Menzies Institute for Medical Research
Honours Projects 2017

If you are interested in undertaking one of these research projects in 2017, please email the corresponding supervisor and make an appointment to meet them. Prior to applying formally for honours ensure that you have clear agreement from that supervisor that they are prepared to supervise you to carry out the project. Please note that even though your research project will be conducted in the Menzies Institute for Medical Research, the honours program is administered through the School of Medicine (this is important when you come to enroll).

NEURODEGENERATIVE DISEASE / BRAIN INJURY THEME

INHIBITORY REGULATION OF MOTOR NEURONS: A NEW TARGET MECHANISM FOR MOTOR NEURON DISEASE?

Supervisory team: *A/Prof Tracey Dickson, Ms Rosie Clark*

Project description: *Amyotrophic lateral sclerosis (ALS) is the most common phenotype of motor neuron disease, and is a devastating neurodegenerative disease for which there is no effective treatment or cure. It involves the progressive loss of movement due to the dysfunction and loss of motor neurons, which universally results in paralysis and death, due to respiratory failure. ALS has a median survival of only three years from symptom onset, with only 4% of people living longer than ten years. There is new clinical, histological and electrophysiological evidence from our research team and others indicating that reduced inhibitory neuronal influences may be at the root of the disturbed glutamatergic transmission occurring in ALS. Through a combination of human and transgenic pathological investigations, performed in parallel with novel targeted in vitro experimental models we will address the novel hypothesis: 'Interneuron pathogenesis is a central mechanism of ALS'*

Key techniques: *immunohistochemistry, cell culture, immunocytochemistry*

Contact: Tracey.Dickson@utas.edu.au

WHAT DO KAINATE RECEPTORS HAVE TO DO WITH MULTIPLE SCLEROSIS?

Supervisory team: *Dr Kaylene Young, Dr Kimberley Pitman and Dr Jac Charlesworth*

Project description: *Mutations within kainate receptors have previously been associated with the development of Schizophrenia, a CNS inflammatory/degenerative disease with many phenotypic similarities to Multiple Sclerosis (age of onset, relapsing remitting course, and underlying intractable neurodegeneration), and a significant overlap between the genetics of MS and schizophrenia has been reported. Kainate receptors are ion channels that, when activated by glutamate binding, open and allow cations (such as calcium and sodium) to flow into the cell. Kainate receptors are known regulators of synaptic transmission and cellular excitability, however, they can also contribute to excitotoxicity and neuronal cell death. Our collaborators recently identified an association between a kainate receptor mutation and the development of Multiple Sclerosis. The main aim of this project is to determine how this mutation alters kainate receptor function, and therefore how it could affect cell health. The student working on this project will express normal and mutant kainate receptors in HEK293T cells and use immunohistochemistry and electrophysiology to investigate their function.*

Key techniques: *cell culture, transfection, immunocytochemistry, pharmacology and electrophysiology.*

Contact: Kaylene.young@utas.edu.au

KEEPING A LID ON OLIGODENDROCYTE PROGENITOR CELL PROLIFERATION

Supervisory team: *Dr Kaylene Young, Mr Loic Auderset and AProf Lisa Foa.*

Project description: *Oligodendrocyte progenitor cells (OPCs) proliferate and make new oligodendrocytes throughout life. We recently identified a novel cell surface receptor that regulate OPC proliferation. The main aim of this project will be to identify the ligand/s that activate these receptors, and the downstream signalling mechanisms involved. The student undertaking this project will culture OPCs in the presence of EdU, a thymidine analogue, to permanently label all cells that divide. These cells can then be exposed to known ligands, in order to determine which ones can alter OPC proliferation. The specificity of this effect will then be confirmed by deleting the receptor from the OPCs, and the downstream protein changes will be interrogated by western blot.*

Key techniques: *cell culture, cre-lox recombination / conditional gene deletion, pharmacology, EdU-labelling (tagging proliferating cells), immunocytochemistry, and western blot.*

Contact: Kaylene.young@utas.edu.au

DO WE NEED NEW OLIGODENDROCYTES TO MAINTAIN OUR MYELIN?

Research discipline: *Neuroscience*

Supervisory team: *Dr Kaylene Young, Ms Renee Pepper and Dr Carlie Cullen.*

Project description: *Oligodendrocyte progenitor cells (OPCs) proliferate and make new oligodendrocytes throughout life. However, it is now known whether these new cells are needed to replace those that die over the lifetime. To examine this, the student taking on this project will use cre-lox transgenic technology to conditionally delete the gene Myrf from OPCs in adulthood. Without Myrf OPCs are unable to mature into new oligodendrocytes. This approach effectively prevents the addition of new oligodendrocytes to the brain of adult mice. The performance of control and Myrf-deleted mice will be compared in a series of motor and coordination tests. These data will reveal whether continued oligodendrocyte addition is required to sustain motor function over time.*

Key techniques: *animal handling, drug administration, cre-lox recombination / conditional gene deletion, behavioural testing, and immunohistochemistry.*

Contact: Kaylene.young@utas.edu.au

DISCOVERING THE TARGETS OF NEURAL STEM CELL TRANSCRIPTION FACTORS

Supervisory team: *Dr Owen Marshall*

Project description: *Neural development is a complex process in which neural stem cells (NSCs) give rise to a large number of highly specific neuronal lineages. A number of key transcription factors are known to be involved in this process, but little is known about their targets or their mode of action. One such transcription factor is called Snail, which is vital for both NSC maintenance and for specifying a subset of neuronal lineages. This project aims to identify the genome-wide binding targets of Snail in NSCs and immature neurons within the brain of the fruit fly,* Drosophila melanogaster. *The results will be integrated with existing expression and epigenetics data to gain an understanding of Snail action within the developing brain.*

Key techniques: *PCR, next-generation sequencing, immunohistochemistry, data analysis using R*

Contact: owen.marshall@utas.edu.au

DEVELOPING AN ALZHEIMER'S DISEASE MODEL IN THE FRUIT FLY

Supervisory team: *Dr Owen Marshall, Dr Elias Polymeropoulos*

Project description: *Alzheimer's Disease (AD) has a major impact on society. Model organisms, such as the fruit fly* Drosophila melanogaster, *provide a useful means to study the mechanisms of the disease progression. However, most fly AD models are driven by the GAL4 expression system, which prevents investigation of transcriptional and epigenetic changes. This project aims to convert a common AD fly model (a human familial mutation in the protein Tau) to the LexA bipartite expression system. If time permits, the new model will be used to profile transcriptional changes occurring in AD-affected neurons.*

Key techniques: *PCR, Gibson Assembly, sequencing, behavioural studies, data analysis using R*

Contact: owen.marshall@utas.edu.au

PUBLIC HEALTH AND PRIMARY CARE THEME

THE PSYCHOSOCIAL DETERMINANTS OF TREATMENT PATHWAYS, CLINICAL OUTCOMES AND COSTS IN ADULTS WITH CHRONIC KIDNEY DISEASE.

Supervisor: *Dr Charlotte McKercher*

Project description and techniques: *Given the increasing social and economic burden of treated end-stage kidney disease both locally and globally, interventions and strategies that prevent or delay the progression of kidney disease are crucial. Utilising a range of individual level, registry and administrative health data this state-wide prospective cohort study will examine the relative influence of both biomedical and psychosocial factors on*

the rate of kidney disease progression, the choice of treatment pathways, hospitalisation, mortality, health-related quality of live and economic outcomes in adults living with chronic kidney disease.

A number of projects are available involving mental health, health economics, public health and nephrology. The student will learn statistical techniques and epidemiology principles, and will perform statistical analyses. An aptitude for biostatistics is essential. In addition to the normal Hons requirements, students are also expected to draft a manuscript with the intention to submit to a peer reviewed journal.

Contact: Charlotte.McKercher@utas.edu.au

IMPROVING THE LIVES OF PEOPLE WITH MS – THE AUSTRALIAN MS LONGITUDINAL STUDY

Supervisory team: *A/Prof Ingrid van der Mei*

Project description: *Multiple Sclerosis (MS) is a debilitating neurological disease affecting many young around the world. The Australian MS Longitudinal Study (AMSLS) has been running for 15 years and has more than 3,500 active participants who are living with MS. Data from the study provides researchers, advocacy groups and government agencies with practical information on how MS is impacting on people's lives. Participants complete a number of surveys each year. In 2016 we will run a Lifestyle and Environment Survey which contains data on height and weight, children, social support, tobacco smoking, marijuana smoking, alcohol use, UV exposure, heat sensitivity, skin type, vitamin D supplementation, physical activity, relaxation activities, diets, dietary intake, stressful life events in the last 12 months, medical conditions. From that data, we will be able to examine how these lifestyle factors are associated with outcomes such as quality of life, MS symptom severity and disability progression. The results will contribute to improving the lives of people with MS e.g. by developing recommendations for people with MS and health professionals, or by developing new interventions.*

Key techniques: *You will gain extensive skills in epidemiology and biostatistics in a very applied/practical manner, and will learn how to analyse data using a statistical package called STATA. If you have some aptitude for maths, then you will probably enjoy this project.*

Contact: Ingrid.vanderMei@utas.edu.au

DIETARY FACTORS ASSOCIATED WITH THE PROGRESSION OF MULTIPLE SCLEROSIS

Supervisory team: *A/Prof Ingrid van der Mei, Prof Wendy Oddy*

Project description: *Many people with MS are motivated to try different diets to see whether this might positively affect their MS. While there is anecdotal evidence that people feel better after removing particular foods from the diet, there is very little research supporting the benefits of these diets. We have a number of high quality datasets available to test whether diet might influence the progression of MS and quality of life. Markers of disease activity include relapses, progression in disability, change in MRI markers, quality of life and MS Symptom Severity. Cancer Council Food Frequency data is available for some datasets, as well as information on specific diets. The work might lead to dietary interventions that can be tested in people with MS.*

Key techniques: *You will gain extensive skills in epidemiology and biostatistics in a very applied/practical manner, and will learn how to analyse data using a statistical package called STATA. If you have some aptitude for maths and an interest in diet/nutrition, then you will probably enjoy this project.*

Contact: Ingrid.vanderMei@utas.edu.au

PREDICTORS OF SMOKING CESSATION IN YOUNGER ADULTS

Supervisory team: *Dr Seana Gall, Ms Jing Tian*

Project description: *Young adulthood is a peak time when smokers to attempt to quit. Understanding the factors that motivate younger smokers to quit, and the methods they typically use, can inform public health strategies to promote quit attempts. This project will use data from over 2,000 people aged 31 to 41 years collected as part of the Childhood Determinants of Adult Health (CDAH) study, to examine these aspects of smoking cessation.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Participants provided information on their smoking history, including attempts to quit, motivations for*

quitting and methods used to quit. Students will learn principles of epidemiology and public health, and will become proficient in analysing quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, psychology/health behaviour, and/or biostatistics.

Contact: Seana.Gall@utas.edu.au

SEX DIFFERENCES IN THE RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HAEMORRHAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Supervisory team: *Dr Seana Gall, Ms Linda Nichols*

Project description: *Aneurysmal subarachnoid haemorrhage (aSAH) is a rare form of stroke that disproportionately affects women compared to men. The reasons for this excess risk are uncertain. This project involves conducting a systematic review and meta-analysis of the risk factors for aSAH in men and women.*

Key techniques: *The student will plan and conduct a systematic review of the literature on risk factors for aSAH in men and women. Using data extracted from studies identified as part of the systematic review, the student will conduct a meta-analysis of the risk factors for aSAH in men and women, separately. The student will learn statistical techniques related to meta-analysis using Stata and R. The project will suit students interested in epidemiology, public health, clinical medicine and biostatistics.*

Contact: Seana.Gall@utas.edu.au

LONG-TERM OUTCOMES AFTER STROKE: A WORLDWIDE REVIEW OF POPULATION-BASED STUDIES

Supervisory team: *Dr Seana Gall, Dr Hoang Phan*

Project description: *While there have been multiple reviews of the short term outcomes of stroke, there has been limited exploration of outcomes into the longer term. This project would address this deficiency using data from an existing dataset including 16,000 strokes from 14 studies around the world to profile long term outcomes including survival and functional outcomes. These data would be supplemented with new data from a systematic review and meta-analysis of other published studies reporting these outcomes from around the world. This study will provide the first comprehensive analysis of these long term outcomes worldwide.*

Key techniques: *The student will develop quantitative skills including in meta-analysis and standard regression techniques including how to use the programs R and Stata. The student will work with a team of researchers from Australia, the USA and Europe, gaining experience in collaborative, inter-disciplinary research.*

Contact: Seana.Gall@utas.edu.au

CAN METABOLOMICS PREDICT THE ONSET OF DEPRESSION AND ANXIETY?

Supervisory team: *Dr Seana Gall, Prof Wendy Oddy*

Project description: *The metabolome represents the metabolic state of a person. It can reveal the biochemical pathways involved in disease. Depression and anxiety contribute substantially to the burden of disease. There has been recent interest in whether metabolomics can be used to better characterize depression and anxiety, particularly in terms of response to treatments, but also whether it could identify people at risk of developing a mental health problem in the future. This project will use data collected as part of the Childhood Determinants of Adult Health (CDAH) study including a metabolomics analysis and psychiatric diagnoses of depression and anxiety in over 2,000 people.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Students will learn principles of epidemiology, and will become proficient in analysing quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, psychology/neuroscience, and/or biostatistics.*

Contact: Seana.Gall@utas.edu.au

ADHERENCE TO MUSCLE STRENGTHENING GUIDELINES: PREDICTORS AND TRENDS OVER TIME

Supervisory team: *Dr Verity Cleland, Dr Costan Magnussen*

Project description: *In 2014, Australia's physical activity guidelines were updated to include a recommendation for muscle strengthening activities on at least two days each week. Little is currently known about the number of people who currently or historically meet these guidelines, or about the demographic (e.g. sex, age, education) and behavioural (e.g. physical activity, diet) factors associated with meeting these guidelines. It is important to identify these trends and predictors, so that strategies to increase adherence to muscle strengthening guidelines can be targeted and tailored to ensure maximum effectiveness.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Australian adults (age 26-36 years at baseline) completed surveys and wore pedometers in 2004-6 and in 2009-11. Students will learn principles of epidemiology and public health, and will become proficient in analysing longitudinal quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, exercise behaviour, and/or biostatistics.*

Contact: verity.cleland@utas.edu.au

WHO CATCHES THE BUS?

Supervisory team: *Dr Verity Cleland*

Project description: *People who use public transport are more physically active than those who use private motor vehicles, and physical activity is an important protective behaviour associated with numerous health outcomes. The use of public transport therefore provides an opportunity to increase population levels of physical activity, but the key barriers and enablers to public transport usage in Tasmania are currently unknown. This information is important, because it can help public transport providers and health planners/policy-makers to better target and tailor strategies to increase public transport usage.*

Key techniques: *This project will involve developing and administering an online survey to Tasmanian adults, exploring public transport usage patterns and key barriers and enablers to public transport usage. Students will learn principles of epidemiology and public health, and will become proficient in the development of surveys and analysis of survey data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, exercise behaviour, travel behaviour and/or biostatistics.*

Contact: verity.cleland@utas.edu.au

FIT AFTER 40: A PEER-SUPPORTED PHYSICAL ACTIVITY PROGRAM FOR WOMEN

Supervisory team: *Dr Verity Cleland, Dr Meredith Nash (Sociology)*

Project description: *Women are less active than men across the life course, and regular activity is critical in preventing conditions such as heart disease, breast cancer, osteoporosis and diabetes as women age. Key barriers to participation in physical activity include a lack of knowledge about how to exercise, lack of experience to exercise alone, and a lack of social support for activity. There is currently little evidence of effective strategies to engage and promote physical activity among women, which are needed to help women become and remain active as they age.*

Key techniques: *This project aims to increase community participation in recreational physical activity by providing social support to women to participate in a free weekly walking/running event ('parkrun'). It will involve establishing the feasibility and/or testing the efficacy of a program to connect currently sedentary women with a parkrun mentor, who will support their mentee in parkrun participation. Students will learn principles of epidemiology, public health and/or sociology, and will become proficient in analysing either quantitative or qualitative data (depending on the focus of the study) using Stata or NVivo software (note that analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, sociology, gender, exercise behaviour, and/or biostatistics. This project would be suitable for one or more students.*

Contact: verity.cleland@utas.edu.au

PATTERNS AND PREDICTORS OF SEDENTARY BEHAVIOUR OVER TIME

Supervisory team: *Dr Verity Cleland, Dr Megan Teychenne (Deakin University)*

Project description: *A body of evidence demonstrating important and independent effects of sedentary behaviours (e.g. sitting, TV viewing) on cardiometabolic health outcomes is accumulating. However, much data is cross-sectional, with little is known about sedentary behaviours over time, and the factors associated with sedentary behaviour. It is important to identify these patterns and predictors, so that strategies to reduce sedentary behaviour can be targeted and tailored to ensure maximum effectiveness.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Victorian women (age 18-45 years at baseline) completed surveys about their sedentary behaviour on three occasions over five years. Students will learn principles of epidemiology and public health, and will become proficient in analysing longitudinal quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, exercise behaviour, and/or biostatistics.*

Contact: verity.cleland@utas.edu.au

WHAT IS THE IMPACT OF RETIREMENT ON OBJECTIVELY-MEASURED PHYSICAL ACTIVITY?

Supervisory team: *Dr Verity Cleland, Dr Dawn Aitken*

Project description: *Evidence suggests the transition to retirement has an impact on physical activity behaviour, but the direction of the effect is unclear with some studies suggesting increases and others suggesting decreases. However, existing studies have predominantly relied upon self-reported surveys to measure physical activity, which are subject to reporting and recall biases and may explain inconsistencies in findings.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Tasmanian adults (age 50-80 years at baseline) completed surveys and wore pedometers on three occasions over ten years. Students will learn principles of epidemiology and public health, and will become proficient in analysing longitudinal quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, exercise behaviour, and/or biostatistics.*

Contact: verity.cleland@utas.edu.au

UNDERSTANDING BIAS IN THE SELF-REPORTING OF HEIGHT AND WEIGHT: DO WE GET WORSE OVER TIME?

Supervisory team: *Dr Verity Cleland, Dr Kylie Smith*

Project description: *Many epidemiological studies rely on self-reported measures of height and weight to estimate obesity. It is well-documented that factors such as sex are related to biases in self-reports – women tend to underestimate their weight, while men tend to over-estimate their height. However, it is currently unclear if there are other factors – such as socioeconomic position, rural/urban status, age – that also bias reports, and it is unknown whether these biases change over time. This information is important for understanding how biases may impact on estimates of obesity in longitudinal studies that often include different or missing measurements over time.*

Key techniques: *This project will involve analysis of observational data from an existing prospective cohort study. Australian adults (age 26-36 years at baseline) had their height and weight measured and self-reported their height and weight in 2004-6 and in 2014-15. Students will learn principles of epidemiology and public health, and will become proficient in analysing longitudinal quantitative data using Stata software (note that statistics/analytic experience is not a pre-requisite). This project will suit students with an interest in epidemiology, public health, exercise behaviour, and/or biostatistics.*

Contact: verity.cleland@utas.edu.au

UNDERSTANDING THE EXPERIENCES OF TASMANIANS WHO UNDERGO BARIATRIC SURGERY FOR WEIGHT LOSS

Supervisory team: *Dr Kim Jose and Professor Alison Venn*

Project description: *Since 2014 a series of qualitative studies have been undertaken as part of a broader project investigating the health service use, costs and policy options with respect to bariatric surgery in Tasmania. The qualitative studies have aimed to capture the experiences and needs of those who have had surgery for weight loss. A number of possible areas for further analysis and investigation have been identified as a result of these studies; including familial surgery, shame and bariatric surgery, ongoing focus on food and sense of personal responsibility following surgery. This project would suit students with a background in health sciences/promotion, medicine, public health, social science, applied science, medical research.*

Key techniques: *This project will involve secondary qualitative data analysis using data that has been collected as part of a broad program of work that has examined the experiences of people in Tasmania who have had weight loss surgery. It may also require collection of further qualitative data.*

Contact: kim.jose@utas.edu.au

AUTOMATED CONTROL OF INSPIRED OXYGEN THERAPY IN NEONATES

Supervisor(s) contact details: *Prof Peter Dargaville, Dr. Tim Gale*

Project description: *Avoidance of hypoxia (low blood oxygen level), and especially for the preterm neonate, hyperoxia (high blood oxygen level), is fundamental in the delivery of respiratory support to the newborn infant with respiratory insufficiency. Hypoxia in preterm infants is most commonly a consequence of respiratory distress syndrome, and, if not adequately treated, substantially increases the risk of mortality. Conversely, unrestricted and/or inadequately regulated oxygen therapy causes overgrowth of vasculature in the developing retina of the preterm infant. This retinopathy of prematurity (ROP) is a continuing problem in NICUs in the Western world, and is a significant concern in developing and newly industrialised countries. At present in most NICUs, moment-by-moment changes to FiO_2 are under the control of the bedside staff, who make adjustments based on the transcutaneous oxygen saturation level (SpO_2). Despite the best efforts of staff at the bedside, neonates on respiratory support spend considerable amounts of time with SpO_2 readings outside the desired or target range. A study conducted at RHH in 2012 by UTAS MBBS Honours student Kathleen Lim (the SNOOT study) found that in preterm infants on non-invasive respiratory support, SpO_2 was maintained in the target range only 31% of the time.*[1]

The data collected in the SNOOT study[1-3] *have aided our efforts to develop an inspired oxygen controller. This is a device that receives transcutaneous oxygen saturation (SpO_2) readings from a bedside oximeter, verifies and processes the oximetry data, compares the SpO_2 readings with predetermined targets in a control algorithm, and sends signal pulses to a servomotor to automatically turn the FiO_2 dial of a gas blender. The control algorithm at the heart of our control device has some unique features that have not been incorporated in FiO_2 feedback control systems previously. We believe these additional features will allow more precise targeting of SpO_2 in preterm infants receiving oxygen than ever before possible with an automated FiO_2 control system. Preliminary studies of 4 h duration under controlled conditions, with a researcher present throughout, have been conducted in 2015 by our current UTAS MBBS Honours student, Gemma Plottier. We have found that in preterm infants our device appears to maintain SpO_2 in the target range more effectively than manual control, with few episodes of hypoxia and hyperoxia. The next stage of development of the oxygen control device is a study (the SANTO-B study) in which automated control will be compared with manual control under standard clinical conditions for 24 h periods, without a member of the research team consistently in attendance. These studies will begin later in 2016, and will continue throughout 2017. The involvement of an Honours student in this next stage would be a great boost for the project, as has been the case in 2012 and 2015.*

Location: Menzies Research Institute and Royal Hobart Hospital, Hobart

1. Lim K, Wheeler KI, Gale TJ, Jackson HD, Kihlstrand JF, Sand C, Dawson JA, Dargaville PA. Oxygen saturation targeting in preterm infants receiving continuous positive airway pressure. J Pediatr (2014); 164:730-736.
2. Fathabadi OS, Gale TJ, Lim K, Salmon BP, Wheeler KI, Olivier JC, Dargaville PA. Assessment of validity and predictability of the FiO2-SpO2 transfer-function in preterm infants. Physiol Meas (2014); 35: 1425-1437.
3. Lim K, Wheeler KI, Fathabadi O, Gale TJ, Dargaville PA. Lost without trace: oximetry signal dropout in preterm infants. Arch Dis Child Fetal Neonatal Ed (2015); DOI: 10.1136/archdischild-2014-308108.

Contact: peter.dargaville@ths.tas.gov.au or tim.gale@utas.edu.au

HOUSE DUST MITE IN AUSTRALIAN HOMES

Supervisory team: *Dr Amanda Wheeler, Dr Fay Johnston*

Project description: *A collaboration with the National Asthma Foundation Australia. There is interest in understanding current exposures to house dust mite in Australian homes. The study will conduct measurements of house dust mite and will develop a housing characteristic survey to understand the levels in homes. Students should have a background in health sciences, public health, applied science, biostatistics, medical research.*

Key techniques: *developing and testing a survey instrument to assess predictors of house dust mite.*

Contact: amanda.wheeler@utas.edu.au

POLLEN EXPOSURES AND RESPIRATORY HEALTH EFFECTS

Supervisory team: *Dr Fay Johnston, Dr Grant Williamson, Dr Amanda Wheeler*

Project description: *The AirRater App has been successfully developed and used to track symptoms and environmental triggers in individuals with asthma and allergies. Environmental triggers include fine particulate matter, pollens and temperature. The study will investigate associations between symptoms and different species of pollens. Students should have a background in health sciences, public health, applied science, biostatistics, medical research.*

Key techniques: *modelling of health effects associated with exposures to pollens.*

Contact: Fay.Johnston@utas.edu.au

CARDIO-METABOLIC HEALTH AND DISEASE THEME

EXERCISE PHYSIOLOGY IN THE IDENTIFICATION AND CONTROL OF HIGH BLOOD PRESSURE: THE EPIC BP STUDY.

Supervisors: *Dr Martin Schultz and AProf James Sharman*

Overview: *An exaggerated exercise blood pressure (EEBP) response to submaximal exercise independently predicts cardiovascular (CV) events and mortality, incident hypertension, and reveals BP abnormalities that are otherwise not detectable via standard screening methods at rest (i.e. masked hypertension). Thousands of individuals are referred for accredited exercise physiologist (AEP) services each year, who routinely undertake submaximal exercise testing with BP measurement a mandatory component. Whether BP readings taken during AEP led exercise testing can aid in the identification of those at increased CV risk related to EEBP is unknown. Furthermore, it is unknown whether targeted AEP exercise intervention can reduce the CV risk associated with EEBP. Thus, the broad aims of the EPIC BP study program are to identify those with EEBP at the time of referral to AEP services in the community, as well as to determine the effect (and optimisation) of AEP intervention on BP control and other hypertension-related markers of CV risk by randomized clinical trial in the AEP community sector.*

The project comprises part of an existing research program, and participation will involve data collection in the Menzies BP clinic, in addition to analysis of existing human physiological data to understand the prevalence of EEBP identified in the AEP community sector. Prospective candidates are encouraged to contact BP research group supervisors for more detail or to discuss other options for related research activities.

Contact: Martin.Schultz@utas.edu.au or James.Sharman@utas.edu.au

MUSCULOSKELETAL HEALTH AND DISEASE THEME

COMPARING VITAMIN D DOSES TO CORRECT VITAMIN D DEFICIENCY IN ADOLESCENTS: A RANDOMISED CONTROLLED TRIAL.

Supervisory team: *Professor Tania Winzenberg, Dr Dawn Aitken, Mr Feitong Wu*

Project description: *Improving children's bone density (a measure of their bone strength) may reduce both the risk of childhood fracture and the risk of fractures due to osteoporosis in older adult life. Vitamin D is important for children's bone health but it is unknown whether correcting mild to moderate vitamin D deficiency in children will result in clinically important improvements in bone density. Adolescents are at particular risk of vitamin D*

deficiency and are also a group who may not take medications regularly. The optimal dosage regimen for adolescents to help them take vitamin D regularly enough to correct deficiency is not known. Therefore, the main aim of this study was to test two different vitamin D dosage regimens to see if they can both correct vitamin D deficiency in adolescents. The study will also provide preliminary pilot data on whether correcting vitamin D deficiency results in significant improvements in bone density.

Key techniques: *This study would suit a person who is keen to pursue an interest in clinical research as the techniques learnt will be applicable to any clinical trial. In this study you will learn how to clean a data set ready for analysis, design and analysis plan and analyse and present data from a randomized controlled trial. Techniques will include approaches to modeling data that is subject to seasonal variation. Statistical supervision and training will be provided. Other skills attained will be the preparation of conference abstracts and presentations and preparation of scientific manuscripts for publication.*

Contact: tania.winzenberg@utas.edu.au

ASSOCIATIONS OF PHYSICAL ACTIVITY, PHYSICAL PERFORMANCE MEASURES AND OBESITY IN CHILDHOOD WITH KNEE CARTILAGE THICKNESS IN ADULTS AFTER 25 YEARS

Supervisory team: *Dr Benny Antony, Prof. Changhai Ding*

Project description: *Osteoarthritis (OA) is characterised by knee pain, osteophyte growth, gradual loss of articular cartilage and other structural changes of articular tissues. Cartilage pathology is the hallmark feature of OA although OA involves the whole joint and eventually leads to total joint replacement. OA is the most common joint disorder in the world and there are no disease-modifying treatments available (1). Identifying the early life modifiable risk factors is an ideal strategy to prevent the development of OA. Strength training and physical activity are widely advised to patients with knee and hip OA for improving their symptoms although the effect of physical activity and fitness on knee structure is controversial (2). We have recently reported that childhood physical performance measures were positively associated with knee bone area and cartilage volume in young adults (3). However, it is unclear whether the increased cartilage volume is just the result of an increased bone area, which might have stretched the overlying cartilage resulting in cartilage thinning (cartilage thinning is an important feature of early OA). This possibility can be resolved by measuring the cartilage thickness in multiple subregions (4).*

Aims: The aim of this study is to determine the association between physical activity, physical performance measures and obesity in childhood, and subregional knee cartilage thickness in young adults 25 years later.

Hypothesis: 1) Childhood physical activity and physical performance measures are positively associated with subregional knee cartilage thickness in adults after 25 years. 2) Childhood obesity measures are negatively associated with knee cartilage thickness in adults after 25 years.

This application takes advantage of a NHMRC funded study ($290,000), which has completed its preliminary analysis and publications. We reported that in children aged 9-18 years, vigorous activity, numbers of sports, type of sports and lower limb muscle strength were positively associated with knee cartilage volume (5), suggesting that physical activity may be beneficial for knee cartilage development. However, when we followed school children over 25 years, we did not find significant associations between childhood physical activity or obesity and adult tibial cartilage volume. This could be due to the effect of physical activity and obesity on weight bearing subchondral bone development. Increased bone growth can lead to stretching of overlying cartilage and can result in increased cartilage volume. Cartilage thickness is a three-dimensional (3D) measure and can be of more use in situations where bone area growth occurs. Further, a study reported that subregional cartilage thickness (4) had a relatively higher sensitivity than cartilage volume in detecting early cartilage changes (6). It is reasonable to hypothesize that physical activity in younger life may lead to long-term benefits on thickness of knee cartilage. This research will be the first long-term study to explore the effect of childhood lifestyle factors on adulthood knee cartilage thickness and will also utilise the pioneering MRI techniques to measure the tibial and femoral cartilage thickness. This topic requires urgent attention given that OA is often regarded as a potential adverse effect of physical activity/body composition in childhood. If a positive association between childhood physical activity and (subregional) adult knee cartilage thickness is demonstrated in our proposed study, it will have important implications for the prevention of OA and will provide reassurance that physical activity recommendations in childhood do not have unintended harmful effects on knee joint. This can reduce OA in the future and can significantly decrease the number of costly joint replacement surgeries resulting from knee OA.

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CANCER, GENETICS AND IMMUNOLOGY THEME

FUNCTIONAL CHARACTERISATION OF FC RECEPTORS IN TASMANIAN DEVILS

Supervisory team: *Dr Andy Flies, Prof Greg Woods, Dr Bruce Lyons*

Project description: *Monoclonal antibody-based immunotherapy has incredible progress in the past years in treating human cancer. A critical, yet often overlooked aspect of monoclonal antibody immunotherapy is the interaction between the antibody isotype and subclass (e.g. IgG1) and the Fc receptors (e.g. FcγRI) that determine how long antibodies persist in a host and whether the antibody has inhibitory or stimulatory effects [12]. Very little is known about Fc receptors in marsupials. Here we will amplify and clone Tasmanian devil Fc receptors and determine which devil antibody isotypes bind to which Fc receptors and also the functional response of antibody-Fc receptor interactions. The information obtained in this study will help guide our ongoing vaccine research efforts for the devil facial tumour disease.*

Aims:

1. *Clone and express all devil antibody isotypes and subclasses.*
2. *Clone and express all devil Fc receptors.*
3. *Characterise functional consequences of Fc receptor-antibody binding.*

Methods: For aims 1 and 2 we will use PCR to amplify the genes that code for key devil immune system proteins. These genes will then be inserted into plasmid DNA expression vectors. The plasmid DNA is then transformed into bacteria to make copies of the plasmid DNA, and then the plasmids DNA is purified, sequenced, and transfected into mammalian cells for protein production. For aim 3 we will replicate a system that was used for characterisation of Fc receptors in dogs[3].

Key techniques: *polymerase chain reaction (PCR), overlap-extension PCR, DNA purification, plasmid DNA construction, Gibson assembly cloning, bacterial transformation, DNA sequencing, cell culture, mammalian cell transfection, analysis of receptor-ligand interactions.*

Recommended reading:

1. *Simpson, T. R. et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti–CTLA-4 therapy against melanoma. J. Exp. Med.* ***210,*** *1695–1710 (2013).*
2. *Pincetic, A. et al. Type I and type II Fc receptors regulate innate and adaptive immunity. Nat. Immunol.* ***15,*** *707–716 (2014).*
3. *Bergeron, L. M. et al. Comparative functional characterization of canine IgG subclasses. Vet. Immunol. Immunopathol. (2013). doi:http://dx.doi.org/10.1016/j.vetimm.2013.10.018*

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BUILDING A TOOLBOX FOR UNDERSTANDING AND MANIPULATING THE IMMUNE SYSTEM OF TASMANIAN DEVILS

Supervisory team: Dr Andy Flies, Prof Greg Woods, Dr Bruce Lyons

Project description: *The Tasmanian devil facial tumour (DFT) disease has been the primary driver for an 85% decline in wild devils. Recently a second type of transmissible tumour was discovered in wild devils and this second devil facial tumour (DFT2) thus far has proven to be 100% fatal [1]. These two transmissible tumours offer a unique opportunity to learn how tumours avoid being killed by the immune system, and the knowledge we acquire from studying these transmissible tumours could have help us to understand cancer and transplant rejection in other species. Efforts to develop a DFT vaccine have made steady progress, but have been hampered by the limited tools available for studying the devil immune system. The goals of this project will be to use cutting-edge molecular biology techniques to develop new proteins and antibodies for studying and manipulating the devil immune system. Blockade of inhibitory checkpoint molecules has revolutionised cancer immunotherapy in humans, and we have already made progress towards replicating these treatments for devils. This project will focus on the next generation of the inhibitory checkpoint molecules (e.g. CD47, VISTA) [23].*

Aims:

1. *Develop expression vectors to make devil proteins that can be used to assess receptor-ligand interactions.*
2. *Characterise receptor expression in response to cytokine stimulation.*

Methods: For aim 1 we will use PCR to amplify the genes that code for key devil immune system proteins. These genes will then be inserted into plasmid DNA expression vectors. The plasmid DNA is then transformed into bacteria to make copies of the plasmid DNA, and then the plasmids DNA is purified, sequenced, and transfected into mammalian cells for protein production. For aim 2 we will amplify sequences from hybridomas and single-

cell sorted B cells so that we can determine the exact coding sequence for the antibodies produced by B cell and hybridomas.

Key techniques: polymerase chain reaction (PCR), overlap-extension PCR, DNA purification, plasmid DNA construction, Gibson assembly cloning, bacterial transformation, DNA sequencing, cell culture, mammalian cell transfection, analysis of receptor-ligand interactions.

Recommended reading:

1. *Pye, R. J. et al. A second transmissible cancer in Tasmanian devils. Proc. Natl. Acad. Sci. (2015). doi:10.1073/pnas.1519691113*
2. *Le Mercier, I., Lines, J. L. & Noelle, R. J. Beyond CTLA-4 and PD-1, the generation Z of negative checkpoint regulators. Frontiers in Immunology* ***6,*** *(2015).*
3. *Ide, K., Wang, H., Tahara, H., Liu, J. & Wang, X. Role for CD47-SIRPα signaling in xenograft rejection by macrophages. Proc. Natl. Acad. Sci. USA* ***104,*** *5062 (2007).*

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RETURNING RESEARCH RESULTS TO BIOBANK DONORS

Supervisory team: *Dr Rebekah McWhirter and Dr Lisa Eckstein (Law)*

Project description: *Biobanks store human tissue samples donated for future health research. Research using stored tissue has the potential to produce results that might be important for the donor's health or reproductive choices, or those of their family. It is currently unclear whether there is an obligation to return clinically-relevant information to donors, or how this should happen. TasBioGRID is a biobank currently being established by the University, and an ethically sound plan for handling return of results needs to be developed. This project will:*

- *analyse survey data to investigate community attitudes,*
- *examine legal obligations to donors and their genetic relatives (relevant legislation and case law),*
- *assess ethical arguments,*
- *integrate the legal, ethical and empirical analyses to provide evidence-based recommendations for biobank governance on return of results.*

Key techniques: *Students will learn statistical, legal and bioethical research techniques, and work with scientists and lawyers to develop answers to real-world problems for biobanks. This project would suit students with a Science/Law, Arts/Science or similar background.*

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GENETICS OF RESPONSE TO ANTI-VEGF THERAPY FOR RETINAL DISEASE

Supervisory team: *A/Prof Kathryn Burdon, Clin A/Prof Nitin Verma, A/Prof Alex Hewitt*

Project description: *Several types of retinal diseases are treated with newly developed antibody based drugs that aim to inhibit the action of a protein called Vascular Endothelial Growth Factor (VEGF). These anti-VEGF agents are used to treat age-related macular degeneration, diabetic maculopathy and retinal vein occlusions. All these diseases affect the vasculature in the retina at the back of the eye and can lead to blindness. The introduction of anti-VEGF therapies has vastly improved the treatment of these conditions, however, not all patients respond to treatment and a portion continue to progress towards blindness. There are many factors that may contribute to the response to therapy in any patient, but genetics is thought to play a role. Some people are more genetically pre-disposed to benefit from these therapies than others. If we could predict who is likely to benefit, patients could be offered appropriate therapy at an earlier stage of disease, or conversely, spared from invasive and ongoing treatments that are not likely to work and be directed towards other options sooner. This project aims to identify genetic variants contributing to response to anti-VEGF therapy. An audit of patients that have received these treatments over the last 5 years will be undertaken to identify appropriate participants and to collect data regarding response to therapy in terms of improvement in vision and changes to the retina. Patients currently undergoing treatment will also be invited to participate. A blood or saliva sample will be collected from participants and DNA extracted for genetic testing. Data analysis will centre around finding genetic variants and other clinical risk factors that predict response to therapy. This project would suit either science (including biomedical) or medical students. The exact scope of the project will be negotiated such that the data collection focus is on clinical aspects including patient recruitment and assessment, or on laboratory work to generate genetic data depending on the interests and skills of the student. Research staff will also be involved to assist with data collection and patient recruitment.*

Key techniques: The techniques used will depend on the focus of the student. Key techniques may include: *Audit of medical records, recruitment of patients into research study including informed consent, specimen collection, DNA extraction, SNP array genotyping, DNA sequencing, statistical methods including genetic association and bioinformatics.*

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IDENTIFICATION OF COMMON GENETIC VARIANTS CONTRIBUTING TO KERATOCONUS

Supervisory team: *A/Prof Kathryn Burdon*

Project description: *Keratoconus is a disorder of the cornea of the eye. The cornea becomes progressively thinner and conical in shape, severely distorting vision. The disease affects people in early adult-hood and results in life long visual impairment. There are some treatments available, including the use of hard contact lenses, or collagen cross linking procedures, but they are not effective or suitable for all patients. Once the disease progresses to an advanced stage, the cornea is replaced with a donor cornea graft. Graft patients require a high level of medical follow-up and the graft is often rejected, resulting in severe visual disability. The molecular and genetic causes of keratoconus are not well understood, but some progress has been made recently with advances in understanding the genetic risk factors.*

Our recent research has highlighted a number of loci that likely harbour genetic variants contributing to keratoconus. This project will involve the detailed resequencing of these loci in keratoconus patients and controls known to carry risk and protective haplotypes in these regions using next generation sequencing techniques. We will identify all the variation present on these haplotypes and use bioinformatics techniques to rank the likely pathogenicity of variants. If time permits, the most likely variants may be genotyped in larger numbers of cases and controls to confirm the association.

Key techniques: *Massively Parallel (Next Gen) sequencing, including capture design, library preparation, and sequencing. Bioinformatics analysis will include sequence alignment and variant calling, variant annotation, pathogenicity prediction. If time permits, SNP genotyping and association analysis will be included.*

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GENE THERAPY FOR BLINDING EYE DISEASES: OPTIMISATION OF ADENO-ASSOCIATED VIRAL VECTORS FOR RETINAL GENE AUGMENTATION THERAPY

Supervisory team: *A/Prof Alex Hewitt; Dr Rick Liu*

Project Description: *Adeno-associated virus (AAV) vectors have emerged as the preeminent gene delivery platform for gene augmentation studies and have now been used in a small number of clinical trials for the treatment of blinding retinal diseases. From these initial studies it is clear that the early generation of AAV vectors have a relatively limited cellular transfection repertoire and poor long-term expression efficiency. Recently, several new AAV serotypes have been developed using innovative in silico and bioinformatics techniques. These novel vectors may provide more robust retinal gene transduction by allowing having broader cell penetration, faster onset and more efficient transgene expression than conventional AAV systems. The specific aim of this project is to screen a variety of novel AAV vectors in the eye, to determine which subtypes provide the most promising delivery vehicle for the next generation of gene augmentation therapies. In this project, we will validate the viral tropism and gene transduction efficacy of 18 specific AAV serotypes in the murine retina.*

Key techniques: *cell culturing, plasmid construction, animal handling, microdissection; histological analysis.*

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CRISPR/CAS CORRECTION OF PATIENT-SPECIFIC CELL LINES WITH BLINDING DISEASE MUTATIONS

Supervisory team: *A/Prof Alex Hewitt; Dr Tony Cook; A/Prof Kathryn Burdon*

Project Description: *Breakthroughs in cellular and molecular technologies have led to the ability to generate induced pluripotent stem cells (iPSCs) from adult somatic cells, which can be subsequently differentiated into*

potentially any cell type. This offers the unique ability to interrogate pathological processes in specific cell types such as retinal cells, which cannot be easily obtained pre-mortem. Further, the adaptation of Clustered Regularly Interspersed Short Tandem Repeat (CRISPR) and CRISPR-associated protein (Cas) technology to mammalian cells has enabled the direct editing of genetic variants with high fidelity. Combing these two technologies, reverse genomic profiling provides the ability to definitively determined the up- and down-stream pathways involved in disease. The overriding hypothesis of this work is that iPSC-derived RPE cells from patients with known disease-causing mutations have fundamentally different functional and molecular profiles to isogenic lines which do not harbour these genetic mutations.

Key techniques: *CRISPR/Cas construct design, cell culturing, plasmid construction, DNA/mutational screening.*

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DETERMINING THE UNDERLYING CAUSE OF CHROMOSOME 7P21 LOSS IN A TASMANIAN PROSTATE CANCER PEDIGREE

Supervisory team: *Dr Liesel FitzGerald; Assoc Prof Jo Dickinson*

Project description: *We have preliminary data that suggests several cases from a large Tasmanian hereditary prostate cancer family exhibit loss or gain of chromosome 7p21, a region that encompasses the ETV1 gene. This gene is a member of the ETS gene family and rearrangements are found in ~7% of prostate tumours. Notably, 13 of 16 PcTas9 tumours had evidence of 7p21 alterations, a prevalence far greater than that documented in sporadic populations. The objective of this honours project is to fine-map and elucidate the underlying cause of 7p21 alterations in the tumours of PcTas9 affected men. Specifically, to determine if this loss or gain is due to translocation of the ETV1 gene to one of its fusion partners. This project will utilise a wide range of laboratory techniques, including: DNA and RNA extraction from archived formalin-fixed, paraffin-embedded tumour tissue; next-generation SNP array hybridisation to fine-map 7p21 loss; 5' rapid amplification of cDNA ends (RACE) and Sanger sequencing to determine fusion products; and fluorescent in-situ hybridisation (FISH) to determine the frequency of fusion products in PcTas9 cases. Results from this project may have a significant impact in this area of prostate cancer research and could result in a publication(s) as well as an opportunity to continue the research as a PhD project.*

Key techniques: *DNA and RNA extraction, SNP array hybridisation, 5' rapid amplification of cDNA ends (RACE), Sanger sequencing, fluorescent in-situ hybridisation.*

Suggested reading: *Tomlins et al. (2005) Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer. Science. 310; 644-48. Attard et al. (2008) Heterogeneity and clinical significance of ETV1 translocations in human prostate cancer. British Journal of Cancer. 99; 314-20*

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