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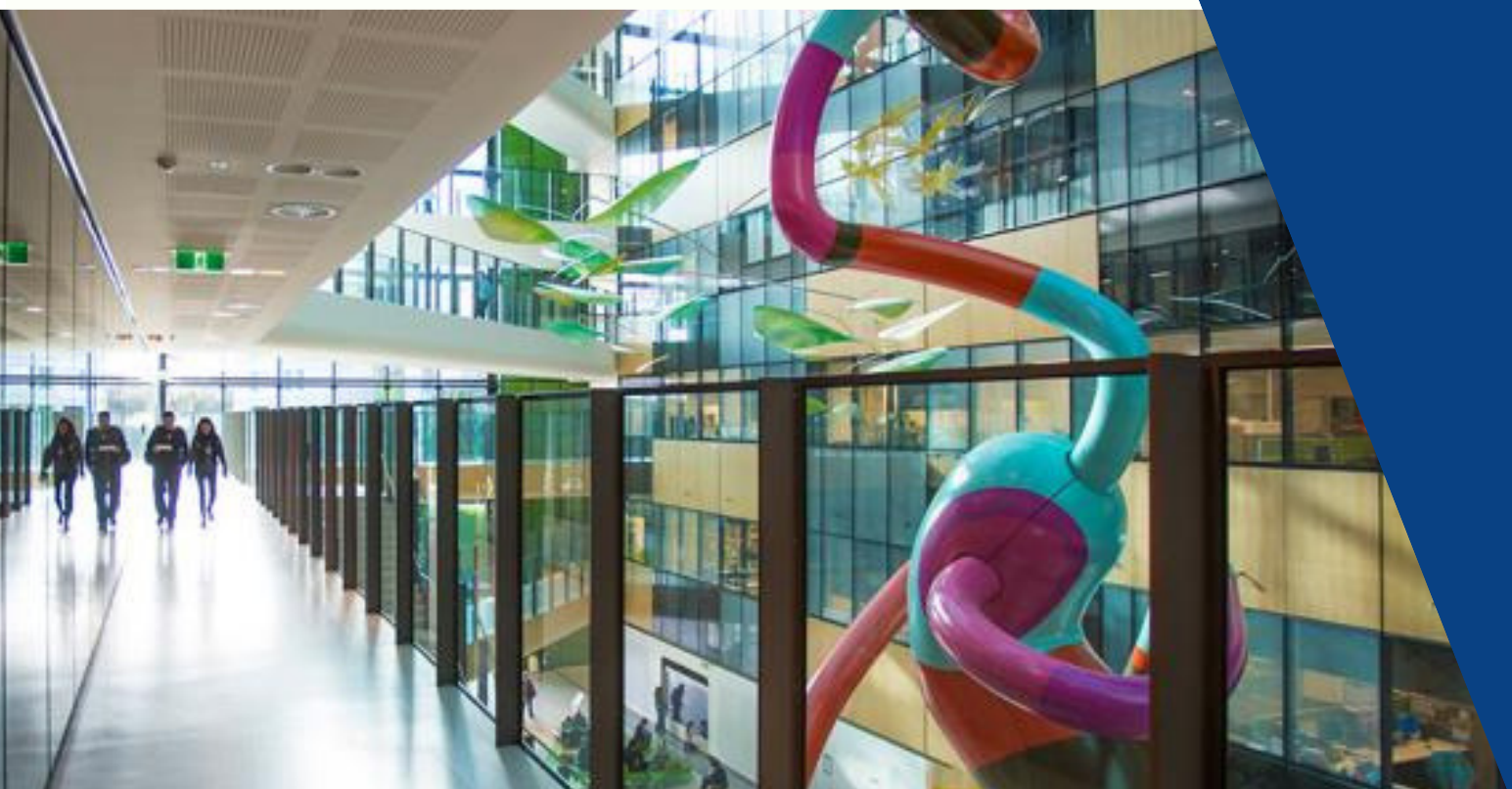
THE UNIVERSITY OF MELBOURNE

2019 HONOURS AND MASTERS PROJECTS

Department of Paediatrics

Faculty of Medicine Dentistry & Health Sciences



CONTENTS

Laboratory-based research

Cell Biology

1. How do monocytes remember? Characterisation of the early life exposures that induce Innate Immune Memory.

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Available as Masters Project: Yes

We all know that the adaptive immune system develops memory following specific antigen exposure, but is the same true for the innate immune system? An emerging field of research tells us exactly this, with epigenetic remodelling as the underlying mechanism. Innate immune cells, such as monocytes and macrophages, form this non-specific memory in response to a variety of exogenous signals. Exposure-induced epigenetic remodelling governs their future response to a range of pathogens. This process can be modelled in vitro, using both yeast and bacterial antigens and metabolites (Novakovic et al. Cell 2016), metabolites (Bekkering et al. Cell 2018), vaccines (Arts at el. Cell Host Microbe 2018) and a range of other stimuli.
During pregnancy, both maternal and foetal monocytes show attenuated pro-inflammatory responses correlated with pregnancy-associated hormones. Additionally, foetal monocytes are exposed to a range of environmental factors. We hypothesise that monocytes remodel their chromatin in response to early life environments, which explains their altered function during pregnancy. To test this hypothesis, we will isolate pure monocytes from human blood, and treat them with various stimuli in vitro. After treatment we will measure cytokine release, RNA expression and epigenetic (histone modification) changes. This project is appropriate for students with an interest in molecular biology and immunology and will utilise monocyte isolation and culture, ELISA, chromatin immune-precipitation (ChIP), DNA and RNA extraction and real-time PCR.

2. How does ACTN3 influence recovery from muscle atrophy?

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Alpha-actinin-3 (ACTN3) is a skeletal muscle protein responsible for maintaining the integrity of the contractile apparatus in fast-glycolytic muscle fibres. We have previously identified a common null polymorphism (R577X) in ACTN3. Approximately 1 in 5 people worldwide are homozygous for the X-allele (ACTN3 577XX), which results in complete deficiency of alpha-actinin-3 protein. While this does not cause disease, the absence of alpha-actinin-3 results in significantly lower muscle mass and strength/power in elite athletes and in the general population. We have generated

an alpha-actinin-3 knockout mouse (Actn3 KO) to model human alpha-actinin-3 deficiency. Using this model, we have shown that alpha-actinin-3 deficiency alters muscle mass, fast fibre size, muscle metabolism,calcium handling, and increases muscle susceptibility to eccentric contraction induced damage - all of which explains the altered muscle function in ACTN3 577XX humans. Recently, we found that the absence of alpha-actinin-3 also alters the pathways that regulate muscle mass. We also found that healthy Actn3 KO mice do not suffer as much muscle mass or strength loss as a result of corticosteroid treatment. Furthermore, Actn3 KO mice show a slower progression in muscle atrophy in response to activin-A over-expression. Increased activin-A is associated with increased muscle wasting during ageing and cancer.
This project will examine the role of alpha-actinin-3 expression in recovery from muscle atrophy. Using an inducible form of recombinant adeno-associated viral (rAAV) vector expressing activin-A, we will turn the gene on to induce muscle wasting, then turn the gene off again to allow for muscle recovery. We will compare the time course of muscle wasting and recovery in wildtype mice and in the Actn3 KO mouse model. This project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and muscle physiology to examine the functional, structural, metabolic and signalling changes in skeletal muscle.

3. How does ACTN3 influence muscle hypertrophy?

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Recently, we found that the absence of alpha-actinin-3 also alters the pathways that regulate muscle mass. We also found that healthy Actn3 KO mice do not suffer as much muscle mass or strength loss (muscle wasting) as a result of corticosteroid treatment. However, it is not yet clear if alpha-actinin-3 deficiency also influences how mature muscles grow in size (hypertrophy).

This project will examine the role of alpha-actinin-3 expression in muscle hypertrophy. Using a recombinant adeno-associated viral (rAAV) vector expressing follistatin to induce muscle growth, we will compare the hypertrophic response relative to dose in wildtype mice and in the Actn3 KO mouse model. This project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and muscle physiology to examine the functional, structural, metabolic and signalling changes in skeletal muscle.

4. Epigenetics as a mediator of gene: environment interactions underlying early life programming of cardiovascular and metabolic risk.

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The world is experiencing an alarming rise in the incidence of cardiovascular disease, obesity and poor metabolic health. Mounting evidence suggests that the period in utero and early postnatally plays a critical role in programming these phenotypes. Both genetic and environmental factors contribute to complex disease risk and are also known to influence epigenetic profile. Thus, epigenetic variation has emerged as prime candidate for the early life programming of later CV and metabolic health. Epigenetic variants have great potential as biomarkers for monitoring ideas progression and may be reversible with appropriate intervention. The overall aims of this project are to examine the association of epigenetic change in early life (with a focus on DNA methylation), genetic variation and environmental exposures, with measures of adiposity and cardiovascular health in the unique Barwon Infant study of 1000 mothers and their children (www.barwoninfantstudy.org.au/). BIS has a wealth of environmental measures and longitudinally sampled biospecimens with genome-wide genetic data already collected, enabling an unprecedented investigation of the role of genes, environment and epigenetics in conferring early life risk of cardio/metabolic health in humans.

5. Does DNA methylation predict a cell's response to environmental exposures?

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The term ''epigenetics'' literally means ''above DNA'' and refers to the study of molecular interactions that in?uence chromosome structure and gene activity. A key property of epigenetic marks, which are valuable in understanding the interaction between DNA and the environment, is that they do not simply indicate the state of the cell at time of collection but can carry the memory of past exposure and in?uence the potential of a cell to respond to future stimuli. Therefore, the epigenome (the complete epigenetic pro?le of a cell) can be said to contain information about the ''past, present, and future'' of a cell. One such epigenetic mark is DNA methylation, which when present at the promoter of a gene is (mostly) associated with gene silencing. Mounting evidence linking environmental exposures in early life to later risk of cardiovascular disease has led to intense interest in the process of vasculature development in utero. The placenta is home to three specific types of endothelial cells, which line the placental arteries: placental artery endothelial cells (PAEC), placental vein endothelial cells (PVEC) and umbilical cord vein endothelial cells (HUVEC). These cells play important roles in foetal development, and have very different DNA

methylation patterns (Joo et al. BMC Genomics 2013; Cvitic et al. Diabetalogia 2018). All major genes involved in vitamin D signalling and metabolism are differently methylated in PVECs compared to PAECs and HUVECs. The functional significance of this remains unclear and will be the focus of this project. We will examine the consequences of vitamin D stimulation of primary cultures of PVECs, PAECs, and HUVECs using RNA sequencing and epigenomic analysis. Following computational analysis, we will identify the cellular pathways differentially regulated in these cells in association with differential methylation of key vitamin D regulators.

6. Human testis organoids - a novel stem cell model for reproductive disorders.

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Often the first question asked when a child is born is "is it a boy or a girl". Unfortunately, a definitive answer cannot be given to the parents of a child born with severe ambiguous genitalia. These cases occur with a frequency of 1 in 4500 births and are part of a large spectrum of disorders known as Disorders/Differences of Sex Development (DSD), which are caused by mutations in the genes that regulate how the testis or ovaries develop and function. Yet, less than 50% of patients with DSD currently receive a clinical genetic diagnosis. This is due to a very poor understanding of the genes that can cause DSDs. We use genomic technologies such as Whole Exome Sequencing to find novel candidate genes that may cause DSDs. We currently test the importance of these gene in the developing gonads (testis or ovaries) using animal models such as mice. However, mouse gonadal development is not always a good model for human gonadal development and disease. Consequently, we are developing stem cell technology to grow human testicular cells in a dish. This project involves optimising the differentiation of human testicular cells from pluripotent stem cells, and growing these to organoid formation. These organoids will then be used to test the importance of new candidate pathogenic gene variants found in DSD patients. This project will be conducted in collaboration with Professor Melissa Little, who has successfully grown human kidney organoids, and used these to model kidney disease. It will suit someone who has an interest in working with cutting edge stem cell technology to study human disorders.

7. Investigating an RNA based treatment for Partial Androgen Insensitivity Syndrome

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Partial androgen insensitivity syndrome (PAIS) occurs with a frequency of 1 in 4500 births and are part of a large spectrum of disorders known as Disorders/Differences of Sex Development (DSD). Children with PAIS can be born with ambiguous genitalia or severe under masculinization. Management often includes surgery and testosterone treatment and there is an increased risk of gonadal tumor, particularly if the testis remains undescended. In PAIS, the (46,XY) patient's testes make testosterone/androgens normally but this does not produce the normal masculinizing effect. PAIS is often caused by partial loss of function variants in the Androgen Receptor (AR) gene. This means that the androgen receptor cannot respond properly to testosterone, resulting in severe under masculinization. PAIS patient's therefore may not respond optimally to testosterone treatment, and as the onset of puberty is unpredictable large doses of androgens may be required to induce adequate virilization. Patients with PAIS often face infertility and high-dose androgens rarely restore fertility. We hypothesize that by boosting the levels of the Androgen Receptor we may be able to bypass its reduced activity and improve the patient's response to Testosterone.

Recently, a novel type of RNA molecule that can boost gene transcription has been described, termed short activating

RNA (saRNA). This project will investigate the use of saRNA technology to increase transcription of the Androgen Receptor in cell culture, as a model for human tissues. You will learn and employ cell culture techniques, cell transfection, DNA cloning and preparation and qRT-PCR. You will also interact with paediatric urologists and

endocrinologists who see patients with PAIS. We will model patient AR gene variants in this system to address the clinical utility of this method. This work will be the exciting first step in an effort to provide novel therapies for patients with PAIS.

8. Identification of new genes that cause Disorders/Differences of Sex Development

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9. Adaptive thermogenesis and the evolution of alpha-actinin-3 (R577X)

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Alpha-Actinin-3 is a skeletal muscle protein expressed primarily in fast-glycolytic fibres. It is responsible for maintaining sarcomeric integrity by cross-linking other muscle proteins, such as skeletal actin. We identified a common null polymorphism (R577X) in human alpha-actinin-3. An estimated 1.5 billion people worldwide are homozygous for the X-allele which results in the complete absence of the alpha-actinin-3 gene and protein. While alpha-actinin-3 deficiency does not cause disease, the 577 X-allele has undergone strong recent positive selection, following the migration of modern humans out of Africa. This data suggests that the absence of alpha -actinin-3 is evolutionary advantageous, however the mechanism of this positive selection has not been determined.
We have developed an alpha-actinin-3 knockout mouse (Actn3 KO) mimics the human muscle phenotype and provides a useful model to assess the role of alpha-actinin-3. Recently alpha-actinin-3 has been identified in Brown Adipose Tissue (BAT), a key heat producing organ, known to influence cold adaptation. While much is known about the role of alpha-actinin-3 in skeletal muscle, we have only just begun to understand its function in BAT.
Using the Actn3 KO mouse, this project will study the role of alpha-actinin-3, in both skeletal muscle and BAT in response

to cold stimuli. The project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and Digital droplet PCR (ddPCR) to further study the role of alpha-actinin-3 in adaptive thermogenesis.

10. Developing 3-dimensional (3D) skeletal muscle cultures from induced pluripotent stem cells (iPSCs)

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This project aims to develop skeletal muscle from induced pluripotent stem cells (iPSCs) to model rare inherited muscle disorders, like Duchenne muscular dystrophy (DMD). Current methods, which have been well described, are being developed in our laboratory and we are now using these technique to generate skeletal muscle in a dish.
A lack of patient based primary muscle means that it is increasingly difficult to study the molecular a pathophysiological aspects of rare inherited muscle diseases. Developing culture based assess like this will greatly enhance our ability to assess and develop novel therapeutic approaches to treat these debilitating conditions in the future. The project will involve the use of stem cells and we will teach you all that is required to grown skeletal muscles in vitro. This includes good ascetic tissue culture techniques as well as laboratory-based methods such as, immunocytochemistry, flow cytometry, western blotting and quantitative real-time PCR (RT-qPCR).

11. Modelling human cartilage and bone disorders using pluripotent stem cells

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Genetic cartilage and bone disorders in children prevent normal skeletal development and function. In Australia around 100 babies per year are born with these debilitating conditions that cause lifelong disability. Of these conditions, osteogenesis imperfecta (brittle bone disease) and dwarfing chondrodysplasias stand out as particularly severe, sometimes lethal, and always having a major impact on quality of life. The overarching aim of this project is to exploit our genomic studies on bone and cartilage disorders to understand how the mutant genes cause disease and test drugs that target these disease pathways. We have developed new methods to differentiate stem cells into cartilage and bone cells and have patient-derived induced pluripotent stem cells (iPSCs), iPSCs with engineered mutations in our genes of interest, and appropriate isogenic controls. These iPSC lines will be used to model cartilage and bone disorders in vitro

Clinical Sciences Laboratory-based research
and the functional consequences of mutations evaluated using RNAseq, proteomics, and advanced microscopy techniques.

Clinical Sciences

12. Developing a small volume flow cytometry-based assay to monitor antiplatelet therapy in children

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Antiplatelet therapy is a crucial life-saving treatment that inhibits platelet activation and is used to treat life-threatening thrombosis (blood clots) in children (e.g. stroke) and to prevent clotting side effects of life-saving interventions such as cardiac surgery and ventricular assist devices (VADs).
There are no studies demonstrating effective monitoring strategies of antiplatelet therapy in children compared to gold standard tests. In fact, many paediatric institutions, including the Royal Children's Hospital do not monitor antiplatelet therapy. Monitoring tests utilised for adults are problematic for children. Specifically, they require large volumes of blood, which simply cannot be obtained from sick children; and their clinical validity in children is unknown.
With no appropriate monitoring tests for children, determining failure of adherence, failure of absorption or true antiplatelet drug resistance has not been possible. There are no strategies for dose escalation and no evidence to support drug choice for each child.
We will develop a small volume microplate flow cytometry monitoring approach. This will allow us to specifically measure the effectiveness of each antiplatelet therapy to build a comprehensive picture of platelet function in a patient receiving one or more therapies, with minimal blood volume. By understanding the level of platelet inhibition for each patient in comparison to their maximal level of inhibition that is possible using that drug, the clinicians will be able to decide whether they need to modify the dose of the drug, or whether they need to consider an alternative approach for platelet inhibition.
This Honours project will focus on establishing the microplate flow cytometry method and will include testing of the in vitro effect of major antiplatelet agents (e.g. aspirin, tirofiban) in blood samples from healthy children and adults.

Genetics

13. Solving Rare Diseases via the Australian Genomics Mitochondrial Disease Flagship

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Genetics Laboratory-based research

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A "rare disease" affects fewer than 1/2000 people but there are over 7000 rare diseases that collectively affect 5% to 10% of the population, many of whom suffer life-threatening diseases or lifelong chronic disease. Rare diseases are thus a major public health problem and affected families have often faced a long diagnostic odyssey in attempting to achieve a diagnosis. Australian Genomics is a collaboration of over 40 Australian centres seeking to translate new genomic technologies into improved outcomes for rare diseases and cancer. Mitochondrial (mito) diseases are one of the first flagship projects. They are the most common group of inherited metabolic disorders and highly complex since they comprise almost 300 different genetic disorders with a wide range of clinical phenotypes and types of inheritance.

In previous studies we have used whole exome sequencing or whole genome sequencing to achieve diagnostic yields of over 60% in retrospective cohorts, identifying over a dozen novel disease genes. This project will focus on a prospective national cohort of paediatric patients who fit entry criteria for having probable mitochondrial disease. Recruitment commenced in early 2017, with half the cohort having whole genome and half whole exome sequencing over a 2-year period. Some patients will have sequence variants identified that have been previously shown to cause disease, which are straightforward to classify. Others will have novel sequence variants identified in known disease genes or in candidate disease genes not previously linked to disease. The project will use a range of bioinformatic, molecular, biochemical, immunochemical and cell biology approaches to investigate causality of novel variants. This will contribute to obtaining definitive diagnoses in previously unsolvable cases, understanding pathogenic mechanisms of disease and developing methods that can be applied to understanding the genetics of a wide range of other rare diseases.

14. Molecular insights into a new neurodegenerative disorder exacerbated by febrile illness

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Metabolites are produced by a complex series of reactions within cells. When a cell is stressed or sick these enzymes can malfunction and produce damaged versions of the same metabolites which is bad news because the damaged metabolites can accumulate and interfere with normal cellular functions. These may include energy production, cell signalling and repair. Because the brain is one of the most 'energy hungry' organs, failure of any metabolite repair enzyme will have dire consequences.

To address this problem, cells have specific sets of enzymes to repair damaged metabolites back to a form which can then be used again by the cell. Specific metabolite repair enzymes are responsible for 'cleaning up' specific metabolites.

Our research team focuses on uncovering the molecular basis of undiagnosed childhood brain disorders using Whole Exome Sequencing or Whole Genome Sequencing. We have recently identified mutations in a new gene in six young children who were born healthy and developed normally until an episode of mild fever or common infection triggered failure of the metabolite repair system. All of these children died rapidly during such an episode. We have shown that these mutations prevent the enzyme from repairing damaged metabolites. We have shown that skin cells from these children had severely compromised mitochondrial energy production and a vast accumulation of damaged metabolites. We have already shown that gene rescue studies with a normal copy of the gene completely clears the damaged metabolites. Mutations in this gene have never been described before in humans.

This research proposal will further our understanding of this new gene deficiency by uncovering molecular pathways

perturbed by loss of gene function and may provide an understanding of therapeutic targets to protect the brain when children with gene mutations suffer illnesses such as fever that would otherwise normally overload the repair system.

15. FBXW7 as a new genetic cause of intellectual disability: exploring the effects of gene variants on developmental and signalling pathways in patient cells.

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F-box and WD repeat domain-containing 7 (FBXW7) is an important component of the SCFFbxw7 complex and can tag target proteins with ubiquitin (so-called ubiquitination), thereby marking them for degradation. FBXW7 mutations have been previously found to influence certain cancers. Loss of FBXW7 has also been shown to impair the ability of neural stem cells to mature into neurons. Moreover, knock-in of several missense mutations have been found to be perinatally lethal in mouse models.
Recently, with overseas collaborators we have identified a number of children with de novo variants in FBXW7 gene. They have intellectual disability, hypotonia and constipation. In this research project, we plan to examine the effect of the identified FBXW7 variants using cell lines from the patients (currently being obtained). We have already examined the effect of FBXW7 depletion on the transcriptome by analysing publicly available microarray data. These preliminary data revealed some interesting pathway changes caused by FBXW7 loss.
Initially, we will perform 3D modelling to predict the changes in protein structure caused by the FBXW7 variants, which we anticipate will yield potential mechanistic insights into the pathogenic nature of these variants.
Next, we will focus on some FBXW7 targets involved in those pathway changes. We will evaluate the expression level and turnover rate of FBXW7 target proteins in cell lines from patients and healthy controls. With those cell lines, the changes in the ubiquitination level of FBXW7 targets will be determined in response to FBXW7 mutations by western blot. We will then examine the effect of FBXW7 variants on signalling pathways associated with FBXW7 targets by quantitative reverse transcriptase polymerase chain reaction.

16. Tuberous sclerosis and epilepsy: using resected tissue to understand pathogenesis

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Tuberous sclerosis complex (TSC) is a multisystem disorder leading to benign tumours in multiple organs including the skin, kidneys, heart, lungs and brain. The most significant clinical features of TSC are neurological, with epileptic seizures being the most common and severe, particularly when they occur in early childhood. Seizures from TSC are often drug-resistant and incomplete control, especially during early childhood, is associated with adverse developmental consequences including intellectual disability and autism.

The seizures of TSC originate in dysplastic lesions known as cortical tubers. Tubers are well circumscribed and usually confined to a single gyrus, often extending into the subcortical white matter. They are characterised by disorganised cortical lamination and abnormal cells including dysmorphic neurons and balloon or giant cells. Our recent experience with modelling tuber microstructure using ultra-high field (16.4 Tesla) ex vivo diffusion MRI acquired from the resected tuber specimens also plausibly demonstrated localisation of dyslaminated cortex and dysmorphic neurons in the tuber centre.

This suggests that it is the tuber centre that is likely to contain the highest density of dysmorphic neurons. We have qualitative data from visual analysis of tubers using routine histopathological techniques to support this, however neither we nor any other group have systematically tested this hypothesis by quantitative analysis of the density of dysmorphic neurons in various regions of a tuber. In this project, the candidate will use immunostaining and stereological techniques to determine the gradient density of dysmorphic neurons in resected tuber tissues. These histology findings will be overlayed with our ultra-high field ex vivo diffusion MRI data to create a 3D reconstruction of tubers.

17. **Using cerebral organoids for the study of tuberous sclerosis complex**

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Tuberous sclerosis (TSC) is a multi-system disorder leading to benign tumours in several organs including the skin, kidney, heart, lung and brain. The most significant clinical sequelae of TSC are neurological, with epileptic seizures being the most common and severe, particularly when they occur in early childhood. The seizures are often resistant to treatment with drugs and arise in abnormal brain regions called tubers. If the seizures are not suppressed or otherwise managed, especially during early childhood, they are often associated with adverse developmental consequences including intellectual disability and autism.
The ability to model neurological disorders utilising cerebral organoids represents an invaluable tool for both delineating disease processes and investigating the fundamental mechanisms required for normal human brain development. Tubers are three-dimensional structures characterised by markedly disturbed cortical layering and morphologically abnormal cell types. Little is known about the molecular mechanisms leading to tuber development or the mechanism of seizure generation.
We are currently developing iPSC-derived cerebral organoid models to investigate the aetiology of tuber formation and resultant epilepsy. In this project the candidate will utilise molecular and cellular techniques including stem cell culturing, differentiation, immunostaining and advanced microscopy to analyse organoid models of TSC.

18. Functional characterisation of a novel gene linked to autism spectrum disorder

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Available as Masters Project: Yes
Autism Spectrum Disorder (ASD) is a complex and highly heritable neurodevelopmental disorder defined by deficits in social communication and repetitive behaviours with restricted interests. Over 300,000 Australians have ASD and the annual national economic cost is ~$9.7 billion. Whilst there have been many studies that have identified variants

which are predicted to predispose to ASD, the challenge is to unravel which variants are truly contributing to the phenotype and the mechanisms by which they do so. Therefore a key requirement for understanding disease pathogenesis is the development of models that recapitulate the disease enabling key insights into basic underlying mechanisms. To this effort, we have already recruited 6 extended families, which consist of grandparents, parents, children, aunts, uncles and cousins. We have performed high throughput genetic screens on 1 family and have identified a candidate mutation and gene that segregates with the disorder.
This project will focus on characterising the function of the gene at a molecular level to understand how it contributes to ASD. Techniques will include differentiation of stem cells into neuron and glial cells and manipulating the cells using various drug treatments to determine ASD pathogenesis. Specific techniques will include tissue culture, real time PCR, western blot and enzyme activity assays.

19. Understanding rab39b-mediated Parkinson's disease

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Available as Masters Project: Yes
The recent advances in our understanding of common and disabling neurodegenerative diseases such as Parkinson and Alzheimer disease has been the result of the identification and analysis of causative mutations in families, where a linkage-based approach can be utilised to identify disease associated genes. We recently identified RAB39B as a

novel gene for Parkinson's disease.
This project will characterise the gene and investigate pathogenic mechanisms underlying disease utilising molecular and cell biology techniques. Studies will utilise newly developed and unique iPSC and mouse models to perform preclinical studies to characterise the disease process and identify potential therapeutic targets.

20. Human Stem Cell Models of Mitochondrial Disease

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Mitochondria are our cellular power plants that burn sugars, fats and proteins to generate energy. Each week in Australia a child is born with a mitochondrial disorder. Many of these children die in the first years of life and most suffer from severe disease, particularly affecting their brain and/or heart. Access to these tissues from patients is limited, making it difficult to assess the impact on mitochondrial and other pathways contributing to disease pathology. This project is part of a 5-year NHMRC-funded study to develop and characterize human stem cell models for over 20 genes in which knockout-type mutations cause inherited disorders of mitochondrial energy generation.
The overall aims are:
1) Assemble a representative panel of cellular models of OXPHOS disease in human Embryonic Stem Cells (hESCs) and human Induced Pluripotent Stem Cells (iPSCs) that can be used to study phenotypic rescue of novel defects, pathogenicity and treatment approaches.
2) Characterize pathogenic pathways in the most relevant cell lineages by assessing the impact of OXPHOS defects on

the mitochondrial and cellular proteome of cardiomyocytes and neural cells generated from hESCs or iPSCs, as well as the impact on mitochondrial function and cellular physiology.
3) Define the impact of targeted therapeutic strategies in these models on the cellular proteome and other markers of cellular homeostasis. The research project will thus involve generation of hESCs with CRISPR/Cas9 mediated gene disruption, or iPCs from mitochondrial disease patient fibroblasts, followed by confirmation of the impact on the targeted gene and pathway. Selected cell lines will then be differentiated to cardiomyocyte and/or neural lineages to enable comparison (with control cells) of the impact of the gene knockout on various aspects of mitochondrial and cellular function. These may include respiration, ATP synthesis, reactive oxygen species, mitochondrial membrane potential, redox balance, cellular stress response and quantitative proteomics.

21. Characterisation of the parkin protein and how it causes parkinson disease

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Parkinson's disease (PD) is a neurodegenerative disorder with a complex aetiology and progression. Mutations in the parkin gene are the most common cause of early onset-PD. Pathologically PD is characterised by loss of dopamine producing neurons and Lewy bodies composed of aggregated of alpha-synuclein. We hypothesise that parkin plays a key role in eliminating toxic proteins such as alpha-synuclein from within the brain. Failure of parkin function results in the accumulation of toxic proteins and results in the development of PD. We are interested in how parkin functions with its co-regulated gene PACRG in protein turnover and neuron function. We have recently aged and a number of unique mouse models that are dysregulated for parkin/PACRG/alpha-synuclein in the laboratory. These will be characterised for markers of altered neuropathology, biochemistry and correlated with behaviour data already obtained.

Infection and Immunity

22. Developing a vaccine to protect children with cystic fibrosis from pathogenic infection

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Cystic fibrosis (CF) is an inherited disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF disease begins in early life and is characterised by a reduced lung function that is related to infection with a number of opportunistic pathogens. These infections drive a chronic airway inflammation that results in pathological structural changes in the lung. In recent years a new lung pathogenic infection, Mycobacterium abscessus, has emerged as an important global threat to individuals with CF. M. abscessus are multidrug-resistant bacteria that are associated with poor clinical outcomes and for which treatment is extremely difficult. Treatment typically involves the long-term use of toxic agents, including the injection of antibiotics that are frequently associated with major side-effects such as deafness and kidney failure. M. abscessus infection can also prevent a CF patient from receiving a life-saving lung transplantation.

AIM: Given the above issues, we believe prevention through vaccination holds the best promise for these patients. The Aim of this project is therefore to identify a vaccine that has the potential to prevent infection with M. abscessus. APPROACH: This project will test a number of different vaccines in a mouse model of M. abscessus infection and determine which provides the best protection against this infection. The immune response induced by these vaccinations will also be measured using standard immunological techniques.

SIGNIFICANCE: Identifying a vaccine that protects against M. abscessus in the mouse model will guide future research aimed at developing a vaccine for protecting children with CF from this important pathogen.

The project will be supervised by Prof Sutton, who is an expert on vaccine development, especially against bacteria pathogens at mucosal surfaces, and Prof Sarath Ranganathan, who is Head of Respiratory Medicine at Royal Children's Hospital and an expert on CF.

23. Streptococcal transmission and disease

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The bacterium Streptococcus pyogenes (group A streptococcus, Strep A) causes a range of mild to severe infections, ranging from sore throat to streptococcal toxic shock syndrome. Importantly, S. pyogenes infections can lead to serious sequelae such as rheumatic fever and rheumatic heart disease. S. pyogenes can also colonise a variety of human tissues including the upper respiratory tract and skin in healthy people.

In a related bacterial species, Streptococcus pneumoniae, we have shown that viral co-infection can enhance bacterial virulence by increasing bacterial density and inflammation in the host, and by driving changes in expression of bacterial virulence genes. There is recent clinical epidemiologic evidence that viruses are also important in S. pyogenes pathogenesis, but little is known about this process.

In this project, you will use a murine model of S. pyogenes colonisation to examine the effect of viruses on S. pyogenes colonisation, transmission (spread to co-housed littermates) and disease, and the mechanisms involved. To achieve these aims, a range of methods will be employed including animal and tissue handling, immunological assays, traditional microbiology and molecular approaches such as qPCR, and gene expression analyses. Your project will provide important novel data on key components of S. pyogenes pathogenesis, and inform a pathway towards improving strategies for preventing S. pyogenes infections.

24. Characterisation of a putative phage-inducible chromosomal island in Streptococcus pneumoniae

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Phage-inducible chromosomal islands (PICIs) are genetic elements that benefit bacteria by restricting bacteriophage replication in favour of their own survival. Upon induction by bacteriophage infection, PICIs block bacteriophage reproduction and preferentially package their own DNA into the bacteriophage-encoded capsid, forming transducing

particles that contain PICI DNA that can be horizontally transferred to a new host. Most research involving functional characterisation of PICIs have been conducted in Staphylococcus aureus; our knowledge of PICIs in other bacteria is limited.
We have identified a putative PICI in a Streptococcus pneumoniae (the pneumococcus) strain isolated from the nasopharynx of a healthy child. In this project, you will investigate the functional significance of this mobile genetic element in pneumococci. You will isolate and characterise pneumococcal bacteriophages and determine whether pneumococci carrying the PICI are protected against bacteriophage infection, as well as investigate other phenotypes the PICI may confer to its bacterial host. You will also conduct molecular screening using clinical samples to determine the prevalence of the PICI. This project will involve a range of skills including traditional microbiological culture and molecular biology techniques.

25. Transcriptional regulation in Streptococcus pneumoniae

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Streptococcus pneumoniae (the pneumococcus) is a leading cause of pneumonia in children world-wide. This bacterium asymptomatically colonises the upper respiratory tract, but can transition to a pathogenic state to cause disease in the lower respiratory tract. We are interested in identifying the genetic factors that trigger this transition and have identified a putative transcriptional regulator we hypothesise may play a role in this process.
In this molecular microbiology project, you will use pneumococcal strains in which the gene encoding the regulator has been deleted or overexpressed to identify which virulence and non-virulence genes are under the control of this regulator, as well as the associated phenotypes. Key approaches include: genetic manipulation of pneumococcal strains, experiments with DNA and RNA, as well as conducting functional assays in vitro and/or in vivo.
Your work in helping us elucidate the function of this regulator will make a substantial contribution to our understanding of how pneumococcal gene expression is regulated and how this is coupled with its pathogenesis.

26. Pathogenesis of pneumococcal pneumonia

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Streptococcus pneumoniae (the pneumococcus) is the most common cause of community-acquired pneumonia and a leading killer of children world-wide. However, it is also commonly found as an asymptomatic coloniser of the upper respiratory tract, particularly in children. We are interested in elucidating the molecular processes by which

the pneumococcus can transition from the carriage to infection state, and identifying signals of pneumococcal pneumonia. Previous work in our laboratory using clinical samples collected from children in The Gambia, West Africa, hospitalised with pneumonia has identified several pneumococcal genes that were upregulated in the lung.
Your project will have two main aims: to elucidate the role of these genes in pneumococcal pneumonia, and to

examine pneumococcal gene expression in samples collected from pneumonia patients at the Royal Children's Hospital. You will use a variety of approaches to identify and characterise pneumococcal genes and proteins involved in pneumococcal pneumonia. This includes genetic manipulation of pneumococci, functional assays to characterise bacterial mutants, and measurement of gene and protein expression using methods such as qRT-PCR, RNA-seq, western blotting, and ELISA.
Access to clinical samples such as pleural fluid provides the unique opportunity to examine pneumococcal gene expression during pneumonia. This project will provide exciting new data on the pathogenesis of pneumococcal pneumonia.

27. HPV immunity as markers of protection against infection

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Cervical cancer is the fourth most common cancer in women worldwide, caused by infections with the human papillomavirus (HPV), with highest rates in low- and middle-income countries. Most cases (70%) are due to oncogenic HPV types 16 and 18 which are included in the two widely used prophylactic HPV vaccines, 2vHPV (Cervarix, GSK Biologicals) or 4vHPV (Gardasil, Merck) given as a 3-dose schedule over six months. We have recently completed a study examining immunity in Fijian girls who received 1, 2 or 3 doses of 4vHPV six years earlier as well after a booster dose of 2vHPV. This project aims to examine the immunological response following HPV vaccination using a combination of methods including neutralisation assays and HPV type-specific ELISAs.

28. Analysis of cord blood immune profiles in preterm and term infants

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Infection and Immunity

Laboratory-based research

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Preterm infants have increased susceptibility to viral and bacterial infectious diseases in comparison to term infants. The reason for this is not well understood but is thought to be due to delayed immune system development in preterm infants. Understanding early life immune responses in preterm infants is important in the development of novel vaccines or therapeutics in the prevention and/or treatment of infectious diseases. This project aims to define differences in cord blood immune responses between preterm and term infants from Vietnam using a range of immunological techniques including cell culture, flow cytometry and cytokine assays.

29. Examining the immunogenicity of a single dose of pneumococcal conjugate vaccine in the second year of life in Vietnamese infants

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Pneumococcal diseases are a common cause of childhood morbidity and mortality globally. Immunisation with pneumococcal conjugate vaccines (PCV) are highly effective in reducing the rates of pneumococcal carriage and disease in almost all settings where they have been introduced. Current recommendations involve a 3-dose schedule in the first year of life abbreviated schedules involving fewer than 3 doses are currently being investigated. We are undertaking a randomised controlled trial in Vietnam of alternative PCV schedules which includes a group of infants randomised to receive a single dose of PCV at 18 months of age. This project aims to measure the immunogenicity of PCV given as a single dose at 18 months using the WHO gold standard opsonophagocytic assay. This project will utilise techniques such as cell culture, bacterial culture and colony counting.

30. Investigating innate immune memory effects of dietary compounds

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Innate immune memory or "Trained Immunity" is a recent concept that describes the ability of certain innate immune cells to exhibit enhanced responsiveness on subsequent encounter to certain pathogens. Previously, this response was

only associated with the adaptive immune system (i.e. T and B cells). A number of training stimuli have been identified to date with their effects largely attributed to epigenetic reprogamming. This 'epigenetic reprogramming' involves changes to DNA-associated proteins and modifications, such as histone modifications and DNA methylation. L-sulforaphane is a dietary derived anti-oxidant that also exhibits histone deacetylase inhibitory (HDACi) properties. This project aims to examine whether novel dietary compounds such as LSF are able to induce innate immune memory in ex vivo human monocytes. It will involve a range of techniques involving cell culture, cytokine assays and epigenetic analyses. This study will provide exciting data on the role of dietary factors that contribute to immune memory.

31. Therapeutic Aerosols: Pulmonary delivery of novel therapeutics to the infant lung

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THE PROBLEM: Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infections in babies less than 2 years, hospitalising approximately 10,000 Australian children each year. No effective RSV vaccine is currently available, with prevention only available with palivizumab at a high cost and requirement for repeated muscular injections. Therefore, novel practical and affordable strategies for protection of all infants from severe RSV disease are urgently needed. The novel approach being explored in our proposal involves targeted aerosol delivery of palivizumab to the lungs to provide enhanced prevention and treatment of severe RSV disease. This approach offers several advantages including ease of delivery and reduced cost, resulting in improved access to a life-saving therapy for babies at highest risk. Our team has developed a novel aerosol delivery system for effective palivizumab delivery in an infant sheep model. THE PROJECT: The student will conduct studies to determine if palivizumab delivery via the aerosol route will induce a strong mucosal immune response, within the lung, and a robust systemic immune response compared to alternative routes of delivery in an infant lamb model. TECHNIQUES: The student will use RSV culture methods and RSV detection assays together with immological assays such as ELISA and molecular assays to validate the immune responses. Students will work closely with a team of immunologists, virologists, molecular biologists, clinicians and engineers. Candidates with a strong interest in immunology or virology other relevant engineering expertise is encouraged to apply. Please submit your interest along with you CV and academic transcripts to anushi.rajapaksa@mcri.edu.au

Population Health

32. Optimising diagnostic testing for tree nut allergy

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Clinical Sciences

Non-laboratory-based research

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Tree nut allergy in children is common, often serious and usually life-long. Recent data from the Health Nuts study (MCRI) has found prevalence of tree nut allergy at age 6 to be as high as peanut allergy (3.1%). Accidental ingestion is common and nuts are the most common trigger of anaphylaxis in
Current diagnosis of tree nut allergy is based on clinical history and skin prick testing (SPT). SPT has a high sensitivity but low specificity and is therefore unable to determine in those without a history of a reaction, clinical allergy or tolerance; necessitating specific nut elimination or oral food challenge.
The HealthNuts study is the world's largest population-based, longitudinal study of food allergy and in early childhood. At 12-months of age, 5300 infants had skin-prick testing, and those with a positive test proceeded to hospital-based food challenges to assess for food allergy. The cohort has been followed up at ages 4 and 6 years and an age 10-year follow-up is underway. A number of measures including blood, have been collected over the years. Therefore ethically approved samples of plasma, peripheral blood mononuclear cells and granulocytes from tree nut allergic and tolerant children are in storage and available for analysis.
This project will be focused on optimising diagnostic testing for tree nut allergy. Using samples from the HealthNuts study, novel laboratory techniques for use in screening, determining severity and reaction thresholds for tree nut allergy will be explored. For example component-resolved diagnostics using specific IgE and basophil activation testing will be compared to skin prick testing for the diagnosis of clinical allergy or tolerance to individual tree nuts.

Non-laboratory-based research

Clinical Sciences

33. How do babies take their first breaths?

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Birth involves the successful transition from a fluid-filled fetal lung state to a lung that is aerated (air filled). This needs to occur quickly to allow other organs to start working. About 10% of term babies, and most preterm babies, do not aerate their lungs properly at birth. These babies often need help with their breathing. We do not yet fully understand how babies take their first breathes at birth and why some have problems. This observational study aims to describe how babies aerate their lungs at birth and develop normal breathing. It will use a new state-of-the-art lung imaging system developed at the MCRI to study newborn babies in the Delivery Room of the Royal Women's Hospital. The successful candidate will then analyse the ventilation, aeration and filling characteristics of each imaged lung. This will help us determine whether the human lung starts breathing in the way we think it does.

34. A qualitative study exploring physical activity in children with a Fontan circulation

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Some of the most severe congenital heart abnormalities result in single functioning ventricle. Many children born with these defects undergo a series of operations to help them survive that ultimately results in a Fontan circulation, where venous return through the lungs bypasses the heart. Although improvements in surgical and medical care have resulted in improved survival, exercise capacity is reduced and may deteriorate over time. Limited evidence has suggested that exercise training is the most effective intervention for improving exercise performance and cardio-vascular health in those with a single ventricle. While we all know that exercise is good for you, and we have now identified that exercise is safe in Fontan patients, a solid evidence base is non-existent. We want to provide a source of information, in the form of a school brochure, for children, parents and teachers as a guide to the types of physical activity and exercise children can participate in.

35. Evaluating the impact of on online social networking platform (Livewire) on the mental health of young people with serious and chronic illness

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Livewire, a program of the Starlight Children's Foundation, is an online community to help young people aged 12 to 20 years, and their siblings, cope with the impact of a serious illness, chronic health condition or disability. Livewire's unique combination of a moderated chat room, mobile-friendly platform, and youth relevant features such as a live newsfeed, articles and a TV platform creates a reliable and engaging point of social connection for young people aged 12-20 years living with illness and disability. Livewire has been delivered successfully to thousands of members since its inception in 2008, and is available to young people living in Australia and New Zealand. Despite its success in linking young people with illness, no research has yet been conducted to explore whether being a part of the Livewire online community has mental health benefits. This study will investigate whether joining Livewire is associated with improvements in mental health for adolescents and young adults with serious or chronic illness.

36. The impact of obesity trajectory on late outcomes after Fontan surgery

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Being born with a single pumping heart chamber is the most severe congenital heart disease condition. These patients may survive late into adulthood provided that they undergo a series of operations. The last one is named the Fontan procedure, after which the blood from the body goes into the lungs without being pumped by the heart. This very special circulation can only work if the passage of blood through the body and the lungs is very fluid. They function better if they have a larger muscle mass.
We have in Australia the largest database of such patients in the Fontan Registry and we are leading this research worldwide. We have anecdotal evidence that obesity is toxic for this population even more so than in the general population as it may cause some of them to die or need a transplantation in their second or third decade. There is to date only one very small retrospective study confirming this suspicion. We have the dataset and the expertise in obesity and its impact in cardiovascular disease to elucidate the impact of obesity on the Fontan circulation. We have demonstrated that trajectories of weight during childhood and adolescence better define obesity than punctual weight measurements and have developed the software necessary to perform these studies.
The project. We will collect the data of weight trajectories of as many of the 1500 patients included in the Fontan Registry to define their obesity status and define the relationship between obesity status and endpoints such as death and transplantation.
Feasibility and future implications. We have past expertise to lead this type of research and possess a large number of the necessary data. This research is likely to have direct clinical implications. It will undoubtedly open a new area of research.

37. The genetic and environmental contributions to blood cell parameters at birth and their association with cardiometabolic outcomes at age six years: a twin study

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Twin studies are ideal for addressing research questions related to the early life origins of chronic disease because of their ability to resolve genetic, shared and individual environments.
Recently, a number of studies have explored the link between blood cell parameters and cardiovascular risk. The most recent and the largest of these studies was completed in 14,362 adults and concluded that the total and differential white blood cell (WBC) count, mean corpuscular volume (MCV), red blood cell distribution width (RDW) and platelet count likely play a role in the aetiology of cardiovascular disease (CVD), with the WBC providing a modest improvement for the prediction of 10-year CVD risk over traditional CVD risk factors in an adult population. However, whether blood cell parameters recorded early in life are able to predict occurrence of CVD early and/or later in life has not been studied to date.
This project will utilize unique data collected in the Peri/postnatal epigenetic Twin Study (PETS). The project will focus on

determining the potential for blood cell parameters collected at birth and 18 months of age to predict cardiometabolic outcomes (e.g. BMI) at 6 years of age. This approach will provide an answer to the question of whether the blood cell parameters can serve as a predictive and/or diagnostic tool early in life.
Secondary aim of this project is to determine the relative contributions of genetics, shared (family) environment and nonshared (specific to each individual) environment to blood cell parameters by comparing these within MZ twins versus within DZ twins.

38. Tracking 'brain age' in childhood using magnetic resonance imaging and machine learning

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Brain development in childhood follows a well-defined path. Connections form, the cortex develops and the brain grows. These anatomical changes results in the development of increasingly sophisticated behavioural and cognitive functions. Neurodevelopmental disorders such as autism, schizophrenia and attention-deficit hyperactivity disorder may stem from deviations from this developmental path.
Modern machine learning methods are able to predict chronological age from the anatomical appearance of the brain using magnetic resonance imaging (MRI). Current theory suggests that delayed cognitive development may reflect a brain that appears to be younger for a given age compared to peers. Similarly, an older appearing brain may reflect advanced development. This notion of a 'brain age' has been tested in both developmental and aging populations, is altered following preterm birth, and in schizophrenic patients. As such, brain age has the potential to act as a marker of typical or atypical development in childhood.
In this project, we aim to test how stable brain age estimates are over time in the same paediatric population. Using MRI scans acquired 1-2 years apart, we will use machine learning to build and test a model of brain age. We will predict age at both timepoints in the same individual and determine how brain age changes over time in the same individual. Further to this, we can examine how changes in brain age related to cognitive development and stages of pubertal maturation.

39. Does skin-to-skin care improve ventilation patterns in newborn infants?

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Available as Masters Project: No

Skin-to-skin care (SSC), also known as Kangaroo Care, involves positioning an unclothed baby directly onto the chest of one of their parents for a period of time. This simple interaction in the stressful period of a Neonatal Intensive Care stay has proven benefits, include regulation of temperature and heart rate, improved breastfeeding rates and reduced infant mortality. However, some caregivers have been reticent to use SSC care for newborn infants receiving respiratory

support (such as with a breathing machine), as the effects on ventilation are unknown. We have developed a method of imaging how gas moves in the lung without radiation or interrupting normal NICU and infant care. This observational study aims to assess the effects of SSC on regional ventilation and breathing patterns in newborn infants cared for in the NICU at The Royal Children's Hospital. Infants will be studied during SSC and when their cots using our state-of-the-art lung imaging system developed at the MCRI. The successful candidate,
under the supervision of experienced clinician researchers, will be directly involved in studying babies, analyse the ventilation, aeration and filling characteristics of each lung, and the breathing pattern of the baby to help us understand the effects of SSC.

40. The ageing Fontan - what's normal?

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Available as Masters Project: Yes

Individuals with complex congenital heart defects end up undergoing a Fontan operation if there is insufficient heart muscle to allow a repair that achieves two ventricular pumping chambers. The Australian and New Zealand Fontan Registry is the largest registry of people with a Fontan circulation in the world. New data is showing improved survival, however the whole of life outcomes for these individuals is unknown, and in particular outcomes in the oldest Fontan patients are not well characterised.
This project will concentrate on in-depth exploration of quality of life (QoL), medical complications and neurodevelopmental function in this subgroup. Previous QoL data has suggested that Australian adults have one of the highest QoL, internationally, in adults with congenital heart disease.
The project will identify all adults in Australia and New Zealand who are a minimum of 30 years post their Fontan surgery. Medical record review will allow description of cardiac function, collation of Fontan related complications, formal exercise testing data, assessment of other organ function (particularly the liver and kidneys) and an in-depth assessment of neurocognitive function. Many of these patients have participated in neuroimaging studies such as brain MRI, and this project will seek to explore further whether there are any concerns about abnormal brain aging on functional assessment. Additionally, patients will be asked to complete in depth QoL questionnaires and the possibility of qualitative study in a subgroup will be explored.

Core Groups

41. Backyard benefits: Do children living in homes with larger and greener backyards have higher levels of physical activity?

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Genetics Non-laboratory-based research

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Available as Masters Project: No

Having places to be active is important for children's physical activity behaviours. Previous research has shown that having parks and open spaces in the neighbourhood are associated with greater physical activity levels in children. However, despite the importance of the home environment for children, there has been little research on whether the size and characteristics of the backyard are correlated with physical activity levels. Existing research suggests that the home backyard might be important for children's physical activity, yet to date characteristics of the backyard lack objective assessment.

The aim of this project is to investigate associations between backyard size and vegetation levels (i.e. 'greenness') and objectively measured physical activity levels in 11-12 year old children. We will use socio-demographic data from Wave 6 (10-11 years) of the Longitudinal Study of Australian Children (LSAC), physical activity data from the Child Health CheckPoint (11-12 years), and geographic information systems (GIS) derived measures of backyard size and vegetation levels.

This project will suit someone interested in epidemiology, statistics, and the use of spatial/GIS/mapping data in health research. The student will work with supervisors to undertake statistical analysis and aspects of the spatial/GIS analysis/mapping.

Genetics

42. Expansion of gait analysis techniques in the paediatric setting

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Available as Masters Project: No

Gait analysis is a powerful clinical tool for studying typical and atypical motor control development. To this end, scientists have begun to tease out the spatiotemporal gait signatures linked to neurodevelopmental disorders. However, expansion of this field in the paediatric setting has been limited by expensive technician run gait laboratories, which impede collection of large data sets to establish control normative ranges, reduce access to patients and reduce the likelihood that a gait assessment will be tolerated by lower functioning children with intellectual disabilities. This project aims to increase adoption of gait analytic techniques in the paediatric setting by studying construct validity of newly available wearable gait analysis technology. These sensors will be used by the student to collect extensive spatiotemporal and 3D path data about stepping during gait from typically developing children. This will be performed whilst the child walks along a mat that is embedded with pressure sensors, in order to provide the first ever large scale validation study of these sensors against the gold standard for spatiotemporal data collection. Using these data the student will also establish paediatric control norms across the following age ranges: 6-7 years; 8-9 years; 10-11 years; 12-13 years (20 children in each age bracket; 50% female). These data will fast track expansion of the new gait analysis

field, facilitating adoption of wearable technology for gait analysis into clinical trials development for children with neurodevelopmental disorders.

43. Predictive testing of minors for Friedreich ataxia - the views of at-risk siblings and health professionals

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Available as Masters Project: Yes

Friedreich ataxia (FRDA) is a life-shortening inherited condition characterised by variable age of onset, with no treatment proven to alter its natural history. Siblings of individuals with FRDA are born with a 25% risk of developing the condition. After the diagnosis of a child with FRDA, clinicians are often faced with requests from parents to predictively test their other children for the condition. Testing at-risk minors for a genetic disease that has no known cure is an issue that has been thoroughly explored in the literature, however there remains limited empirical evidence to substantiate or justify the arguments put forth for and against such testing. Further research regarding the impact of such testing, as well as the views of at-risk individuals and clinicians with expertise in FRDA, is required in order to develop an appropriate, balanced framework for dealing with this contentious issue. This study, comprising two arms, aims to ascertain the opinions and experiences of at-risk individuals (siblings) and health professionals with clinical experience in FRDA or neurogenetics, regarding predictive testing of minors. Arm 1 of the study will include individuals who are at risk of FRDA (siblings) and will have an emphasis on exploring the views of those at risk of FRDA on predictive testing of minors for FRDA, using semi-structured interviews. Arm 2 will target health professionals either with clinical experience in FRDA or neurogenetics and will again focus upon predictive testing of minors for FRDA, using an online questionnaire. Establishing the opinions and experiences of these two key groups is essential so an appropriate framework for dealing with this contentious issue can be developed.

Infection and Immunity

44. Epidemiology of bronchiectasis in children in Victoria

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Available as Masters Project: No

Bronchiectasis refers to irreversible lung damage which can be caused by a range of underlying conditions including inherited congenital conditions where airway clearance is impaired such as Cystic Fibrosis and Primary ciliary dyskinesia, inherited or secondary immunological defects or the consequences of single severe or recurrent lower airway infections.

In 2017 a dedicated multi-disciplinary bronchiectasis clinic was established to supervise the ongoing clinical care of these patients. This study will examine the patients seen in this clinic for range of diagnosis, diagnostic tests utilised to make each diagnosis and over a 12 month period the pharmacology utilised by patient, change in lung function and nutritional parameters over that period and associated quality of life. Most publications from non CF bronchiectasis clinic stem from clinics heavily influenced by indigenous persons - studies from Auckland, Darwin, Alaska and South Africa all repot a different patient basis than the RCH clinic.

45. Risk factors associated with pneumococcal carriage in healthy children in Mongolia in the era of pneumococcal conjugate vaccine introduction

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Available as Masters Project: No

Pneumonia is the leading infectious cause of mortality in young children with 95% of deaths occur in low- and middle-income countries. Streptococcus pneumoniae is amongst the commonest causes of acute respiratory infections. Nasopharyngeal pneumococcal carriage is considered the precursor to disease and carriage rates vary by age with the highest rates reported in children. Carriage rates also vary in different settings and countries. We have ongoing surveillance and studies in Mongolia to define the impact of pneumococcal vaccine introduction on pneumococcal disease and carriage in this country. In this study we hope to determine risk factors for carriage in children in this country.

46. Observational study of intravenous fluid use in neonates

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Available as Masters Project: No

There is little research regarding the incidence and consequence of hyponatraemia (low blood sodium) in neonates receiving intravenous fluid. Hyponatraemia in older children has been associated with adverse neurological consequences, including death.

Clinical research conducted at The Royal Children's Hospital and Murdoch Children's Research Institute provided strong evidence that prescribing an isotonic intravenous fluid containing a similar sodium concentration to plasma reduces hyponatraemia (low sodium blood level) in older children. This has led to global changes in the intravenous fluid administered to children over three months of age, but it is unknown whether this evidence applies to neonates. Neonates continue to be prescribed intravenous fluid with profoundly low sodium concentrations, and there is very limited evidence regarding the consequence of this.

This project will be an observational study of neonates in non-tertiary special care nurseries across Victoria who are receiving intravenous fluid. The study will determine the composition of fluid being prescribed and the impact on serum sodium levels. The results will provide important data to inform a clinical trial, to ascertain the ideal composition of intravenous fluid in neonates.

Project techniques - Observational study

Project resources - This study will utilise the resources of the newly formed Inpatient General Paediatric Research Network. This has been identified as a priority research area for the network.

Population Health Non-laboratory-based research

Student benefit - The student will get experience in: Observational study design and conduct, Statistical analysis, Using software: RedCap and Stata. Leadership experience, liaising with multiple paediatric departments across the state.

Population Health

47. Understanding the psychosocial aspects of period and pelvic pain in adolescents.

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Available as Masters Project: No

Period pain occurs in up to 80% of adolescent women. Significant period and pelvic pain results in school absenteeism and young women missing out on social and sporting activities. Recurrent period pain is now considered a potential precursor for chronic pelvic pain in adult women.
There has been some work that has demonstrated that central sensitisation may contribute to the experience of more severe period and pelvic pain, yet there is no understanding as to why this occurs in some and not others. There has been no work done to explore the psychosocial aspects of why the pain is more substantial in some young women than others. There is data in adults in other pain areas, that pain catastrophisation [measured using the pain atastrophisation score (PCS)] may exacerbate and influence the pain experience, management and long term outcomes. There is only limited work looking at PCS in the setting of period and pelvic pain, but none in adolescents.
Parental emotional, cognitive and behavioural responses are highly influential on their childs' pain and functional outcomes. This aspect of a young womans experience of period and pelvic pain is as yet unexplored.
This project will recruit young women with period and pelvic pain who attend the Royal Children's hospital gynaecology service, and their parent to study these issues.

48. Parental anxiety from early targeted cytomegalovirus (CMV) screening through the Victorian Infant Hearing Screening Program (VIHSP)

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Available as Masters Project: No

Cytomegalovirus (CMV) is the most common infectious cause of congenital hearing loss. Recent international guidelines recommend screening for congenital CMV for at risk infants due to evidence that early antiviral treatment can improve outcomes. From 2018 to 2019, VIHSP, in collaboration with four Victorian maternity hospitals, will pilot a program of targeted saliva CMV screening (HearS-cCMV) to see whether it is feasible and acceptable for future statewide roll-out. Measuring parental anxiety with and without this pilot program will inform whether the additional saliva CMV screening affects levels of anxiety in parents of newborn babies who require a diagnostic hearing test.

49. Aetiology, developmental trajectories and health service use in children with congenital hearing loss

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Congenital hearing loss affects 1-3 in 1000 children and is the most prevalent childhood disability diagnosed through newborn screening. In Victoria, despite a robust universal hearing screening program, there has until recently been no universal pathway to ensure each baby receives appropriate clinical care once a hearing loss diagnosis is made. The Royal Children's Hospital Caring for Hearing Impaired Children (CHIC) clinic was set up in 2016 to deliver coordinated medical and developmental shared care to these families, while enabling participation in research. The clinic's opening coincided with the roll-out of the electronic medical record system EPIC, with clinicians collecting rich data recorded systematically.

50. The epidemiology of food allergy and other allergic diseases

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Available as Masters Project: No

An epidemic of allergic diseases has occurred, marked by the rapid rise of asthma, eczema and allergic rhinitis during the 1990s, followed by an alarming increase in food allergies in the 2000s. The determinants, natural history and impact of allergic diseases, in light of the increased prevalence, remains largely unknown. This includes whether the new wave of infant food allergy will persist later into childhood, and the role of food allergy in the development of other allergic diseases such as asthma.
The HealthNuts study is the world's largest population-based, longitudinal study of food allergy and other allergies in early childhood. At 12-months of age, 5300 infants underwent skin-prick testing, and all positives proceeded to hospital-based food challenges to test for food allergy. The cohort has been followed up at ages 4 and 6 years and an age 10 year follow-up is underway. Objective data on the full range of allergic outcomes (asthma, eczema, allergic rhinitis and food allergy) including lung function testing, food challenges and skin prick tests, as well as other measures of their physical and psychosocial health have been collected.
A position is available for an honours student to investigate a number of potential research questions related to the determinants, natural history and consequences of food allergy and other allergic diseases. This is an exciting opportunity to undertake epidemiological research in a large, longitudinal study.

51. Equivalence curves: Trading off lifestyle behaviours

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Population Health

Non-laboratory-based research

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Available as Masters Project: Yes

The way we use our time affects our health. In general, more sleep, more physical activity and less sitting are good for us. But we only have 24 hours in a day, and our choices are often constrained. If we have to choose which behaviours to modify, how should we choose? What is the "exchange rate" between behaviours in terms of health outcomes? For example, if both physical activity and sleep are good for quality of life, how much longer would I need to sleep to get the same benefit as say 30 min of physical activity each day?
This project will suit someone who enjoys working with numbers, and is considering a future career in biomedicine, medicine, public health, sports science, epidemiology and/or biostatistics.

52. Residential air pollution effects on cardio-respiratory health in early and mid-life: A population-based study

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The adverse effects of air pollution exposure are well documented and wide-ranging. Exposure to particle matter (PM2.5), even at low levels, has been associated with cancer, cardiovascular- and respiratory-related morbidity/mortality, eczema, allergies, reproductive issues and low birth weight. In particular, the intermediate and long-term effects on cardio-respiratory health have been studied widely in other countries. However, Australian data are lacking and very few studies have considered these effects early if life, which is important given that the pathogenesis of cardio-respiratory diseases begins in childhood.

Although Australia's air quality is considered favourable in the global perspective, recent data shows that even these low levels account for more deaths annually than the current road toll. Recent emission trends, particularly from diesel vehicles, are also of concern. Unlike other countries that have begun to implement policy changes to reduce traffic emissions, diesel car ownership has recently increased by 60% in Australia and new road infrastructure continues to be rolled out without mitigation systems to reduce air pollution (e.g. lack of filtration on tunnels).

Novel statistical methods now allow us to estimate Australian's air pollution exposure using geographic information system technology. By combining this with The Child Health CheckPoint's unique cardio-respiratory data (i.e. spirometry, carotid IMT, cardio-metabolic profiles and vascular function data), we have a unique opportunity to examine whether residential air pollution is associated with cardio-respiratory health at 11-12 years and mid-life in a well-phenotyped sample.

53. Australians' views on an electronic health record

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Available as Masters Project: No

In 2017, the Australian Productivity Commission noted overwhelming benefits to Australians and Australia of a universal electronic health record to improve health care, cut down on waste and errors, and support use of data to improve health. The record has been piloted extensively over the last 4 years, with millions of Australians already having a record. As of July 2018, all Australians were given 3 months to 'opt out' of having their electronic health record created. Despite similar initiatives overseas being well received and operating smoothly, and the large pilot operating without incident, the public discourse across the media was almost universally negative. It focused heavily on perceived risk, with little consideration of benefit. At point of writing, the extent of resulting My Health Record opt-out remains uncertain. This project will (1) use qualitative research methods to analyse the public discourse across themes and across time as the opt-out period progressed; (2) conduct a systematic review of successful engagement methods to improve acceptance of and support for electronic health records; and (3) make recommendations regarding public engagement strategies to support the use and sharing of children's electronic data for public-good research.

54. 'Beating the odds': Early life experiences influencing the association between genetic prediction and health characteristics in mid-childhood

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Available as Masters Project: No

In the modern age of complex population epidemics, such as obesity, cardiovascular disease, and the substantial

divide between socioeconomic classes in health and wellbeing, early intervention can have a remarkable impact on long-term quality of life. However, many non-communicable diseases and outcomes involve a complex interaction between 'nature' (genetic pre-disposition) and 'nurture' (lifestyle stressors). In a large cohort of Australian 11-12 year old children and mid-life adults, this project aims to investigate the association between genetic prediction and the measurement of a health characteristic, and the early life exposures that overcome genetic predisposition to improve outcomes in children with poorer genetic profiles.

The Child Health CheckPoint was a physical health and biospecimens module nested within the Longitudinal Study of Australian Children (LSAC), a national, population-derived cohort assessing children and their families every two years since birth. The CheckPoint includes detailed outcome measurements at 11-12 years in almost 2000 children and one of their parents, and from which DNA has been collected and genotyped for over 1700 children and 2500 adults for 7 million genetic variants. A wide range of outcome measures are available, including anthropometrics, physical health in cardiovascular, respiratory, musculoskeletal, renal, hearing and visual systems, physical activity and sleep, allergies, pain, mental wellbeing, and societal outcomes such as educational attainment.

The student will (1) use previously published results to generate a polygenic risk score within the CheckPoint cohort for a characteristic of interest to the student. The student will then (2) examine the association between the generated polygenic risk score and the phenotype measured in the CheckPoint cohort, and (3) investigate the mediation of this genetic- phenotype association by a range of relevant lifestyle exposures in the preceding decade, such as home environment, activities, diet, community and health service use, parental involvement, socialisation and family demographics.

55. Obese parents, obese child? Investigating the resilience factors amongst children of obese parents who maintain normal weight throughout childhood.

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Available as Masters Project: No

Overweight clusters in families, due to shared genetics, environments and lifestyle behaviours. Approximately 75% of children have an overweight or obese parent. Mainstream advice to prevent or treat overweight by 'moving a little more, eating a little less' isn't working to reduce the prevalence of overweight/obesity down from a quarter of Australian children and two thirds of Australian adults. Insights into protective factors against childhood overweight may be found by studying children of obese parents who maintain normal weight. This group of children, who are so-far 'beating the odds' by not realising their high risk for obesity, may hold the key for halting intergenerational transmission of overweight and its associated health consequences.
Using data from the Longitudinal Study of Australian Children (LSAC, n 3500 families), a wide range of predictors of child body mass index (BMI) status can be examined, including sociodemographic, lifestyle, psychosocial, parenting and cognitive characteristics. This project can also analyse the data from LSAC's Child Health CheckPoint study (n 1900 families) to characterise the physical health (e.g. cardiovascular, renal, bone, respiratory) and genetic risk of obesity of children from obese and non-obese families.
These datasets could be analysed to explore numerous related research topics including:
Do the predictors (including protective factors) of future BMI status differ between children of obese ('higher-risk') and non-obese ('lower-risk') parents?
What is the typical profile of normal weight children of obese parents, and do multiple factors interact to protect children from future overweight?
How strongly do child lifestyle and environment factors predict future weight status, compared to parental BMI and genetic risk of obesity?
How accurately can we predict the future BMI status of the children of obese parents?
The project will suit someone interested in health, epidemiology and/or statistics, and working closely with a strong interdisciplinary team.

56. Linking early life environment with child health: a longitudinal twin study

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Population Health

Non-laboratory-based research

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Available as Masters Project: Yes

What happens in the womb can last a lifetime. Factors such as maternal diet and lifestyle during pregnancy are linked with a lifetime risk for chronic diseases, ranging from cardiometabolic to neurodevelopmental. Twin studies are ideal for studying such diseases because of their ability to resolve genetic, shared (maternal and early life) and individual environments. For example, comparing twins within a pair enables regression of within-pair differences in pre- and perinatal factors on within-pair differences in health outcomes, controlling for genetics and shared environment.
This project takes advantage of the unique data collected in the Peri/postnatal epigenetic Twin Study (PETS) of Drs. Craig and Saffery. In this study, women pregnant with twins were recruited in mid gestation, extensive data were collected on maternal diet and lifestyle and on the twins themselves multiple times in utero, at birth, 18 months and
6 years of age. This rich dataset enables a number of potential projects based on the student's interests and is ideal for a wide range of disciplines from genetics to medicine. Our main outcomes of interest are cardiometabolic (weight, height, skin fold thickness, blood pressure) and infectious and other illnesses. Specific research questions include, but are not limited to:
1. Are shared maternal factors such as smoking, gestational weight gain, diet and stress associated with health outcomes in 6 year-olds?
2. Are twin-specific prenatal factors such as intrauterine growth rate, placenta weight, and location of cord insertion into the placenta associated with within-pair differences in health outcomes in 6 year-olds?
3. Do factors such as maternal smoking in pregnancy predict within-pair discordance in child health outcomes?
4. Are twin zygosity, sex and chorionicity associated with child health outcomes?
Each specific research project will be supported by experts in specific domains of child health.

57. Case control study identifying modifiable health system factors associated with asthma re-admissions

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Available as Masters Project: Yes

Asthma is the most common chronic childhood illness affecting approximately 10% of Australian children. Asthma hospitalisations are associated with serious outcomes including worse lung function, functional limitations, future admissions and increased risk of mortality. In addition, hospitalisation poses a significant burden on hospitals with asthma accounting for approximately 3% of all hospitalisations for Australian children aged 5-14 years in 2015-6. Hospitalisations also place an economic burden on families with time off work. With the increasing burden of chronic and complex paediatric illnesses on hospital resources, new models of care that shift care to the community are necessary for sustainability. The overall aim of this project is to identify modifiable and translatable factors associated with asthma re-admissions in order to inform new models of care to keep children out of hospitals.
The candidate will undertake a retrospective hospital record analysis comparing children with frequent admissions for asthma (>2 per year) with children with no asthma admissions (only seen in ED or clinics). Through a case control analysis the candidate will identify modifiable health system factors associated with re-admissions above and beyond known child, family and environmental factors that contribute to poor asthma control.

UNIVERSITY OF MELBOURNE HONOURS

Honours entry requirements

To be eligible to enter the Bachelor of Biomedicine (Degree with Honours) or the Bachelor of Science (Degree with Honours), applicants must satisfy both:

- the Faculty of Medicine, Dentistry and Health Sciences (MDHS) or Faculty of Science entry requirements;
- the requirements of the department offering the Honours program.

Please note: demonstrated eligibility does not guarantee a place in the Honours program. All successful applicants will also need to be selected for admission by the Department. The University of Melbourne handbook contains detailed information about the subjects available and entry requirements for departments offering Honours. https://handbook.unimelb.edu.au

For further details, see the Department of Paediatrics: http://medicine.unimelb.edu.au/school-structure/paediatrics

Murdoch Children's Honours Website: www.mcri.edu.au/students/honours-students

MDHS website: http://studentcentre.mdhs.unimelb.edu.au/entry-requirements

Honours course work

BIOM40001 Introduction to Biomedical Research – 12.5 points (February)

1. 10 x 2hr tutorials
2. Two written reports (each not exceeding 3000 words) (50% each)

PAED40002 The Biology of Human Health and Disease – 12.5 points (Year Long)

1. Literature review, - Hurdle requirement
2. Assignment 1: (Individual) coming to grips with your research project 34%
3. Assignment 2: (Group) Bioinformatics – Hurdle requirement
4. Assignment 3: (Group) using biostatistics in your Honours thesis – 33%
5. Assignment 4: (Group) Critical thinking and data analysis – 33%

Honours research project

Students will enrol in both the research project subjects indicated below to complete a total of 75 points for the research project by the end of their course.

PAED40001 Paediatrics Research Project Part 1 – 31.25 points (semester 1)

PAED40005 Paediatrics Research Project Part 2 – 43.75 points (semester 2)

The research project will be completed under the supervision of experienced senior scientific researcher/s and work within a research group at the Murdoch Children's Research Institute. The student's original research project will be assessed by the following criteria:

1. A written report (thesis) of 10,000 – 12,000 words (80%)
2. An oral presentation on the research project (20%)

How to apply – MDHS Honours

Course Codes:
Bachelor of Biomedicine (Honours) – **BH-BMED** Bachelor of Science (Honours) – **BH-SCI**
RCH Academic Centre Enrolling Unit is: **Department of Paediatrics**
If you wish to be considered for Honours in 2019, and you would like to undertake your project and coursework with the Murdoch Children's Research Institute, Royal Children's Hospital, Academic Centre, Faculty of Medicine and Dentistry Sciences with the enrolling unit being Department of Paediatrics, you will need to carry out a FOUR STEP PROCESS.

STEP 1: Contact Potential Supervisor(s): You will need to decide which Supervisor(s) and Project(s) that you wish to apply for. To do this, contact potential supervisors listed in this Handbook, you should speak to them and organise a meeting to discuss the project further. Projects available for 2019 are also listed on the Murdoch Children's Research Institute and Department of Paediatrics websites.

STEP 2: Online application: Lodge an online course application by Friday 26 October 2018 and select 'MDHS Specialisations' as the discipline.
http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

STEP 3: Project Preference: Once you have submitted an online course application, you will receive an email within 3 working days with login details to access the Honours Project Preference System - SONIA. You may select up to 4 project preferences. You must only preference projects after making contact with the relevant supervisor(s). You are allowed to log into Sonia to change your preferences any time by the closing date, Sunday 28 October 2018.

STEP 4: Offers: Round 1 offer for entry into 2019 will be sent to you by Friday 7 December 2018. Students must accept their offer by the Offer Lapse Date noted in their offer letter. Students who meet the minimum entry requirements but are not made a Round 1 offer may be considered for Round 2 and Round 3.

UNIVERSITY OF MELBOURNE MASTER OF BIOMEDICAL SCIENCE

The Master of Biomedical Science is a coursework program (Course code **MC-BMEDSC**) offered through the Department of Paediatrics. This program offers graduates a pathway into research or other science based careers, and can lead on to PhD studies. Students may consider undertaking a Masters as an alternative to the Honours Program.
Students undertake a major research project and discipline-specific coursework subjects offered by MDHS. A range of professional development subjects are offered to complement and enhance the research undertaken and to progress students' career opportunities.
MDHS website: http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/overview

Masters research project

The Master of Biomedical Science is a two year full time course (four years part time) and mid-year entry is available. Students must complete 200 credit points comprising:

- Discipline-specific subjects (50 credit points)
- Professional skills subjects (25 credit points)
- Research subject (125 credit points)

The research subject is completed as a project under the supervision of experienced senior scientific researcher/s within a research group at the Murdoch Children's Research Institute.
To organise the research project, students must speak to the prospective supervisor/s listed in this Handbook for projects marked as available for Masters. Students should meet with the supervisor/s to discuss the project further. Projects available for 2018 are also listed on the Murdoch Children's Research Institute and Department of Paediatrics websites. For commencement in semester one 2019, applications close: 23 November 2018
http://futurestudents.unimelb.edu.au/admissions/applications/grad-dom

Contact us:
Gr-mc@unimelb.edu.au or students@mcri.edu.au