2018 HONOURS AND MASTERS PROJECTS
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Laboratory-based Research Projects

Cell Biology

1. Effect of ACTN3 on corticosteroid response in Duchenne muscular dystrophy

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**Available as Masters Project:** No

Duchenne muscular dystrophy (DMD) is the most common, inherited childhood muscle disease and affects 1 in 3500 boys. Most patients succumb to the disease in their 20's due to cardiac and respiratory failure. DMD is caused by the loss of a critical skeletal muscle protein, dystrophin, and results in recurrent muscle damage. There is currently no cure for DMD, but corticosteroids are effective in reducing inflammation and slowing disease progression. Long term corticosteroid use however causes weight gain and muscle loss, which creates additional health problems for patients with DMD.

ACTN3 is known as “the gene for speed” and is associated with muscle strength and power. Approximately 1 in 5 people worldwide do not produce the ACTN3 gene product, alpha-actinin-3, in their muscles and have slightly lower muscle strength (within normal human variation) than people who have alpha-actinin-3. Interestingly, we found that muscles lacking alpha-actinin-3 are partially protected from damage in mouse models of DMD and ACTN3.

Recently, we also found that healthy mice lacking alpha-actinin-3 do not suffer as much corticosteroid-induced muscle loss. Our aim now is to determine if the presence or absence of alpha-actinin-3 will influence how muscles respond to corticosteroids using mouse models of DMD. This research will provide valuable preclinical data to identify DMD patients who may experience greater muscle loss with corticosteroid treatment, and may otherwise respond better to other classes of anti-inflammatory drugs that carry fewer side effects.

This project will involve animal handling and laboratory-based techniques such as molecular biology, immunohistochemistry, western blotting and muscle physiology to examine the structural, metabolic and signalling changes in skeletal muscle.

2. Examining the evolutionary role of alpha-actinin-3 in adaptive thermogenesis

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**Available as Masters Project:** Yes

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 quantitative real-time PCR (RT-qPCR) to further study the role of alpha-actinin-3 in adaptive thermogenesis.

3. Examining the effect of alpha-actinin-3 deficiency in skeletal muscle injury

We have identified a common genetic variant in the alpha-actinin-3 (ACTN3 R577X) gene that results in absence of the fast muscle fibre protein, in ~20% of the world's population. This equates to ~1.5 billion people worldwide being completely deficient in alpha -actinin-3. Loss of alpha -actinin-3 does not cause disease but its absence significantly influences muscle function in both the general population and elite athletes by altering the muscles structure and metabolism.

We have developed a model of alpha -actinin-3 deficiency in mice (Actn3 KO). The Actn3 knockout (KO) mouse model mimics much of what we seen in humans. Actn3 KO mice run further on a treadmill, are able to train more efficiently and have an altered metabolic profile, due to a shift in the muscle to a more oxidative phenotype. Our data, generated over the last 8 years, provides strong evidence that alpha -actinin-3 influences normal variation in skeletal muscle function.

This project aims to determine how alpha -actinin-3 deficiency influences the muscles response to damage and its ability to regenerate following acute injury. We will use notexin to induce targeted muscle damage in both Actn3 WT and KO mice and examine the molecular and histological changes over time. The project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and quantitative real-time PCR (RT-qPCR) to further study the role of alpha-actinin-3 in muscle damage/regeneration.

4. Modelling childhood leukaemias using human pluripotent stem cells

We have identified a common genetic variant in the alpha-actinin-3 (ACTN3 R577X) gene that results in absence of the fast muscle fibre protein, in ~20% of the world's population. This equates to ~1.5 billion people worldwide being completely deficient in alpha -actinin-3. Loss of alpha -actinin-3 does not cause disease but its absence significantly influences muscle function in both the general population and elite athletes by altering the muscles structure and metabolism.

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This project aims to determine how alpha -actinin-3 deficiency influences the muscles response to damage and its ability to regenerate following acute injury. We will use notexin to induce targeted muscle damage in both Actn3 WT and KO mice and examine the molecular and histological changes over time. The project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and quantitative real-time PCR (RT-qPCR) to further study the role of alpha-actinin-3 in muscle damage/regeneration.

Available as Masters Project: Yes
Although the prognosis of childhood leukaemia has improved, there are still children with types of leukaemias for whom survival remains poor. A particular group with difficult to treat leukaemia are those who develop the disease in infancy. In a high proportion of these children, their leukaemic cells have a specific genetic abnormality that involves the abnormal fusion of the MLL1 (KMT2A) gene to variety of other partner genes. There has been significant progress using mouse models to increase our understanding of the manner in which MLL fusion proteins activate genes and drive cancer. However, progress is limited by the lack of robust human cell systems to study these childhood leukaemias and to use as a screening platform for potential therapeutic agents.

We have developed methods to differentiate human pluripotent stem cells (PSCs) into blood cells that resemble precursors of haematopoietic stem cells, the cell type that sustains blood formation throughout life (Ng et al, Nat Biotechnology 2016). Using this system, we can generate precursors of all the blood lineages, including cell types in which MLL mutations are first thought to arise. This capacity places us in a position to model the development of blood cells and to understand how MLL fusion genes cause childhood leukaemia. This endeavour will greatly expand our possibilities for understanding disease mechanisms and for studying the potential of new therapeutics in human cells.

In this project, MLL fusion genes will be put into the hPSCs and the effects on differentiation and cell growth will be studied. We will also determine the susceptibility of oncogene expressing cells to anti-cancer drugs.

5. Engineering artificial bone marrow

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**Available as Masters Project:** Yes

Haematopoietic stem cells give rise to all of the various cell types found in the blood, including those belonging to erythroid (red cells), myeloid and lymphoid (immune cells) lineages. In bone marrow failure syndromes, HSCs are lost, eventually resulting in the collapse of the blood system, a scenario that is sometimes fatal. The generation of haematopoietic stem cells (HSCs) from the in vitro differentiation of human pluripotent stem cells would benefit individuals with bone marrow failure who lack a perfectly matched HSC donor. However, the generation of HSCs in vitro has proved elusive, reflecting a failure to generate the correct cells and/or to provide a suitable stem cell niche. We have improved pluripotent stem cell differentiation methods to yield cells that are transcriptionally similar to ‘preHSCs’ that develop during early human embryogenesis. However, these cells still require further maturation to become therapeutically useful HSCs.

In adults, HSCs reside in the bone marrow, where they interact with a variety of endothelial and stromal cells. In this project we will generate an artificial human bone marrow-like microenvironment into which we can seed pluripotent stem cell-derived ‘preHSCs’ and determine whether this enables further maturation to yield true HSCs. Reconstruction of an artificial bone marrow will require the generation cell types such as cartilage precursors, macrophage like osteoclasts and vascular and haematopoietic components.

This project will involve generating the above cell types and combining them to generate an artificial bone marrow-like culture system.

6. In vitro models of type 1 diabetes

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Type 1 diabetes is a condition in which the immune system destroys the body’s cells that produce insulin, the hormone controlling the level of glucose in the blood stream. Because of this, individuals with Type 1 diabetes must assiduously monitor their blood glucose levels and inject insulin 3-4 times per day. This condition affects around 110,000 Australians and, as yet, neither cause nor cure has been identified. In this project, we will use stem cell models to investigate mechanisms underlying type 1 diabetes, with particular emphasis on the interaction between cells of the immune system and insulin producing beta cells.

Beta cells reside in pancreatic islets, small clusters of endocrine cells that secrete hormones directly into the blood stream. In type 1 diabetes, residual islets can contain a mixture of different immune cells, including effector cells such as CD4 and CD8 T-cells and NK cells, as well as antigen presenting cells like macrophages, dendritic cells and B-cells. We have developed methods for generating many of these different cell types from human pluripotent stem cells. We also have protocols for deriving insulin producing beta cells from the same pluripotent stem cell lines, providing an opportunity to directly observe interactions between beta cells and cells of the immune system.

This project will involve generating combinations of the above cell types and observing their direct interactions using time lapse microscopy.

The gut’s own nervous system, the enteric nervous system (ENS), arises early in development from migratory precursor cells. In Hirschsprung disease, the distal-most colon is not colonised by these cells and so it fails to develop an ENS. This means the colon cannot function once the baby is born. The current treatment for this fatal birth defect is to surgically remove the non-functional part of the baby’s colon, and join the upstream functional colon to the rectum. This saves the patient’s life but loss of distal colon results in poor quality of life. Recently the notion has been presented that the ENS of the distal colon could be repopulated with ENS precursor cells at neonatal stages, so avoiding surgical colon removal. The two crucial questions are: 1) How to obtain the appropriate cells in appropriate numbers, and 2) How to transfer these cells into the distal colon. This project focuses on the second question, using firstly an animal model, the avian embryo, and secondly, pig colon tissue obtained at surgery. The avian model is chosen because the tissue maturity of the late stage embryonic avian colon resembles that of a human neonate, and because avian ENS precursor cells are readily obtainable. The pig model closely resembles human tissue in structure and size. Labelled ENS precursor cells will be seeded and grown on a polymer membrane which will then be wrapped onto the outer surface of the colon. The ability of the ENS precursor cells to penetrate the colon tissue will be assayed to test the practical efficacy of this method of cell transfer.
The gut's own nervous system, the enteric nervous system (ENS), arises early in development from migratory precursor cells. In Hirschsprung disease, the distal-most colon is not colonised by these cells and so it fails to develop an ENS. This means the colon cannot function once the baby is born. The current treatment for this fatal birth defect is to surgically remove the non-functional part of the baby’s colon, and join the upstream functional colon to the rectum. This saves the patient's life but loss of distal colon results in poor quality of life. Recently the notion has been presented that the ENS of the distal colon could be repopulated with ENS precursor cells at neonatal stages, so avoiding surgical colon removal. The two crucial questions are: 1) How to obtain the appropriate cells in appropriate numbers, and 2) How to transfer these cells into the distal colon. This project focuses on the first question, using firstly real embryonic ENS precursor cells from an animal model, the avian embryo, since these are easily and cheaply obtained. A second source will be human ENS precursor-like cells induced from human pluripotent cells. Both these cell types will be exposed to growth factor and small molecule regimes to inhibit cell differentiation and promote cell proliferation, the regimes being based on known effectors of normal ENS development. This project will increase our ability to produce ENS precursor cells in large numbers for proposed therapeutic use.

Clinical Sciences

9. Haemostatic system in Fontan patients with liver dysfunction

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Available as Masters Project: No

The Fontan procedure is the last of a series of operations offered to children with a single functioning ventricle. It is widely accepted that patients with a Fontan are at an increased risk of thrombosis due to a number of factors associated with their surgical procedure. These include: abnormalities in blood flow, endothelial dysfunction, as well as inherent abnormalities to the coagulation system. Furthermore, it is now recognised that liver dysfunction is common in this population, particularly due to increased systemic pressure.

The impact of liver dysfunction on the coagulation system of Fontan patients has never been investigated. Considering that the liver plays an essential role in the production of coagulation proteins, the impact of abnormalities in liver function may play a significant role in the dysregulation of the coagulation system that lead to thrombotic complications in this patient population.

This will be a detailed, laboratory-based clinical study investigating the blood clotting system in Fontan patients with liver disease.

Note: Samples and clinically relevant data for this study have been collected and the primary role of the Honours student will be to complete the laboratory testing and correlate the results to the known clinical outcomes.

10. Characterisation of the specificity and activity of bio-engineered antibodies in children

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Available as Masters Project: No
This is a collaborative project between the Haematology Research laboratory at the Murdoch Children's Research Institute and the NanoBiotechnology laboratory at the Australian Centre for Blood Diseases.

The project will utilise recently developed antibody fusion molecules and targeted nanoparticles for the sensitive detection and safe treatment of thrombosis. These specifically modified recombinant antibodies can deliver imaging tracer and a therapeutic payload with high precision and reduced adverse effects; this is achieved by using novel bio-enzymatic conjugation methods allowing site-specific modification without affecting antibody function.

Specific state of the art antibodies targeting activated platelets and fibrin have previously been made and extensively characterised by A/Prof Hagemeyer at the ACBD. Whilst the specificity and activity of these antibodies have been tested in animal models of human disease and on human tissue ex vivo there are currently no data on the specificity and effect of these antibodies in blood samples obtained from children.

The fact, that the blood clotting system changes with age, concept known as Developmental haemostasis, has been proven conclusively. The Haematology Research Team at MCRI leads the World in this field with both laboratory and clinical research. Our studies have demonstrated age specific differences in concentration, function and structure of key haemostatic proteins and their response to anticoagulants. We have also shown differences in platelet phenotype and response to agonists, as well as differences in the mechanism of thrombin generation and clot structure in neonates and children compared with adults.

Considering these key age-specific differences in the blood clotting system, it is crucial to investigate the specificity and activity of existing bio-engineered antibodies in blood samples obtained from children; with a view of their possible use for disease detection and treatment in children affected by thrombosis and potentially the biotechnological generation of new, unique antibodies more specially tailored for children.

11. Investigation of the in vitro effect of the antiplatelet drug Tirofiban in children

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Available as Masters Project: Yes

Tirofiban (Aggrastat) is an antiplatelet drug that functions by inhibiting the glycoprotein IIb/IIIa platelet receptor. This synthetic non-peptide inhibitor is specifically responsible for blocking the interaction between fibrinogen and the GP IIb/IIIa receptor on the platelet surface, and hence preventing platelet aggregation.

Despite its current use in hospitalised children, the safety and efficacy of Tirofiban have never been established in this especially vulnerable population. In fact, to date, there has not been a single study of Tirofiban in children, with all evidence arising from adult studies.

Considering that:
1. Bleeding is the most common adverse reaction associated with the use of Tirofiban.
2. Antiplatelet therapy is not routinely monitored in children at the Royal Children's Hospital (RCH).
3. There are fundamental differences in platelet phenotype and response to agonists that exist between children and adults (Yip et al 2013; Yip et al 2015).

It is imperative to understand the effect of Tirofiban on platelets from children. This study will utilise flow cytometry, as a robust and sensitive tool for measurement of platelet function, to determine the differences in the in vitro effect of Tirofiban in infants, children and adults.

This first ever study of Tirofiban effect on platelets from children of different ages will provide essential data that will guide future use of this drug in hospitalised children. The results of this study will directly inform clinical practice at the RCH, and will be used by clinicians nationally and internationally.
12. Investigation of the age-specific changes in Blood Microparticles

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**Available as Masters Project:** Yes

Cellular Microparticles are heterogeneous membrane vesicles that are shed by almost all cells in response to cellular activation and apoptosis. The process of microparticle formation is a physiological phenomenon. However, increase in microparticle formation has been associated with inflammatory and autoimmune diseases, atherosclerosis, as well as malignancies.

Microparticles vary in size from 100 - 1000 nm and express antigens specific to their parental cells. The complexity of surface receptors in addition to the content of cytokines, signaling proteins, mRNA, and microRNA confirms the role of microparticles in exchange of biological signals and information.

Blood microparticles arise from the cellular components of blood, as well as the endothelial lining of blood vessels. Each of these individual populations of microparticles (i.e. platelet microparticles, endothelial microparticles) have been studied in the setting of disease.

While studies in adults demonstrate that platelet microparticles constitute 70-90% of the microparticles in the bloodstream, this has never been investigated in children. In addition, to date, there have been no investigations of the age-specific differences in the composition of the blood microparticles. Question such as: “Do particular microparticles dominate early in life and does this change during the process of ageing?” is yet to be answered.

Characterization of the age-related differences in the microparticles of the healthy population will provide new insights into normal growth and development and in our understanding of developmental biology. Given that the incidence of majority of diseases (i.e. diabetes, thrombosis, cardiovascular disease, cancer) increase with age, these results will provide the basis for understanding the age of onset of these diseases, as well as identification of potential biomarkers and therapeutic targets. This has the potential to impact on high frequency, high importance disease of adults.

13. Modulating fibrosis and myocardial injury in Muscular Dystrophy

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**Available as Masters Project:** Yes

Duchenne muscular dystrophy (DMD) is an X-linked muscle-wasting condition that affects approximately 1 in 3600 boys. It is caused by a mutation in the dystrophin gene, which results in the complete absence of the dystrophin protein. The absence of dystrophin significantly weakens the connection between the muscle cytoskeleton and extracellular matrix, leading to mechanical instability of the sarcolemma, inflammation, necrosis, and the replacement of muscle tissue with fat and fibrotic tissue. This deterioration is most obvious in skeletal muscle, initially affecting the limbs, before spreading to respiratory muscles and heart by the second decade of life. Currently there is no cure or effective therapy to prevent DMD from progressing to premature death.
The skeletal muscle pathology is currently treated using glucocorticoid drugs. However, the management of cardiac dysfunction is more commonly addressed after heart symptoms first present. The current standard of care in the management of cardiac dysfunction involves the use of angiotensin-converting-enzyme (ACE) inhibitors and β-adrenoceptor blockers, an approach arising from heart failure management in adults, but with relatively limited study in DMD children.

Recent work has proposed the involvement of mitochondria-dependent cell death and irreversible opening of the mitochondrial permeability transition pore (MPTP) in the pathogenesis of the dystrophic myopathies. Early enhanced opening of the MPTP increases the susceptibility of dystrophin-deficient muscle to stress-induced cell injury. The genetic ablation of the MPTP-sensitizing protein cyclophilin-D has been reported to reduce fibrosis in dystrophic muscle, and improve muscle function in mouse models of muscular dystrophy, i.e., mdx mouse. This study aims to test whether pharmacological targeting of the MPTP ameliorates the cardiac pathology in mdx mice. The work will inform whether the clinical use of perindopril in DMD patients may be augmented by the inclusion of an additional class of drugs that directly target muscle cell death via MPTP control.

Genetics

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

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Available as Masters Project: Yes

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 quantitative 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.
15. Using cerebral organoids for the study of tuberous sclerosis complex

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**Available as Masters Project:** Yes

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.

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

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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.
17. Understanding RAB39B-mediated Parkinson's disease

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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 and we are currently investigating how RAB39B may be involved in the development of 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 induced pluripotent stem cells (iPSC) and mouse models to perform pre-clinical studies to characterise the disease process and identify potential therapeutic targets. Specific techniques will include tissue culture, real time PCR analysis, western Blot analysis, confocal microscopy.

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

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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.
19. 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.

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 iPSCs 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.

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Available as Masters Project: No

The CDKL5 disorder is a rare X-linked neurodevelopmental disorder characterised by severe intellectual disability and seizures which appear in the first few months of life. There is no treatment for this devastating disorder and little is known about the biology of CDKL5 disorder.

The proposed research project will address the large knowledge gap on CDKL5 by examining if there is functional overlap between CDKL5 and MeCP2 (the gene responsible for Rett syndrome, which causes health problems that have a strong clinical overlap with the CDKL5 disorder) in regulating microtubule dynamics. Microtubules are the 'train tracks' that nerve cells use to deliver critical cargo to nerve connections called synapses. Any problems in the regulation of microtubules will impair nerve function. We have previously shown that microtubule dynamics are affected in Rett syndrome caused by mutations in MECP2.

Specifically, we plan to use cutting edge technologies developed by researchers at the MCRI that enable us to convert skin cells from patients with Rett syndrome and the CDKL5 disorder to develop a 'disease in a dish' model. We have already created induced pluripotent stem cells (iPSC) from patient fibroblasts with pathogenic CDKL5 variants, and have generated isogenic iPSC controls for each CDKL5 cell line using CRISPR-Cas9 gene correction. We will then differentiate iPSC into neurons and capture the overall gene profile in differentiated neurons carrying the CDKL5 mutations using RNA-seq. This will provide a global perspective of gene expression changes in response to CDKL5 mutations. Similar methodology has provided novel insights into gene regulation in a mouse model of RTT carrying Mecp2 mutations [32] and in the frontal cortex of the human Rett syndrome brain [33]. We will determine the validity of our candidate genes by high-throughput quantitative reverse transcriptase polymerase chain reaction.

22. HDAC6 inhibitors as a treatment for Rett syndrome: Resolving neuronal trafficking deficits

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Available as Masters Project: No

Rett syndrome is an incurable progressive genetic disease that causes girls to develop catastrophic severe motor, cognitive, neurological, and behavioural abnormalities. It is an X-linked genetic disorder most commonly caused by de novo mutations in the methyl-CpG-binding (MECP2) gene, which encodes a key transcriptional regulator protein, and affects about 1:9000 female births. MeCP2-deficient neurons have a defective cytoskeletal architecture that compromises the trafficking of synaptic components such as mitochondria along the microtubule network. We have strong evidence that mitochondrial function and movement is disrupted in MeCP2-deficient fibroblasts. We are currently generating MECP2 mutant human neuronal cells. These will be generated from induced pluripotent stem (iPS) cells generated from Rett syndrome patients and differentiated into a neuronal lineage. From these cells we will assess mitochondrial activity (respiration, enzyme activity and ATP content) in MECP2-deficient neuronal cells. We hypothesize that correcting this cytoskeletal defect could underlie a therapeutic solution for Rett syndrome. Our research has
identified histone deacetylase 6 (HDAC6), an enzyme that post-translationally modifies microtubules, to be upregulated in MeCP2-deficient cells. As HDAC6 is a key regulator of the stability of the microtubule network it is a strong target for therapeutic intervention. Our laboratory has exciting preliminary data showing that inhibitors of HDAC6 can ameliorate the effects of MECP2 mutations in patient fibroblast cell lines and in a mouse model of Rett syndrome. We will determine the expression levels of key proteins known to be involved in Rett syndrome, and determine whether HDAC6 inhibition restores expression of these key targets. From the MECP2-deficient neuronal cells we will also determine whether there are off-target effects of HDAC6 inhibition on mitochondrial function using a new class of drugs currently under investigation. If there are side-effects of these drugs, it may have relevance to their translation into clinical trials.

Infection and Immunity

23. Developing a new treatment for stomach cancer

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Infection with the cancer-causing bacteria Helicobacter pylori starts in childhood and lasts for life. This infection causes a chronic inflammation (gastritis) that can result in stomach cancer, globally the 3rd leading cause of cancer-related death. We have identified a genetic variant (a polymorphism) that increases the susceptibility of some people to this cancer. Individuals who have this polymorphism are five times more likely to get stomach cancer when infected with H. pylori, and this gene is highly expressed in cancer biopsies. Drugs against this gene target are already clinically available, meaning this discovery has the potential for a completely new treatment for stomach cancer. Stomach cancers arise as a result of severe inflammation driven by H. pylori mediated activation of the immune system, so this effect is likely due to genetic regulation of the immune cell response to bacterial stimulation.

AIMS: Key questions to be addressed by this project include 1) how this gene (and its polymorphism) make some people susceptible to stomach cancer and 2) whether drugs can protect against this cancer.

APPROACH: Human cell lines will be genetically modified with the latest genome editing technology and then stimulated with H. pylori. The immune response will then be quantified by measuring the cytokine response by ELISA. This will show how this gene affects the inflammatory response of human cells to these cancer-causing bacteria. Drugs that target this gene will also be tested in these assays, in order to identify candidates that might be used for the prevention or treatment of cancer.

24. Analysis of gene regulations on gonocyte transformation into spermatogonial stem cells

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Undescended testis (UDT) is a major health problem, affecting over 2-4% of males at birth. Boys with UDT face two major problems later in life (20-40 years of age) even after surgically correcting the testis position. One of the problems is infertility, in which 30-60% of males with cryptorchidism will be infertile; and the other is testicular cancer, where the risk of testicular cancer in cryptorchidism is 5-10 fold higher than for normal young men. Infertility and testicular cancer are likely caused by failed transformation of gonocytes (neonatal germ cells) into spermatogonial stem cells (SSC).

Currently UDT surgery is recommended at 6-12 months, but it is not known whether this is the right time as there is insufficient knowledge about early postnatal germ cell development. The aim of the project is to understand the molecular mechanism and regulation of early postnatal germ cell development/transformation of gonocytes into spermatogonial stem cells to provide possible
clues for optimal timing of surgery for UDT to prevent infertility and testicular cancer. This project will focus on analysis of the gene regulations in gonocyte transformation and the effect of congenital UDT on gonocyte transformation using animal models and human UDT biopsies. The study will involve molecular biology, cell biology, histology.

25. The immune response to infection in early cystic fibrosis

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Cystic fibrosis (CF) is an inherited disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The commonest cause of death in CF is respiratory failure as a consequence of bronchiectasis (airway destruction). Disease begins in early life and is characterised by a diminished lung function that is related to infection with opportunistic pathogens, airway inflammation and structural changes. However, mucosal immunity in the early CF lung is not well studied and mechanisms of specific immune events that occur early in CF lungs are poorly understood. Immune factors that modify inflammation in the CF lung are likely to play a critical role in determining disease progression.

1) Characterise the mucosal immune response in the lungs of children with cystic fibrosis during the early stages of disease  
2) Examine how this immune response changes with pathogenic infection

Bronchoalveolar lavage (BAL) cells and fluid from children less than 6 years of age will be analysed. The types of immune cells present in their lungs will be determined by flow cytometry. Existing immunity in BAL fluid from CF lungs will be measured by ELISA. The immune response of the BAL cells to infection will be measured by stimulating BAL cells in culture with pathogenic bacteria. The results will be related back to the clinical and infection status of the patient.

The immune response elicited to lung infections plays a critical role in modifying inflammation in the CF lung. Characterisation of this mucosal immune response will identify potential therapeutic targets via which inflammatory responses can be modified, with the potential of significantly impacting the extent and quality of life for patients suffering from CF.

26. Targeting stem cells as a new treatment for stomach cancer

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Stomach cancer has the 3rd highest mortality rate of all cancers worldwide and results largely from chronic inflammation caused by the bacterium, *Helicobacter (H.) pylori*. Current treatments, based on antibiotic eradication of *H. pylori*, have become progressively less effective, sparking efforts to find new ways to combat stomach cancer. Using a range of mouse genetic, cell/molecular and in vivo lineage mapping tools, this project will investigate the role of a recently discovered gastric epithelial 'reserve stem cell' population in the origins of stomach cancer, define molecular and/or *H. pylori*-related inflammatory signals that reprogram these cells into stomach-specific cancer stem cells (CSC) to give rise to tumour lineages, or premalignant precursor lesions, and establish translational rationale for targeting these cells to restrain or block disease progression.

Recent progress in cancer biology has been achieved by studies of CSC. The clinical potential of CSC in stomach cancer has been recognised but, until now, remains unexploited for therapy. Outcomes of this project will contribute to our understanding of (i) gastric reserve stem cells as inflammation-inducible CSC, (ii) how these cells impact cancer progression and (iii) how they might be targeted therapeutically to prevent disease. This information will help to inform novel approaches for stomach cancer prevention.
and treatment. This project would suit an ambitious and highly motivated individual who is keen to develop advanced skills in advanced cell/molecular biology and in using mouse genetic models of human disease.

27. Bacterial gene expression in pneumococcal pneumonia

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Streptococcus pneumoniae is the most common cause of community-acquired pneumonia, which is a leading killer of young children worldwide, and can also colonise the upper respiratory tract of healthy children. Our laboratory is interested in identifying genes involved in pneumonia pathogenesis, particularly those that are differentially expressed in disease vs colonisation. These genes could be candidates for novel prevention strategies and improved diagnostics for pneumococcal pneumonia. Using a combination of clinical samples collected from healthy children and pneumonia patients as well as in vitro assays, this project will examine pathogen gene expression and genomics using a variety of molecular methods.

28. Synergistic interactions between Streptococcus pneumoniae and respiratory viruses on bacterial pathogenesis

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Co-infections with influenza virus and bacterial pathogens (e.g. Streptococcus pneumoniae) can lead to severe respiratory infections. Clinical evidence suggests that a similar synergy exists between S. pneumoniae (the pneumococcus) and other viruses that are more commonly major causes of respiratory infection and hospitalisation of young infants. Using in vivo models, this project will investigate how respiratory viruses such as influenza, can 1) augment various aspects of pneumococcal pathogenesis and 2) how prevention strategies targeting one pathogen can indirectly impact the other.

29. Bacterial factors for pneumococcal transmission

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Streptococcus pneumoniae (the pneumococcus) is a leading killer of children worldwide. Transmission between hosts is a key step of pathogenesis and also underpins herd protection. Despite this importance, little is known about the bacterial factors that mediate transmission. This project will use mutagenesis (targeted, and transposon mutagenesis with next-gen sequencing) to identify the bacterial factors, and to assess their importance in our established in vivo transmission model.
30. Examination of cross-neutralising immunity following HPV vaccination in Fiji

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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. Three other oncogenic HPV types 31, 33, and 45, represent an additional 15% of cervical cancer cases. For countries using 2vHPV or 4vHPV, cross-neutralising antibodies to non-vaccine types HPV31/33/45 are important as it may provide broader protection against a wider range of oncogenic HPV types. 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 Honours project aims to specifically examine cross-neutralising immunity in blood following 4vHPV using a combination of approaches, including HPV neutralisation assays and cellular immune assays. This is the first such study to examine the persistence of cross-neutralising antibodies following HPV vaccination.

31. Molecular Epidemiology of Severe Respiratory Syncytial Virus Infections in Children under 2 years of age

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Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infections in young children. It is a major reason for hospitalisation worldwide and a leading cause of infant mortality particularly in low-resource settings. Whilst most children are infected with RSV in the first two years of life, it is unclear why some children develop more severe disease whilst others develop only mild symptoms. This may be due to host factors such as the immune response or characteristics of the virus e.g. specific variations in the virus genome. The aim of this study is to identify the major risk factors of severe RSV infection in young children with a specific focus on the genetic characteristics of the RSV strains circulating in Australia.

32. Immunomodulatory effects of Vitamin D on the host response to bacterial and viral infections

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Infections with the Streptococcus pneumoniae and Respiratory Syncytial Virus are a major cause of morbidity and mortality in children less than 5 years of age. In particular, bacterial-viral co-infections cause substantial more inflammation and disease. The host response to infection involves activation of both innate and adaptive immunity both in the mucosal tissue as well systemically. Vitamin D has been shown to have a variety of biological effects including beneficial effects on the immune system. These include modulation of cytokine production, T-lymphocyte function and inflammatory responses, suggesting that Vitamin D may have an
important function in the control of bacterial and viral infections. This project aims to characterise the effects of Vitamin D on immune cell populations in response to bacterial and/or viral co-infection. This study will use a variety of techniques including human immune cell culture and stimulation, flow cytometry and cytokine assays.

33. Inhaled RSV therapeutics: Aerosol delivery of novel therapies to the infant lung

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Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection in young children <5 years. There is no RSV vaccine currently available. The only preventive treatment available is passive protection with Palivizumab, an RSV specific monoclonal antibody (mAb). However, this is costly, at A$7,500 per course and requires repeated injections throughout the RSV transmission season. Developing safe and effective methods of therapeutic administration to protect infants at the highest risk of respiratory illness from RSV has been challenging, and advances are urgently needed. Aerosol delivery of a RSV mAb to the deep lung may be the most effective method, to protect infants from RSV. Our team has developed a novel aerosol delivery system does not produce these disruptive processes, and we have shown that the nebuliser can efficiently deliver biomolecules in sheep models. This project aims to explore a novel strategy for RSV therapeutic delivery. We will test whether using a novel method of delivery for Palivizumab, a respiratory syncytial virus (RSV) specific mAb, will effectively prevent and reduce severe RSV infections in neonatal lambs. The student will conduct studies to determine if therapeutic mAb delivery via the aerosol route will be effective to prevent RSV disease in an infectious infant lamb model. The student will use clinical measurements, viral assays, immiological assays and molecular assays to validate the responses. Students will work closely with a team of molecular biologists, clinicians and engineers.


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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
Population Health

Laboratory-based Research Projects

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.

Population Health

35. The early origins of autism: a focus on epigenetic differences within identical twin pairs

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Autism is a complex and heterogeneous neurodevelopmental disability that impacts social communication and behaviour. Currently, behaviour-based assessment is needed for diagnosis, along with clinical assessments. Despite international effort and funding, progress has been slow towards finding its biological basis. It is likely to originate before birth in most cases but is often not diagnosed until at least 2-3 years of age.

An increasing number of genetic abnormalities are being found in some children with autism, but none are sufficiently common or specific to act as diagnostic tests. There is an increasing understanding that most human disease results from genetic and environmental interactions, the latter arising very early in life. Epigenetics, the molecular "switches" that turn genes on or off, are helping us to understand how environment might mediate changes to gene expression that result in predisposition to disease. Importantly, it may be possible to change the epigenetic "switches." Identical twins are ideal for studying epigenetics because they are otherwise genetically identical. In this project we bring together expertise in epigenetics and clinical care. No-one has previously taken this approach.

In our definitive study we want to discover genes that have a different epigenetic state in autism to improve our understanding of causative mechanisms and identify potential biomarkers for risk. This is also the latest in a series of similar projects we have offered, each one leading to a successful Honours thesis.

36. The application of a novel dried blood spot collection device for future diagnostic applications

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Available as Masters Project: No

The dried blood spot technique, in which heel prick (babies) or finger-tip blood (children and adults) blood is dried onto filter paper is the leading method in screening for inherited metabolic diseases. A growing field of research is addressing the use of this technique in other clinical applications including genetic testing for a wide variety of conditions, metabolomics, lipidomics and proteomics. There are, however, some limitations to the filter paper approach.
Clinical Sciences

We are working with a novel, easy-to-use pen-like device, HemaPEN, which will be used as an alternative to venous blood and dried blood spot collection. We are currently testing the precision, integrity and ease of use of this device and optimising protocols for DNA extraction and storage. This project will involve a parallel analysis of other applications such as metabolites and/or proteins. It will build on the experience of A/Prof's Craig's group who have pioneered the use of dried blood spots for genetic and epigenetic analysis and the group's collaboration with Trajan Scientific and Medical. This lab-based project is ideal for a student with an interest in biological sampling, biochemistry and/or diagnostic and predictive testing.

Non-laboratory based Research

Clinical Sciences

37. Investigation of inter-arm blood pressure differences during paediatric exercise testing

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Available as Masters Project: No

Blood pressure provides important information about cardiovascular health in children. In the Cardiology clinic at the Royal Children's Hospital, blood pressure is routinely measured before and after exercise testing to assess the heart's response to stress; this can reveal problems that may not be detectable under resting conditions. Previous studies have shown that the blood pressure response to exercise in children provides important information about current heart health and also the risk of developing cardiovascular problems in the future. Blood pressure is currently measured in one arm, but studies in adults have shown that, during exercise, about one third of individuals display an interarm blood pressure difference (i.e. a significantly higher pressure in one arm compared with the other). There is also evidence in adults that interarm blood pressure differences are indicative of an elevated risk of mortality. Although current guidelines suggest blood pressure should be measured in both arms, this recommendation is rarely followed in practice. The aims of this project are to i) establish the existence and frequency of interarm blood pressure differences in children at rest and after exercise, ii) investigate whether such differences are more prevalent in normal children versus those with diagnosed cardiovascular disease and iii) investigate the potential physiological mechanisms underlying interarm blood pressure differences. This study may lead to a stronger rationale for measuring blood pressure in both arms, thus leading to a measurable impact on clinical practice.

38. Haemostatic abnormalities in children with venous thromboembolism and stroke

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Thrombosis in children is an ever-increasing problem. The two most common clinical presentations in children are venous thromboembolism (VTE) or arterial ischaemic stroke (AIS). While VTE and AIS are very different clinical entities, they are linked pathophysiologicaly. Specifically, both diseases involve the pathological formation of a blood clot, which is in turn based on the dysregulation of the key haemostatic protein, thrombin. VTE has significant adverse outcomes for children who would otherwise survive their primary health problems unscathed. AIS is among the top ten causes of death in children and is associated with significant social and economic burden, as more than 50% of survivors have long-term neurological impairments. Reducing the rates of thrombosis and its associated sequelae in children represent major clinical challenges.
This project will investigate the haemostatic abnormalities and the mechanism of thrombosis in two extensively phenotyped core family cohorts of children with thrombosis (VTE and Stroke) and their asymptomatic siblings.

Note: Samples, clinically relevant and laboratory data for this study have previously been collected and the primary role of the Honours student will be to analyse this existing data. There is potential for a pilot laboratory study to be carried out during this Honours project.

39. Understanding brain development in ADHD using longitudinal, multimodal neuroimaging.

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**Available as Masters Project:** Yes

The neurobiological substrate of attention deficit hyperactivity disorder (ADHD) is an area of active research. Compared to typically developing children, those diagnosed with ADHD demonstrate deficits on tasks of sustained, complex, and divided attention. A number of studies have reported differences in brain structure and function between children with ADHD and typically developing controls. As a part of the Neuroimaging of the Children's Attention Project (NICAP) study, we are in the process of collecting longitudinal neuroimaging data on children with and without ADHD from ages 9.5 to 12.5 years. The aim of this project is to investigate to what degree these differences in brain structure and function explain the observed cognitive impairments.

40. Peak exercise capacity in patients with a Fontan circulation

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**Available as Masters Project:** No

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. While North American data has demonstrated a slow deterioration in peak oxygen uptake, serial assessment of peak exercise capacity, measured with cardiopulmonary exercise testing has not been reported in a large Australian cohort.

41. Placental dysfunction in the causal pathway to cerebral palsy

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**Available as Masters Project:** Yes

Cerebral palsy affects about one in 500 children, however in most cases the exact cause is unknown. We hypothesise that in some cases of CP, placental dysfunction in early pregnancy is part of the causal pathway to CP. This project will involve data linkage
between two large and existing databases. The first is the Victorian Cerebral Palsy Register, which collects clinical and epidemiological data for Victorian children with cerebral palsy. The second is the Victorian Clinical Genetics Services Maternal Screening service, which undertakes testing of most pregnant mothers in Victoria. Although this testing is focused primarily on screening for Down syndrome, bHCG and PAPP-A measurements can also be used as a measure of placental dysfunction. We hypothesize that compared with pregnancies that result in a non-CP child, pregnancies that result in the birth of a child with CP will have different levels of bHCG and PAPP-A. In addition these differences may vary with the sub-type of CP. If such differences are detected, bHCG and PAPP-A levels could be used to identify pregnancies at risk of CP, providing the potential for intervention and prevention.

42. Cardiovascular Risk in Nephrotic Syndrome

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The damage to arteries that eventually leads to cardiovascular disease (e.g. heart attack and stroke) starts in early childhood. Identification of those at highest risk early in life offers a considerable potential to reduce adult cardiovascular disease. Nephrotic syndrome is a poorly understood condition characterised by massive urinary protein loss, resulting in swelling of subcutaneous tissues (oedema), and abnormal blood lipids. It affects about 15 children per year at the Royal Children's Hospital. There are limited data suggesting that nephrotic syndrome may be associated increased long term cardiovascular disease risk, but definitive studies are lacking. This study will investigate whether children who have had nephrotic syndrome 5-15 years previously have markers of increased CVD risk, compared to healthy controls. Cardiovascular disease risk will be assessed using non-invasive techniques, including blood pressure and ultrasound, as well as blood markers. The findings will enable identification of children who are at increased cardiovascular disease risk, and explore the underlying biological mechanisms. The long-term goal is to identify those at heightened risk early and develop interventions that aim to reduce the potential later risk burden, by minimising vascular injury early in the disease. The student will work within an interdisciplinary team of medical researchers (including a ultrasound research technician) and will coordinate/perform patient recruitment, data collection and analysis.

43. What are the education and training needs of health professionals incorporating genomics into healthcare? A mixed methods study

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Available as Masters Project: Yes
The Australian Genomics Health Alliance (Australian Genomics), funded by the NH&MRC, brings together more than 70 partner organisations committed to integrating genomic medicine into healthcare across Australia (www.australiangenomics.org.au). Australian Genomics aims to shorten diagnosis times, enable early intervention and provide access to treatment for people with genetic disorders by translating genomic technology into clinical practice for patients and family benefit. Within Australian Genomics, Program 4 is conducting research around education and training needs of the genomic workforce, as well as ethical and patient perspectives of genomic medicine. The Program 4 working group consists of experts in genetics/genomics education, clinical practice, evaluation, mixed methods research, genetic counselling, social science, science communication and ethics.

The aim of this project is to inform strategies around education and training of health professionals to enable them to incorporate genomic medicine into their future practice. The project is suitable for two Honours students or one Masters student. Student/s will use a mixed methods approach, combining interviews and surveys to gather data from a range of perspectives, including health professionals, genomic specialists, educators, patient groups, professional organisations and other stakeholders. Student/s will be trained in quantitative and/or qualitative methods to develop needs assessment surveys and/or interview schedules based on existing literature and other data obtained by Program 4. For the survey component, the student would develop a draft online survey which would then undergo a process of iterative revision with content and educational experts (a process known as the Delphi technique), piloted then deployed and analysed using descriptive and inferential statistics. For interviews, student/s would be trained in developing an interview schedule, interviewing technique and qualitative data analysis, such as inductive thematic analysis.

44. Susceptibility to adult disorders in carriers of Mendelian alleles

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The most common and pervasive human health problems are caused by diseases with complex aetiologies. Humans differ greatly in their genetic vulnerability to these common diseases. Mechanisms that underlie disease susceptibility and progression are, with few exceptions, influenced by numerous genetic, developmental and environmental factors. For the most part, complex disorders are difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. By contrast, Mendelian or monogenic disease are caused by mutations in one gene and they often run in families and can be dominant or recessive, and autosomal or sex-linked. It is recognised that complex disorders also often cluster in families but they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of developing disease.

One way to investigate the genes associated with complex disease is genome-wide association study (GWAS). GWAS investigate the entire genome and identify SNPs and other variants in DNA associated with a disease, but they cannot on their own specify which genes are causal. We hypothesise carrier status of a gene that is known to causes a Mendelian childhood illness will increase and individuals risk for adult onset illness. To date, hundreds of GWAS on thousands of individuals with diverse disease have been performed and to our knowledge no one has interrogated them to determine if there is an over-representation of known disease genes.

In the project the candidate will interrogated the literature and publically housed genetic databases to determine if there is a correlation between genes that cause childhood Mendelian disease and the genes that cause complex adult onset disease.

45. Burden of disease associated with genetic aetiology at a paediatric hospital

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It is well recognised that genetic disorders contribute significantly to paediatric mortality and morbidity. Previous audits (unpublished) carried out at the Royal Children's Hospital (RCH) show that individuals with genetic conditions make up a significant proportion of the hospital population and often have longer and more frequent hospital stays. The aims of this study are to 1) determine the proportion of admissions to the RCH in a 2-week sample of patients in 2017 that have a genetic component, using nine genetic ‘load’ categories previously determined; 2) describe characteristics of inpatients with these genetic conditions and their hospitalisation; 3) identify the number of RCH patients who were referred to or received consultations with Victorian Clinical Genetic Services (VCGS) and 4) determine whether there have been any changes in these observations over four sample time periods of 1985, 1995, 2007 and 2017. Awareness of the past and current magnitude of the influence of genetic load on hospital admissions is important for health service planning and for monitoring the influence of new genetic technologies on future paediatric hospital admissions.

46. BiliNappy: Novel low cost point-of-care diagnostic for Jaundice embedded in a newborn nappy

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Severe jaundice is a life threatening condition. Currently, the diagnosis of neonatal jaundice requires a blood test. Bilirubin blood testing is routine in both provincial and tertiary referral hospitals. For remote locations and developing economies this diagnostic testing is not readily available leading to delays in treatment. There is an urgent need to identify a suitable, reliable and affordable bedside test to positively impact upon the lives of millions of children worldwide by facilitating effective early intervention. Our group has developed a non-invasive, affordable (~AUD$0.10 per test), bedside test for neonatal jaundice using a urine detection method placed in a newborn's nappy, referred to as BiliNappy. This project will evaluate the reliability of BiliNappy and to determine its usefulness in maternal units as a screening method in newborn infants susceptible to treatment. The student will use biochemical sensing methods to quantify the bilirubin in urine. The techniques developed will be validated against gold standard methods of diagnosis using blood tests. This project is a collaborative effort between Engineering, Chemistry and Clinical sciences.

47. Risk factors associated with pneumococcal carriage in healthy children in Mongolia prior to 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.

54. Biomarkers of human papillomavirus-related cancers

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Human papillomavirus (HPV) causes cervical, other anogenital, anal and skin cancers. Many people who eventually develop HPV-related cancer were first exposed to HPV in adolescence or young adulthood, with cancers taking decades to develop. Early detection of precancers or small cancers improves prognosis and quality of life. HPV-associated cancers disproportionately affect disadvantaged and/or marginalised populations such as Australian Indigenous and Torres Strait Islander peoples (ATSI), women in low- and middle-income countries (LMIC), immunocompromised and/or HIV-positive people, and gay and bisexual men (GBM). Prevention of cervical cancers has been very successful in higher-income countries such as Australia using intensive, technically-demanding screening programs, however these types of screening programs are unfeasible in many low-resource settings, and are more technically difficult for other HPV-related cancers such as anal cancer. The identification and development of simple to implement, sensitive and specific biomarkers for cancer risk in HPV-positive individuals has the potential to significantly decrease the burden of these cancers. Cancer development is preceded by certain molecular changes; these include epigenetic modifications such as methylation of viral gene promoters, and changes to the expression of viral and cellular gene products. This project will involve the characterization of molecular patterns in clinical samples from people with and without HPV-related disease – including cancer - with a view to determining the potential of each marker to contribute to effective screening for people at risk of HPV-related cancer. This project will involve laboratory work in the Molecular Microbiology Department of the Royal Women's Hospital, including nucleic acid purification, polymerase chain reaction (PCR) including real-time PCR, digital droplet PCR, reverse transcriptase PCR to detect messenger RNA (mRNA) transcripts, epigenetic studies including detection and quantification of methylation, and others. Data entry, database design and data manipulation including the possibility of some basic programming, and statistical analysis in the Stata statistics package, will be important for this project. Other tasks may involve co-ordination of sample collection, receipt and processing. For longer projects (i.e. PhD, Masters), additional tasks may include assay design and development, and application and/or reporting for ethics approvals. The RWH Molecular Microbiology Department is affiliated with the University of Melbourne, the Royal Women's Hospital, the Royal Children's Hospital and Murdoch Childrens Research Institute. We collaborate with numerous other institutions in Australia and internationally including primary health care, research institutions, and private industry including private pathology and biotechnology/pharmaceutical companies, with numerous opportunities for multi-disciplinary engagement.

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Available as Masters Project: Yes

**Background:** Treatment for mental health problems in children varies greatly. Some children get lots of care whilst others get very little. Clinician and family factors likely contribute to variation in care. Modifying these factors could reduce variation, but this requires accurate understanding of which factors to modify.

**Aim:** To identify potentially modifiable clinician and/or family factors associated with variation in treatments provided to children with the most prevalent mental health disorders (i.e., attention deficit/hyperactivity disorder [ADHD], anxiety, depression) in low versus high socioeconomic areas and in major city versus other locations.

**Study:** Nested within an NHMRC project grant, this study will collect qualitative data from in-depth one-on-one interviews (approximately 30-45 mins duration) with clinicians (GPs, paediatricians, psychologists, and child psychiatrists) and/or caregivers of children diagnosed with ADHD, anxiety or depression.

**Data collection:** Data are being collected from clinicians and/or caregivers in Victoria and South Australia, from a spread of socio-demographic areas, major city/regional areas, and public/private settings. The students will be involved with active data collection including contacting potential participants, conducting qualitative interviews, and data entry, cleaning, and analysis.

**Measures:** The interview questions will explore a range of factors (e.g., clinician knowledge of best practice care, availability of other clinicians to whom to refer, barriers for parents accessing treatment such as cost, stigma, wait lists) and also to uncover previously unreported influences, such as established local practices, social and school contexts, and personal beliefs and values.

**Analyses:** Interview data will be analysed qualitative methods using a software program called NVivo. Students will be provided with close supervision and guidance during the analysis process. Students will be able to choose an aspect of the project (eg interviews with families in rural areas or interviews with psychologists in low socioeconomic areas etc) which suits their interest.

49. The epidemiology of childhood food allergy and other allergic diseases

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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 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, and healthcare utilisation across the early years, will be available.

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. Possible research projects include:
- To explore the role that infantile food allergy plays in the development of other allergic diseases
- To determine which children with early-life wheezing will go on to develop asthma
- To describe the prevalence and identify risk factors of food and aeroallergen sensitisation in a population-based cohort

50. Measuring low value care across inpatient, outpatient and emergency department settings

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Available as Masters Project: Yes

Low value, or unnecessary care, is care that provides little or no benefit, may cause patient harm, or yields marginal benefits at a disproportionately high cost. Identifying and reducing low value care is now an international priority for a sustainable healthcare system (e.g. Choosing Wisely campaign). For example, in children, the use of chest x-rays is considered unnecessary for the diagnosis of asthma, yet these tests are still conducted. Unnecessary testing may cause harm to the child (radiation) and the healthcare system (increased costs).

To identify an instance of low value care at the Royal Children’s Hospital (RCH), and to measure for these tests (i) the frequency across ED, inpatient and/or outpatient settings; (ii) the costs to the hospital/patient; and (iii) factors associated with unnecessary testing (eg. child, clinician or setting).

In a sample of children at the RCH, the proportion of unnecessary testing will be high for common conditions, and factors associated with unnecessary testing will include child age (younger child), clinician factors, and setting (ED, OP, IP). 3-month prospective audit drawing upon RCH patient data recorded in Epic. Patients with planned admissions for chronic illnesses (eg chemotherapy) will be excluded. Bivariate and logistic regression analysis to determine child (eg age, gender, family SES), clinician and other factors (eg seasonality) associated with unnecessary testing. Cost analysis of unnecessary testing, scaled up to healthcare system costs over 1 year. Interest and time permitting, interviews with 5 key hospital clinicians to determine why they request unnecessary testing.

Before trialling interventions to reduce unnecessary testing, we first need to identify which children and which conditions are associated with unnecessary testing and any potentially modifiable risk factors associated with such tests. Results will inform a peer-reviewed publication and planned intervention trials to reduce unnecessary testing.
51. Measuring low value care in the emergency department; a multi-site study

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Low value, or unnecessary care, is care that provides little or no benefit, may cause patient harm, or yields marginal benefits at a disproportionately high cost. Identifying and reducing low value care is now an international priority for a sustainable healthcare system (e.g. Choosing Wisely campaign). For example, in children, the use of chest x-rays is considered unnecessary for the diagnosis of asthma, yet these tests are still conducted. Unnecessary testing may cause harm to the child (radiation) and healthcare system (increased costs).

To identify low value care in emergency departments (ED) at 1-4 hospitals, and to measure for these tests, at each site (i) the frequency of low value testing; (ii) the costs to the hospital/patient; and (iii) factors associated with unnecessary testing.

In a sample of children presenting to ED at multiple hospitals, the proportion of unnecessary testing will be high for common conditions, and factors associated with unnecessary testing will include child age (younger child), clinician factors, and hospital type (general or paediatric).

3-month prospective audit drawing upon data recorded in ED electronic records at each site. Patients with complex conditions will be excluded. Bivariate and logistic regression analysis to determine child (e.g. age, gender, family SES), clinician and other factors (e.g. seasonality) associated with unnecessary testing. Cost analysis of unnecessary testing, scaled up to healthcare system costs over 1 year. Interest and time permitting, interviews with 5 key hospital clinicians to determine why they request unnecessary testing.

Before trialing interventions to reduce unnecessary testing, we first need to identify which children and which conditions are associated with unnecessary testing and any potentially modifiable risk factors associated with such tests. Results will inform a peer-reviewed publication and planned intervention trials to reduce unnecessary testing.

52. The feasibility and acceptability of a mindfulness meditation program within the preschool setting

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The use of mindfulness meditation and mindfulness based curriculum has become increasingly popular in primary and secondary schools. There is less evidence detailing the use of mindfulness meditation in the pre-school years and the impact such programs may offer in fostering mental health, wellbeing and early learning skills in young children.

To evaluate the feasibility, acceptability and fidelity of a newly developed mindfulness program within early learning centres (ELCs)

This pilot study will be conducted in ELCs to assess the content usability of a newly developed mindfulness program. The study will examine educator fidelity with the program content, their experience of the program, their sense of competence using the program and their knowledge of mindfulness practice since implementation. Data will be collected from early childhood educators, via online questionnaires and qualitative interviews.

The measures used in this study will likely on educator experience, satisfaction, and content knowledge. The interview questions will explore educator's experience of the mindfulness program. Quantitative measures will be scored/interpreted as required by the measure, while interview data will be analysed using thematic analysis. Students will be provided with close supervision and guidance during the analysis process.
53. The ‘Premmie Health Profile’: Do babies born early or small have distinct patterns of health and metabolic disparities?

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Premature birth and being born small for gestational age (SGA) are costly to the healthcare system and elicit substantial concern amongst parents and clinicians. There is increasing interest in those born late preterm and early term, who make up a significant proportion of total births. Preterm children are more likely to experience health, cognitive and academic deficits than their peers in early childhood. Most studies evaluate outcomes in one domain but not multiple domains simultaneously in a single cohort to look for a cross-domain profile associated with prematurity.

Aside from being premature, being born small at any gestational age may also have a lasting legacy on later health. Previous studies have focussed on SGA children, but there may be impacts on later health across the full continuum of gestational size. In a large national cohort of Australian 11-12 year old children, we will investigate the cross-domain profile associated with gestational age and birth weight, considering physical health, metabolomics, psychosocial and cognitive domains. The Longitudinal Study of Australian Children (LSAC) is a national, population-derived cohort of Australian children.

Commencing in 2004, soon after the children were born, the study has assessed the children and their families every two years, and in 2015-16, conducted a comprehensive physical health assessment and biosample collection module called the Child Health CheckPoint. This project will utilise pregnancy and birth data from LSAC Wave 1 (child age 0-1 year), cognition, academic outcome and emotional/mental health data from LSAC Wave 6 (10-11 years), and physical health (cardiovascular, renal, bone, respiratory, body composition) and biologic data from the CheckPoint (11-12 years). The project will suit someone interested in health, epidemiology and/or statistics, and working closely with a strong interdisciplinary team. Given the large, high quality data available, findings are likely to be published in a quality journal.
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 2018, 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 2018 are also listed on the Murdoch Children’s Research Institute and Department of Paediatrics websites.

**STEP 2:** Online application: Register for the Honours Application Tracking System (SONIA) before making your application in SONIA. Lodge an online application between Friday 26 August and Friday 10 November 2017:

http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

**STEP 3:** Project Preference: Applications for specific projects are entered into SONIA in order of preference, however you can change or re-order your project preferences at any time, up until Friday 24 November 2017.

**STEP 4:** Offers: Round one offers for entry into 2018 will be made by Friday 22 December 2017. Students must accept their offer by the Offer Lapse Date notes 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 in mid-January.

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.


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 2018, applications close: 30 November 2017

http://futurestudents.unimelb.edu.au/admissions/applications/grad-dom

Contact us:

Gr-mc@unimelb.edu.au or students@mcri.edu.au