Menzies Institute for Medical Research
Honours Projects 2018

If you are interested in undertaking one of these research projects in 2018, 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).

PROJECTS LISTED BY THEME

NEURODEGENERATIVE DISEASE AND BRAIN INJURY THEME

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

Supervisory team: A/Prof Tracey Dickson and Dr 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

TARGETING SPINES IN ALS-FTD: PROTECTING AGAINST CASCADING SYNAPTIC DEFICITS

Supervisors: Dr Catherine Blizzard and A/Prof Tracey Dickson

Project description: Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) exist on a disease spectrum that is absent of any effective treatments. In the clinic, ALS and FTD both present with abnormalities in neuronal excitability in the cortex and a plethora of experimental models have now demonstrated that alterations in excitability are an important pathogenic event, occurring both in sporadic and familial forms of disease and prior to the onset of symptoms. We have found that TDP-43, the protein that is most frequently found in large cytoplasmic aggregates in both ALS and FTD, is involved in maintaining neuronal synapses – regulating the number and maturation of dendritic spines. Spine changes occurred well before symptom onset in the motor cortex but not in the somatosensory cortex, indicating that this is one of the earliest pathological changes associated with TDP-43 and that the motor cortex is specifically affected. It is now time to draw upon these findings and unravel the motor cortex specific mechanism behind this disruption in spine function and establish a therapeutic intervention point. This project involves culturing motor neurons, in vitro, derived from a novel mouse model in which TDP-43 expression, targeted to the synaptic compartment, can be selectively 'turned on' and 'turned off', to investigate the specific mechanism of TDP-43 at the synapse and how to rescue this.

Key techniques: cell culture, tetracycline-controlled transcriptional activation, immunocytochemistry

Contact: Catherine.Blizzard@utas.edu.au

UNDERSTANDING OLIGODENDROCYTE PROGENITOR CELL BIOLOGY TO DEVELOP NEW TREATMENTS FOR MULTIPLE SCLEROSIS AND OLIGODENDROGLIOMA

Supervisory team: Dr Kaylene Young

Project description: Oligodendrocyte progenitor cells (OPCs) proliferate and make new oligodendrocytes throughout life. We recently identified novel cell surface receptors that regulate OPC proliferation as well as the way these cells contact and interact with other cells in the brain. The main aim of this project is to identify the ligand/s that activate these receptors, and the downstream signaling 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 maturation of these cells into oligodendrocytes and the way they interact with each other, as well as nearby neurons and astrocytes. 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

HOW DO OLIGODENDROCYTES DIE IN THE HEALTHY AND DISEASED BRAIN?

Supervisory team: Dr Kaylene Young, Dr Nicole Bye and Dr Brad Sutherland.

Project description: Oligodendrocytes die in multiple sclerosis and stroke lesions. The mechanism of oligodendrocyte death is not fully understood, meaning that we have no way of blocking this death therapeutically. It is also not known whether oligodendrocytes die in the normal healthy or ageing brain. This project aims to determine (i) the extent to which mature oligodendrocytes, generated during development, die over the lifetime, (ii) how they die and (iii) whether the mode of death is the same under disease conditions. This project requires the use of cre-lox transgenic technology to fluorescently label developmentally-generated oligodendrocytes, allowing us to follow them over time, immunohistochemistry and confocal microscopy to determine whether they die by apoptosis or ferroptosis, and drug administration to attempt to block oligodendrocyte death.

Key techniques: animal handling, DNA extractions, PCR, cre-lox recombination, oxygen-glucose deprivation of tissue ex vivo, immunohistochemistry, western blot, confocal microscopy, cell quantification and statistical analysis.

Contact: Kaylene.young@utas.edu.au

WHAT DO KAINATE RECEPTORS HAVE TO DO WITH MULTIPLE SCLEROSIS?

Supervisory team: Dr Kimberley Pitman, Dr Kaylene Young, Dr 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 whole cell patch clamp electrophysiology to record electrical currents in response to kainate receptor activation.

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

Contact: Kimberley.Pitman@utas.edu.au

DISCOVERING THE TARGETS OF NEURAL STEM CELL TRANSCRIPTION FACTORS

Supervisory team: Dr Owen Marshall, Dr Caroline Delandre

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 family of transcription factors are the bHLH genes that respond to Notch signalling. These are vital for both NSC maintenance and for specifying a subset of neuronal lineages. This project aims to identify the genome-wide binding targets of these transcription factors in NSCs and immature neurons within the brain of the fruit fly, Drosophila melanogaster, using the Targeted DamID technique and next-generation sequencing. The results will be integrated with existing expression and epigenetics data to gain an understanding of how the brain develops.

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 Caroline Delandre

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

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 ran a Lifestyle and Environment Survey which contains data on height 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. It also tells us what people with MS do themselves to improve their symptoms, allowing them to learn from each other. A study with real life implications! 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

EXPLORING THE PUBLIC HEALTH IMPACT OF NOVEL SETTINGS FOR PHYSICAL ACTIVITY PROMOTION

Supervisory team: Dr Verity Cleland, Dr Meredith Nash

Project Description: Physical inactivity is a significant risk factor for a range of common and chronic diseases, and places substantial economic burden on governments, communities and individuals. Given that the prevalence of inactivity has remained stable over the past three decades, exploration of novel settings and strategies to increase physical activity is required. There are a number of opportunities to work across three key applied research program areas: increasing active travel behaviours, exploring parkrun as a setting for physical activity promotion, and understanding rural physical activity environments.

Key techniques: Projects may be quantitative or qualitative in nature, and students may be involved in analysing existing data and/or collecting new data from observational and/or intervention studies. Students will be able to apply principles of epidemiology and public health, will become proficient in analysing data using appropriate software packages, will gain experience in academic writing, and will contribute to research dissemination and translation. This project will suit students with an interest in epidemiology, public health, psychology, sports/exercise science, transport planning, and/or biostatistics

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UNDERSTANDING THE HEALTH IMPACTS OF THE HAZELWOOD COAL MINE FIRE

Supervisory team: Dr Fay Johnston, Dr Shannon Melody

Project description: A fire in the Hazlewood coal mine blanketed Morwell and the surrounding area in brown coal smoke and ash for six weeks in February and March 2014. In response to community concerns about long-term health effects, the Victorian Department of Health and Human Services commissioned the Hazelwood Health Study. This project will contribute to the early childhood component of this study by conducting a data linkage analysis to explore associations between hospital attendances and how much smoke a child (or, if they were not yet born, their mother) was exposed to. This will help build an understanding of the impact of smoke exposure on early childhood health and development. The student should have a solid grounding in statistical modelling.

Key techniques: The student will gain skills in data linkage and population-scale epidemiological analysis. Students will develop strong skills in quantitative analysis (using R). This project will suit students with an interest in epidemiology, public health, environmental health and/or biostatistics.

Contact: Fay.Johnston@utas.edu.au

IS IT POLLEN OR IS IT FUNGI? DETERMINING THE CAUSE OF ALLERGIES IN TASMANIA

Supervisory team: Dr Fay Johnston, Dr Grant Williamson, Penelope Jones

Project description: Fungi are known to be a major trigger for allergies and asthma, yet across Australia a paucity of fungi-based studies means that we have very little understanding about their contribution to asthma and allergy symptoms at a population scale: in particular, how they compare to and/or interact with pollen and smoke as asthma and allergy triggers. This project will provide the first systematic analysis of the contribution of fungal spores to asthma and allergies by:

1) Counting the number of allergenic fungal spores on daily microscope slides (previously collected for pollen analysis by the 'AirRater' project); and
2) Building a model that tests associations between fungal spore abundance and asthma and allergy symptoms reported by users of the 'AirRater' app.

This will provide an important platform for understanding the role of fungi in asthma and allergies in Tasmania, and the degree to which they should be prioritised in clinical and public health settings.

Key techniques: The student will gain skills in both microscope identification and the statistical analysis of epidemiological data. Students will develop strong skills in quantitative analysis (using R) and an appreciation for the challenges and opportunities in utilising crowd-sourced symptom data: a rapidly emerging but challenging field. This project will suit students with an interest in epidemiology, public health, environmental health and/or biostatistics.

Contact: Fay.Johnston@utas.edu.au

DO TASMANIAN NATIVE PLANTS CAUSE ALLERGIES?

Supervisory team: Dr Fay Johnston, Dr Grant Williamson, Penelope Jones

Project description: Pollen is a major cause of allergic disease, with over 20% of the Tasmanian population suffering regularly from hay fever (allergic rhinitis). However, diagnosis and treatment of pollen allergies is limited by a lack of information about which pollen types are the most prevalent allergy triggers. In particular, almost nothing is known about the allergenicity of native pollen types and whether

they should be considered as clinically-relevant. This project uses symptom data collected by the 'AirRater app' and other methods to test whether native pollen types should be considered as allergy triggers. This highly novel research will have the potential to significantly contribute to improved allergy treatment and diagnosis in Tasmania.

Key techniques: This project will utilise a mixture of epidemiological and immunological techniques. It will suit students with a background in public health, applied science, biostatistics, and/or immunology.

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IS THERE AN ALLERGY 'HOT SPOT' IN HOBART? COMPARING POLLEN ALLERGEN EXPOSURE ON HOBART'S EASTERN AND WESTERN SHORES

Supervisory team: Dr Fay Johnston, Dr Grant Williamson, Penelope Jones

Project description: Pollen is a major cause of allergic disease with over 20% of the Tasmanian population suffering regularly from hay fever (allergic rhinitis). Understanding where and when people are exposed to pollen can help significantly in reducing the associated burden of disease. AirRater is a novel smartphone app and environmental monitoring system that is helping to map population exposure to pollen (as well as smoke and temperature extremes) across Tasmania. This includes monitoring atmospheric pollen levels at both Sandy Bay and Mornington, providing a unique opportunity to compare population exposure to allergenic pollen types on Hobart's eastern and western shores. This project will contribute towards this by analysing the pollen slides from Mornington to build a picture of eastern shore pollen exposure. You will then compare the data with those from Sandy Bay and use this to develop a basic spatial model of pollen variability across Hobart.

Key techniques: The project will involve the identification of pollen on microscope slides and statistical analysis of pollen, meteorological and land use data. Statistical analysis will be conducted using R. The project will suit a students with an interest in transdisciplinary approaches to public health, environmental health and/or epidemiology.

Contact: Fay.Johnston@utas.edu.au

CAN PORTABLE AIR CLEANERS REDUCE EXPOSURE TO OUTDOOR SMOKE AND PROTECT HEALTH?

Supervisory team: Dr Amanda Wheeler, Dr Fay Johnston

Project description: Funded by the Tasmanian Community Fund. There is interest in understanding exposures to smoke in Australian homes. The study will conduct indoor and outdoor measurements of smoke and will develop a housing characteristic survey to understand the levels in homes. A number of different interventions will be included to see which is the most successful at reducing air pollution in homes. Residents will track their health symptoms through the AirRater app. Students should have a background in health sciences, public health, applied science, biostatistics, medical research.

Key techniques: Conducting data collection and interpreting data to understand the impact of interventions on indoor air quality and health.

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PSYCHOSOCIAL PREDICTORS OF LATENT BODY MASS INDEX TRAJECTORIES ACROSS THE LIFECOURSE

Supervisor: Dr Costan Magnussen, Marie-Jeanne Buscot

Project description and techniques: The prevalence of overweight and obesity has increased substantially in both adults and children in the last 30 years. Excess weight and weight gain in youth are associated with adverse long-term cardiometabolic risk markers and with increased cardiovascular disease morbidity and mortality in adulthood. A recent study, using data from a multi-wave longitudinal cohort, demonstrated that there are multiple developmental patterns of body mass index (BMI) from childhood to adulthood, and showed that these distinct BMI trajectories classes were associated with different levels of cardiometabolic risk in adulthood.

However, this study did not investigate the role of psychosocial determinants in predicting the development, stabilisation or resolution of obesity from childhood to adulthood. Cross sectional studies have highlighted the importance of factors such as occupation, education, self-esteem, and mental health in predicting obesity in adults, as well as parental education, familial socio-economic status, and anxiety in the aetiology of childhood obesity. However no study investigated whether some of these factors, in childhood or adulthood, or change in risk factor level over time, distinguished the different BMI trajectory classes across the life course. Identifying these risk factors could help identify different subgroups at risk of developing obesity at different critical periods in the life course. In doing so, psychosocial predictors pertaining to the development of obesity may be useful in determining factors to target for primary prevention, and they may also be of relevance for secondary prevention, since they may be applicable to recurrence of obesity in formerly obese patients. The purpose of this study will be to study the predictors of latent BMI trajectory class membership identified via Growth Mixture Modelling in the previous study.

Key techniques: Key techniques will include coding and standardization of all covariates, multiple imputation of predictor variables, and multinomial logistic regression analyses of BMI trajectory class membership status with psychosocial factors as predictors. An aptitude or interest for biostatistics is essential. You will learn 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: cmagnuss@utas.edu.au, m.buscot@utas.edu.au

ASSOCIATION BETWEEN LONG-TERM BLOOD LIPID TRAJECTORIES AND SUBCLINICAL CARDIOVASCULAR OUTCOMES IN MID-ADULTHOOD

Supervisor: Dr Costan Magnussen, Marie-Jeanne Buscot

Project description and techniques: Abnormal circulation lipid levels, also known as dyslipidemia, is a major risk for atherosclerosis, a leading cause of cardiovascular disease worldwide. To assess pre-clinical vascular change, the presence of increased carotid intima-media thickness (cIMT) and coronary artery calcification (CAC), can be detected non-invasively and reliably by ultrasound. These two commonly used markers of structural atherosclerosis strongly correlate with the severity of coronary atherosclerotic lesions and with the rate of future cardiovascular events. Adverse serum lipid profiles in young adulthood are associated with adult atherosclerosis, but the condition is known to begin in childhood: Cross-sectional and longitudinal studies have shown that exposure to atherogenic lipid profiles in early life was associated with the development of atherosclerosis.

However, at present, limited data allow linking long-term blood lipid profiles to later cardiovascular disease endpoints and it remains poorly understood whether distinct blood lipid trajectories from childhood to adulthood predict different levels of cIMT or CAC, or whether a specific long-term serum lipid pattern is more strongly associated with pre-clinical atherosclerosis than others. In particular, no study to date has determined whether early onset dyslipidemia is associated with worse cIMT / CAC compared to later onset dyslipidemia.

The purpose of this project will be identify latent serum lipid trajectories in a large multi-wave cohort study from age 6 to 49 years, and to examine whether latent class membership predicts subclinical cardiovascular outcomes such as cIMT and CAC, while adjusting for potential time-varying confounders (such as sex, and developmental trajectories of BMI- and blood pressure).

Key techniques: Key techniques will include identification of latent serum lipid trajectory classes using state of the art Latent Class Growth Mixture Modelling (LCGM), and Poisson regression analysis with robust error variance. An aptitude or interest for biostatistics is essential. You will learn 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.

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OVERCOMING THE PHYSIOLOGICAL EFFECTS OF APNOEA IN PRETERM INFANTS

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

Project description: The respiratory course for a very preterm infant during first hospitalization is most usually characterized by a protracted requirement for non-invasive respiratory support and oxygen therapy. This is a period of vulnerability, with reliance on an infant's spontaneous respiratory effort to maintain cardiorespiratory stability at a time when respiratory pause events or apnea are frequent. Apnea (cessation of breathing for > 20 sec or > 10 sec if accompanied by physiological destabilisation) is a well-recognized cause of episodes of hypoxemia (low oxygen level) and/or bradycardia (low heart rate), which in turn appear to have lasting neurodevelopmental consequences in preterm infants.

Our combined Medical and Engineering research group (the "GREMLINS")[1] is investigating ways to better support and control the respiratory system of the preterm infant. In the past 5 years, and with the aid of 3 MBBS Honours students (Kathleen Lim, Gemma Plottier and Oliver Ladlow), along with numerous UTAS Engineering Honours students, we have developed and clinically tested a device to automatically control inspired oxygen concentration (FiO_2) in preterm infants on continuous positive airway pressure (CPAP).[2,3] This device, the function of which is under further study during 2017, shows a clear capacity to keep the oxygen saturation (SpO_2) in the desired target range for more of the time than manual control of FiO_2 by bedside staff. We have also begun to understand the factors that contribute to instability of SpO_2 in preterm infants, with apnoea and loss of CPAP pressure being two major contributors. We have recently found that even brief pauses in breathing (5-9 sec in duration) are enough to cause significant hypoxic and bradycardic episodes in infants on CPAP. We are now investigating whether a similar feedback-controlled device can: i) "cut short" a pause in breathing and thus avoid the physiological instability that often follows, and/or ii) deliver a brief pulse of increased oxygen to avoid or foreshorten a hypoxic event. A series of bench top and clinical studies is planned to investigate each of these questions. These studies will be conducted in 2018 and beyond in collaboration with UTAS School of Engineering, and will be largely based in the Neonatal and Paediatric Intensive Care Unit at the Royal Hobart Hospital.

1. GREMLINS: **Gr**oup of **E**ngineers and **M**edics **L**aboriously **I**nvestigating **N**eonatal **S**ystems
2. Dargaville PA, Sadeghi Fathabadi O, Plottier GK, Lim K, Wheeler KI, Jayakar R, Gale TJ. Development and pre-clinical testing of an adaptive algorithm for automated control of inspired oxygen in the preterm infant. Arch Dis Child Fetal Neonatal Ed 2017; 102: F31-F36.
3. Plottier GK, Wheeler KI, Ali SKM, Sadeghi Fathabadi O, Jayakar R, Gale TJ, Dargaville PA. Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support. Arch Dis Child Fetal Neonatal Ed 2017; 102: F37-F43.

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CHILD MUSCULAR FITNESS AND INFLAMMATORY BIOMARKERS IN YOUNG ADULTHOOD: A 20-YEAR COHORT STUDY

Supervisor: Dr Costan Magnussen

Project description: Cardiovascular disease remains the major contributor to health care costs in Australia and worldwide. Although the major health complications of cardiovascular disease do not typically occur before middle age, the disease process begins early in life and progresses through adolescence and young adulthood. Current evidence suggests multiple child and adolescent risk factors such as adiposity, blood pressure, smoking, blood lipid levels, and parental and socioeconomic factors predict cardiovascular disease in adulthood. Higher levels of cardiorespiratory fitness have been shown to protect against a number of health outcomes including cardiovascular disease. However, interest has recently turned toward the potential independent importance of muscular fitness, a unique type of fitness. For example, data from a multi-country study has shown that low grip strength in adults

associates with all-cause death, cardiovascular death, and cardiovascular disease. Importantly, low grip strength was more strongly associated with all-cause and cardiovascular mortality than hypertension – a well-established risk factor. These data have highlighted the potential long-term benefits of increased muscular fitness to important health outcomes, especially cardiovascular health. The major underlying cause of cardiovascular disease is an inflammatory process that begins early in life. However, the association between childhood muscular fitness levels with adult markers of inflammation has not been examined.

Aim: To examine the independent association of child muscular fitness (strength, endurance, power) with adult biomarkers of inflammation (high-sensitivity C-reactive protein, fibrinogen, GlycA).

Study overview: This project will use data from approx. 2000 participants in the Childhood Determinants of Adult Health (CDAH) study. This study first measured participants from across Australia when they were aged 7-15 years old in 1985, who were again measured 20 years later as adults. In both the child and adult stages of the study, participants were measured for muscular and cardiorespiratory fitness, as well as cardiovascular risk factors. In adulthood, biomarkers of inflammation were measured from blood samples collected from participants.

Skill development: To get the most from this project, you will require (or attain) an interest in statistical analysis methods, which we will help you to develop using a statistical package called STATA or R. You will be taught different epidemiological principals, such as confounding, causality, bias, and effect modification. The skills you develop working in an epidemiological study such as this are broadly applicable to a number of research enquiries in medical research. There will be opportunities to interact with a group of researchers working on related projects, and your work will form the basis of a paper that will be submitted to a journal to be published.

Suggested readings:

1. Fraser BJ, Huynh QL, Schmidt MD, Dwyer T, Venn AJ, Magnussen CG. Childhood Muscular Fitness Phenotypes and Adult Metabolic Syndrome. Med Sci Sports Exerc. 2016;48:1715-22
2. Gall SL, Jose K, Smith K, Dwyer T, Venn A. The Childhood Determinants of Adult Health Study: A Profile of a Cohort Study to Examine the Childhood Influences on Adult Cardiovascular Health. Australasian Epidemiologist. 2009;16:35-9.
3. Steene-Johannessen J, Kolle E, Andersen LB, Anderssen SA. Adiposity, aerobic fitness, muscle fitness, and markers of inflammation in children. Med Sci Sports Exerc. 2013 Apr;45(4):714-21.
4. Agostinis-Sobrinho CA, Moreira C, Abreu S, Lopes L, Sardinha LB, Oliveira-Santos J, Oliveira A, Mota J, Santos R. Muscular fitness and metabolic and inflammatory biomarkers in adolescents: Results from LabMed Physical Activity Study. Scand J Med Sci Sports. 2016 Nov 23.
5. Artero EG, España-Romero V, Jiménez-Pavón D, Martinez-Gómez D, Warnberg J, Gómez-Martínez S, González-Gross M, Vanhelst J, Kafatos A, Molnar D, De Henauw S, Moreno LA, Marcos A, Castillo MJ; HELENA study group. Pediatr Obes. 2014 Oct;9(5):391-400.

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CARDIO-METABOLIC HEALTH AND DISEASE THEME

GROWTH, TEMPORAL TRENDS, AND CLINICAL IMPACT OF CARDIOVASCULAR MEDICATIONS IN AUSTRALIA

Supervisors: Dr Ricardo Fonseca and Prof. James Sharman

Overview: Population growth, higher life expectancy, new technologies, and growth of burden of chronic diseases, have contributed to the increase of the health expenditure in Australia. Cardiovascular disease remains associated with the highest level of mortality, burden of illness, and health care spending, and has been a primary contributor to the rise in health costs.(1-3)

This study aims to determine the growth and regional differences in the use of the cardiovascular medications, and its impact on cardiovascular outcomes. The project will involve collection and analysis of data from Medicare statistics, Australian Bureau of Statistics (ABS) and ABS Health Survey, and Australian Workforce data.

Aims of the project:

1. To understand the associations between the use of cardiovascular medications and cardiovascular mortality.
2. To determine the temporal trends and regional variation in the utilisation of different cardiovascular medicines in Australia.

Key techniques: This study would suit a student who is interested in the use of medical services and its economic and clinical impact. The student will learn how to collect and analyse data using statistical methods.

References

1. OECD. Cardiovascular Disease and Diabetes: Policies for Better Health and Quality of Care: OECD Publishing.
2. Australian Institute of Health and Welfare. Australia's health 2016. Australia's health series no. 15. Cat. no. AUS 199. Canberra: AIHW. 2016.
3. Australian Institute of Health and Welfare. Health expenditure Australia 2014–15. Health and welfare expenditure series no. 57. Cat. no. HWE 67. Canberra: AIHW. 2016.

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

Supervisors: Dr Martin Schultz and Prof 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 of AEP intervention on BP control and other hypertension-related markers of CV risk.

The project comprises part of an existing research program, and participation will involve assistance with data collection, 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

AORTIC RESERVOIR AND NOVEL BLOOD PRESSURE PHENOTYPES

Supervisors: Dr Martin Schultz, Dean Picone and Prof James Sharman

Overview: Cardiovascular disease is the number one risk factor for mortality worldwide and blood pressure (BP) is the leading risk factor. We have recently discovered four BP phenotypes from intra-arterial recordings that are not differentiated by conventional cuff BP, despite distinct differences in aortic BP and BP waveform characteristics. Two phenotypes have substantially elevated aortic BP, suggesting these patients are at increased cardiovascular risk. The reservoir-excess pressure paradigm is a relatively new method to analyze arterial pressure waveforms. Work from our group and others has shown the reservoir-excess pressure model is both physiologically plausible and clinically relevant. This model has never been applied to these BP phenotypes, but would greatly improve the physiological understanding of each phenotype. The aims of this project are to apply the reservoir-excess pressure model to intra-arterial BP waveforms from four BP phenotypes to determine differences in waveform characteristics. Additionally, the clinical relevance of the reservoir-excess pressure parameters to target organ damage will also be assessed.

The project comprises part of an existing research program in collaboration with the Royal Hobart Hospital cardiology department. Participation will involve data collection at both RHH and at the Menzies Institute clinical research facilities, in addition to analysis of existing human physiological data. Prospective candidates are encouraged to contact BP research group supervisors for more detail or to discuss other options for related research activities.

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COMPARING SELF-REPORTED PHYSICAL ACTIVITY TO OBJECTIVE MEASURES OF PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS

Supervisory team: Prof. James Sharman, Niamh Chapman (PhD candidate).

Project Description: Increased levels of cardiorespiratory fitness (CRF) and greater physical activity (PA) habits are inversely associated with cardiovascular and all-cause mortality, making it desirable to assess CRF and PA patterns in clinical encounters. Direct and indirect methods of estimating PA are available, such as indirect monitoring devices (pedometer, accelerometer) or activity logs and directly measuring oxygen uptake (VO_2). The drawbacks of these methods result in these important health determinants rarely being assessed during clinical visits. Self-report questionnaires (SRQs) have been used extensively in epidemiological research to estimate PA levels. Indeed, recent evidence indicates that a single PA question can be used to gather sufficient information regarding PA to improve risk stratification by 23% or estimate CRF if other variables such as resting heart rate are available. While lengthy PA questionnaires have been validated, they do not provide a feasible alternative for the clinical environment. Relatively few studies have measured both PA and CRF in the same cohort. The aim of this study is to compare a single PA question as part of a SRQ to objective measures of PA and CRF.

This project forms part of a larger research program for the IDEAL (Improved cardiovascular Disease hEALth service delivery in Australia) study. Participation will involve data collection on a broad range of cardiovascular health parameters in the Menzies Blood Pressure Clinic. This study would suit a person with a keen interest in clinical research, public health and physical activity behaviours.

Contact: James.Sharman@utas.edu.au or Niamh.Chapman@utas.edu.au

PREDICTORS OF SMOKING CESSATION IN YOUNGER ADULTS

Supervisory team: Dr Jing Tian, Dr Seana Gall

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: J.Tian@utas.edu.au

THE ROLE OF EMERGENCY SERVICES IN THE MANAGEMENT AND OUTCOMES OF ANEURYSMAL SUBARACHNOID HAEMORRHAGE

Supervisory team: Dr Seana Gall, Ms Linda Nichols

Project description: Aneurysmal subarachnoid haemorrhage (aSAH) is a rare form of stroke that results in death in up to 40% of people by 1 month later. There is very little known about the role of emergency services in the pre-hospital management of aSAH. We have established a Tasmania-wide population-based study of all cases of aSAH that occurred between 2010 and 2014. As a part of this study we have gathered information from Ambulance Tasmania about care provided by the ambulance service. This project will involve examining activation of emergency services in people with aSAH, aspects of the clinical care provided and how it relates to people's outcomes.

Key techniques: The project involve analysis of data from our retrospective cohort study using epidemiological methods. 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, medicine, paramedicine, and/or biostatistics.

Contact: Seana.Gall@utas.edu.au

CAN CHANGES IN THE PROFILE OF CARDIOVASCULAR HEALTH HELP US TO UNDERSTAND THE GROWING INCIDENCE OF STROKE AMONG YOUNGER PEOPLE?

Supervisory team: Dr Seana Gall, Mr Berhe Sahle

Project description: There is growing concern about the rising incidence of stroke among younger people worldwide. In an attempt to understand these trends we will analyse data from repeated National Health Surveys conducted by the Australian Bureau of Statistics to look at the cardiovascular health profile of different age groups over time. This will allow us to understand the key risk factors driving the increase in younger aged people to inform intervention strategies.

Key techniques: The student will develop skills in quantitative analysis as well as epidemiology. They will learn how to use the statistical program Stata. This project will suit students with an interest in epidemiology, medicine, public health and/or biostatistics.

Contact: Seana.Gall@utas.edu.au

USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY TO UNDERSTAND HOW AGING AFFECTS CORTICAL CONTROL OF BALANCE

Supervisory team: Dr Rebecca St George, Dr Michele Callisaya, Dr Mark Hinder

Project Description: Balance is critical to avoid falls and injury and becomes worse as people age. Balance control is largely considered an automatic process involving brain stem and spinal reflexes. However, there is evidence that as people age there is increased cortical involvement to compensate for deteriorating sensory and motor systems. Performing a cognitive task while performing a balance task is a way of probing the involvement of the cortex for balance. Direct measurement of cortical activity during standing balance has traditionally been problematic as fMRI scanners require subjects to be lying still. However, a new neuroimaging technique called Functional Near-Infrared Spectroscopy (fNIRS) can be performed during movement. Subjects wear a light-weight headband that wirelessly transmits the hemodynamic responses associated with neuron behaviour. This technique will provide

greater insight into the role of the cortex for balance control and how this role changes with age.

Key techniques: The project will involve testing old and young subjects on standing balance and gait while performing dual cognitive tasks. Cortical activity will be measured with functional near-infrared spectroscopy, while balance control will be measured via standing force plates and a gaitmat.

Contact: Dr Michele Callisaya: michele.callisaya@utas.edu.au

MUSCULOSKELETAL HEALTH AND DISEASE THEME

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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A RANDOMISED TRIAL OF CURCUMAL LONGA FOR TREATING SYMPTOMS AND EFFUSION-SYNOVITIS OF KNEE OSTEOARTHRITIS (CURKOA TRIAL)

Supervisory team: Dr Benny Antony

Project description: Osteoarthritis is a common joint disorder for which there is no cure. Inflammation of the joint lining (synovitis and excess joint fluid) is now recognised as a key part of osteoarthritis that predicts the progression of the disease including total joint replacement. Curcuma longa (commonly known as the turmeric plant) has anti-inflammatory, cartilage and bone protective properties, and can potentially be used to treat osteoarthritis patients with an inflammatory form of osteoarthritis. Previous studies of Curcuma longa have been of dubious quality and did not select patients with knee swelling,

which is a clinical indication of inflammation. The aim of this clinical trial is to determine the efficacy of Curcuma longa extract for treating knee osteoarthritis symptoms and effusion-synovitis (assessment of excess joint fluid using MRI). If successful, treatment with Curcuma longa can be easily implemented as it is inexpensive, safe and available over-the-counter.

The aim of this study is to compare the efficacy of Curcuma longa vs. identical placebo to treat knee pain and excess joint fluid in 70 older adults with clinical knee osteoarthritis, significant knee pain and local inflammation (effusion) on MRI using a randomised, double–blind, placebo–controlled clinical trial over 12 weeks.

This will be the largest clinical trial of Curcuma longa and the first to investigate use in a targeted population using imaging outcomes of effusion-synovitis. We will also determine the changes in inflammatory markers and cartilage degradation markers in the blood and urine. If Curcuma longa can improve both symptoms and effusion-synovitis in osteoarthritis, it may slow OA progression. The proposed study represents an innovative approach to this and lends itself to easy implementation as Curcuma longa is already available over-the-counter.

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IMPROVING THE NON-DRUG MANAGEMENT OF OSTEOARTHRITIS - AN EMPHASIS ON THE ROLE OF EXERCISE

Supervisory team: Dr Dawn Aitken, Prof Tania Winzenberg, Dr Laura Laslett

Project description: Osteoarthritis is a highly prevalent, painful, disabling, and costly condition that affects over 2.2 million Australians. It is the main reason for joint replacement surgery. Conservative (non-surgical) management is recommended for the treatment of osteoarthritis at all disease stages. The core treatments include patient education and self-management, exercise and weight loss support. Access to joint replacement is recommended when, and only when, conservative management no longer provides adequate pain relief or maintenance of function. Despite this, in Australia referral to a surgeon is five times more common than referral to a physiotherapist or dietitian (someone that can help with weight loss).

Key techniques: This project will involve a synthesis of the literature to gain a better understanding about why conservative management of osteoarthritis is so poor. There is an opportunity to perform a systematic review and meta-analysis in this area, which will inform strategies to improve the care of osteoarthritis patients. Students will learn the techniques of systematic review and meta-analysis and how to prepare conference abstracts and presentations and prepare a scientific manuscript for publication. Statistical supervision and training will be provided.

Contact: Dawn.Aitken@utas.edu.au

HOW DO FAT AND MUSCLE INTERACT TO INFLUENCE THE RISK OF OSTEOARTHRITIS DEVELOPMENT AND PROGRESSION?

Supervisory team: Dr Dawn Aitken, Saliu Balogun, Professor Graeme Jones

Project description: Osteoarthritis is a highly prevalent, painful, disabling, and costly condition that affects over 2.2 million Australians. Obesity is one of the most important risk factors for osteoarthritis. Other risk factors include low muscle mass (sarcopenia) and low muscle strength (dynapenia). The combination of obesity with low muscle mass and strength is termed sarcopenic obesity and dynapenic obesity, respectively.

Key techniques: This project will examine whether obesity combined with low muscle mass or low muscle strength (sarcopenic obesity/ dynapenic obesity) are associated with a greater risk of osteoarthritis development and progression, compared to obesity alone. It will use data from a 10-year Tasmanian cohort study that has measures on obesity, muscle and osteoarthritis outcomes (including MRI scans) at multiple time points over 10 years. Students will learn how to clean a data set ready for analysis, perform statistical analysis, interpret study results, prepare conference abstracts and presentations and prepare a scientific manuscript for publication. Statistical supervision and training will be provided.

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DO LIGAMENT AND ENTHESIS ABNORMALITIES PREDICT PAIN?

Supervisory team: Dr Laura Laslett, Dr Benny Antony

Project description: Knee pain is extremely common. One potential source of pain is abnormalities in ligaments and the point at which ligaments enter the bone (entheses). There is little population-based data on these abnormalities, and even less in younger populations.

Key techniques: This project will involve viewing MRI scans to collect data on ligament abnormalities and using statistical techniques to investigate associations between these abnormalities and knee pain and disability. These scans will come from data that has already been collected on younger adults (20's and 30's).

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PREDICTORS OF FALLS IN MIDDLE-AGED WOMEN: THE ROLE OF BALANCE AND LOWER LIMB MUSCLE STRENGTH (THE PRE-FALL STUDY).

Supervisory team: Dr Feitong Wu, Prof Tania Winzenberg, Dr Michele Callisaya

Project description: Falls are a major health issue among older people (>65 years) - approximately 1 in 3 community-dwelling older people fall each year. Falls cause considerable injury, morbidity, mortality and costs. Falls increase with age and most work to date on falls prevention has occurred in older adults (>65 years). However, a high incidence of falls in middle-aged women has also been reported. **This middle-aged group of women has largely been ignored in the context of falls prevention.** An additional concern is that a single fall is one of the strongest risk factors for future falling. Therefore, developing early interventions to prevent a first fall is also an important strategy to reduce long-term falls risk. To address this issue, there is an urgent need to understand both the circumstances and risk factors for falls in middle-aged women.

Our data show that in middle-aged women, weaker muscle strength is associated with poorer balance. These results suggest that improving muscle strength and balance in midlife may be beneficial for preventing falls in late midlife and even older age. However, evidence is needed to support a direct link between falls risk factors in middle-age and future falls before development of early intervention programs can be justified.

We have a unique existing cohort of middle-aged women (mean age 55 years in 2017) in whom we have measures of lower limb muscle strength and balance made in 2011-12, as well as of other potential falls risk factors. With these as baseline data, a further follow-up in 2017-18 will enable us to determine (a) whether modifiable falls risk factors in middle-age predict falls in later life; and (b) if deterioration in these factors create an additional risk of falling in later life.

Key techniques: Students will learn how to clean a data set ready for analysis, perform statistical analysis, interpret study results, prepare conference abstracts and presentations and prepare a scientific manuscript for publication. Statistical supervision and training will be provided.

Recommended reading: Feitong Wu, et al. Both Baseline and Change in Lower Limb Muscle Strength in Younger Women Are Independent Predictors of Balance in Middle Age: A 12-Year Population-Based Prospective Study. JBMR 2017 (32): 1201-08

Contact: Feitong.Wu@utas.edu.au

ASSOCIATIONS OF INFLAMMATORY MARKERS AND ADIPOKINES WITH MUSCULOSKELETAL HEALTH OUTCOMES IN MIDDLE-AGED WOMEN

Supervisory team: Prof Tania Winzenberg, Dr Feitong Wu

Project description: Participants were from a 10-years additional follow-up of 2-year randomised controlled trial conducted in 2000 in Southern Tasmania, Australia. The present project will be a cross-sectional analysis of 347 women retained in the study at 12 years (mean age of 50.0 years, 36.2 to 56.8 years of age). Inflammatory markers and adipokines included hs- CRP, interleukin -6 (IL-6), tumour necrosis factor alpha (TNF-α), adiponectin, resistin, visfatin and leptin. Outcomes were lumbar spine

and femoral neck bone mineral density, lower limb muscle strength and balance/mobility measures (timed up and go test, functional reach test, lateral reach test and step test). Linear regressions will be used to describe the association of inflammatory markers and adipokines with all outcomes.

Key techniques: Students will learn how to perform statistical analysis, interpret study results, prepare conference abstracts and presentations and prepare a scientific manuscript for publication. Statistical supervision and training will be provided.

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UNDERSTANDING DOMAINS IN THE PAIN TRAJECTORIES

Supervisory team: Dr Feng Pan, Prof Graeme Jones

Project description: Pain is a very complex process affected by multiple interactive pathways including genetic, environmental, socio-economic and psychological factors. Risk factors, such as environmental and psychosocial factors for pain, have been extensively investigated in previous epidemiology studies, although the potential mechanisms of these factors contributing to pain are not yet well understood. Knee pain is the most prominent symptom of knee osteoarthritis and generally gets worse with time. It is reported that approximately 21-35% of people aged 45 or over have had persistent knee pain lasting for at least one week during a month period. Although knee pain level and course over time can be very different among patients, there might have existing subgroups which follow similar courses (trajectories) over time. Successful identification of determinants and structural damage to different pain trajectories might lead to effective and targeted interventions to defined pain subgroup.

Key techniques: This project will utilise data from a 10-year Tasmanian Older Adult Cohort study where genetic, environmental, socio-economic and psychological factors have been collected. The student will gain skills in longitudinal study analysis using advanced statistical methods.

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CANCER, GENETICS AND IMMUNOLOGY THEME

MAPPING TRANS-ENDOCYTOSIS OF IMMUNOMODULATORY PROTEINS

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

Project description: We have recently developed a system to track immunomodulatory proteins that can be transferred between cells through processes called trans-endocytosis and trogocytosis[1–3]. Trans-endocytosis is where a protein on a cell (i.e. cell A) strips a protein off of a different cell (cell B) and brings the protein into cell B. Trogocytosis is where cell A strips the protein from cell B, and then the protein can be detected on the surface of cell B. Understanding these processes can shed light on how the immune system is regulated, particularly for anti-cancer immunity. The goals of this project are to use cutting-edge molecular biology techniques to map trans-endocytosis and trogocytosis of key immunomodulatory proteins. Our primary focus is on the Tasmanian devil immune system, but we also will apply the techniques to the human and canine immune systems. Our initial focus will be on the CTLA-4 protein and its ligands CD80 and CD86, but the project is readily adaptable to other key immunomodulatory proteins.

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, monitoring of trans-endocytosis, confocal microscopy, flow cytometry.

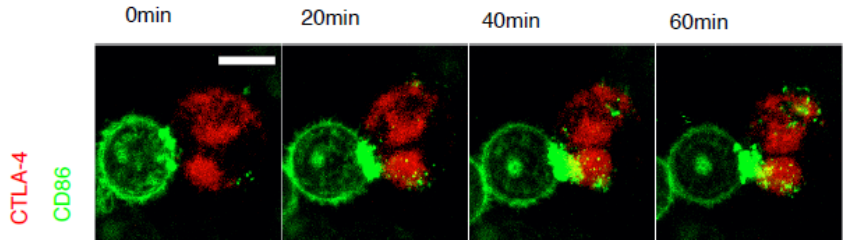

Fig. 1. Transendocytosis of CD86-GFP by cells expressing CTLA-4-RFP. Figure S4 Qureshi et al. 2011 shows that CD86-GFP (green) is rapidly transferred to cells that express CTLA-4-RFP (red)

Recommended reading:

1. Qureshi, O. S. et al. Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. Science (80-.). **332,** 600–3 (2011).
2. Qureshi, O. S. et al. Constitutive clathrin-mediated endocytosis of CTLA-4 persists during T cell activation. J. Biol. Chem. **287,** 9429–9440 (2012).
3. Briggs, Z. CD28 costimulation in T cells: requirements, outcomes and regulation. (2014).

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ASSESSING THE ROLE OF CYTOKINES IN THE DEVIL FACIAL TUMOUR DISEASE

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 help us to understand cancer and transplant rejection in other species, including humans. 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[2]. The goals of this project will be to use cutting-edge molecular biology techniques to develop new proteins (i.e. recombinant cytokine receptors) for studying and manipulating the devil immune system. Successful completion of the project will result in a better understanding the immunophenotype of devil immune cells and tumour cells, and will shed light on potential vaccine and immunotherapy pathway for the DFT diseases.

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, flow cytometry, immunofluorescence.

Recommended reading:

1. Pye, R. J. et al. A second transmissible cancer in Tasmanian devils. Proc. Natl. Acad. Sci. **113,** 201519691 (2016).
2. Flies, A. S., Blackburn, N. B., Lyons, A. B., Hayball, J. D. & Woods, G. M. Comparative analysis of immune checkpoint molecules and their potential role in the transmissible tasmanian devil facial tumor disease. Front. Immunol. **8,** 513 (2017).

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INVESTIGATION INTO AN OVERLOOKED PATHWAY IN THE CANCER-IMMUNITY CYCLE

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

Project description: Immunotherapy that works by blocking interactions between immune checkpoint molecules has revolutionised cancer immunotherapy in recent years 1,2. The most broadly effective immunotherapy to date works by neutralising the inhibitory effects of immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and immunoreceptor tyrosine-based switch motifs (ITSMs), which block activation of T cells. ITIM and ITSM phosphorylation in response to ligand binding (e.g. PD-1 binding to PD-L1) recruits phosphatases that dephosphorylate activation signals, such as the CD28 co-stimulatory signal that is necessary for T cell activation, which ultimately inhibits anti-tumour immune responses. The aim of this proposal is to investigate the function of previously overlooked ITIM sequences in checkpoint molecules.

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, flow cytometry.

Recommended reading:

1. Topalian, S. L. et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N. Engl. J. Med. 366, 2443–2454 (2012).
2. Postow, M. A. et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. N. Engl. J. Med. 372, 2006–2017 (2015).

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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. A biobank is 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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EVALUATING / OPTIMISING WHOLE GENOME SEQUENCING OF SALIVA SAMPLES FOR GENETICS RESEARCH

Supervisory team: A/Prof Kathryn Burdon, Dr Bennet McComish, Dr Jac Charlesworth

Project description: Whole genome sequencing is widely used in research to identify variants that lead to disease. DNA can be obtained from any tissue in the body, but is most commonly collected from whole blood. When a patient does not like the idea of a needle based blood test, or if a child is being tested, DNA can be obtained non-invasively from saliva. Saliva samples have been routinely used in genetics research for over a decade. It is well recognised that saliva DNA contains a high proportion of bacterial DNA. This is not typically a problem for traditional analysis methods that rely on PCR or other enrichment techniques for the DNA of interest. Whole genome sequencing, however, does not use any enrichment technique and bacterial DNA contamination can be a major problem.

This project will explore existing whole genome sequencing data from whole blood and saliva to determine if the quality of data from saliva is acceptable for research purposes. It will determine the extent of bacterial contamination, how this affects alignment and quality metrics, and determine if there are systematic gaps in coverage or errors in variant calling. The project is primarily analytical, but a laboratory component may be incorporated; such as testing laboratory-based methods for improving sequence coverage from saliva samples

Key techniques: Bioinformatics including analysis of whole genome sequencing data (such as alignment, quality metrics, variant calling, coverage analysis). Laboratory based DNA extraction and sample preparation prior to sequencing may be incorporated.

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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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INVESTIGATING THE ROLE OF SHORT TANDEM REPEAT SEQUENCE VARIATION IN MULTIPLE SCLEROSIS

Supervisory team: Dr Bennet McComish, Dr Jac Charlesworth, A/Prof Kathryn Burdon

Project description: Multiple sclerosis has a strong genetic component and genome-wide association studies have identified 103 loci associated with MS risk, but these account for less than 30% of the

predicted MS heritability. The remaining "missing heritability" may be due in part to variants in the human genome that are currently inaccessible at a population scale. One such class of variation is short tandem repeat (STR) unit-number variation. STRs (often known as microsatellites) are highly polymorphic variants that are ubiquitous in the human genome, but remain understudied in terms of their relationship to human phenotypes. STR mutations are known to be responsible for several neurological diseases with motor involvement, such as Huntington's disease, amyotrophic lateral sclerosis (ALS), and certain types of spinocerebellar ataxia. Disease severity is often correlated with the extent of abnormal repeat expansion.

This project will use whole-genome sequence data from extended families with a dense clustering of MS cases to identify and characterise rare STR variants associated with MS. We will analyse these variants for correlations between STR allele length and the severity and age of onset of MS. The project is primarily analytical, but a laboratory component may be incorporated to confirm genotypes for any STR loci identified.

Key techniques: Bioinformatics including analysis of whole genome sequencing data (e.g. alignment, quality metrics, STR variant calling, coverage analysis). Laboratory based DNA extraction, PCR and capillary electrophoresis may be incorporated.

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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-SPECFIC CELL LINES WITH BLINIDING 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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