**Form B: (BSc Students) - Permission to enrol in a science research project/special topics unit**. Must be signed by PHY3990 Unit Convenor and yourself and returned to the Science faculty office by FRIDAY 16th NOVEMBER**for semester 1, 2019 (semester 2 and summer unit 2019 TBC).

## *If you are a Bachelor of Biomedicine Student- Form A and Form C;*

**Form A: Department of Physiology Application for PHY3990 Project S1 or S2**. Must be signed by Supervisor, PHY3990 Unit Convenor or Assistant Convenor and yourself and returned to Tomris Mustafa (26 Innovation Walk (Building 13F), Room 221)) by **FRIDAY 16th NOVEMBER** for semester 1, 2019 (semester 2 and summer unit, 2019 TBC).

**and**

**Form C: (BBiomed Students) – Application form for Research in Action Units**. Must be signed by PHY3990 Unit Convenor and yourself and returned to SOBS by **FRIDAY 16th NOVEMBER** for semester 1, 2019 (semester 2 and summer unit, 2019 TBC).

*Sounds simple enough but....*I have a few questions.

# Who should I ask?

**Professor Marcello Rosa**
**Physiology 3990 Chief Examiner &**
**Unit Co-convenor.**
1st Floor Room C194 (Annex)
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**Dr Tomris Mustafa**
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**Dr Leo Lui**
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**Professor Helena Parkington**
**Physiology 3990 Summer Unit Co-ordinator**
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Email: helena.parkington@monash.edu

# Important information for Honours and PHY3990: Obligatory orientation session

Please note that all Honours and PHY3990 students are expected to attend a compulsory orientation session during orientation week (18th – 22nd February for semester 1 and 15th – 19th July for semester 2, 2019), with the exact date, time and venue to be announced. This means that before you enrol in these subjects you need to consider travel plans and work commitments during orientation week.

Working in a research laboratory carries specific responsibilities, and it is imperative that you attend this session to be induced on aspects of Occupational Health and Safety, legal obligations related to work involving animals, library sessions and other training sessions as directed by your supervisor.

Normally, non-attendance to the orientation session will result in cancellation of enrolment. In specific cases, involving major illness or other justifiable reasons (note: being away on travel is not considered a justifiable reason) the coordinators will allow enrolment to continue provided that the student's supervisor agrees to take responsibility for this training. A form to this effect can be requested from the Student Administrative Officer.

# RESEARCH FIELDS

## CARDIOVASCULAR & RENAL PHYSIOLOGY P16

Cardiovascular disease is the leading cause of death and disability in developed nations such as Australia. In Australia alone, cardiovascular disease affects 3.5 million people, and is responsible for one death every 10 minutes. It is well recognised that high blood pressure and kidney disease are major risk factors for premature death, particularly from cardiovascular events such as heart attack and stroke or chronic heart failure. However, the mechanisms underlying the development and progression of these diseases are not clearly understood. Our group utilises techniques ranging from whole animal physiology and state-of-the-art imaging modalities through to tissue and molecular based techniques. We also collaborate with clinical researchers, epidemiologists and biomedical engineers. Our multi-facetted research approach allows for detailed investigation of complex research questions. Our global aim is to determine the mechanisms underlying the development and progression of high blood pressure, kidney disease and heart failure and thus provide novel therapeutic targets and diagnostic tools to treat and prevent cardiovascular disease. We offer projects based within the Department of Physiology as well as projects with our collaborators based at Monash Health or the Baker Heart and Diabetes Institute.

## SYSTEMS NEUROSCIENCE P24

The main focus of this research theme is to understand the processes and neural pathways involved in the brain's control of important physiological functions including learning and memory, pain processing, nutrient sensing and social interactions. Another focus of this research theme is to investigate changes in neural connectivity in response to brain injury (ischemic stroke, traumatic brain injury). Projects will utilize a range of *in vitro* (electrophysiological recordings, histological staining), and *in vivo* (whole animal behaviour) techniques and will involve the use of transgenic animal models of neurodegenerative diseases as well brain injury.

## OBESITY & METABOLIC PHYSIOLOGY P29

This group has a primary focus on central neural and peripheral mechanisms involved in the regulation of metabolism. As shown by the diversity of ongoing research projects, our scientific interests span across disciplines including the neurosciences, endocrinology, metabolism, pharmacology, electrophysiology and immunology. We are trying to understand:

- how peripheral signals of energy state are integrated in specific brain centres
- how these signals from the body lose the ability to regulate body weight when the individual is obese or very lean

- how the body escapes the brain's normal homeostatic regulation of body weight and gives way to obesity
- how changes in metabolic state (i.e. obese vs. very lean) affect neural function and influence the process of degeneration

Projects will utilise telemetric and calorimetric devices in conscious experimental animals to measure multiple aspects of metabolism, immunocytochemistry, in situ hybridisation, intracerebral injection of specific antagonists, real time PCR, imaging including PET and MRI, mouse mutagenesis models, mouse knock out models, and regulation of genes in cell culture to study cell signalling.

## CANCER ENDOCRINOLOGY P39

The primary focus of this research theme is to study the biology of the tumour cells and the tumour microenvironment and its influences on tumour growth. The projects will utilize immune-deficient animal models, ex vivo culture and human explants and cell culture techniques.

## REPRODUCTIVE PHYSIOLOGY P41

The reproductive system is essential for production of offspring and human life. Whilst the male reproductive system is required to produce sperm and deliver them to the female for fertilization, the female reproductive system has the more complex role of developing a fertilised ovum into a new human being. Both male and females possess internal and external genitalia which develop in utero and during puberty under the control of endocrine hormones. The overall goal of this group of researchers is to understand the normal physiological function of each reproductive system, and how aberrations to these normal processes lead to infertility and/or diseases including cancer.

## SENSORY & COGNITIVE NEUROSCIENCE P44

The laboratories in the Sensory and Cognitive Neuroscience Group study the structure and function of sensory systems in the brain. The laboratories have specific strengths in studying the auditory, somatosensory and visual systems. Lines of investigation include understanding how individual neurons represent sensory stimuli in the environment, the functional connectivity that exists between brain regions and how neuronal activity contributes to perception and action. The Group is also involved in efforts to develop a cortical visual prosthesis - a bionic eye. With over 10 full-time staff investigating different aspects of brain function, the Department of Physiology at Monash University is the home of one of the strongest sensory systems neuroscience groups in Australia.

## MUSCLE, EXERCISE & PROPRIOCEPTION P51

Our research group is interested in two areas of human physiology: Proprioception and muscle injury. Proprioception has been described as our "sixth sense" and is arguably the least well understood of all our senses. How do we know quite accurately where our limbs are and what they're doing even when we can't see them? We use simple position matching tasks and techniques that disturb muscle receptors to help us understand how the brain integrates sensorimotor information. This research has implications for areas including falls-related injuries in the elderly and phantom limb pain. Muscle strain injuries remain one of the most common injury types in sports and exercise, and the effects on human performance and function can be irreversible. Our research uses mechanical measures of skeletal muscle to help us understand what factors make muscle vulnerable to damage and how we can optimise its capacity to adapt and recover from injury or disuse.

## SLEEP AND SLEEP DISORDERS PHYSIOLOGY P52

Sleep is a vital physiological process with important restorative functions that are essential for optimal day-time functioning. Insufficient or poor quality sleep has been associated with neurocognitive impairments, end-organ dysfunction and chronic health conditions, and increased mortality. Sleep-disordered breathing (SDB) is a broad term that encompasses a range of breathing disorders, from primary snoring through to obstructive sleep apnoea (OSA). One of the major focuses of our research is to better understand the pathogenesis of OSA, an increasingly prevalent disorder characterised by repetitive collapse of the airway during sleep and associated with serious health consequences. The goal of our work is directed at providing a set of clinical tools for phenotyping patients with OSA and identifying patient-specific treatments to revolutionize how OSA is currently managed: this advance beyond the current treatments for OSA (which are poorly tolerated) would offer patients a greater range of treatment options, and thereby improve treatment adherence as well as quality of life and health outcomes.

# OFF-CAMPUS SUPERVISORS

## BAKER IDI HEART & DIABETES INSTITUTE

Baker IDI is one of the few institutes in the world where the work of our staff spans from benchtop to bedside. The Institute has more than 360 scientists, scientific support staff, clinicians, health professionals and students who work across a range of laboratories undertaking research to tackle the deadly trio of diseases: cardiovascular disease, diabetes and obesity. This multi-faced approach ensures that the Institute brings everything to bear on these challenging health issues. Go to https://bakeridi.edu.au/ for further information.



## HUDSON INSTITUTE:



## THE BE ACTIVE SLEEP EAT FACILITY:

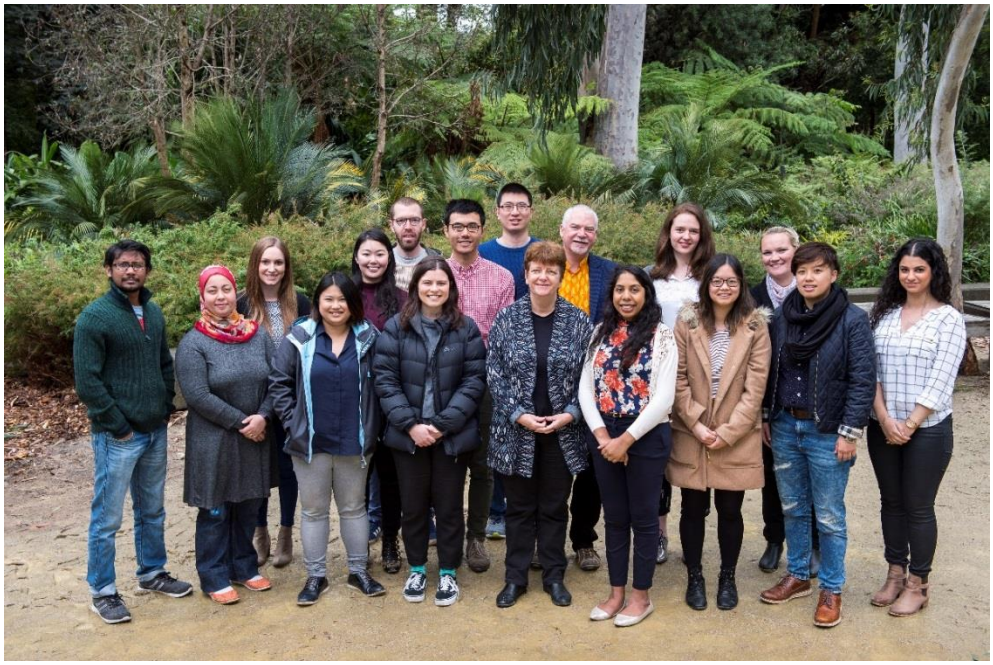
## DEPARTMENT OF NUTRITION, DIETETICS AND FOOD

# ON-CAMPUS SUPERVISORS

## I. DEPARTMENT OF PHYSIOLOGY CLAYTON:

# CARDIOVASCULAR & RENAL PHYSIOLOGY

**Our group consists of independently funded researchers working in a cooperative and supportive research environment**



*Kate Denton*

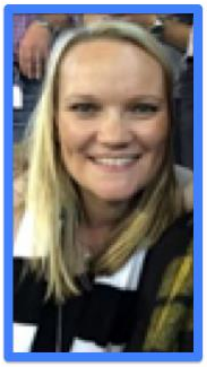
*Roger Evans*

*Lucinda Hilliard*

*Reetu Singh*

*Jennifer Ngo*

*Sarah Walton*



*Joanne Caldwell*

*Katrina Colafella*

## Regulation of kidney oxygenation when acute kidney injury progresses to chronic kidney disease

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: blood vessels, chronic kidney disease, integrative physiology, kidney physiology
Supervisors: Prof Roger Evans (Rm F274), Prof John Bertram (Department of Anatomy and Developmental Biology), Dr Jennifer Ngo (Department of Physiology)
Phone: 9905 1466 (RE), 9902 9100 (JB), 99024308 (JN)
Email: Roger.Evans@monash.edu, John.Bertram@monash.edu, Jennifer.Ngo@monash.edu

When someone develops acute kidney injury, clinical care is directed towards supporting them to allow their kidneys to repair. Sometimes this is not successful, so patients require permanent renal replacement therapy (dialysis and/or a kidney transplant). But often patients apparently fully recover and are discharged from hospital. We used to think that there were no further consequences of their episode of acute kidney injury. But we now know it greatly increases their chances of developing chronic kidney disease. One of the factors that may be driving the development of 'chronic on acute kidney disease' is loss of capillaries in the kidney. We have two projects investigating this problem. In one, we will use multiphoton microscopy to characterize, in three dimensions, the changes in the renal vasculature that occur in rats during progression from acute kidney injury to chronic kidney disease. In the other project we will study the functional implications of these changes in renal vascular structure for regulation of kidney oxygenation. The data generated in these projects will also be used by colleagues at Murdoch University and the University of Western Australia to develop sophisticated mathematical models of the renal circulation.

## Kidney oxygenation during cardiopulmonary bypass

For: Honours only
Key words: acute kidney injury, oxygen, integrative physiology
Supervisors: Prof Roger Evans (Rm F274), Dr Yugeesh Lankadeva (Florey Institute of Neuroscience and Mental Health)
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Email: Roger.Evans@monash.edu, yugeesh.lankadeva@florey.edu.au

Acute kidney injury occurs in approximately 25% of patients who undergo cardiac surgery requiring cardiopulmonary bypass. During cardiopulmonary bypass, the roles of the heart and lungs are taken over by a machine. This renders the kidney susceptible to hypoxia, which in turn appears to be one of the factors that leads to development of acute kidney injury. To find ways to improve kidney oxygenation during cardiac surgery, we are using an

experimental model in sheep to examine the effects of changing the perfusion conditions maintained by the heart-lung machine. This project would be partly based in the Department of Physiology and partly based at the Florey Institute of Neuroscience and Mental Health, on the Parkville Campus of the University of Melbourne.

**Urinary oxygen tension: a new biomarker of risk of acute kidney injury?**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: acute kidney injury, clinical, oxygen, integrative physiology, kidney physiology
Supervisors: Prof Roger Evans (Rm F274), Prof Amanda Thrift (Monash Medical Centre)
Phone: 9905 1466 (RE), 8572 2656 (AT)
Email: Roger.Evans@monash.edu, Amanda.Thrift@monash.edu

Acute kidney injury can occur in multiple hospital settings, including after major surgery (particularly when cardiopulmonary bypass is required), when patients develop sepsis, or when patients are administered drugs or contrast agents that are toxic to the kidney. Currently available diagnostic procedures can tell us that a patient has developed renal dysfunction as a result of acute kidney injury (increased serum creatinine concentration) or that their kidney is injured (e.g. increased urinary concentration of neutrophil gelatinase associated lipocalin). But there are no available methods to assess risk of injury, at a time when it is not too late to intervene to prevent development of acute kidney injury. We have been conducting studies in experimental animals and in patients undergoing cardiac surgery, to assess the potential of continuous measurement of urinary oxygen tension ($PO_2$), using a fibre-optic probe, to provide an 'early warning' of hypoxia in the renal medulla, and thus risk of acute kidney injury. We have generated a large body of data, so can now explore the relationships between urinary $PO_2$ and other physiological variables such as urine flow and systemic oxygenation. Eventually, these analyses will form the basis for development of mathematical models to predict renal medullary $PO_2$ from measurements of urinary $PO_2$.

## Shared Team Approach between Nurses and Doctors for Improved Risk factor Management (STAND FIRM)

For: Honours only
Key words: cardiovascular disease, clinical trial, stroke, feasibility, risk factors
Supervisors: Prof Amanda Thrift (Monash Medical Centre), Prof Roger Evans (Rm F274)
Location: Monash Medical Centre, Clayton Rd, Clayton
Phone: 8572 2656 (AT), 9905 1466 (RE)
Email: Amanda.Thrift@monash.edu, Roger.Evans@monash.edu

This large-scale clinical trial is aimed at improving management of risk factors in survivors of stroke. Time is one of the greatest barriers faced by general practitioners (GPs) in assessing and providing ongoing monitoring of their patients' risk factors. In this research we overcome this barrier by preparing and providing individualised management plans to the patients' GPs. Chronic disease management plans, such as these, attract a Medicare benefit that provides an incentive for GPs to participate in the study, and further provides a mechanism for implementation/translation of our findings. There are many potential projects available within this clinical trial. These include data linkage to other datasets to determine how adherence to medications is associated with outcome, as well as patient satisfaction with the program.

## Identifying factors associated with hypertension, and barriers to the control of hypertension in the setting of poverty, overcrowding and infection

For: Honours only
Key words: hypertension, barriers to control, poverty
Supervisors: Prof Amanda Thrift (Monash Medical Centre), Prof Roger Evans (Rm F274)
Location: Monash Medical Centre, Clayton Rd, Clayton
Phone: 8572 2656 (AT), 9905 1466 (RE)
Email: Amanda.Thrift@monash.edu, Roger.Evans@monash.edu

We know a lot about risk factors for hypertension in people who live in high income countries and in urban and relatively wealthy regions of low to middle income countries. However, the specific risk factors for hypertension in disadvantaged regions, and the barriers to control of risk factors, are largely unknown because most previous studies have been conducted in regions where obesity and physical inactivity are prevalent. Our preliminary work shows that people in rural disadvantaged regions are developing hypertension despite being thin and physically active. There is also evidence that those with hypertension are not adequately treated and their blood pressure is not controlled. We are therefore investigating what barriers there are to the control of hypertension in a community that is subject to extreme

poverty. There are many aspects to this study that are suitable for both Honours and PhD projects.

### Protecting the kidney from loss of function

For: Honours only
Key words: kidney disease, fibrosis, insulin-related aminopeptidase, mice
Supervisors: Prof Kate Denton (Rm F266), Dr Sarah Walton (Rm F254), Dr Lucinda Hilliard (Rm F259)
Phone: 9905 9553 (KD), 9905 5130 (SW), 9905 3191 (LH)
Email: Kate.Denton@monash.edu, sarah.walton@monash.edu, Lucinda.Hilliard@monash.edu

Chronic kidney disease (CKD) is a major health problem, leading to end-stage kidney disease (ESKD) or early mortality due to cardiovascular sequelae. Both CKD and ESKD involve renal inflammation and fibrosis. Current treatment options for CKD are far from effective and new approaches are required. Angiotensin IV (AngIV), an inhibitor of the enzyme insulin-regulated amino-peptidase (IRAP) which we have in the brain, vasculature, and heart, has been shown to have anti-inflammatory and anti-fibrotic actions, but the effects of IRAP inhibition have not been examined in the kidney. This project will determine if targeting the AngIV-IRAP axis, a pathway in the greater renin-angiotensin system (RAS), has reno-protective actions that prevent the age-related loss of renal function and progression of CKD. Our exciting data suggest that IRAP inhibition can slow the age-related decline in GFR by reducing collagen accumulation and may therefore be able to achieve one of the holy grails in the treatment of CKD, the preservation of renal function. The aim of this project is to examine the potential of IRAP inhibitors to prevent CKD in animal models of disease.

### Can pharmacological interventions early in life prevent onset of hypertension in an ovine model of solitary functioning kidney?

For: Honours only
Key words: kidney function, sheep, fetal surgery, nephron number, renin-angiotensin system, nitric oxide
Supervisors: Dr Reetu Singh (Rm F259), Prof Kate Denton (Rm F266)
Phone: 9905 9553 (KD), 9905 2285 (RS)
Email: Kate.Denton@monash.edu, Reetu.Singh@monash.edu

In children born with a solitary functioning kidney the onset of hypertension and renal disease is from early in life. Our group has established a model of solitary functioning kidney in sheep where one kidney is removed by performing nephrectomy in the ovine fetus. We have demonstrated that unilateral nephrectomy in the ovine fetus results in elevated blood pressure and renal dysfunction from 6 months of age. In the present study, we will investigate

whether pharmacological interventions early in life (from 4 weeks of age) can prevent the onset of hypertension in this model. The outcomes of this project will inform whether pharmacological interventions early in life are a feasible and effective therapy to manage hypertension and renal dysfunction in children born with a solitary functioning kidney.

### Novel therapeutic approaches to maintain cardiovascular health: role of the renin-angiotensin system

For: Honours only
Key words: ageing, arterial pressure, renin-angiotensin system, hypertension
Supervisors: Prof Kate Denton (Rm F266), Dr Katrina Colafella (Rm F259)
Phone: 9905 9553 (KD) 9905 3191 (LH)
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Before menopause, women have lower blood pressure compared to men of similar age. However, after menopause a woman's risk of developing hypertension increases greatly, and more women than men have hypertension after age 65. We have gained strong evidence that this sex difference in the development of hypertension is associated with differences in one of the key hormonal systems that controls blood pressure, the renin-angiotensin system (RAS). Our studies demonstrate that the depressor arm of the RAS, which elicits blood pressure-lowering effects, is enhanced in females by estrogen. Furthermore, we now have evidence that suggests the depressor pathways are no longer protective in females with advancing age, due to a decline in estrogen production.
Ongoing studies examine: 1. Whether it is possible to restore or enhance the depressor RAS pathways in aged males and females using drugs that target this system; and 2. Whether the pregnancy hormone relaxin contributes to these protective pathways. Results from these studies may lead to the identification of new strategies that reduce the risk of developing hypertension and associated disease.

### Targeting Angiotensinogen for the treatment of Hypertension

For: Honours only
Key words: arterial pressure, renin-angiotensin system, hypertension
Supervisors: Dr Katrina Colafella (Rm F259) & Prof Kate Denton (Rm F266)
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Hypertension is one of the most important risk factors for the development of cardiovascular disease and chronic kidney disease. We recently investigated small interfering (si)RNA targeting angiotensinogen (AGT) as a novel antihypertensive approach. In spontaneously hypertensive rats (SHRs), we found that AGT siRNA causes a similar antihypertensive effect as valsartan, but with a lower dosing frequency. Therapeutic effects are now reported to last

up until six months. The long duration of effectiveness of AGT siRNA is obviously lauded, considering its great potential for resolving problems with therapy adherence in a non-invasive manner, especially in patients with apparent treatment-resistant hypertension. Yet, it is also regarded with caution. AGT siRNA may limit the ability to respond to physiological challenges, as upregulation of angiotensin II plays an important role in correcting both acute hemodynamic changes, such as hemorrhage, and more slowly developing hypovolemia, such as dehydration. Prevention of hypovolemic shock would then be dependent solely upon compensatory upregulation of the sympathetic nervous system, which might be insufficient. Therefore, before we can start human trials, we need to assess hemodynamic responses, in rats treated with AGT siRNA, to acute hypovolemic challenges (i.e. hemorrhage) or chronic hypotension (i.e. low salt diet). In addition, considering that an antidote to acutely break AGT siRNA down is not yet available, we need to evaluate whether acute infusion of angiotensin II, noradrenaline or dopamine can restore normotension, and whether this can be maintained with chronic, non-intravenous treatment.

### Angiogenesis inhibition-induced hypertension and renal injury: prevention by aspirin?

For: Honours only
Key words: arterial pressure, angiogenesis, hypertension, chronic kidney disease
Supervisors: Dr Katrina Colafella (Rm F259) & Prof Kate Denton (Rm F266)
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Angiogenesis, the formation of new blood vessels from the existing vasculature, is essential for tumor growth and metastasis. In the last decade, angiogenesis inhibitors directed at the vascular endothelial growth factor (VEGF) pathway have become a first line treatment for several malignancies, including some previously untreatable cancers. However, VEGF inhibitors (VEGFi) can induce severe cardiovascular, most frequently hypertension, and renal (proteinuria, glomerular endotheliosis) toxicities. As such, patients treated with VEGFi may have improved cancer outcomes, but at the cost of an increased risk of cardiovascular disease. Furthermore, dose intensity and prolonged use of VEGFi may be limited by cardiovascular side effects, requiring dose reduction and/or early termination of treatment which compromises VEGFi efficacy and patient survival. Novel strategies to prevent these unwanted side effects during angiogenesis inhibition are urgently needed to improve quality of life and survival in cancer patients. In this project we will test the hypothesis that aspirin confers protection during VEGFi therapy with benefits for both the control of arterial pressure and renal function.

**Sex hormones influence heat stress tolerance times in women**

For: Honours and adaptable for PHY3990
Supervisors: Dr Joanne Caldwell and Dr Belinda Henry
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Exposure to extreme environmental temperatures poses an increased risk of heat illness in military populations. Serious heat illness may result in heat exhaustion, heat stroke and even death. Identification of high-risk individuals is one of the mitigation procedures utilized to reduce the incidence of heat illness. Woman appear to have a significantly greater risk of experiencing heat illness compared to men in a healthy, active population. Female sex hormones alter body temperature across the menstrual cycle, where the luteal phase is characterized by an increased basal body temperature (~0.5$^{o}$C) due to higher progesterone levels in plasma, whereas the follicular phase is characterized by higher levels of estrogen. The resultant thermoregulatory changes observed during the luteal phase are increased core temperature, elevated threshold for shivering and sweating as well as cutaneous vasodilatation. In addition, sex steroids regulate non-shivering thermogenesis. Adaptive thermogenesis is a specialized process that occurs in brown adipose tissue (BAT), whereby energy is dissipated through heat production. The purpose of this project is to explore the thermogenic relationship between female sex hormones and heat stress tolerance in women who are either taking oral contraceptives or not taking oral contraceptives.

# SYSTEMS NEUROSCIENCE

## Development of inhibition in the hippocampus – the GABA switch

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: traumatic brain injury, synaptic function LTP, electrophysiology, brain slices
Supervisors: Dr Harry Coleman (Rm F131), Prof Helena Parkington (Rm F133)
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*Harry Coleman & Helena Parkington*

In adults, GABA is the major inhibitory neurotransmitter in the brain. However, during development GABA is excitatory. The timing of GABA excitation-to-inhibition switch has been described only for rats, whose brain is very much less well developed at birth than the brain of humans. The importance of knowing the timing of the GABA excitation-to-inhibition switch emerges from our recent observations that administration of a hormone, normally present in the brain, can protect the brain from exposure to low oxygen in the fetus in late pregnancy. This hormone acts on GABA receptors. We have NHMRC funding to determine the timing of the GABA excitation-to-inhibition switch in guinea-pigs, in which the brain is more developed at birth. We will also explore the timing of the switch in marmosets.
Experiments will involve recording electrophysiological activity in neurons of guinea-pig and marmoset hippocampus. Molecular biological approaches will be used to determine the mechanisms implicated in the switch.

## Consequences of insult in the fetus on brain function in adulthood – can we save it?

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: synaptic plasticity, LTP, electrophysiology, perinatal hypoxia, synaptic potentials
Supervisors: Dr Harry Coleman (Rm F131), Prof Helena Parkington (Rm F133)
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In ~10% of pregnancies the placenta fails to perform optimally. This results in fetal growth restriction, early labour and consequent premature birth, the frequent occurrence of fitting in the neonate, and enhanced risk of cerebral palsy. Oxygen and nutrient deficit can result in direct death of neurons, dysfunction of astrocytes, and impair blood flow within the brain.
We are investigating whether giving the mum injections of the hormone melatonin can protect the brain in these infants. In this project we use an intrauterine growth restricted (IUGR) sheep which is a very good model of IUGR in human infants. MRI on IUGR neonatal lambs shows brain problems that are reduced by melatonin. In this project we will use brain slices to better understand what is going on. We use electrophysiology, determine reactive

oxygen species and mitochondrial function, and conduct behavioural tests to understand the cause of the fitting and how to optimize melatonin treatment to reduce or eliminate fitting and brain dysfunction.

### Consequences of maternal obesity in pregnancy on brain function in adulthood offspring

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: synaptic plasticity, LTP, electrophysiology, perinatal hypoxia, synaptic potentials
Supervisors: Dr Harry Coleman (Rm F131), Prof Helena Parkington (Rm F133)
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The population is becoming overweight and obese, including in pregnant women.
Hippocampal hyperactivity has been strongly implicated as underlying at least some of the age-related cognitive impairment. We tested the effects of obesity on aspects of hippocampal function and associated behaviours in adult rats that had been gestated in a high fat environment. A significant observation was that in all our obese males, slices of hippocampus had a dramatically greater tendency to produce oscillatory network (epileptiform) activity. Cognitive function was also altered in these rats. It is critically important to understand such obesity-related impairment and underlying mechanisms now, at a relatively early stage, so that preventive steps can be taken to ward off potentially very significant additional health, economic, and social costs. Importantly, treatments that target the hyperactivity can improve neural function, though this could be improved with a better understanding of underlying mechanisms.

### Toxins from marine venoms, – novel tools and potential therapies

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: ion channels, cell calcium, neurons
Supervisors: Prof Helena Parkington (Rm F133)
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Most venoms are designed to kill. Yet, judicious tweaking of venom toxins has provided a wealth of compounds important in the combat of disease. A critical approach in harnessing a killer for the good is a deep understanding of how the toxin acts. We have recently made significant strides, and have identified two important actions in neurons. In this project a student will learn how to isolate protein toxins from venom. We will then test the effects of these toxins on ion channels, transmitter release and calcium handling in neurons, using patch clamp electrophysiology and calcium imaging. To achieve this, the student will learn how to isolate cells from the hippocampus and culture then for a week before testing toxin. Neuron type will then be determined using immunohistochemistry.

## Glucose-sensing neurons in the brain: how do they do it?

*Prof David Spanswick*

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: hypothalamus, glucose, patch clamp electrophysiology, neuronal plasticity
Supervisors: Prof David Spanswick (Rm F206)
Phone: 9902 4307 (DS)
Email: David.Spanswick@monash.edu

Brain areas dedicated to controlling food intake and body weight include aspects of the hypothalamus and brainstem: key centres for sensing, integrating and formulating appropriate behavioural responses to changes in energy status. One nutrient that is controlled and maintained within narrow limits is glucose. Glucose levels are maintained by a network of interacting peripheral and central glucose-sensing systems. Consequently understanding the fundamental mechanisms by which function-specific glucose-sensing neurons and networks detect, respond and formulate appropriate output and if and how they are subject to dysfunction in obesity and diabetes is critical to developing future intervention strategies. This project aims to characterise the subtypes of POMC/CART and NPY/AgRP glucose sensing neurones in the arcuate nucleus of the hypothalamus and ionic mechanisms underlying glucose-induced changes in electrical excitability of these neurones using whole-cell patch clamp electrophysiological recording techniques in isolated brain slices.

## Motivation and reward: glucose, ghrelin and the mechanisms regulating the dopaminergic neural circuits of the ventral tegmental area

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: arcuate nucleus, ATP-sensitive potassium channels, patch clamp electrophysiology, pacemaker neurones, glucose, orexin
Supervisors: Prof David Spanswick (Rm F206)
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The motivation and drive to eat is driven by both homeostatic and hedonic, reward-based neural circuits in the brain. The ventral tegmental area (VTA) dopaminergic neurons are key components of the hedonic pathways driving food-related reward-based behaviour. However, the central neural mechanisms by which these dopaminergic neural circuits, deect and respond to nutrients and neurohormonal inputs and co-ordinate their output to other brain areas remains largely unknown. Recent work in our lab identified novel mechanisms by which both dopaminergic VTA neurons and interneurons synchronise and co-ordinate their activity and this activity is regulated by both glucose levels and the hunger hormone ghrelin. The aim of this project is to characterise the mechanism by which these cells co-ordinate and

synchronise release of dopamine from the VTA, the mechanisms underlying glucose-sensing by these neurones and how ghrelin activates these circuits.

Siew Yeen Chai

**Does diet-induced obesity exacerbate Alzheimer's disease?**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: *obesity, dietary fats, Alzheimer's disease*
Supervisor: Assoc Prof Siew Yeen Chai (Rm F247)
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A high body mass index (a clinical measure of adiposity) at mid-life is an acknowledged risk factor for Alzheimer's dementia (AD). Potential mechanisms linking adiposity to AD include peripheral hyperinsulinemia altering brain insulin levels, the generation of advanced glycosylation end products which causes end organ damage and cerebrovascular dysfunction and disease. The aim of this project is to investigate if dietary fats alter the development of AD pathology and the associated cognitive and memory deficits in mouse models of AD. Additionally, we also aim to investigate if the AD phenotype alters peripheral glucose clearance and the development of insulin-resistance in response to a high fat diet. Our hypothesis is that a high fat diet exacerbates AD pathology (amyloid plaques and cerebral amyloid angiopathy) and memory dysfunction resulting in a less favourable outcome than mice on a normal diet.

**Role of IRAP in the pathogenesis of Alzheimer's Disease**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: *neuroinflammation, Alzheimer's disease*
Supervisor: Assoc Prof Siew Yeen Chai (Rm F247)
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Alzheimer's disease (AD) is a progressive brain disease which is results in memory loss and cell death. All currently prescribed drugs treat the memory loss but are unable to stop the deterioration of brain cells. We have developed a class of drugs that reverse memory loss. These drugs target the enzyme, insulin-regulated aminopeptidase, IRAP. We recently found that these drugs also reduce the disease pathology. The aim of this project is to investigate the role of IRAP in the pathogenesis of AD. Our hypothesis is that IRAP participates in the inflammatory process associated with AD progression by regulating the release of pro-inflammatory cytokine from activated astrocytes and microglia that infiltrate the damaged regions of the brain, causing the polarization of microglia to the M2 phenotype to facilitate AD engulfment and clearance.

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## IRAP contributes to the neuroinflammatory response in ischemic damage

For: Honours only
Key words: *neuroinflammation, ischemic damage*
Supervisors: Assoc Prof Siew Yeen Chai (Rm F247),
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Stroke is Australia's second greatest cause of death after coronary heart disease and is a leading cause of disability. We have four independent observations that provide clear evidence for the involvement of IRAP in ischemic damage (1) markedly reduced damage in the brains of the IRAP knockout mice following middle cerebral artery occlusion, (2) the detection of IRAP immunostaining in activated astrocytes and microglia after damage, (3) IRAP inhibitor treatment attenuated volume of ischemic damage and (4) IRAP inhibitor treatment reduced expression of pro-inflammatory cytokines. This project will elucidate a role for IRAP in the brain following focal or global ischemia and develop the concept of IRAP inhibitors as a potential treatment.

# OBESITY & METABOLIC PHYSIOLOGY

**Adjustable Gastric Band (AGB) surgery, an animal model – does tightening your belt help to enhance weight loss?**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: obesity, surgery, hunger, food intake, metabolism
Supervisors: Prof Brian Oldfield (Rm F216), Dr Aneta Stefanidis (Rm FG12)
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*Brian Oldfield*


*Aneta Stefanidis*

Despite the success of Adjustable Gastric Band surgery we have no good idea of how signals generated by the action of the band on the stomach act in the brain to reduce hunger. This series of projects capitalises on our development of a miniaturized band fitted to the rat stomach and a range of approaches to map the pathways to the brain that are recruited by adjustment of the band. Specifically, individual projects will examine i) the activation by the band of neural links between the stomach and the brain via the vagus nerve, ii) the expression of feeding related genes following tightening of the band and iii) adjunct therapies that may be employed to improve the effectiveness of the band. These experimental approaches will provide valuable information about the mechanisms underlying the effectiveness of this approach in human patients.

**The neurobiological basis of anorexia nervosa? Impact of an animal model and insights into brain reward pathways**

For: Honours only
Key words: eating disorders, anorexia nervosa, animal models of human disease
Supervisors: Prof Brian Oldfield (Rm F216), Dr Aneta Stefanidis (Rm FG12)
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While obesity and its related issues command most attention in considerations of body weight, anorexia nervosa is situated at the other end of the spectrum and represents a very significant problem amongst affected individuals. There is no effective treatment and there is only a sketchy understanding of the neurobiological etiology of the disorder. It is likely that there is some interference with reward pathways and as such a better understanding of these mechanisms may have the dual advantage of casting light on the neurobiological basis of the disorder and insight into the role of reward pathways in eating behaviour. This series of projects is based on an activity based rodent model of anorexia which mimics a number of the key characteristics of the disease. Projects will involve genetic and pharmacological

manipulation of mesolimbic reward pathways in an attempt to reduce weight loss associated with the model of AN.

### Brown fat the Great White Hope

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: brown adipose tissue, metabolism, weight loss, energy expenditure
Supervisors: Prof Brian Oldfield (Rm F216), Dr Aneta Stefanidis (Rm FG12)
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Brown Adipose Tissue (BAT) for many years was thought to be important in small mammals to help regulate temperature and body weight by burning energy and producing heat. The unequivocal identification of functional BAT in adult humans and its important contribution to obesity was established once and for all in 2009. The challenge now is to understand how its function is regulated so that it can be harnessed as an anti-obesity therapy. This exciting series of projects looks at the role of the brain in the control of BAT and involves a number of molecular and pharmacological approaches. In particular, we will investigate how specific macronutrients operating in the periphery and in the brain will influence BAT function.

### Smart foods may be the key to weight loss

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: nutrients, brown adipose tissue, metabolism, weight loss, energy expenditure
Supervisors: Prof Brian Oldfield (Rm F216), Dr Aneta Stefanidis (Rm FG12)
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We have known for quite a while that certain macronutrients, protein, fats, carbohydrates have different effects on appetite. This is the basis of diets such as Atkins and others that produce short term weight loss mainly through an initial impact on glycogen stores. We have an interesting collaboration with Professor Steve Simpson the head of the Charles Perkins Centre in Sydney and world expert in the role of protein in mediating food intake. In this experiment that will be undertaken in rats we will introduce specific macronutrients directly into the gut then measure how they effect changes ion energy expenditure. The hope is that we will find single nutrients, or even more likely, combinations of nutrients that will maximize energy expenditure in brown adipose tissue. This development of a “smart diet” that will sustain weight loss by a persistent impact on energy expenditure has clear implications for the treatment of overweight and obesity.

## Pituitary control of blood glucose levels

Prof Michael Cowley

For: Honours only
Key words: obesity, fat distribution, melanocortins, insulin resistance
Supervisors: Prof Michael Cowley (Rm F280)
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Diabetes is a failure to properly regulate blood glucose levels, and it causes a wide variety of deleterious effects, specifically increasing risks for vascular disease and neuropathies, as well as tissue infection. Blood glucose levels are controlled on several levels, but it has recently emerged that the pituitary can regulate blood glucose levels, by endocrine actions on muscle. The major aim of our study is to determine the mechanisms of action of □ - MSH effects on muscle. This project will combine whole animal physiology, surgical techniques, invitro studies in cell culture, and ex vivo studies with animal tissues, as well as animal experimentation with thermogenesis studies and hepatic glucose production and insulin sensitivity. This project will provide the successful applicant with experience in animal handling, collection of blood and tissues samples from mice with subsequent analysis by radioimmunoassay, immunohistochemistry analysis of proteins, microarray to assess gene expression as well as several physiological and analytical techniques.

## How does estrogen act to protect the heart?

For: Honours only
Key words: obesity, metabolic syndrome, estrogen, menopause, cardiovascular disease
Supervisors: Dr Stephanie Simonds, Prof Michael Cowley (Rm F280)
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It is established that estrogen is cardioprotective, and this is likely the reason why pre-menopause women have lower rates of heart disease than men, but similar rates after menopause. Estrogen acts on vascular walls to decrease tone, and causes reduced peripheral vascular resistance, but additional mechanisms may be in place as well. We have recently identified a hypertensive effect of leptin in mice and in humans; leptin acts on the brain to increase activity of the sympathetic nervous system, and increase blood pressure. We also have preliminary evidence that estrogen acts on the brain to decrease blood pressure. This project will determine the mechanism of the effect of estrogen in the brain to decrease blood pressure. The project will provide experience with animal handling, animal surgery, cardiovascular telemetry, immunohistochemical staining of mouse brains, experience with cre-lox gene deletion technology, gene expression arrays and hormone assays.

## How do neurons regulate blood glucose levels?

For: Honours only
Key words: obesity, metabolic syndrome, glucose
Supervisors: Dr Stephanie Simonds, Prof Michael Cowley (Rm F280)
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Diabetes affects 6-9% of the Australian population, and its incidence is increasing. Although there are some reasonable therapies for diabetes, there remains a clear need for better therapies. Using advanced neuroscience techniques we can rapidly active and inhibit neurons in the hypothalamus. In doing this we have discovered that these neurons can rapidly change blood glucose levels. This project will investigate how these neurons can so rapidly control blood glucose, and if the effect might be used as a therapeutic for the treatment of diabetes. This project will involve a combination of surgery, virology, FdG PET, microCT, blood glucose measurements, and in vivo pharmacology using lean and obese mice.

## How does pregnancy increase blood pressure?

For: Honours only
Key words: obesity, metabolic syndrome, estrogen, pregnancy, cardiovascular disease
Supervisors: Dr Stephanie Simonds, Prof Michael Cowley (Rm F280)
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It is known that estrogen is protective against cardiovascular disease. However in pregnancy there are cases where blood pressure rises dangerously (pre-eclampsia). Estrogen acts on vascular walls to decrease tone, and causes reduced peripheral vascular resistance. We have recently identified a hypertensive effect of leptin in mice and in humans; leptin acts on the brain to increase activity of the sympathetic nervous system, and increase blood pressure. We also have preliminary evidence that estrogen acts on the brain to decrease blood pressure. Leptin levels increase during pregnancy, but there is no data on whether the effect of pregnancy on blood pressure is due to leptin. This study will examine the role of leptin and estrogen and determine the mechanism of the increase in blood pressure during pregnancy. The study will involve in vivo pharmacology, surgery, implanted radio telemetry, and immunoassays.

**Combination therapy for the treatment of obesity. The impact on the cardiovascular system.**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: obesity, drug therapy, cardiovascular diseases, diabetes
Supervisors: Dr Stephanie Simonds, Prof Michael Cowley (HOD
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Combination therapies are used in many disease states and will be used in obesity to ensure the greatest weight loss. Before combination therapies can be used for weight loss, the actions of combination therapies have to be assessed on key systems, including the cardiovascular system and system that regulate glucose homeostasis.
In this project, students will have the opportunity to be involved in research investigating obesity drugs on the market and the impact of combination therapies on the cardiovascular system.
This project will provide the successful applicant with experience in animal handling, collection of blood and tissues samples from mice with subsequent analysis by radioimmunoassay, immunohistochemistry analysis of proteins, microarray to assess gene expression as well as several physiological and analytical techniques.

**Alteration of hypothalamic leptin and insulin signalling in obesity**

For: Honours and/or PHY3990
Key words: Hypothalamus, signaling pathways, immunohistochemistry, stereotaxic surgery, metabolic hormones
Supervisors: Prof Michael Cowley (HOD), Dr Eglantine Balland (room F221)
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Leptin is a hormone produced by adipocytes in proportion to fat mass. Leptin acts on the hypothalamus to control energy metabolism in order to maintain an appropriate body weight. Insulin is another peripheral hormone, produced by the pancreas, which plays a critical role in the regulation of metabolism since insulin controls glycaemia through its action on peripheral tissues and on the brain. In obesity, the hypothalamus fails to respond adequately to both hormones leading to the development of type 2 diabetes.
In this project, we will use stereotaxic injection of tracers in the hypothalamus of mice combined with immunohistochemical study of leptin and insulin signalling to better understand these neuronal networks and gain knowledge on the molecular mechanisms of hypothalamic leptin and insulin resistance in obesity.

## Non-Human Primate Model of Diet-Induced Obesity; Characterization and Biomarker Discovery

For: Honours Only
Key words: Non-human primate, Obesity, Insulin-Resistance, Metabolism
Supervisors: Dr Tomris Mustafa and Professor Michael Cowley
Phone: 9905 2526 or 9902 4019

The prevalence of obesity and associated disorders such as diabetes, cardiovascular and liver disease are on the rise calling for the development and use of more relevant translational animal models to help improve our understanding and treatment of these conditions. To do so, we are in the process of developing a non-human primate model of diet-induced obesity with unique preclinical translational features. Just like humans, these non-human primates develop spontaneous and diet-induced obesity with similar metabolic progression consisting of changes in body fat composition and development of insulin-resistance and impaired glucose tolerance prior to overt type-II diabetes.
This project is an ongoing progressional study that closely monitors body composition and glucose homeostasis changes on a regular basis to assess and monitor the status of the model. During this time a number of specimens are collected such as blood, tissue biopsies, urine and stool. The first part of this project will involve utilizing these biosamples to validate the model and confirm the molecular, biochemical and morphological changes that occur in response to obesity and insulin-resistance compared to healthily control count parts utilizing a range of molecular, biochemical (immunoassay) and histological techniques. Once the model has been fully validated and show to present all the expected hallmarks of obesity-induced insulin resistance and related comorbidities a more detailed analysis of the samples will be undertaken for discovery of novel biomarkers that will better our understanding of the mechanisms underlying this metabolic syndrome that could lead to the development of better diagnostic tools and pharmacological agents for therapeutic intervention.

## Characterization of diet induced chronic gastrointestinal inflammation in non-human primates as an inflammatory bowel disease model for human

For: 3990 and/or Honours
Key words: Inflammatory bowel disease, biomarkers, animal model, immunohistochemistry
Supervisors: Prof. Mark Sleeman
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Inflammatory bowel disease (IBD) is a chronic inflammation in the gastrointestinal tract caused by dysregulated immune responses. Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common types of IBD in human, but the exact cause is still unknown. Understanding the regulatory mechanisms of the intestinal immune system is the key to uncovering the cause, validating novel diagnostic markers and identifying new therapeutic targets for IBD. In our laboratory, we have developed a proprietary diet, that induces inflammation in the gastrointestinal tract of non-human primates (NHP), modelling the

effects of IBD observed in humans. The effects can also be reversed through dietary intervention.
In this project, we will characterize diet-induced chronic gastrointestinal inflammation in NHP as an animal model of IBD model. By targeting the involvement of a number of known and novel biomarkers in the pathogenesis of IBD, we will firstly compare the expression of these markers in gastrointestinal tissue using immunohistochemistry (IHC), secondarily assess markers from IBD human UC or CD biopsies samples and thirdly between normal and IBD patients using a combined approaches of IHC, western blotting and real-time PCR. These experiments will help characterize a new animal model of IBD, providing a validated platform for discovering diagnostic/prognostic biomarkers and investigating the effect of novel therapeutic targets.

## How does the brain sense a change in body weight?

*Zane Andrews*

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: Ghrelin, motivation, starvation, appetite, ghrelin receptors, neuroscience
Supervisors: A/Prof Zane Andrews (Rm 215), Dr Romana Stark
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Ghrelin is a peripheral signal that tells the brain that the body has declining levels of energy (stored fat). In the brain, ghrelin targets ghrelin receptors on different populations of neurons and causes a number of physiological adaptations designed to conserve energy such as increasing food intake, glucose from the liver and a sense of smell and decreasing energy expenditure. It also regulates stress, addictive behaviour and memory, all of which help the organism to prevent starvation by navigating a complex environment, in the face of stress to find the most calorically dense food. The brain pathways regulating these functions are unknown. We hypothesize that different populations of ghrelin receptor neurons control different aspects of behaviour and energy balance and in this project we aim to identifying different ghrelin-receptor pathways regulating different behaviours. We will use sophisticated neuroanatomical viral tracing and to identify ghrelin receptor brain circuits. We will also use novel designer drugs exclusively activated by designer drugs (DREADDs) to remotely control different populations of ghrelin receptor neurons and measure food intake, body weight, stress, memory. These studies are very novel and will help us understand how the brain is “weird” to prevent starvation and thus maintain energy balance. These studies are most relevant to obesity, diabetes and mood disorders.

## How do brain regions communicate with each other to control food intake and body weight

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: Insula cortex, lateral hypothalamus, risk behaviour, reward behaviour, appetite
Supervisors: A/Prof Zane Andrews (Rm 215)
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Human brain imaging consistently show different patterns of activity in the brains of lean people and people with obesity. A number of these regions are in the cerebral cortex, an area of the brain not traditionally associated with the homeostatic control of food intake and body weight. In this project, we aim to isolate pathways in the brain that connect the cortex with the hypothalamus and remotely control these pathways to test their effects on food reward behaviour, food risk/reward behaviour, food intake and body weight. We will use sophisticated neuroanatomical viral tracing combined with novel designer drugs exclusively activated by designer drugs (DREADDs) to remotely control different pathways from the cortex to the hypothalamus and examine animal behaviour (food reward behaviour, food risk/reward behaviour, food intake and body weight). These studies will help us understand how the brain integrates multiple stimuli to influence food intake and body weight. It may help us understand why under certain conditions the brain no longer responds to homeostatic signals, a common feature of anorexia nervosa and obesity.

## Stress, weight loss and predisposition to obesity

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: cortisol, thermogenesis, stress responsiveness and obesity
Supervisors: Dr Belinda Henry (Rm F222)
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*Belinda Henry*

This project will use cortisol responsiveness as a marker for propensity to become obese. We have established a simple test, an ACTH challenge, which identifies individuals with either high (HR) or low (LR) cortisol responses. Those characterised as HR are more prone to becoming obese when fed a high energy diet. This project will detail the physiological mechanisms that underpin innate differences in energy balance in HR and LR. This project combines various in vivo and in vitro. We will measure temperature in brown adipose tissue and skeletal muscle in HR and LR animals after dietary manipulation ie after energy supplementation or food restriction. It will involve analyses of gene expression using real-time PCR, as well as radioimmunoassay and Western Blotting. There will also be an opportunity to undertake clinical work during this project.

## Ageing, Gender, sex steroids and energy expenditure

For: Honours only
Key words: estrogen, testosterone, thermogenesis, obesity
Supervisors: Dr Belinda Henry (Rm F222)
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Adipose tissue exhibits sexual dimorphism, whereby females are more likely to accumulate fat subcutaneously and males are more likely to accumulate fat within the viscera. As women age this distribution shifts so that adipose tissue is accumulate viscerally. This fat distribution is controlled by the sex steroids. This project will investigate the effects of sex steroids on energy expenditure. To measure energy expenditure we will use infrared thermography to measure supraclavicular temperature as an index of thermogenesis (the dissipation of energy through heat production). This project will investigate changes in BAT activity across the menstrual cycle in women across the menopausal transition. The work will involve radioimmunoassays to measure various hormones in human serum and relate this these changes to altered thermogenic output.

## Does IRAP regulate glucose and fat metabolism?

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: obesity, fat metabolism
Supervisors: Assoc Prof Siew Yeen Chai (Rm F247)
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Insulin-regulated aminopeptidase, IRAP, is highly expressed in fat and skeletal muscle where is it found to accompany the insulin-responsive glucose transporter, GLUT4. In the brain, this enzyme is found in brain regions involved in controlling appetite and food intake. In characterising the phenotype of the IRAP knockout mice, we observed that these mice, when placed on a Western high fat diet, were not susceptible to weight gain, in contrast to their wildtype controls. We postulate that IRAP plays a role in the absorption and deposition of fat and in the absence of IRAP (either with gene deletion or inhibition of its activity); the mice have impaired fat absorption and/or enhanced fat clearance. This project will investigate if the IRAP KO mice or mice treated with IRAP inhibitors are protected against the health complications associated with diet-induced obesity.

## The rise in caesarean deliveries: obesity is the culprit

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: uterus, obesity, labour
Supervisors: Prof Helena Parkington (Rm F133), Dr Harry Coleman (Rm F131)
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The number of caesarean deliveries has doubled in the past ten years, and the increase almost exclusively involves obese women. Obese women go into labour less easily, and require induction. During the process, the labour in obese women has an increased tendency to stall, contractions die away despite infusion of inducing hormone. This necessitates emergency caesarean delivery in labour and puts subsequent pregnancies at risk of excessive bleeding, misplaced placenta etc. We have recently discovered the presence of a potassium channel, normally occurring in the heart, in human uterus. Activity of this channel is very much enhanced in the uterus of obese pregnant women. The channel suppresses electrical activity and contraction and explains the poor labour in obese women. We are now determining how this ion channel is regulated in obesity and in the transition into labour and are testing drugs that may inhibit it in the uterus, but not strongly in heart.

# CANCER ENDOCRINOLOGY

## Bipolar androgen therapy in prostate cancer


Renea Taylor

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: prostate cancer, androgen signalling, human tissue
Supervisors: Dr Renea Taylor
Prof Gail Risbridger
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Email: Renea.Taylor@monash.edu

Hormones control and promote tumour growth in men with prostate cancer; when tumours become aggressive, hormones are removed using targeted therapies. This treatment known as androgen deprivation therapy (castration therapy), has unpleasant side effects for men such as loss of libido and metabolic syndrome. Newer evidence suggests that androgens can have a biphasic effect on tumour growth and bipolar androgen therapy [where the men are given episodic deprivation and supplementation of androgens], controls tumour growth but prevents the m from experiencing the deleterious effects of ADT. In this project, we will mimic bipolar androgen therapy using new tumour lines that are castration sensitive. The findings will provide important results using novel patient derived tumours to show proof of concept and some mechanistic insight to how this therapy might work.
This project will utilise techniques common in cancer research, including working with human tumours, cell culture, immunohistochemistry and pathology.

## Understanding fatty acid metabolism in prostate cancer

For: Honours
Key words: prostate cancer, metabolism, androgens
Supervisors: Dr Renea Taylor
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Altered metabolism is a hallmark of cancer pathogenesis and is required to support the malignant properties of cancer cells. Previous studies have focused extensively on the roles of glucose, glutamate and fatty acids derived from *de novo* lipogenesis in modulating the bioenergetic processes and macromolecule synthesis required to sustain growth and proliferation. Fatty acids are also derived from adipose tissue lipolysis or the breakdown of triglycerides contained in circulating chylomicrons and lipoproteins. Recent work from our laboratories shows that fatty acid uptake is increased in malignant human prostate tissue and that the influx of fatty acids leads to increased lipid storage. This process is regulated by molecular reprogramming of genes and proteins encoding lipid metabolism in human

prostate cancer. Specifically, the expression of *CD36*, which encodes the major fatty acid transporter, is associated with reduced survival in prostate cancer patients. In this project, we will explore the link between CD36 and androgen receptor signaling. Androgens are the major hormones regulating prostate cancer progression, and their link to fatty acid metabolism are currently unexplored. A variety of techniques will be used including animal models of prostate cancer, immunohistochemistry, PCR and Western blot and lipid metabolism assays. The identification a link between fatty acid metabolism and androgen signalling has the potential to lead to significant new therapeutic interventions in patients with prostate cancer.

# REPRODUCTIVE PHYSIOLOGY

## Therapeutic potential of TGF-β proteins for the diagnosis and treatment of female infertility

Craig Harrison

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: folliculogenesis, GDF9, BMP15, cumulin
Supervisors: Dr Craig Harrison and Dr Kelly Walton
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The oocyte-secreted factors, bone morphogenetic protein 15 (BMP15) and growth differentiation factor 9 (GDF9), are essential for the acquisition of oocyte developmental competence during folliculogenesis. As such, these growth factors may provide both the means to predict and promote oocyte quality. We have pioneered the BMP15 and GDF9 field for over a decade and are poised to exploit their utility as biomarkers of oocyte quality. Furthermore, we recently established that individual subunits of BMP15 and GDF9 form a heterodimer with dramatically (>1000-fold) enhanced activity towards granulosa/cumulus cells. We are one of only two labs in the world to have produced this new molecule, which we have called cumulin. Although the physiology of cumulin requires further study, we have already demonstrated its remarkable therapeutic potential to increase porcine and human oocyte and embryo yield in vitro maturation (IVM). We hypothesize that the development of GDF9, BMP15 and cumulin as diagnostic markers and therapeutics will significantly improve the efficiency of IVF and IVM, thereby transforming the management of female infertility.

## Physiological Consequences of the Loss of Inhibin Activity

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: ovary, inhibin, activin, bone
Supervisors: Dr Craig Harrison and Dr Kelly Walton
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Gonadal-derived inhibin A and inhibin B are essential factors in mammalian reproduction, negatively regulating pituitary production of follicle stimulating hormone (FSH). Remarkably, declines in inhibin levels across the menopause transition do not only correlate with an increase in FSH, but also a rapid decrease in bone and muscle mass. Based on these clinical findings, and our recent demonstration that transgenic inhibin A increases bone mass and strength, we hypothesise:
That inhibin A and B have important physiological roles outside the reproductive axis, primarily the stimulation of bone and muscle growth.

That inhibin mimetics could be utilised as novel therapeutics to treat postmenopausal complications, including osteoporosis and sarcopenia.

## Mysterious places of uterine regulation

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: uterus, ion channels, cell calcium, labour
Supervisors: Prof Helena Parkington (Rm F133), Dr Penny Sheehan (Royal Women's Hospital)
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Despite much study, our knowledge of how contractions of the pregnant, uterus are regulated is still not well understood. In recent studies in our lab, we have found that an important relationship exists between the plasma membrane (PM), the endoplasmic reticulum (ER) that contains an important store of calcium, and mitochondria, the powerhouses of cell energy. In this study we will use state-of-the-art techniques, imaging, patch-clamp electrophysiology and siRNA techniques to determine the molecules in the PM, ER and mitochondria that are responsible for calcium handling, permitting its availability and removal. The relationship between these three compartments in uterine smooth muscle remains a mystery, with most of our understanding coming from vascular smooth muscle.
We will determine the contribution of this system to the development of strong contractions during labour and whether dysfunction is associated with labours that occur too early or too late.

## Preeclampsia: a major disease of human pregnancy

For: Honours and adaptable for PHY3990 (discuss with supervisors)
Key words: Human and rat pregnancy, artery contraction & relaxation, placental oxidative stress determination, circulating cytokines
Supervisors: Prof Helena Parkington (Rm F133), Dr Padma Murthi (RWH)
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Preeclampsia (PE) is a disease of human pregnancy. It occurs in approximately 10% of pregnancies and is responsible for significant morbidity and mortality in both the mother and offspring. The incidence of PE is increased in women with high BMI or older primigravidae, both of which are increasing in the pregnant population. Diabetes is also a risk factor for PE. Pregnant women destined to develop PE have elevated levels of leptin throughout pregnancy. Leptin has been associated with atherosclerosis, vascular fibrosis, oxidative stress and hence hypertension, coronary artery disease and stroke. Leptin is a cytokine and binds to its receptor in the region of its cytokine homologue region (CHR), the extremity of the extracellular terminal of the receptor. This CHR region can be free in the circulation, hence called the soluble leptin receptor (sLepR), and is the main circulating binding protein for leptin. While sLepR in the circulation is reduced in obesity and diabetes-related pathologies, we have

recently found that sLepR is elevated in the circulation and placenta of women with PE. We have also identified neutrophil adhesion in these women.

# SENSORY & COGNITIVE NEUROSCIENCE

**How does transcranial stimulation of prefrontal cortex influence cognitive abilities?**

For: Honours only
Key words: prefrontal cortex, Non-invasive brain stimulation, cognitive abilities
Supervisors: Dr. Farshad Mansouri (13F, Room 112)
Phone: 9902 0114 (FM)
Email: Farshad.Mansouri@monash.edu

*Farshad Mansouri*

Recently, the technique of transcranial Direct Current Stimulation (tDCS) of dorsolateral prefrontal cortex (DLPFC) has gained much attention for potential management of neurological and neuropsychiatric disorders such as depression and schizophrenia, pain, substance craving in addicts, obesity and stroke. Recent studies have shown that the modulatory effects of tDCS on cognitive abilities is not limited to basic sensory-motor processes and can influence higher brain functions such as working memory. Compared to other brain stimulation techniques tDCS appears to be the safest and the most suitable for clinical applications. However, the neural substrate and mechanisms underlying the effects of tDCS on cognitive and affective processes remain unknown. We would like to study the modulatory effects of tDCS of DLPFC on cognitive flexibility and executive control. These studies will be conducted in the context of clinically relevant cognitive tests. We will examine how contextual factors such as emotional state and environmental factors interact with tDCS to influence cognitive functions. In this project, the students will learn how to assess cognitive functions in the context of behavioural tests and will also become skilled at these brain stimulation techniques. My emphasis is that the students also learn about preparing hardware and software and become independent in establishing a psychophysical testing setup for various cognitive tests.

This project is part of a multidisciplinary approach to understand the function of prefrontal cortex in cognition.

## How do populations of neurons represent the world?

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: neuroscience, vision, perception, eye movements
Supervisors: Dr Nicholas Price (13C, Rm 196), Prof Marcello Rosa (13C, Rm 194)
Phone: 9905 5131 (NP), 9905 2522 (MR)
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*Nicholas Price*

Conscious visual perception depends upon the collective activity of thousands of neurons. Yet, traditionally, visual neuroscientists have been able to record the activity of just one or a few sensory neurons at a time. This project will use cutting-edge electrophysiology techniques to simultaneously record the activity of up to 100 neurons in visual cortex of an anaesthetised animal, as a range of dynamic visual stimuli are presented. This will allow us to characterise how small populations of neurons represent the environment. Specifically, we will examine how the activity of neurons in the middle temporal area encodes the speed and direction of moving stimuli, and how the responses of these neurons changes over time with prolonged stimulation. During this project, you will learn electrophysiological techniques, and apply sophisticated computational analyses to neuronal data sets. It is suited to students with strong computational or mathematical skills.

## Study of the connections of areas of the cerebral cortex

For: Honours only (other projects in our research area can be discussed)
Key words: neuroscience, anatomy, connections, cerebral cortex, plasticity
Supervisors: Prof Marcello Rosa (13C Rm 194), Dr David Reser
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*Marcello Rosa*

The aim is to create a “wiring diagram” of how different areas of the cerebral cortex are connected to each other, and to other parts of the brain. This type of information will allow the modelling of the information flow through the brain, and allow the development of better artificial systems capable of vision. We will also be studying the consequences of brain lesions early in life – how the neuronal circuits reorganise to make use of the parts of the brain that are unaffected. This has direct implications for future attempts to cure certain types of blindness. These experiments use fluorescent tracer substances which, when placed in a point of the brain, migrate along the axons to reveal the cells that send information there. You will be trained in surgical techniques, histological techniques, and microscopy, including image processing techniques. These projects also offer opportunities for students with interest in computer graphics, through the development of better tools for the visualisation of complex networks of data.

## Seeing the forest for the trees: how visual contrast is put together to represent a scene

For: Honours only (other projects in our research area can be discussed)
Key words: vision, behaviour, perception, computational model
Supervisors: Dr Elizabeth Zavitz (13C, Rm 101), Dr Nicholas Price (13C, Rm 196)
Phone: 9905 2503 (EZ)
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Although we perceive a holistic image of the visual world, each neuron in early visual cortex represents only a small part of the scene. In each stage of visual processing, activity from earlier stages is combined to represent both successively larger areas of visual space and more complex visual attributes. Exactly how this activity is combined has been studied for simple stimuli that are barely visible, but not for stimuli that better represent the goals and richness of everyday vision. This project will examine how the responses of neurons that represent different regions of visual space are combined. We aim to understand how human perception of large visual stimuli depends on the spatial distribution of contrast. During this project you will learn how to collect and analyse human behavioural data, design and test visual stimuli, and relate human performance to the predictions of neuronal models.

*Elizabeth Zavitz*

## We're different, we're the same (with apologies to Sesame Street)

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: vision, perception, individual differences
Supervisors: Dr Nicholas Price (Room C196) and Dr Adam Morris (Room C197)
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Philosophers have long argued about whether subjective experiences of the world differ between individuals. For example, is my experience of red the same as yours?
Neuroscientists know that individuals have different objective experiences of the world – some people are more accurate at discriminating faces or detecting patterns in noise. In this project, a large cohort of rats will be trained to discriminate between basic visual patterns. We expect that performance on this task will differ between animals, therefore, in the same animals we will also record neuronal activity in multiple areas of the brain in order to determine how behavioural differences can be attributed to different neural processing.
During this project you will learn how to design and implement experiments that precisely quantify animal behaviour. In addition, you will learn sophisticated computational and mathematical techniques for data analysis.

## Tuning-in to the sensory world

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: vision, behaviour, neurons, computational model
Supervisors: Dr Adam Morris (Room C197) and Dr Nicholas Price (Room C196)
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Email: Adam.Morris@monash.edu

Single neurons show remarkable selectivity for features of the visual world. For example, a neuron might respond strongly when an object moves from left-to-right but remain virtually silent for movement in the opposite direction. Nevertheless, this neuron would have virtually zero influence on our perception of visual motion; after all, it's just one voice in a crowd of zillions. Our perception arises not from single neurons but rather from coherent patterns of activity across a network of interconnected neurons (to further the crowd analogy, consider a "Mexican wave" at a sporting event). This project will examine how visual information is encoded in these patterns of neural activity and how they are altered in response to changing sensory environments and task demands. You will learn how to make precise measurements of visual perception using behavioural methods and to compare the data with the predictions of a computer-based, artificial network of sensory neurons.

*Adam Morris*

## How does the brain separate the signal from the noise?

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: vision, behaviour, computational model
Supervisors: Dr Adam Morris (Room C197) and Dr Shaun Cloherty (Room C196)
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Email: Adam.Morris@monash.edu, Shaun.Cloherty@monash.edu

Humans and other animals use sensory input to guide behaviour. A key aim of neuroscience is to understand neurons code features of the world, such as the positions and movements of objects in a visual scene. It turns out that our perception arises not from the activity of single neurons but rather from patterns of activity across many neurons. This is known as "population coding". We have built an artificial model of a neural network to study how signals are encoded, and how they are read out for perception, decision-making, and behaviour. In this project, you will test predictions of the model using behavioural measurements of perception and (if interested) use the data to extend the computational model. You will learn how to collect and quantify behavioural data and how to study the brain using computer-based simulations of neural networks.

*Shaun Cloherty*

## Neural Plasticity in the Visual Cortex

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: visual cortex, single cell recordings, functional recovery, cortical reorganisation
Supervisors: Dr Leo Lui (F123a) and Dr Maureen Hagan (C1.101)
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Humans have amazing abilities to recover function after damage to the brain. This recovery can best be demonstrated by improvements in sensory and motor function after the initial injury. While these are well documented, the neural mechanisms underlying such measurable behavioural improvements still very much remain unknown. This project will investigate mechanisms underlying neural plasticity after damage to the primary visual cortex (V1). Upon damage to V1, patients will lose conscious vision in some of the contralateral visual field; however, subconscious visual experiences still remain. Moreover conscious visual perception can be recovered upon training using simple visual tasks. Using animal models with comparable visual systems, we will investigate the physiological and anatomical changes that enable visual function to recover. Students in this project will be given extensive training in physiological (neural recordings), anatomical and computational skills (data analysis).


*Leo Lui*

## How are we able to perceive motion in real-life situations?

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: visual cortex, single cell recordings, complex motion
Supervisors: Dr Leo Lui (F123a)
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Simple visual motion, where a single stimuli will move in the same direction, as proven to be one of the most successful paradigms in uncovering the relationship between the activity of single neurons and perception. However, this type of motion rarely occurs in the world. Instead, we are bombarded by different types of motion all at once, most of which are created by our own movements. For example, when sitting in a moving car, we are able to determine which parts of the visual scene are in motion due to our own movements and other parts of which are due to object motion, even if these objects are travelling in completely different directions. This project will investigate how these computations are performed in the brain by recording neural activity on multiple single cells in “higher-order” the visual cortex. Students in this project will be given extensive training in physiological (neural recordings), anatomical and computational skills (data analysis).

## Functional Connections of the Cerebral Cortex

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: visual cortex, single cell recordings, anatomical connections, brain areas
Supervisors: Dr Leo Lui (F123a), Dr Sofia Bakola (F123b) and Dr Maureen Hagan (C1.101)
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Email: Leo.Lui@monash.edu

Neurons that fire together wire together, this has been a long standing principle of Neuroscience. While response properties of single neurons, particularly in the visual cortex, has been studied intensively; much less is known about how response properties of neurons relate to anatomical connections, which may ultimately provide evidence to their function role in perception and behaviour. In this project, we will investigate the responses properties of single neurons in the cortex. Furthermore, we will also investigate the anatomical connections of these neurons, either by placing an anatomical tracer in the area of the recorded neurons, or a downstream area where direct anatomical connections are expected. By combining these techniques, we hope to place these neurons into functional circuits, to determine their contribution to perception and action. Students in this project will be given extensive training in physiological (neural recordings), anatomical and computational skills (data analysis).

## Towards the bionic human

For: Honours
Key words: vision, motor decoding, Biomedical engineering, neural prostheses
Supervisors: Dr Yan Wong (13C, Rm 193)
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*Yan Wong*

Neural prostheses such as cortical vision prostheses offer hope to restore sight to the blind, while devices such as brain machine interfaces aim to read out brain activity to help quadriplegics control devices such as robotic arms. However, work towards making these devices clinically relevant has been difficult due to lack of efficacy in early trials. While the target patients may be diverse, common to all these prostheses is the use of electrodes that are implanted into the brain. These electrodes can used to deliver electrical stimulation to brain cells to elicit certain perceptions such as spots of light for blind subjects or to record from brain cells to read out a subject's intentions. This project will discover ways to improve prostheses that interface with the brain by using a brain signal called the local field potential. By monitoring this signal we will be able to measure the performance of the prostheses as we compare different parameters such as the location electrodes and time of stimulation.

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**How inhibitory neurons are represented in the neocortex?**

For: Honours (adaptable for PHY3990 as well)
Key words: Neuroscience, Cerebral cortex, Plasticity, and Inhibitory neurons
Supervisors: Dr Nafiseh Atapour (F1 Rm 30), Prof Marcello Rosa (13C Rm 194)
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The inhibitory neurons of the cerebral cortex are a diverse population of cells. Their diversity is manifested in their different morphological, electrophysiological and neurochemical features. While these GABAergic interneurons constitute only around 20-30% of all cortical neurons, their reciprocal connections with glutamatergic principal neurons provide cortical networks with a balanced excitation to inhibition, shaping cortical function. Disturbances in this balance, if not compensated, lead to major cortical malfunction and diseases.

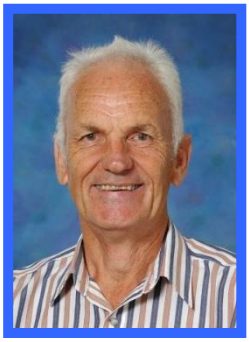
We aim to find out the distribution and density of interneurons, as classified based on their neurochemical features, in all areas of neocortex from anterior to posterior of the brain. Creating such distribution maps of cortical interneuron density offers basis for understanding of inhibitory neuronal circuits and their functional relevance.

During this project you will learn how to visualize cortical interneurons using immunohistochemistry and to perform stereological cell counting and related analyses.

# MUSCLE, EXERCISE & PROPRIOCEPTION

## The contribution of muscle spindles to proprioception

*Trevor Allen*



*Uwe Proske*

For: Honours only
Key words: proprioception, position sense, exercise, muscle spindle
Supervisors: Dr. Trevor Allen, Prof. Uwe Proske
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Our ability to determine where our limbs are in space, if we are not looking at them, depends on signals from sensors in our muscles, as well as signals generated within the brain. In this project we want to test for the contribution of muscle length sensors, the muscle spindles, to limb position sense during forearm matching tasks. Muscle spindle signals can be manipulated by contracting elbow muscles at different arm positions before each matching task. We will test whether matching accuracy and variability is altered by a variety of conditioning procedures for each arm. This research will help us to better understand how the brain processes sensory information to tell us about the position and movement of our bodies. This has wider implications including for reducing fall-related injuries in the elderly and for intractable clinical problems such as anorexia nervosa and phantom limb pain.

## Effect of stretch on passive and active tension in human skeletal muscle

For: Honours only
Key words: passive tension, warm-up, stretch, injury, muscle mechanics
Supervisors: Dr. Trevor Allen, Prof. Uwe Proske
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Warm-up stretches remain a common part of preparation for sports and exercise. However, the potential benefits for injury prevention and human performance remain disputed. This is because our understanding of the mechanisms involved are not fully understood. A large amplitude stretch of locomotor muscles causes an immediate fall in passive tension, but how long it lasts has not been investigated while controlling for muscle history effects (also known as 'thixotropy'). Does muscle stretching actually reduce the risk of muscle injury? Does it impair muscle performance? The aim of this study is to understand the mechanisms responsible for temporal changes in muscle passive and active tension after stretch in human subjects. Measurements will include passive torque, joint angle, electromyogram (EMG), and active torque. This research has implications for reducing exercise-induced injury and human performance.

# SLEEP AND SLEEP DISORDERS PHYSIOLOGY

**Understanding the causes Obstructive Sleep Apnoea and predicting responses to existing and novel therapies**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: sleep apnoea, sleep physiology, respiratory control, muscle physiology
Supervisors: Dr Brad Edwards, Dr Shane Landry, Dr Simon Joosten & Associate Professor Garun Hamilton
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*Brad Edwards*

Obstructive sleep apnoea (OSA) is a common disorder characterized by repetitive upper airway collapse during sleep. It has a number of adverse cardiovascular, neurocognitive, and daytime functioning consequences. Therefore, understanding the pathophysiology and developing effective treatments is a research priority. Unfortunately, the leading treatment for OSA, continuous positive airway pressure (CPAP), is poorly tolerated by many patients. Furthermore, treating all patients with CPAP employs an overly simplistic "one size fits all" approach that fails to take account of multiple "phenotypes" or traits now recognised to comprise OSA. Thus, newer treatment strategies, individualised to an OSA patient's requirements, are urgently needed. Importantly, this approach will require a strategic change to current diagnostic & treatment practices.

In order to revolutionise the way OSA is currently treated, several gaps in our knowledge must first be overcome: (1) a better understanding of how major risk factors (i.e. obesity & ethnicity) alter the pathophysiological traits or mechanisms known to cause OSA (2) the development of clinically validated practical methods to identify OSA phenotypes, and (3) personally-tailored treatment plans to best target the patient's particular underlying physiological abnormalities. As such, this research program includes a number of individual projects suitable for an Honours year that are focused around:

1. Understanding the mechanisms through which key OSA risk factors predispose an individual to OSA.
2. Developing techniques to non-invasively characterise the traits causing OSA using available clinical data.
3. Developing and test non-CPAP therapies targeted towards an individual's abnormal trait(s) with the aim of abolishing their OSA.

If any of these topics interest you, please feel free to come and discuss!

**Understanding the relationship between obesity and sleep problems**

For: Honours only
Key words: obesity, sleep apnoea, integrative physiology, sleep physiology
Supervisors: Dr Brad Edwards & Associate Professor Garun Hamilton
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Obesity is a major risk factor for developing obstructive sleep apnoea (OSA), and most individuals with OSA are either overweight or obese. However, many overweight/obese individuals do not have OSA for reasons that remain unclear. Interestingly recent evidence suggests that overweight/obese individuals without OSA exhibit markedly enhanced upper-airway muscle responsiveness compared with overweight/obese patients with OSA. However, we have no way of easily identifying those obese individuals that are likely to have OSA versus those that do not without invasive measurements. This project therefore aims to explore the differences in the clinical characteristics of obese individuals with and without OSA. The knowledge provided by the findings of this project may ultimately offer a refinement to the diagnosis and management of sleep disorders in the community.

**Novel diagnostic techniques to improve our classification of the hypoxaemic burden in sleep disorders**

For: Honours
Key words: obesity, sleep apnoea, integrative physiology, sleep physiology, hypoxia
Supervisors: Dr Brad Edwards, Dr Shane Landry, Dr Simon Joosten & Associate Professor Garun Hamilton
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Sleep disorders often expose the sufferer to intermittent hypoxia and hypercapnia which have important deleterious cardiovascular consequences. However, our current metrics for capturing the 'degree' of the hypoxaemic burden are relatively superficial (i.e. they simply count the number of times/hr your oxygen levels fall). Therefore, this project will employ a novel tool-kit to objectively analyse the overnight oxygen profile and determine how these novel metrics are correlated to self-reported sleepiness and cardiovascular disease.

# OFF-CAMPUS SUPERVISORS

## II. BAKER HEART & DIABETES INSTITUTE:

# NEUROPHARMACOLOGY LABORATORY



*Geoff Head* *Pamela Davern* *Kristy Jackson*

**Role of Ganaxolone in treating neurogenic hypertension in mice**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: Hypertension, brain, GABA receptors, allopregnanolone, stress, sympathetic nervous system
Supervisors: Prof Geoff Head (Baker), Dr Pamela Davern (Baker), Dr Kristy Jackson (Baker), Prof Roger Evans (Rm F274)
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We have shown that genetically hypertensive mice (BPH, Blood Pressure High) have hypertension due to an overactive sympathetic nervous system compared with control mice (BPN, Blood Pressure Normal). The mechanism is related to GABA receptor dysfunction and allopregnanolone (AlloP) is an endogenous neurosteroid and allosteric modulator of GABA receptors. We hypothesise that reductions in brain AlloP cause reduced inhibitory GABAergic activity in the amygdala and hypothalamus leading to elevated sympathetic nerve activity and neurogenic hypertension. Our aim is to investigate the effectiveness and mechanism of action of treatment with an AlloP analogue Ganaxolone, for the treatment of neurogenic hypertension. In this study Ganaxolone or vehicle will be administered via minipump for 2 weeks to male and female BPN and BPH mice. Mice will undergo a range of stress and anxiety tests (eg restraint, cage swap, and elevated maze) both before and after treatment and blood pressure and heart rate will be recorded via radiotelemetry probes. At the end of the experimental period brains will be examined by immunohistochemistry and real time quantitative PCR to assess the influence of GABA receptors.

## Central effects of chronic stress and mild activation of the renin angiotensin system on blood pressure

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: hypertension, chronic stress, renin angiotensin system, brain, sympathetic nervous system
Supervisors: Prof Geoff Head (Baker), Dr Pamela Davern (Baker), Dr Kristy Jackson (Baker), Prof Roger Evans (Rm F274)
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The effects of acute stress have been well documented in the literature but the mechanisms by which chronic stress or repeated daily exposure to acute stress contributes to sustained elevations in blood pressure is not well understood. The critical factor leading to a marked amplification of cardiovascular responses does not appear to arise from chronic stress per se but requires a combination with either (i) a follow up acute "novel" stress experience or (ii) low subpressor increases in circulating angiotensin II. Our laboratory has data that indicates elevated neuronal nitric oxide synthase and NADPH oxidase in neurons that are activated in response to novel stress. This observation is also associated with elevated blood pressure and identified in brain regions such as the amygdala and hypothalamus that are known to regulate sympathetic output to influence the kidney. In this study we will repeatedly expose mice administered a mild subcutaneous dose of angiotensin II via a minipump or vehicle to a stress on a daily basis over two weeks and record their blood pressure, heart rate and activity continuously via radiotelemetry devices. Following a final "novel" acute stress cardiovascular parameters, neuronal activation and associated neurochemical signatures will be immunohistochemically examined.

## Role of renal microRNA181a in hypertension in mice

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Key words: Hypertension, microRNA, sympathetic nervous system
Supervisors: Prof Geoff Head (Baker), Dr Pamela Davern (Baker), Dr Kristy Jackson (Baker), Prof Roger Evans (Rm F274)
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We have shown that genetically hypertensive mice (BPH, Blood Pressure High) have hypertension due to an overactive sympathetic nervous system and renin angiotensin system compared with control mice (BPN, Blood Pressure Normal). These hypertensive mice also have elevated renal renin mRNA which is associated with low levels of its negative regulator,

microRNA181a. Similarly, mice with global knockout of the mir181a gene (miR181a KO), also have elevated renal renin mRNA and elevated blood pressure compared with control C57Bl6 mice. We hypothesise that reduced levels of miR181a in the tubules of the kidneys results in elevated renin production causing activation of the intrarenal renin angiotensin system and hypertension. Our aim is to investigate the effective of reintroducing/increasing mir181a in the kidney of mir181a KO and BPH/2J mice respectively. In this study, all mice will undergo telemetry surgery to enable us to measure blood pressure in conscious and unrestrained mice. Mice will have baseline measurements before undergoing surgery to deliver a virus to overexpress miR181a in the kidney. The blood pressure response will be measured following this intervention and kidney function will be measured using metabolic cages to collect urine and determine glomerular filtration rate. At the end of the experimental period kidneys will be removed and *in situ* hybridisation will be used to confirm the overexpression and localisation of the miR181a and real time quantitative PCR will be used to quantify mir181a and renin mRNA levels.

# HEART FAILURE PHARMACOLOGY LABORATORY

*Rebecca Ritchie and Lab*

**Role of Inflammation in the Cardiac Complications of Diabetes**

For: Honours and PHY3990
Key words: diabetes, heart failure
Supervisors: Prof Rebecca Ritchie (Baker), Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
Phone: 8532 1392 (RR)
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Diabetes is Australia's fastest growing chronic disease. The disease affects almost 2 million Australians; diabetes increases heart failure risk 2.5-fold and accelerates its onset. Our laboratory has an established track record for identifying mechanisms of diabetes-induced cardiomyopathy. Building on this experience, we have obtained recent evidence that cardiac inflammation is a key contributor to myocardial damage in the diabetic heart. GENERAL HYPOTHESIS: Enhancing anti-inflammatory annexin – A1 in the heart limits diabetes-induced cardiomyopathy by reducing cardiac inflammation and protecting cardiac contractile function and cardiac muscle relaxation.

AIMS: To compare the time-course of cardiac inflammation and impaired cardiac function, in both type 1 and type 2 diabetes, and to investigate annexin – A1 cardioprotection for the cardiac complications of the disease in vivo.

METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac function and biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence.
SIGNIFICANCE: These interventions may ultimately limit progression to heart failure and death in diabetes-affected patients.

### Role of Altered Cardiac Glucose Metabolism in the Cardiac Complications of Diabetes

For: Honours and PHY3990
Key words: diabetes, heart failure
Supervisors: Prof Rebecca Ritchie (Baker), Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
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Diabetes affects almost 2 million Australians, increasing heart failure risk and accelerating its onset. Our laboratory has an established track record for identifying mechanisms of diabetes-induced cardiomyopathy, many of which target reactive oxygen species (ROS, also known as free radicals). Building on this experience, we have obtained recent evidence that maladaptive cardiac glucose metabolism, via hexosamine biosynthesis (an alternative fate of glucose), has now emerged as a contributing factor to the cardiac complications of diabetes.
GENERAL HYPOTHESIS: that the combined impairments in both systemic glucose handling and cardiac levels of ROS together provide an additional drive towards maladaptive cardiac glucose metabolism, negatively impacting cardiac function and mitochondrial integrity.
AIMS: To demonstrate that cardiac-directed therapeutic targeting of this axis delays or even overcomes diabetes-induced cardiac dysfunction in the intact heart in vivo.
METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac and mitochondrial function, mitochondria isolation. Biochemical techniques: Westerns, ELISA, ROS detection, Seahorse Bioanalyzer, real-time PCR, histology, immunofluorescence.
SIGNIFICANCE: These interventions may ultimately limit heart failure in diabetes-affected patients.

### Using the NO Redox Sibling Nitroxyl to Overcome Diabetes-induced Impairments in Cardiac NO Signalling

For: Honours and PHY3990
Key words: heart disease, nitric oxide, diabetes
Supervisors: Prof Rebecca Ritchie (Baker IDI), Dr Marianne Tare (Rm F131)
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In patients with cardiovascular disease, impaired NO signalling predicts poor outcomes, including mortality. This loss of NO-responsiveness (termed ‘NO-resistance’) is particularly

debilitating in type 2 diabetes, where cardiovascular emergencies occur more frequently, but NO-based pharmacotherapies are unable to effectively counteract platelet aggregation and vasoconstriction. We have now obtained the first evidence that the myocardium, like platelets and vessels, is also susceptible to NO-resistance such that NO can no longer enhance cardiac relaxation. However, the novel NO redox sibling, nitroxyl (HNO), may overcome this. This project explores the extent of NO resistance in type 2 diabetes, and whether HNO can overcome this, in the short-term. Whether HNO over the longer-term limits diabetes-induced myocardial dysfunction and changes in cardiac structure (and whether HNO is superior to NO in this context). Putative independent mediators of HNO cardioprotection include cGMP-mediated ROS suppression, and thiol-mediated preservation of cardiac calcium handling proteins, whose activity is abnormally affected in cardiac pathologies such as diabetes. Ultimately, HNO-based strategies may offer new treatment options for cardiac disease. Methods include: in vivo models of diabetic cardiac disease, isolated rodent hearts, assessment of cardiac and vascular function, biochemical techniques: Westerns, ROS detection, ELISA, real-time PCR, histology.

**Combining Drug and Gene Therapy Approaches to Limit Diabetes-induced Cardiac Fibrosis**

For: Honours and PHY3990
Key words: diabetes, heart failure
Supervisors: Prof Rebecca Ritchie (Baker), Dr Marianne Tare (Rm F131)
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Diabetes affects almost 2 million Australians, increasing heart failure risk and accelerating its onset. Two key structural changes in the diabetic heart are cardiac fibrosis and hypertrophy of cardiac myocytes, which contribute to the impaired cardiac function evident in the diabetic heart. This project explores whether specifically limiting diabetes-induced cardiac fibrosis, using a cardiac-selective gene therapy approach, alone or combined with targeting diabetes-induced cardiac myocyte hypertrophy via histone deacetylase inhibition, protects cardiac function in the context of type 2 diabetes in vivo.
METHODS INCLUDE: in vivo models of diabetic cardiac disease, assessment of cardiac function, Westerns, ELISA, real-time PCR, histology, immunofluorescence.
SIGNIFICANCE: These interventions may ultimately limit progression to heart failure and death in diabetes-affected patients.

**Role of Inflammation and its Resolution in the Acute and Chronic Cardiac Response to Myocardial Infarction (Heart Attack)**

For: Honours and PHY3990
Key words: heart attack
Supervisors: Prof Rebecca Ritchie (Baker), Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
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Myocardial infarction (MI, sustained impairment in coronary blood flow) and the resultant heart failure is a major cause of death. Cardiac contractile function often remains impaired over the longer-term, yet there is a paucity of effective treatments for managing MI beyond restoring vascularization in the first few hours. We have shown that the endogenous anti-inflammatory mediator annexin – A1 (ANX-A1) has powerful protective actions against cardiac injury and loss of cardiac contractile function. The GPCR family of formyl peptide receptors (FPRs), and activation of cell survival kinases, are both integral to ANX-A1 cardioprotection. Our most recent work reveals that the ANX-A1/FPR system can reduce early cardiac necrosis, as well as reducing the early inflammatory response to MI. This project explores the potential for novel ANX-A1 mimetics to reduce cardiac ischaemia-reperfusion injury, over the short- and longer-term, and to investigate the FPR-mediated mechanisms involved. The project provides the opportunity for learning a range of molecular and biochemical techniques (including FPR signalling fingerprints, Westerns, ELISA, real-time PCR, histology, immunofluorescence) as well as physiological in vitro and/or in vivo models of cardiac ischaemia, for studying cardiac function and structure.

# OXIDATIVE STRESS LABORATORY

***A/Prof Judy de Haan***

**Activating the major regulator of oxidative stress, Nrf2, with novel small molecules to limit diabetic vascular complications**

For: Honours and PHY3990
Key words: diabetes, atherosclerosis
Supervisors: A/Prof Judy de Haan (Baker IDI), Dr Arpeeta Sharma, Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
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Diabetic patients are 2-4 times more likely to suffer from cardiovascular disease leading to heart attacks and/or stroke. Understanding the mechanisms leading to increased vessel

damage and atherosclerosis has been a major focus of the de Haan laboratory. We have shown that compromised antioxidant defences, together with the increased production of reactive oxygen species (ROS), drives oxidative stress that accompanies diabetic atherosclerosis. We therefore consider the bolstering of the cell's endogenous antioxidant defences as an important and superior strategy to vitamin therapy that has not held up to its promise in clinical trials to lessen heart disease. Nrf2 is the major regulator of oxidative stress and bolstering its function is known to lessen oxidative stress. This project will investigate novel small molecule indanedione-derivatives that have shown Nrf2 on-target activation as well as anti-oxidant and anti-inflammatory potential. Mechanistic analysis of its action will be studied in cultured vascular cells, including its impact on cellular metabolism. The protective effect of indanedione derivatives on atherosclerosis will be investigated in diabetic mouse models after several weeks of drug administration.
AIMS: To assess the protective effect of novel antioxidant and anti-inflammatory compounds on the development of artery disease in a diabetic setting.
METHODS INCLUDE: in vivo models of diabetic vascular disease, cell culture, assessment of endothelial cell function including mitochondrial function by Seahorse Bioanalyser, gene silencing, RNA isolation and qRT-PCR, protein isolation and Western blotting, ELISA, en face plaque analysis, histology and immunohistochemistry.
SIGNIFICANCE: This novel approach may reduce vascular plaques to lessen the risk of heart attack and/or stroke and death in diabetic patients.

**Improving endothelial dysfunction through the use of Nrf2 activators as a novel treatment strategy to lessen diabetes-associated hypertension**

For: Honours and PHY3990
Key words: diabetes, endothelial dysfunction, Hypertension
Supervisors: A/Prof Judy de Haan (Baker), Prof Geoff Head, Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
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Hypertension is a major risk factor for cardiovascular disease, affecting more than 600 million people worldwide. Within the broader group of hypertensive patients there are subgroups of patients where an associated pathology might drive the hypertension. One such group includes diabetes-associated hypertension and is the focus of this project.
Experimental evidence shows that reactive oxygen species (ROS) play an important role in the pathophysiology of diabetes-associated hypertension. Damage to the vascular endothelium, also known as endothelial dysfunction (ED), is an early event and a major player in the pathophysiology of hypertension. Recent studies indicate that oxidative stress leads to ED and is increased in patients with hypertension. Furthermore, oxidative stress is found to be associated with inflammation and vascular remodeling.
We have access to novel activators of a key regulator of oxidative stress, the transcription factor Nrf2. We will use these activators to investigate the role of Nrf2 activation in limiting oxidative stress and inflammatory activities in mouse models of diabetes-associated

hypertension. This will be investigated in diabetic Schlager inbred hypertensive mice. Our approach has the potential to establish Nrf2 activation as a unique treatment option for diabetes-associated hypertension.
AIMS: To assess the protective effect of novel antioxidant and anti-inflammatory compounds on the development of endothelial dysfunction in a hypertensive and diabetic setting.
METHODS INCLUDE: in vivo models of diabetes and hypertension, vascular reactivity studies, RNA isolation and qRT-PCR, protein isolation and Western blotting, ELISA, histology and immunohistochemistry.
SIGNIFICANCE: This study has the potential to identify a novel therapy to lessen vessel damage as a consequence of elevated blood pressure in a diabetic setting, thereby potentially improving the lives of diabetic patients.

## Inhibition of the NLRP3-inflammasome as a novel strategy to limit diabetic cardiomyopathy

For: Honours and PHY3990
Key words: diabetes, endothelial dysfunction, NLRP3 inflammasome
Supervisors: A/Prof Judy de Haan (Baker), Prof Rebecca Ritchie, Dr Marianne Tare (Rm F131)
Location: Baker Heart & Diabetes Institute, Commercial Rd, Prahran
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Diabetes increases the risk of heart failure by 2.5-fold and leads to cardiac injury including cardiac remodeling (hypertrophy) and/or cell death. Inflammation is a major driver of the diabetes-mediated injury seen in heart failure. Activation of the NLRP3-inflammasome accelerates the processing of pro-inflammatory cytokines such as IL-1β and IL-18, resulting in cardiomyocyte injury and death. This project will use newly identified inhibitors of the NLRP3-inflammasome to investigate whether inflammasome inhibition limits diabetic cardiac injury. These pre-clinical studies will be performed in diabetic mouse models as well as tissue cultured cells exposed to elevated glucose. Endpoints to be investigated include cardiomyocyte hypertrophy, cardiac fibrosis, inflammation and oxidative stress.
AIMS: To assess the protective effect of inflammasome inhibition on the development of cardiac injury in a diabetic setting.
METHODS INCLUDE: in vivo models of diabetes, cell culture of human and mouse cardiomyocytes, RNA isolation and qRT-PCR, protein isolation and Western blotting, ELISA, histology and immunohistochemistry.
SIGNIFICANCE: This study will determine whether inhibition of the NLRP3 inflammasome protects against diabetic cardiac injury, thereby establishing inflammasome inhibition as a potential therapy to protect against diabetic cardiac injury.

# METABOLIC & VASCULAR PHYSIOLOGY LABORATORY

**Laboratory Head: Professor Bronwyn Kingwell**

The Metabolic and Vascular Physiology Laboratory takes a multidisciplinary approach to discovery and translation of novel molecular mechanisms to clinical application with a focus in the following areas:

- Advancing mechanistic insights into the negative impact of overconsumption of sugar-sweetened beverages
- Identification of novel drugs and mechanism to protect heart muscle during heart attack
- Brown fat-targeted therapies to prevent obesity-induced metabolic diseases
- Preventing cardiometabolic dysfunction during cancer treatment via physical activity interventions
- Understanding the molecular mechanisms responsible for the health benefits of reduced sedentary time.

Laboratory members and key collaborators have a broad collective skill base and range from molecular biologists through to endocrinologists, epidemiologists and cardiologists. These skills are integrated to investigate novel diagnostics and therapeutic approaches to the disease continuum linking obesity, type 2 diabetes and cardiovascular disease.

Current pipeline projects available for Honours and/or PhD are outlined below.

**Sugary drinks: Understanding and minimising metabolic complications**

For: Honours
Key words: sugar sweetened beverage, glucose metabolism, prolonged sitting, sedentary time, metabolic disease, type 2 diabetes
Supervisors: Prof Bronwyn Kingwell
Location: Baker Heart & Diabetes Institute, Commercial Rd, Melbourne Phone: 8532 1518
Email: bronwyn.kingwell@baker.edu.au

A high proportion of young Australian adults consume harmful quantities of sugar-sweetened beverages (SSBs). Beyond increasing body weight, observational research has linked sugary drink consumption to development of metabolic disease. However, evidence from intervention studies is needed to better inform public health messages about sugary drink alternatives. We are studying the mechanisms underlying the negative health consequences of consumption of sugary drinks and interventions to reverse these outcomes.

## Novel drugs targeting cardiac metabolism during acute heart attack

For: Honours
Key words: heart disease, glucose metabolism, inflammation, cardiac function, type 2 diabetes
Supervisors: Dr Adele Richart, Prof Bronwyn Kingwell
Location: Baker Heart & Diabetes Institute, Commercial Rd, Melbourne Phone: 8532 1265 (AR), 8532 1518 (BK)
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Cardiovascular disease resulting in myocardial infarction (heart attack) is the leading cause of death worldwide. Moreover, this is particularly the case in patients with type 2 diabetes where energy metabolism in the heart and other organs is disrupted. We recently showed in mice that a single injection of apoA-I nanoparticles (the main protein component of HDL particles) protected the heart muscle from damage immediately after the heart attack. Current projects expand this work to study other drugs and mechanisms which may provide protection from myocardial infarction-induced heart muscle damage. These include drugs we hypothesise will improved fat and glucose metabolism in organs such as the heart, fat tissue, skeletal muscle and the liver.

## Brown adipose tissue activation to improve metabolism

For: Honours
Key words: obesity, brown adipose tissue, energy expenditure, adrenergic receptor agonist, type 2 diabetes
Supervisors: Dr Andrew Carey, Prof Bronwyn Kingwell
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We have published a series of studies dedicated to examining the potential for certain drugs to increase brown adipose (fat) tissue energy expenditure as a means to protect people from obesity-associated disease. This work has expanded our understanding of human brown fat physiology and highlighted the importance of human clinical studies in development of therapeutic strategies for metabolic diseases. We are currently investigating a new drug candidate which is better targeted to brown fat, to study whether activation of brown fat energy expenditure can improve metabolic health.

## Managing cardiometabolic disease in haematological cancer patients

For: Honours
Key words: haematological cancer, exercise capacity, cardiac function, inactivity, heart disease, sedentary time, vascular function, metabolic function
Supervisors: Dr Erin Howden, Prof Bronwyn Kingwell
Location: Baker Heart & Diabetes Institute, Commercial Rd, Melbourne Phone: 8532 1861 (EH), 8532 1518 (BK)
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Hematological cancer survivors are highly vulnerable to cardiometabolic disease, impacting long-term health, quality of life and survival. Haemopoietic allogeneic stem cell transplant (SCT) can be a lifesaving procedure for patients with haematological cancer, but survivors have increased risk for diabetes and up to a five-fold increase in serious cardiovascular events. Increasing physical activity has the potential to benefit these patients, by both preventing loss of fitness as well as countering the negative effects of cancer drugs. We are investigating whether a novel physical activity intervention can improve cardiometabolic function in people undergoing SCT.

## The integrative biology of prolonged sitting

For: Honours
Key words: sedentary, behaviour, activity breaks, metabolic disease, obesity
Supervisors: Prof Bronwyn Kingwell
Location: Baker Heart & Diabetes Institute, Commercial Rd, Melbourne Phone: 8532 1518
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Sitting for extended periods during waking hours is associated with deleterious health outcomes. We and our colleagues in the Physical Activity Laboratory have extended these observations to laboratory interventions, showing changes in important clinical health markers and molecular processes with prolonged sedentary time, as well as how these can be alleviated by breaking up prolonged sitting. Current studies are investigating the mechanisms underlying the negative health consequences of excessive sitting, how these are mitigated by breaks in sitting time and the interaction between excessive sedentary behaviour, specific metabolic diseases and harmful nutrition practices.

# III. HUDSON INSTITUTE, MONASH MEDICAL CENTRE:

# CARDIOVASCULAR ENDOCRINOLOGY GROUP

## Introduction: Cellular localisation of mineralocorticoid receptor-mediated vascular inflammation and cardiac fibrosis

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Supervisors: Dr Morag Young
Location: Hudson Institute of Medical Research
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*Morag Young*

MR signalling in the context of high salt leads to inflammation, fibrosis and ultimately heart failure. We have used the Cre-Lox technique to delete MR expression (i.e. gene knockout) in a cell-specific manner in the cardiovascular system to identify the cells types critical for the development of vascular inflammation and cardiac fibrosis. Identification of the critical cell types will allow a focused investigation of the cellular mechanisms involved in the establishment and progression of this pathology.

One of these studies has shown that deleting the MR gene knockout in macrophages (immune cells) prevents the development of cardiovascular disease and, surprisingly, hypertension as well. A central research theme in our laboratory is to now identify and investigate the novel signalling pathways for the MR in inflammatory cells and to determine how the MR regulates the macrophages to promote cardiac remodelling.

## Understanding the signaling mechanisms for MR regulation of cardiomyocyte function in heart disease

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Supervisors: Dr Morag Young
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This project will involve molecular and immunohistochemical analyses of hearts, aortas and kidneys from transgenic mice generated by a specific breeding program and subject to treatment that causes heart failure. New studies will address the novel mechanisms that have been identified in previous work. These studies identified circadian signalling as a novel

downstream signaling pathways that we directly investigate using in vivo and in vitro models to determine its regulation by the MR and the specific role in the development of heart failure. The goal of projects undertaken in this topic is to identify novel therapeutic targets for a broad range of cardiovascular diseases that are cardiac selective, and thus have fewer side effects associated with MR actions in other tissues and organs. In addition to in vivo analysis of animal disease models, techniques will include immunohistochemistry, RNA isolation, cell culture, western blotting and RT PCR techniques.

**Nuclear receptor co-regulators in heart disease and inflammation**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Supervisors: Dr Morag Young, Dr Colin Clyne
Location: Hudson Institute of Medical Research
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Nuclear receptors associate with coregulatory proteins in order to modulate gene transcription: These coregulators can have profound effects on receptor activity and may be targeted therapeutically for the treatment of a range of diseases. We have identified novel mineralocorticoid receptor (MR coregulators from the heart and kidney and this project will characterize their activity in heart and kidney cells as well identify the molecular mechanisms of their activity. A separate project involves a T7 screen to identify novel MR coregulators in macrophage, validation as true coregulators and characterization of their activity in immune cells.

**To define the role of macrophage MR signalling in adipose tissue inflammation and glucose tolerance**

For: Honours only
Supervisors: Dr Morag Young
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Mineralocorticoid receptors (MR) play a pivotal role in regulating the macrophage inflammatory phenotype. Targeting the MR in macrophages using gene targeting in mice prevents inflammation and fibrosis in heart disease. We have preliminary data to show that mice lacking the MR in macrophages are protected from glucose intolerance due to obesity. This project aims to identify the mechanisms of this protective effect in fat, muscle and liver and will involve analysis of animal tissue by RT PCR, histology and cell culture approaches to investigate MR signalling in adipocyte and macrophage biology.

## Nuclear receptor co-regulators in heart disease and inflammation

For: Honours only
Supervisors: Dr Morag Young
Location: Hudson Institute of Medical Research
Phone: 9594 4286
Email: morag.young@hudson.org.au
www.hudson.org.au

Nuclear receptors associate with coregulatory proteins in order to modulate gene transcription: These coregulators can have profound effects on receptor activity and may be targeted therapeutically for the treatment of a range of diseases. We have identified novel mineralocorticoid receptor (MR coregulators from the heart and kidney and this project will characterize their activity in heart and kidney cells and other cell based models as appropriate to identify the molecular mechanisms of their activity. A separate project involves a T7 screen to identify novel MR coregulators in macrophage, validation as true coregulators and characterization of their activity in immune cells and is more suited to a PhD applicant. This project will include a suit of molecular biology techniques, cell culture, western blotting and RT PCR.

## Identification of mineralocorticoid receptor signalling pathways in macrophages; a role in heart disease

For: Honours only
Supervisors: Dr Morag Young
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The global importance of addressing cardiovascular disease and hypertension cannot be overestimated; this field needs new insights and novel strategies. The mineralocorticoid receptor (MR) is classically associated with the regulation of sodium, potassium, fluid balance and blood pressure control. It is also present in various non-epithelial cell types including cardiac myocytes, vascular smooth muscle, brain and immune cells such as macrophages. In these cells, the actions of the MR are not completely characterised but in many cases do not relate to salt or fluid regulation. At present, the cascade of events leading to MR activation and how MR activation results in inflammation and fibrosis is not completely defined. In animal models, cardiac fibrosis is exacerbated by mineralocorticoid/salt administration but attenuated by receptor blockade and absent in mice specifically lacking cardiac myocyte MR or macrophage MR. The recent identification of the cardio-protective effects of macrophage-specific deletion of the MR provide supportive evidence for targeted therapeutics specifically designed for macrophages for the treatment of cardiac failure and hypertension. Previous data from the host laboratory demonstrate a critical role for MR signalling in the

monocyte/macrophage lineage, a cell type in which the role of MR signalling is poorly defined. The goal of this project is to define and characterise these pathways. In this way we hope to identify novel mechanisms of inflammation in heart disease that may also apply to other diseases.

# The Be Active Sleep Eat (BASE) facility Department of Nutrition, Dietetics and Food

**The effect of meal timing on gene activity**

For: Honours and adaptable for PHY3990 (discuss with supervisor)
Supervisors: Dr Chiara Murgia, Assoc Prof Maxine Bonham, Dr Belinda Henry
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Nutritional genomics is the study of how foods and its components affect our genes and how individual genetic differences can affect the way we respond to diet and nutrients. Shift workers are more likely to suffer from health issues such as obesity, sleep disorders and cardiovascular disease compared with workers conforming to the normal sleep-wake cycle. Eating and sleeping at irregular times was shown to lead to disturbances in metabolism and energy imbalance promoting chronic disorders. Postprandial metabolites and hormones released in blood modulate the activity of genes of target tissues including blood cells. This project aims to define the metabolic impact of meal time by testing how postprandial gene expression of Peripheral Blood Mononuclear Cells (PBMC) is affected by meal time. A small cohort of participants will be recruited and offered the same defined meal at different time of the day, PBMC will be collected and gene transcription modulation of insulin responsive and inflammatory related genes will be evaluated. The project will allow the application of a nutrigenomics approach to contribute to the understanding of metabolic response and has the potential to favorably impact on the health of shift workers by providing information to develop strategies to improve their metabolic response. This project will be located at the Be Active Eat and Sleep facility in Notting Hill (www.med.monash.edu.au/base/) and the Physiology Department at the Clayton campus of Monash University.
Skills acquired: blood sampling and processing methods, RNA extraction and analysis techniques, understanding of gene-nutrient interaction implications.