The Melbourne Children’s Campus:

Murdoch Childrens Research Institute & Department of Paediatrics

Faculty of Medicine, Dentistry & Health Sciences

HONOURS & MASTERS PROJECTS 2017

www.mcri.edu.au/students

Student Information Evening: 13 September 2016, 5-7pm
Laboratory Based Research Projects

Cell Biology

1. Development of a method for transferring neural precursor cells to the aneural colon for cell therapy for the birth defect Hirschsprung disease.
2. How does ACTN3 influence muscle wasting during active ageing?
3. Adaptive thermogenesis and the evolution of alpha-actinin-3 (R577X)
4. Examining the effect of alpha-actinin-3 deficiency on skeletal muscle injury
5. Epigenetics and other stress-related biomarkers in depression
7. The utility of epigenetic profiling to improve outcome in childhood CNS tumours.
8. Prognostic utility of epigenetic biomarkers in paediatric leukaemias.
9. Detecting and Investigating the molecular biology of novel translocations and mutations in paediatric cancer
10. Understanding the causes of craniofacial birth defects
11. Induction of different cell lineages from PIK3CA mutation-carrying iPSC cells
12. Rapamycin effect on endothelial thrombogenic potential

Clinical Sciences

13. Towards developing an individualised approach to neonatal respiratory support: Assessing the usefulness of biomarkers of lung injury and function

Genetics

14. Solving Rare Diseases via the Australian Genomics Health Alliance
15. Human Stem Cell Models of Mitochondrial Disease
16. Master regulator of chromosome compaction, DNA repair and gene expression, and impact on disease aetiology
17. The role of centromere defects in cancer formation and progression
18. Genome-editing: applications in stem cells and gene therapy
19. Epigenetic modifications of the human beta-globin locus: new therapeutic targets for haemoglobin disorders
20. Does skewed X-linked inactivation predict the severity of Rett Syndrome?
   M1. Developing a diagnostic blood test for autism
21. Investigating repeat-associated disease mechanisms in Friedreich ataxia
22. Investigating the factors involved in FXN silencing in Friedreich ataxia
23. Determining the genetic basis of novel neurogenetic disorders
24. Investigating the molecular basis of Parkinson’s disease
25. Identifying the genetic causes of brain malformation in children
26. Identifying novel genetic targets that underlie Synucleinopathy and Tauopathy.
27. Characterisation of the parkin protein and how it causes Parkinson’s disease
28. A genetic approach to identifying drug targets for prevention of deafness

Infection & Immunity

29. Streptococcus pneumoniae gene expression and pathogenesis
30. Investigating the pneumococcal whole cell vaccine in an infant mouse model of pneumonia
31. Interactions between Streptococcus pneumoniae and respiratory viruses
32. Immunomodulatory effects of Vitamin D on the host response to respiratory infections
33. Exploring a new approach for preventing stomach cancer
34. Animal model with undescended testes may provide the key to understanding cellular interactions necessary for testicular descent
35. Effect of congenital UDT on Gonocyte development
M2. Pneumococcal carriage dynamics in children hospitalised with acute respiratory infection in Fiji
72. Impact of multiple pathogen infection on respiratory syncytial virus evolution

Population Health

36. Developing novel methods to diagnose and predict the prognosis of food allergy

All numbered projects are available for Honours, and available as Masters Projects if marked above the project description.
Projects numbered ‘M’ is Masters only. Find out about University Requirements for Honours and Masters.

MCRI & Dept of Paediatrics Honours/Masters Projects 2017
Non-Laboratory Based Research Projects

Cell Biology

37. How early-life adversity gets under the skin: the role of epigenetics
38. The impact of stress on mental health
39. Molecular classification tools to improve outcome in childhood cancers

Clinical Sciences

40. A clinical trial of lung protective ventilation during neonatal surgery and transport (Go with the flow 2)
41. Using complexity theory to model the newborn lung at birth
42. How do we help sick babies breathe? Understanding the role of ventilator synchronisation on lung protection
43. Does non-invasive ventilation alter ventilation patterns in preterm infants?
44. How do babies take their first breaths?
45. Understanding brain development in very preterm children using novel diffusion magnetic resonance imaging measures of white matter microstructure
46. Understanding brain development in very preterm children using in vivo myelin mapping based on magnetic resonance imaging
47. Does cortical thickness mediate cognitive deficits in ADHD.
48. Modelling the cardiovascular birth transition in vulnerable infants
49. Modelling cardiovascular development during childhood
50. "Are we truly engaged or is this a token?" Effective community engagement in research.
51. Measuring movement variability with inertial measurement units
52. Impact of pregnancy on women with Fontan circulation.

Genetics

53. Educational and training needs assessment of health professionals to inform implementation of genomic medicine
54. 'Genomic wellness' - exploring experiences and expectations of personal genomic testing in alternative medicine

Infection & Immunity

55. Risk factors for severe childhood pneumonia in Lao PDR

Population Health

56. Linking early life environment with child health: a longitudinal twin study
57. The epidemiology of childhood food allergy and other allergic diseases
58. Habitual dietary intake, snacking behaviour and oral health in 11-12 year old children and their parents
59. Parent-child concordance in oral health
60. Delving into adolescents' dispositional optimism/pessimism and exploring its association with cardiovascular health in 11-12 year olds: a population-based study
61. Delving into adolescents' dispositional optimism/pessimism and exploring its association with health-related quality of life in 11-12 year olds: a population-based study
62. Delving into adolescents' dispositional optimism/pessimism and exploring its social determinants in 11-12 year olds: a population-based study.
63. Changes in adolescents' time use over the past decade
64. How early life factors influence cardiovascular function at age 11-12 years: a population-based longitudinal study
65. How 10-year diet and body composition trajectories influence bone health at two important life stages: Early adolescence and mid-life
66. How 10-year diet and body composition trajectories influence lung function at two important life stages: Early adolescence and mid-life
67. Unnecessary use of pathology testing in hospital admissions.
68. Insights into the conundrums of managing mild congenital hearing loss
70. Trends in additional health and developmental needs over time: Evidence from three cohorts of the Australian Early Development Census

All numbered projects are available for Honours, and available as Masters Projects if marked above the project description. Find out about University Requirements for Honours and Masters.
1. Development of a method for transferring neural precursor cells to the aneural colon for cell therapy for the birth defect Hirschsprung disease.

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Available as Masters Project: Yes

In Hirschsprung disease, the distal-most colon is not colonised by neural precursor cells embryonically and so it fails to develop an intrinsic enteric nervous system (ENS). This means the colon cannot function once the baby is born. The current treatment for this fatal birth defect is, at neonatal stage, to surgically remove the non-functional part of the colon, and join the upstream functional colon to the rectum. This saves the patient's life but loss of distal colon typically 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 partial 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 late embryo avian embryo, and secondly, human and pig colon tissue obtained at surgery. The avian model is chosen because the maturity of the late embryo avian colon resembles that of a human neonate, and because avian ENS precursor cells are readily obtainable, and the pig model closely resembles human tissue in structure and size. We have carried out successful preliminary experiments using this approach on neonatal mouse colon, but this tissue is too immature to be an appropriate model for the human neonatal colon. Labelled ENS precursor cells will be seeded and grown on a polymer membrane which will then be wrapped onto the outer or serosal surface of the colon. The ability of the ENS precursor cells to penetrate (transmigrate across) the serosa will be assayed, and chemical manipulation of the serosa will be attempted to increase cell penetrability.

2. How does ACTN3 influence muscle wasting during active ageing?

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Available as Masters Project: Yes

Alpha-Actinin-3 (ACTN3) is a skeletal muscle protein responsible for maintaining the integrity of the contractile apparatus in fast-glycolytic muscle fibres. We have previously identified a common null polymorphism (R577X) in human alpha-actinin-3. Approximately 1 in 5 people worldwide are homozygous for the X-allele, which results in complete absence of alpha-actinin-3 protein. While this deficiency does not cause disease, its absence results in significantly lower muscle mass and strength/power, but provides a benefit for endurance performance in elite athletes and in the general population. We have generated an alpha-actinin-3 knockout mouse model (Actn3 KO) that mimics the human muscle phenotype. Using this model, we have shown that the absence of alpha-actinin-3 in muscle changes muscle metabolism, calcium handling, and increases susceptibility to eccentric contraction induced damage - all of which explains the alterations in muscle performance in mice and humans. Muscle wasting is the loss of muscle mass and strength, and is caused by ageing, chronic illnesses or prolonged bed rest. It is associated with increased disease morbidity and mortality and reduced quality of life. This project will study how alpha-actinin-3 expression influences muscle wasting during active ageing. Wildtype and Actn3 KO mice (aged 24-27 months) will be placed under voluntary freewheel exercise for one month and compared to age-matched sedentary mice. This project may require some animal handling and will involve laboratory-based techniques such as immunohistochemistry, western blotting, molecular biology and muscle physiology to examine the structural, metabolic and signalling changes in skeletal muscle.

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

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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) that mimics the human muscle phenotype and provides a useful model to assess the role of alpha-actinin-3. Recently alpha-actinin-3 has been identified in Brown Adipose Tissue (BAT), a key heat producing organ, known to influence cold adaptation. While much is known about the role of alpha-actinin-3 in skeletal muscle, we have only just begun to understand its function in BAT. Using the Actn3 KO mouse, this project will study the role of alpha-actinin-3 in both skeletal muscle and BAT in response to cold stimuli. The project will involve animal handling and laboratory-based techniques such as immunohistochemistry, western blotting and digital droplet PCR (ddPCR) to further study the role of alpha-actinin-3 in adaptive thermogenesis.
4. Examining the effect of alpha-actinin-3 deficiency on skeletal muscle injury

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Available as Masters Project: Yes

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 see 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.

5. Epigenetics and other stress-related biomarkers in depression

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Available as Masters Project: Yes

Stress is a risk factor for a range of non-communicable diseases (NCDs), including cardiovascular disease, diabetes and depression, and can also contribute to cancer incidence and survival. Stress has been described as the 21st century health epidemic. It remains unclear however, how the timing, severity and accumulation of stress exposure can influence mental health, in particular depression and anxiety. The underlying biological mechanisms driving these associations are also unclear.

The aim of this project is to identify novel stress-related biomarkers which are associated with the prevalence and incidence of depression. This project will use data gathered from a large prospective study of over 2000 individuals, with detailed measures on recent stressful events, major lifetime traumas and childhood events (DSM diagnosed), as well as thorough medical, social and lifestyle information. Data on a range of stress-related biomarkers (inflammation, metabolic, magnetic resonance imaging) and genotyping is already available. Stored DNA samples will be used to measure telomere length and candidate gene DNA methylation levels. The student working on this project will learn advanced laboratory techniques and develop skills in the analysis of data gathered from a large cohort study. This project would suit a candidate with some experience molecular biology and an interest in mental health.


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Available as Masters Project: Yes

The world is experiencing an alarming rise in the incidence of cardiovascular disease, obesity and poor metabolic health. Mounting evidence suggests that the period in utero and early postnatally plays a critical role in programming these phenotypes. Both genetic and environmental factors contribute to complex disease risk and are also known to influence epigenetic profile. Thus, epigenetic variation has emerged as prime candidate for the early life programming of later CV and metabolic health. Epigenetic variants have great potential as biomarkers for monitoring ideas progression and may be reversible with appropriate intervention. The overall aims of this project are to examine the association of epigenetic variation 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.baronwinfantstudy.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.
7. The utility of epigenetic profiling to improve outcome in childhood CNS tumours.

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**Available as Masters Project:** Yes

Childhood tumours of the central nervous system are the second most common group of cancers behind leukaemias, yet account for a disproportionate majority of cancer deaths. To date, the primary cause(s) of such tumours, and the molecular mechanisms that lead to poor outcome, remain unclear. The key to addressing these knowledge gaps lies in developing the appropriate tools for risk stratification of disease, increasing our understanding of the oncogenic pathways within prognostic subgroups, and developing novel therapies targeting key pathways to facilitate a 'personalised' approach to treatment. We hypothesise that the combined profiling epigenetic disruption (by methylation arrays), copy number variation and mutation status (exome:seq), and gene expression (by RNA:seq) has potential to refine tumour risk stratification, inform treatment responsiveness and improve long term outcome for childhood CNS cancers. This project will utilise (i) archival CNS tumour samples housed in RCH Anatomical Pathology and (ii) fresh/frozen tissue from the Childrens Cancer Centre Tissue Bank and (iii) matched clinical data, to identify molecular biomarkers for refining diagnostic and prognostic sub-groups and the identification of potentially reversible epigenetic marks important in tumour aetiology.

8. Prognostic utility of epigenetic biomarkers in paediatric leukaemias.

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**Available as Masters Project:** Yes

Leukaemias are the most common form of cancer in children. Despite intensive investigation, the primary cause(s) of disease remain unclear and a proportion of children still succumb to disease. The MCRI/RCH has one of the largest collections of archival patient-derived leukaemic bone marrow in existence internationally, with a complementary ongoing prospective collection of tumour and matched blood samples. During the course of recently completed Masters and PhD projects, we identified a panel of DNA methylation markers and miRNAs that are common to childhood ALL and AML. More recently we have identified signatures with potential prognostic utility and for monitoring minimal residual disease in both childhood ALL and AML.

9. Detecting and Investigating the molecular biology of novel translocations and mutations in paediatric cancer

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The Children's Cancer Centre Research Laboratory aims to understand the molecular basis of childhood cancer and to use this knowledge to develop better diagnostics and treatments for children with malignant disease. Associate Professor Paul Ekert leads the laboratory. His research has focused on aspects of programmed cell death (or apoptosis), particularly on the intersections between cytokine signaling pathways and cell death pathways. The team also studies acute myeloid leukaemia to examine cytokine signaling in this cancer and how new drugs might target these pathways.

An important project within the laboratory is the study of cancer samples deposited in the Children's Cancer Centre Tissue Bank. We use RNA sequencing to detect novel translocations and mutations that drive childhood cancer. In this project, you will take one of these translocations, and using the tools of molecular and cellular biology, you will clone the fusion gene arising from the translocation and develop new cell line models expressing the fusion to determine how it drives oncogenic transformation and potential therapeutic approaches that may target the fusion. There will also likely be opportunities to learn new skills in the generation and analysis of RNA sequencing data.

10. Understanding the causes of craniofacial birth defects

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**Available as Masters Project:** Yes

Birth defects involving the face affect approximately 1% of all babies but the genes involved in most of these conditions are unknown. The olfactory receptors are a large group of genes involved with enabling a sense of smell but have never been linked to birth defects. We have identified an uncharacterised olfactory receptor, known as Olfr603, which is crucial for early embryonic development. Mice harbouring a mutant Olfr603 have midfacial clefting and severe brain abnormalities that model a group of conditions known as frontonasal dysplasia. Analysis of gene expression changes in mutant mice demonstrate that Olfr603 signalling is required to regulate patterning of the cranial neural tube and differentiation of a wide range of neural and craniofacial derivatives. In parallel to these animal model studies we are using exome sequencing to identify genes for frontonasal dysplasia in humans.
Examination of candidate genes from frontonasal dysplasia patients in our mouse models is highlighting novel mechanisms resulting in craniofacial birth defects.

This project will involve a range of human genetics, molecular and developmental biology approaches to investigate human birth defects. Upon completion of this project, students will be in a strong position to participate in research into the genetic and developmental basis of human birth defects.

11. Induction of different cell lineages from PIK3CA mutation-carrying iPSC cells

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PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) mutations are identified in a diverse group of rare disorders called PIK3CA-Related Overgrowth Spectrum (PROS). These conditions are due to somatic activating mutations identified in the phosphatidylinositol-3-kinase/AKT/mTOR pathway. The PROS umbrella covers some vascular malformations, fibroadipose hyperplasia or overgrowth (FAO), hemihyperplasia multiple Lipomatosis, (HHML), Congenital lipomatous overgrowth, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome, Klippel-Tranauany syndrome, macrodactyly, fibroadipose infiltrating lipomatosis, and the related megalencephaly syndromes, megalencephaly-capillary malformation (MCAP or M-CM) and dysplastic megalencephaly (DMEG).

To date, we have produced 2 induced-pluripotent stem cell (iPSC) cell lines carrying single point PIK3CA mutations from a CLOVES patient and a Klippel-Tranauany patient, where both syndromes are characterised by tissue overgrowth and include lymphatic malformation as part of their clinical presentation. Tissue, blood and derived cells from these patients were subjected to whole exome sequencing in collaboration to confirm a single base point mutations in PIK3CA gene. The next step in this repertoire is to differentiate the derived iPSCs that carry known PIK3CA mutations into skeletal and fat cells.

12. Rapamycin effect on endothelial thrombogenic potential

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Recent reports have indicated that rapamycin (sirolimus), a drug with a long history of use as an immunosuppressant, is effective in the treatment of some types of vascular anomalies, the inborn errors of the vascular and lymphatic systems. Rapamycin acts via Mammalian Target of Rapamycin (mTOR) signalling pathway which is involved in regulation of cell proliferation, survival and metabolism. Rapamycin-mediated inhibition of the mTOR pathway may potentially occur via two mTOR associated complexes: mTOR complex 1 (mTORC-1) or mTOR complex 2 (mTORC-2). As each complex performs different functions in cells, different cellular processes will be affected. Although rapamycin improves symptoms in patients, clinical studies in other conditions have suggested that rapamycin can increase thrombosis and the risk of fatal pulmonary embolism. How this may occur is unknown.

This project proposes to clarify the ability of rapamycin to induce clot formation by examining how rapamycin affects the expression of endothelial cell molecules involved in thrombus formation and thrombolysis. This will be done by assessing the expression of these cellular markers following treatment in vitro with rapamycin both under static and shear stress conditions.
13. Towards developing an individualised approach to neonatal respiratory support: Assessing the usefulness of biomarkers of lung injury and function

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Preterm infants often need prolonged respiratory support (mechanical ventilation) to survive, however, ventilation of these immature lungs can lead to the development of ventilation-induced lung injury (VILI), which is associated with prolonged hospital stay and long-term morbidity. Lung injury is a complex interaction between intrinsic biological and developmental factors and the way in which mechanical ventilation is applied. We know that the volume and pressure used to inflate the lung has the potential to be harmful as well as beneficial. Identifying biomarkers that can accurately predict the early development of the many different forms of lung injury will be essential to improving outcomes for preterm infants.

The goal of this project is to perform a controlled validation of both current and recently unveiled indicators of lung injury and function in preterm lambs who have undergone various, clinically relevant ventilation strategies. To do this students will employ a range of techniques including qPCR, histology, immunohistochemistry, image analysis and protein based technologies to study the Neonatal group preterm lamb tissue bank. In addition to aiding the development of essential monitoring tools, this project has the potential to unravel not only how currently monitored markers relate (or actually don't relate) to each other, but also assess the validity of the injury/function parameters across a range of ventilation strategies.
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. 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 are known to cause inherited disorders of mitochondrial energy generation. The overall aims are to: 1) Assemble a representative panel of cellular models of OXPHOS disease in HEK293T cells and human Embryonic Stem Cells (hESCs) 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, as well as the impact on mitochondrial function and cellular physiology. 3) Define the impact of targeted therapeutic strategies in these cellular models on the cellular proteome and on other markers of cellular homeostasis.

The research project will thus involve generation of hESCs with CRISPR/Cas9 mediated gene disruption, followed by confirmation of the impact on the targeted gene and pathway assessment of the molecular karyotype and retention of pluripotency. Selected cell lines will then be differentiated to cardiomyocyte and/or neural lineages to enable comparison (with isogenic 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.

16. Master regulator of chromosome compaction, DNA repair and gene expression, and impact on disease aetiology

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Available as Masters Project: Yes

In order for our genetic material to be faithfully segregated into two daughter cells, the DNA must compact 10,000 fold to visible X-shaped structures known as mitotic chromosomes. Proper compaction of DNA also underpins the regulation of DNA repair and global gene expression. A master regulator in these fundamentally important processes is the multi-subunit protein complex, condensin, for which an increasing number of cancers and diseases have now been linked to its defect.

The aims of this project are to understand how condensin and its affiliated components affect chromosome folding, DNA repair and global gene expression, using integrated proteomics, biochemistry and cell biology approaches. Specific techniques employed will include genome editing and conditional gene knockout, next gen sequencing, proteomics and live cell imaging. The knowledge gained will have major implications for understanding the underlying causes of a wide range of diseases.

15. Human Stem Cell Models of Mitochondrial Disease

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Available as Masters Project: Yes

Mitochondria are our cellular power plants that burn sugars, fats and proteins to generate energy. Each week in Australia a
17. The role of centromere defects in cancer formation and progression

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Available as Masters Project: Yes

The centromere is an essential chromosome structure required for the transmission of replicated DNA to daughter cells during cell division. It has been shown that chromosome instability (CIN) driven via disruption of centromere function, formation of dicentric chromosomes (and its associated amplification of oncogenes via chromosomal Breakage-Fusion-Bridge cycles), and the overexpression of centromeric repeats may be associated with cancer development, but there have been no systematic study of the role of the centromere in different cancer types. We have preliminary data showing that a major driving force in liposarcoma development is through the formation of oncogenic neocentromeres that contain ectopic centromeres or neocentromeres - a phenomenon first described by us. Owing to the typical association of centromeres with highly-repetitive satellite DNA, current efforts including the International Cancer Genome Consortium to conduct large-scale nextgen sequencing of cancers cannot reveal changes to the number, structure or function of the centromere in tumours.

Our hypothesis is that centromere abnormalities are common and a key factor in cancer development, and propose to determine the extent, form and functional significance of centromeric defects within cancer.

Our specific aims are 1) To investigate the frequency and forms of centromere abnormalities in cancer development in a panel of paediatric tumours samples and cell lines from many different cancer types that we have assembled; and 2) To determine the role aberrant expression of centromere transcripts play in cancer development. This will be the first in-depth study of the association of centromere defects with tumorigenesis. The study that will yield valuable insight into the roles centromeres play in the onset and progression of cancer.

This knowledge will complement existing large-scale cancer genome sequencing projects and translate into a better understanding of the causes and biomarkers of cancer.

18. Genome-editing: applications in stem cells and gene therapy

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Available as Masters Project: Yes

The recent development of targetable nucleases has introduced a highly flexible technique for modification of specific genomic sequences. CRISPR-Cas9-generated double stranded breaks (DSB) may be resolved by the host cell through either non-homologous end joining (NHEJ), or homology directed repair (HDR) given the presence of an appropriate DNA template. The latter carries great promise for the field of gene therapy as it can be utilised for the correction of disease-causing mutations. Several groups have demonstrated the potential for site-specific modification of the beta-globin locus by HDR following generation of a targeted DNA break. However, for modification of patient primary HSCs to be clinically useful, the genetic alteration must be made as uniformly as possible throughout the entire cell population.

This project aims to develop strategies for targeted modifications of haematopoietic stem cells using the CRISPR-Cas9 targetable nuclease. Conversion of the fluorescent reporter gene GFP to BFP fluorescence will be used to monitor efficiency of genome editing. Initial studies will be conducted in vitro and will involve culture of both cell lines and primary cells expressing GFP. In vitro differentiation will be used to assess the capacity of modified stem cells to differentiate along multiple lineages. Further studies will also be conducted in vivo using our unique humanised beta-thalassaemia mouse models.

19. Epigenetic modifications of the human beta-globin locus: new therapeutic targets for haemoglobin disorders

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Available as Masters Project: Yes

Haemoglobin disorders, such as sickle cell disease and Ï€-thalassaemia are the result of mutations in the adult beta-globin gene. When these disorders are co-inherited with hereditary persistence of fetal haemoglobin, (high levels of gamma-globin gene expression in adult life) the disease phenotype is much reduced. Therefore, understanding the mechanism of gamma-globin globin gene regulation through development has been the subject of intense investigation for many years. These studies led to an appreciation of the role of epigenetic modifications such as DNA methylation and histone acetylation in globin gene expression and regulation. As a result, considerable efforts have been focused on the pharmacolologic induction of fetal haemoglobin (HbF) using epigenetic-specific agents. However, the role of individual epigenetic regulators in globin gene expression is not very well understood.

This study will investigate the potential impact of epigenetic regulators on globin gene expression. Functional genomic screening strategies will be performed using RNA interference (RNAi) or CRISPR/Cas9 genome editing to either suppress or knockout the expression of specific epigenetic regulators in erythroid cells modified to express fluorescent reporter genes under the control of the gamma-globin promoter. Flow cytometry, real-time PCR and western blot analysis will be used to monitor gene expression. Positive outcomes of such studies could pave the way for better treatment strategies for sickle cell anaemia and beta-thalassaemia patients by targeting epigenetic regulators to increase fetal globin expression.
20. Does skewed X-linked inactivation predict the severity of Rett Syndrome?

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Available as Masters Project: Yes

Rett syndrome (RTT) is a severe neurodevelopmental disorder, where most cases arise from mutations within the MECP2 gene (RettBASE: http://mecp2.chw.edu.au). The great majority of MECP2 gene mutations occur on the paternally inherited X chromosome. Specific mutations can affect clinical severity, but skewing of X-inactivation is proposed to also modulate the phenotype in RTT. X-linked inactivation is a process whereby one copy of the X-chromosome is randomly transcriptionally inactivated.

We hypothesise that the proportion of RTT cells with an MECP2 mutation on the active X chromosome at birth decreases over time because of selection disadvantage. This is reflected by a significant change in X chromosome methylation between birth and later on in the childhood, and its relation with transcription of RTT related genes. The rate of this change may be correlated with the severity of clinical involvement. This project will examine X chromosome methylation using previously developed methods shown to identify skewed X-chromosome inactivation in X-linked disorders, including fragile X syndrome and sex chromosome aneuploidies (Godler et al 2013 HMG; Inaba et al 2013 Med Genet; Godler 2015 Ex Rev Mol Med).

Aim 1: To examine methylation patterns in a cohort of clinically mild and severe RTT patients carrying known MECP2 gene mutations.

Aim 2: To examine methylation in newborn blood spots retrospectively retrieved from 100 RTT patients, and in blood collected at time of recruitment, and compared to control data.

Aim 3: To examine transcription of RTT related genes by absolute RNA quantification using droplet digital PCR.

Outcomes: Relationships between DNA methylation and clinical severity, changes in methylation over time, and RTT specific mRNA levels will be analysed. These findings could lead to development of a novel way to predict increased risk of developing severe RTT phenotype from methylation analysis of newborn blood spots, well before symptoms become apparent.

M1. Developing a diagnostic blood test for autism

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Masters Project Only

Autism is a complex, heterogeneous neurodevelopmental disorder with an early childhood onset and a lifelong course. The identification of biomarkers to define biologically homogeneous subgroups, predict risk, and aid the diagnosis of autism would greatly facilitate the management of this common disorder, which affects ~1% of the population.

This research project seeks to identify circulating RNA biomarkers that are dysregulated in autism and, using this information, to develop a diagnostic blood test for autism. In this way, the research seeks to overcome the current difficulties that exist around obtaining a diagnosis of autism and, by doing so, should help to facilitate intervention and thus improve outcomes for autistic children and their families. Students will develop skills in RNA biology, next generation sequencing, and bioinformatics.

21. Investigating repeat-associated disease mechanisms in Friedreich ataxia

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The debilitating neurodegenerative disease Friedreich ataxia results from a trinucleotide (GAA) repeat expansion in the FXN gene. FXN encodes frataxin, a mitochondrial protein important in iron homeostasis and iron-sulfur cluster assembly. Low levels of frataxin is considered the main driver of disease. In the repeat-associated diseases spinocerebellar type 8 and myotonic dystrophy, a unique translational process known as repeat-associated non-ATG (RAN) translation was demonstrated to be pathogenic. RAN translation does not require a start codon and produces homopolypeptides. We hypothesise that the GAA triplet repeat expansion in Friedreich ataxia expresses homopolypeptides via RAN translation in both the sense and anti-sense directions. Our preliminary data indicate increased signal intensity and differential localisation of a specific homopolypeptide in key tissues of pathology in Friedreich ataxia mice compared to wild-type mice.

This project will evaluate the expression of GAA repeat-associated RNAs and homopolypeptides in animal and cellular models of Friedreich ataxia. Endogenous repeat-associated RNAs will be examined in transcriptome analyses of primary cells from individuals with Friedreich ataxia and control subjects. In human cell lines, plasmid-based expression of repeat-associated peptides tagged in multiple open reading frames will be evaluated via western blot. Repeat-associated homopolypeptide expression will also be examined in tissues from Friedreich ataxia mice, as well as sensory neurons in induced pluripotent stem cell-derived neurospheres from individuals with Friedreich ataxia and control subjects. This study will increase our understanding of the molecular mechanisms in Friedreich ataxia.
22. Investigating the factors involved in FXN silencing in Friedreich ataxia

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The debilitating neurodegenerative disease Friedreich ataxia results from a trinucleotide (GAA) repeat expansion in the FXN gene. FXN encodes frataxin, a mitochondrial protein important in iron homeostasis and iron-sulfur cluster assembly. Low levels of frataxin is considered the main driver of disease. Our team has shown a characteristic DNA methylation pattern surrounding the expansion in Friedreich ataxia (FRDA) where methylation is increased upstream of the DNA expansion and decreased downstream. We showed that when methylation increased at a specific dinucleotide (UP-CpG1) near the expansion, FXN expression decreased. We also found that FXN expression inversely correlated with the clinical features of FRDA, including disease severity.

This project will investigate a novel repeat-associated factor and its contribution to FXN silencing. We recently demonstrated a nuclear protein binds at/near UP-CpG1, and that this binding increases when UP-CpG1 is methylated. Using TRANSFAC (Biobase), we found putative binding sites for three known transcription factors in this region. This project will characterise this protein and examine its effect on FXN expression. FXN transcript and frataxin protein will be measured in a series of over-expression and knock-down studies in human cell lines. FXN reporter constructs will also be generated to identify the exact protein binding site. Binding in intact human cells will be characterised using chromatin immuno-precipitation.

This study will increase our understanding of the molecular mechanisms underlying Friedreich ataxia and could identify much-needed therapeutic targets for treatment development.

23. Determining the genetic basis of novel neurogenetic disorders

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Available as Masters Project: Yes

The identification and characterisation of genes underlying Mendelian disorders has been responsible for unprecedented advances in our understanding of human disease. Very recently, gene discovery has been driven by advances in genetic technologies, particularly the ability to routinely sequence entire genomes. This project will utilise clinical resources of the Victorian Clinical Genetics Services and modern molecular genetic and bioinformatic technologies to identify novel genes for neurogenetic disorders. In addition, the function of these genes will be investigated in cell and animal models to determine underlying disease pathogenesis. These studies have application in the field of personalised medicine, where the knowledge of an individual's genetic make-up can be utilised to predict disease development, influence decisions about lifestyle choices and tailor medical practice to the individual.

24. Investigating the molecular basis of Parkinson's disease

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Available as Masters Project: Yes

The recent advances in our understanding of common and disabling neurodegenerative diseases such as Parkinson and Alzheimer disease have 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 have identified several families who demonstrate clinical features of early-onset parkinsonism and intellectual disability. Modern genomic technologies have allowed us to identify the gene responsible, which represents a novel gene for Parkinson's disease. This project will characterise the gene and investigate pathogenic mechanisms underlying disease utilising molecular and cell biology techniques with the aim of translation into cell and animal models.

25. Identifying the genetic causes of brain malformation in children

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The human cortex is the surface of the brain that enables advanced intellectual function. It forms through a series of overlapping steps involving neuronal proliferation, migration and differentiation. Abnormal formation of the cortex causes a group of disorders known as malformations of cortical development (MCD), which can result in epilepsy, intellectual disability and cerebral palsy. There is considerable evidence that gene mutations cause MCD, but to date few of the genes involved have been identified.

This project will utilise modern genomic technologies, including whole exome and genome sequencing, to identify the genetic basis of MCD in patients treated by the Children's Epilepsy Program at the Royal Children's hospital. The function of these genes will be investigated in cell and animal models to determine underlying disease pathogenesis.
26. Identifying novel genetic targets that underlie Synucleinopathy and Tauopathy.

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The Parkinson disorders (PDs) all present with selective vulnerability of nigrostriatal dopaminergic populations and abnormal aggregates of the proteins alpha synuclein (asyn) and/or microtubule associated protein tau (tau). This has led to the classification of PDs as either synucleinopathies or tauopathies. However, the pathologies are not isolated categories but rather form a continuum and co-occurrence of asyn and tau pathology is common. This observation suggests that PDs represent a spectrum, rather than discrete disorders and the hypothesis that shared underlying pathways are dysregulated.

A fundamental question that needs to be resolved is what factors (genetic and environmental) underlie these related but diverse clinical presentations and individual patient outcomes. Our hypothesis is that the variable clinical presentation and outcomes of individuals with Parkinson disorders are mediated by the interaction of many genes. The identification of these genes will allow us to dissect the complex interactions that underlie disease aetiology and identify novel therapeutic targets for effective treatment and/or cure of these disorders. We have used the MPTP-induced Parkinsonism model in a panel of recombinant inbred mice to identify strains that are susceptible to dopaminergic neurons loss. This project will involve the identification of susceptible and resistant strain using immunohistochemistry and stereology to determine the number of dopaminergic neurons in the substantia nigra remaining after MPTP exposure. Biochemical quantification of steady-state asyn and tau will be performed in parallel to identify the genes underlying variability of these important disease associate proteins.

27. Characterisation of the parkin protein and how it causes Parkinson's 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, and altered parkin function is a risk factor for several different neurodegenerative diseases. We hypothesise that parkin plays a key role in eliminating toxic proteins within the brain. Failure of parkin function results in the accumulation of toxic proteins and results in the development of PD. We have a number of projects in progress or development that investigate the function of parkin and other related proteins. In particular, we are interested in how parkin functions with its co-regulated gene PACRG in protein turnover and neuron function in the brain. Projects that investigate this relationship between parkin and PACRG can be tailored to the interests and strengths of the right candidate(s). For example, investigation of the significance of the biderational promoter, e.g., luciferase and qPCR; molecular mechanisms altering protein turnover, e.g., protein-protein interactions modifying key residues.

Furthermore, we have recently generated a number of unique mouse models in the laboratory that can be characterised for markers of altered neuropathology, as well as biochemical and behavioural analyses.

28. A genetic approach to identifying drug targets for prevention of deafness

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Available as Masters Project: Yes

THE PROBLEM:
Acquired hearing loss is prevalent within our community. There are several clinical situations that can result in inadvertent damage of the cochlea and acquired hearing loss. These include treatment with platinum based chemotherapy drugs and (somewhat counter-intuitively) cochlear implantation with an electrode array. Previous research has revealed that in most cases of acquired hearing loss, it is death of sensory cells within the cochlea that results in the hearing loss. The aims of this project are to identify molecular targets that can be blocked therapeutically to prevent acquired hearing loss.

THE PROJECT:
Our laboratory uses mouse models to study the genetics and molecular basis of progressive forms of hearing loss. We have a collection of mouse strains with chemically-induced genetic mutations that are resistant to progressive deafness. An opportunity exists for an Honours Student to fully characterise one of these models. The aims of this Honours project are to figure out which gene is mutated in the mouse strain, and to work out how disruption of this gene results in resistance to progressive hearing loss. This project will provide valuable information about the molecular pathways that underpin hearing and may help us identify potential drug targets for preventing deafness. In the long-term we hope to use this information to inform development of drugs that can be used to treat and prevent acquired hearing loss.

TECHNIQUES:
The student will use a wide variety of genetic, molecular biology and auditory biology techniques including: linkage mapping, genomic DNA isolation, single nucleotide polymorphism genotyping, massively parallel DNA sequencing, polymerase chain reaction and dideoxy DNA sequencing, auditory brainstem response testing, micro-dissection of the auditory system and histological analysis of cochleae.

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29. Streptococcus pneumoniae gene expression and pathogenesis

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Streptococcus pneumoniae (the pneumococcus) is a major cause of pneumonia and other severe infections worldwide. In addition to causing disease, the pneumococcus can also colonise the nasopharynx (nose and throat) of healthy individuals. This colonisation is most common in young children and is considered a precursor to disease.

Our laboratory is interested in investigating pneumococcal pathogenesis and the processes by which this bacterium transitions from the colonising to the infectious state. Using a combination of clinical samples and experimental models, gene expression studies will identify genes of interest. Candidate genes will be examined by mutagenesis and functional assays conducted to investigate their role in pathogenesis.

30. Investigating the pneumococcal whole cell vaccine in an infant mouse model of pneumonia

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Pneumonia is the leading killer of children under five years of age worldwide, and Streptococcus pneumoniae (the pneumococcus) is the most common cause. Pneumococci commonly colonise the nasopharynx of healthy individuals, and can disseminate from this site to infect other tissues of the respiratory tract. The pneumococcal whole cell vaccine (WCV) aims to induce immunity against non-capsular antigens and is currently undergoing clinical trials. Previous studies in our laboratory have shown WCV can reduce pneumococcal density in the nasopharynx and ears of infant mice co-infected with pneumococci and influenza A, but its effect on lung disease remains unknown. There is no experimental model which fully recapitulates pneumococcal disease pathogenesis, particularly the transition from colonisation to lung infection, in a paediatric setting.

This project will investigate specific triggers that disrupt pneumococcal biofilms in the nasopharynx and lead to aspiration of the bacterium into the lungs, in order to establish an infant mouse model of pneumococcal pneumonia. Disease pathology and other clinical signs will be assessed, including measuring local and systemic immune responses by flow cytometry, ELISA and gene expression. The model will then be used to assess the impact of WCV on pneumococcal lung disease in the context of pre-existing carriage, important because children in high disease-burden settings commonly carry pneumococci at the time of vaccination.

31. Interactions between Streptococcus pneumoniae and respiratory viruses

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Co-infections with viral and bacterial pathogens can lead to severe respiratory infections. These interactions have been well-documented between the bacterium Streptococcus pneumoniae (the pneumococcus) and influenza virus. Clinical evidence suggests that a similar synergy exists between pneumococcus and respiratory syncytial virus, a major cause of respiratory infection and hospitalisation of young infants.

Using in vivo models, this project will investigate the interactions between these two pathogens and generate novel data on the impact of viral infection on pneumococcal colonisation, transmission, and pneumonia.

32. Immunomodulatory effects of Vitamin D on the host response to respiratory infections

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Respiratory infections such as those by the pneumococcus and RSV are a major cause of morbidity and mortality in children less than 5 years of age. The host response to infection involves activation of both innate and adaptive immunity both in the mucosal tissue as well systemic immune system. These include modulation of cytokine production, T-lymphocyte function and inflammatory responses. Vitamin D has been shown to have a variety of biological effects including beneficial effects on the immune system that may help resist against respiratory infections.

In this study, we aim to characterise the effects of Vitamin D on human immune cell populations. We will measure cytokine production and immune cell function in peripheral blood mononuclear cells (PBMCs) and isolated subpopulations when stimulated with various pathogen ligands in the presence of Vitamin D. We will also examine the effect of Vitamin D on functional responses such as bacterial killing. This study has important implications for developing preventative and/or therapeutic strategies in individuals at high risk of disease.
33. Exploring a new approach for preventing stomach cancer

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Infection of the stomach with the bacterium *Helicobacter pylori* typically starts in childhood and lasts for life. This infection causes a chronic inflammation (gastritis) that in some people drives the development of stomach cancer, globally the 3rd leading cause of cancer-related death. Why some people but not others develop disease is complex but includes the effects of important host regulatory factors. We have identified a new factor, a potassium channel, which plays such a role. Experiments in mice have indicated that this channel plays a role in inhibiting gastritis and therefore protecting against *H. pylori*-associated disease. Importantly we have also found that people with particular genetic variants in this channel have a greatly increased susceptibility to gastric cancer, showing this is relevant to humans. As drugs are already available that clinically target this channel, this discovery raises the possibility of a new treatment to prevent stomach cancer. However we need first to confirm that this factor does indeed play a key role in human cells.

AIM: This project aims to explore the functional role of this important host factor in the response of human cells to *H. pylori* infection.

APPROACH: To achieve this, the student will first use molecular techniques to modify the expression of this channel in human cells, then stimulate these cells with *H. pylori* before measuring cytokine secretion (by ELISA and real time PCR) in order to observe how modifying the potassium channel changes the inflammatory response of human cells to bacterial stimulation. Drugs that modify this potassium channel will also be tested in the same system, to commence exploring potential candidates for therapeutic use.

34. Animal model with undescended testes may provide the key to understanding cellular interactions necessary for testicular descent

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Congenital undescended testes (UDT), or cryptorchidism, is extremely common, affecting 2-4% of boys. Surgery to pull the testes down is currently recommended at 6-12 months, aiming to prevent deranged postnatal germ cell maturation, secondary to high temperature that eventually causes cancer and infertility. The testis forms inside the abdomen near where the kidneys are. The genito-inguinal ligament, or ‘gubernaculum’, initially anchors the testis to the groin and then migrates through the abdominal wall and down into the scrotum, pulling the testis inside an extension of the peritoneal membrane, the processus vaginalis (PV). Gubernacular migration is controlled by androgens via the genitofemoral nerve (GFN), which releases calcitonin gene-related peptide (CGRP) to direct migration and control PV closure after descent. Our recent study has indicated that neorotrophins, such as CNTF and BDNF and their respective receptors, are expressed in the inguinocrotal fat pad in response to androgen to masculinise each GFN.

The project aims to examine interactions between the inguinal fat pad, the GFN and the gubernaculum, and the molecular signals that trigger gubernacular outgrowth from the abdominal wall, for migration to the scrotum. The study will involve the use of immunohistochemistry, confocal microscopy, PCR and Western blotting.

35. Effect of congenital UDT on Gonocyte development

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Undescended testis (UDT) is a major health problem, affecting over 2-4% of males at birth, and with a long-term risk of infertility (30-60%) and a 5-10 fold increase in testicular cancer in young men. Infertility and testicular cancer are likely caused by failed transformation of primitive sperm cells (gonocytes) 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 project will analyse the effect of congenital UDT on gonocyte transformation using animal models and human biopsies. The study will involve the use of immunohistochemistry, confocal microscopy, PCR
M2. Pneumococcal carriage dynamics in children hospitalised with acute respiratory infection in Fiji

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Masters Project Only

Pneumonia is the commonest infectious disease causing childhood death worldwide. Pneumococci are responsible for about 1/3 of all pneumonia deaths. We have a number of studies in Fiji documenting the impact of pneumococcal vaccine on pneumococcal disease in Fiji. In this study, we will determine how antibiotics effect the dynamics of pneumococcal carriage.

72. Impact of multiple pathogen infection on respiratory syncytial virus evolution

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Host immune responses have been shown to have an impact on respiratory syncytial virus (RSV) molecular evolution. Multiple viral co-infections are frequent in children and multiple infections can promote competition between the different strains in terms of host receptors to induce different host immune responses compared to single infections. Our hypothesis is that there are different patterns of molecular characteristics of RSV strains between single RSV infections and those from RSV co-infected (or superinfected) with other viruses. We will use in-vitro models and clinical samples from our Mongolia pneumonia project to test this hypothesis. This project will add valuable data for a better understanding of multiple pathogens co-infection/superinfection roles on RSV evolution for future RSV vaccine design.
36. Developing novel methods to diagnose and predict the prognosis of food allergy

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Australia has the highest rate of IgE-mediated food allergy in the world, with the prevalence more than doubling over the past decade to 10%. There is a recognised need for further studies into developing new novel diagnostic methods that are readily available for clinicians to accurately predict disease phenotypes and prognostic outcomes without food challenges. Currently, the only tool available for monitoring the natural history of food allergy is the Skin Prick Test (SPT) response or serum specific IgE (sIgE) level.

Our group was the first to generate SPT and sIgE 95% predictive probability thresholds for predicting peanut and egg allergy resolution using samples from the internationally unique NHMRC-funded HealthNuts study, the world's largest single centre population based, longitudinal study of food allergy. Despite these findings, the sensitivity of the thresholds were low. We recently developed an algorithm which includes the measurement of Ara h 2 sIgE (a single peanut allergen) using component resolved diagnostics (CRD) instead of using whole peanut extracts (not yet validated for clinical use for many foods), which increased the accuracy of peanut allergy diagnosis and reduced the need for oral food challenges by four-fold (4). In a landmark New England Journal of Medicine article, successful resolution of peanut allergy correlated with the increase of serum specific IgG4 (sIgG4) and not IgE. While IgE levels can be indicative of current disease, IgG4 may be important for determining the prognosis of a food allergic patient, however is not yet validated in a large population cohort.
37. How early-life adversity gets under the skin: the role of epigenetics

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Increasing evidence highlights the importance of the early life environment in shaping our health and risk for disease in later life. Under this Developmental Origins of Health and Disease Model, exposures occurring during the crucial phase of early life can become biologically embedded, with the potential for long-term effects. Epigenetics which can regulate gene expression without altering the underlying DNA sequence, could be one mechanism by which these effects occur. Indeed, the epigenome of the developing fetus may be particularly vulnerable to exposures received in utero, and early-life stress has been linked with a modified epigenetic profile in the neonate. Epigenetic marks might also be valuable tools used to predict future health outcomes.

The Australian Temperament Project (ATP) is one of Australia's oldest longitudinal studies of social and emotional development. The study has followed 2000 infants and parents across 30 years (15 waves) from 1983 and has detailed information on temperament, social and emotional development, and family and social context. It is now following cohort offspring to create a 3-generation resource (ATP Generation 3 Study), with offspring assessments in trimester 3, at birth, 8 weeks, 12 months and beyond. At 12-months, infants undergo a clinical assessment with their primary caregiver to assess attachment behaviour, which takes into account both infant temperament style and parent care giving behaviour. A DNA sample is also collected, allowing DNA methylation (a key epigenetic mark) to be measured. This study will use new epigenome-wide methylation data gathered on a sub-set of infants assessed at 12 months, comparing two extreme groups based on their attachment classification. The aim will be to investigate the role of DNA methylation in mediating the association between prenatal exposure and infant attachment security. This project would suit a student interested in epigenetics and keen to develop skills in data analysis.

38. The impact of stress on mental health

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Available as Masters Project: Yes

Depression is a major public health problem with high prevalence rates worldwide and an increased risk of comorbidity and mortality. Depression is considered a dimensional disorder whose severity is determined by multiple genes with small effects and complex interactions between genetic predisposition and environmental factors. Indeed, it has been shown that stressful or traumatic life events, particularly those in childhood, can lead to an increased risk of depression in later life for certain genetically predisposed individuals. The molecular mechanism for this gene-environment interaction however remains unknown, but epigenetic mechanisms are likely to play a role. This project, as part of a wider collaboration with a French research team, will make use of data gathered from the longitudinal population-based ESPRIT study.

This study, currently in its fifteenth year, has gathered extensive biological, structural (MRI) and clinical data, including past and current depression diagnosis, detailed histories of stressful and traumatic events across the lifetime, as well as physiological markers of stress response (cortisol measured under basal and stress conditions) and genotyping data. DNA methylation data is also available for a number of candidate genes. This project will focus on the role of stress in depression, using extensive data already collected in this study. It will suit a student interested in epidemiology and biological psychiatry, and will enable then to develop skills in data analysis.

39. Molecular classification tools to improve outcome in childhood cancers

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Available as Masters Project: Yes

The accurate classification of individual cancer patients into risk classes that predict long-term outcome at diagnosis is key to making informed therapeutic decisions. In recent years both gene expression and genetic data have been successfully used to complement the clinical and histological criteria traditionally used in such prediction. Many "molecular signatures" have been developed, primarily in an adult cancer setting. In contrast to their adult counterparts, childhood tumours show a relatively low mutational burden, despite exhibiting widespread gene dysregulation. Much of this is due to extensive epigenetic changes, including changes in DNA methylation profile.

The aim of this study is to use modern machine learning algorithms to develop molecular classification tools based on DNA methylation, gene expression and genetic variation data that accurately predict outcome in childhood cancers. Such classifiers are key to improving outcome in childhood cancers that represent the second most common cause of childhood mortality in developed countries. This project would be suitable for students with a background in Computer Science and/or Machine-based learning.
40. A clinical trial of lung protective ventilation during neonatal surgery and transport (Go with the flow 2)

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The newborn lung is particularly prone to serious lung injury when sick or diseased. Increasingly, clinicians are aware of the potential of the mechanical ventilators to damage the fragile newborn lung. This creates a paradox, as neonatal ventilators are often lifesaving treatments in this population. Excessive tidal inflations (volutrauma) are a particularly injurious mechanism. Consequently, the limitation of tidal inflations to 4 - 8 mL/kg is an established method of maximising lung protection in babies receiving Neonatal Intensive Care. We have recently shown that for babies leaving the NICU for surgery delivered tidal volumes are variable, and often outside of the accepted safe range. This project is a clinical trial of direct feedback clinical monitoring of lung function during transport and surgery in babies versus current therapy to determine if this results in more tidal inflations being in the lung protective range. The project will use our groups existing methods of recording high-fidelity physiology measurements of lung function. It is hoped that this will lead to improved practice for this vulnerable population in the RCH and international guidelines. The successful candidate will have the potential to access additional resources and funding support through the NHMRC Preterm Infants Centre of Research Excellence.

41. Using complexity theory to model the newborn lung at birth

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Available as Masters Project: Yes

The very first breaths of life are one of the most remarkable events in human life. Ery quickly the lung needs to adapt from a liquid-filled state to an air-filled one and start the cascade of events that allow the heart and other organs begin ex-utero life. The physiological mechanisms that underpin this respiratory process are multi-factorial and understood. Unfortunately, our understanding of these processes is limited to models and concepts that consider the lung as a whole. In reality the lung is millions of alveoli, each with their own physiological mechanical properties. Increasingly researchers are acknowledging that the respiratory processes at birth are intrinsically heterogeneous at an alveoli level. Recently advanced imaging methods have become available to describe the physiological transition of the lung at an almost alveolar level. This provides a unique data set that can be exploited to better our understanding of the lung during its first breathes of life. Complexity theory is one method that maybe useful in describing the behaviour of the lung at birth at an alveolar level. Valid complexity theory models of the lung would allow the development of better mechanical ventilator and monitoring algorithms and, hopefully, improved clinical care for sick babies at birth. This project aims to evaluate and test different complexity theory models of alveolar behaviour at birth in an existing data set of 200 high-fidelity regional lung imaging recordings (using electrical impedance tomography) of preterm lambs during the first breathes of life. The project is suited to a candidate with a mathematical background wishing to develop practical mathematical solutions to an important human problem.

42. How do we help sick babies breathe? Understanding the role of ventilator synchronisation on lung protection

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Available as Masters Project: Yes

The diseased newborn lung is particularly prone to injury that can persist throughout life. Increasingly, we are aware that allowing a mechanical ventilator to synchronise with a baby's own breathing pattern reduces the risk of lung injury. Ventilation within the diseased lung is complex and rarely the same throughout the lung. This project aims to understand how synchronisation influences the behaviour of tidal ventilation throughout the lung. It will involve directly studying newborn babies receiving Intensive Care at the Royal Children's and Women's Hospitals using advanced lung imaging techniques. The student will take detailed recordings of lung mechanics and ventilation in babies receiving mechanical ventilation and describe the breath-to-breath characteristics of synchronised and unsynchronised breaths to determine whether lung protection is being achieved and whether it is uniform within the lung. The successful candidate will have the potential to access additional resources and funding support through the NHMRC Preterm Infants Centre of Research Excellence.

43. Does non-invasive ventilation alter ventilation patterns in preterm infants?

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Preterm infants often have trouble breathing after birth and need respiratory support. But, the preterm lung is particularly prone to injury. Increasingly clinicians are using non-invasive ventilation (NIV) as a gentler way of helping preterm babies breathe. There are now different types of NIV; CPAP, high-flow nasal cannula, nHFO and NIPPV. Each is slightly different and clinical trials have not shown a huge efficacy difference. This project aims to understand how each influences the behaviour of tidal ventilation throughout the lung. It will involve directly studying newborn babies receiving Intensive Care at the Royal Children's and Women's Hospitals using advanced lung imaging techniques. The student will take detailed recordings of lung mechanics and ventilation in babies receiving mechanical ventilation and describe the breath-to-breath characteristics of in babies receiving different types of NIV to determine whether tidal ventilation differs within the lung, and conform with our understanding of lung protection. The successful candidate will have the potential to access additional resources and funding support through the NHMRC Preterm Infants Centre of Research Excellence.
44. How do babies take their first breaths?

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

45. Understanding brain development in very preterm children using novel diffusion magnetic resonance imaging measures of white matter microstructure

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Available as Masters Project: Yes

Scientific question: Very preterm birth (less than 30 weeks of gestation and/or less than 1250 grams birth weight) is associated with brain injury, altered brain development and long-term deficits in cognitive, behavioural and motor function. Novel magnetic resonance imaging (MRI) analysis techniques are emerging that enable in vivo quantification of the brain’s white matter microstructural and axonal properties. The aims of this study are to determine whether white matter microstructure is altered in very preterm-born children compared to healthy term-born children at 13 years of age, and to determine if white matter microstructure is associated with concurrent cognitive, behavioural and motor functioning in very preterm children.

Basic experimental approach / general tasks: Advanced diffusion MRI techniques can be used to generate quantitative measures of the brain's white matter microstructure, such as axon density. Furthermore, advanced neuroimaging techniques enable analysis of microstructure measures across the entire white matter of the brain and within specific white matter fibre pathways. General information: The Victorian Infant Brain Study (VIBeS) research group explores brain injury and brain development in premature infants using state-of-the-art neuroimaging techniques. We also focus on identifying factors that influence brain maturation and determining how brain maturation contributes to neurobehavioural development. Furthermore, the team is involved with developing interventions to improve outcomes for premature children.

46. Understanding brain development in very preterm children using in vivo myelin mapping based on magnetic resonance imaging

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Scientific question: Very preterm birth (less than 30 weeks of gestation and/or less than 1250 grams birth weight) is associated with brain injury, altered brain development and long-term deficits in cognitive, behavioural and motor function. Magnetic resonance imaging (MRI) analysis techniques are emerging that enable in vivo quantification of the brain's white matter myelin content. The aims of this study are to determine whether white matter myelin content is altered in very preterm-born children compared to healthy term-born children at 13 years of age, and to determine whether white matter myelin content is associated with concurrent cognitive, behavioural and motor functioning in very preterm children.

Basic experimental approach / general tasks: Myelin mapping is an advanced neuroimaging technique that involves combining T1-weighted and T2-weighted magnetic resonance images to non-invasively examine myelin content. Furthermore, advanced neuroimaging techniques enable quantitative analysis of myelin content across the entire white matter of the brain and within specific white matter fibre pathways. General information: The Victorian Infant Brain Study (VIBeS) research group explores brain injury and brain development in premature infants using state-of-the-art neuroimaging techniques. We also focus on identifying factors that influence brain maturation and determining how brain maturation contributes to neurobehavioural development. Furthermore, the team is involved with developing interventions to improve outcomes for premature children.
47. Does cortical thickness mediate cognitive deficits in ADHD.

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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 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 explain the observed cognitive impairments.

48. Modelling the cardiovascular birth transition in vulnerable infants

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Birth is arguably the most crucial and most complex event of life. Immediately after birth, rapid and profound changes occur in the cardiovascular system to facilitate the shift from placental respiration to breathing with the lungs. However, premature birth, congenital heart disease and/or birth complications (such as fetal or newborn asphyxia) can cause problems with the birth transition that may have long lasting consequences for the child (e.g. brain damage, requirements for intensive care, greater long-term risk of cardiovascular disease). The precise nature of the perinatal cardiovascular complications, and how they might be treated better or avoided altogether, are very difficult to study in human babies due to ethical and practical constraints.

In this project, the student will develop a state-of-the-art computational modelling platform for studying the birth transition and challenges encountered by vulnerable infants. A key benefit of a modelling approach is the lack of ethical constraints and great flexibility in studying the problem. The project will be integrated with world-leading parameters by our group on fetal modelling and experimental studies of the birth transition in lambs, and will benefit from our links with the neonatal intensive care unit at the Royal Children's Hospital.

49. Modelling cardiovascular development during childhood

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It is increasingly being recognised that the precursors to adult cardiovascular disease begin in childhood. However, we currently have limited information about the normal development of the cardiovascular system during childhood and how this normal development is interrupted by problems such as congenital heart disease.

One-dimensional modelling is a powerful tool for studying the cardiovascular system but currently no models of the growing circulation exist. Based on existing state-of-the-art models of the adult and newborn cardiovascular systems, developed by our group, the student will incorporate childhood growth and physiological development. The model will be validated against measurements in children. The resulting model will allow simulation of blood pressure and flow throughout the circulation of a representative normal child at any time during childhood. By perturbing parameters of the normal development model, new insights will be gained into problems faced by children with congenital heart disease and why some children have a high risk of developing cardiovascular disease as adults.
50. "Are we truly engaged or is this a token?" Effective community engagement in research.

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How can researchers best work with the community to benefit from their experience and incorporate feedback into research programs? What makes for good engagement, and where does it typically go wrong? How can the process be improved to support a satisfying and constructive relationship between researchers and community members?

The NHMRC-funded Centre of Research Excellence in Cerebral Palsy (CRE-CP) is a five year project that aims to improve the health and well-being of all people affected by cerebral palsy and their families. One of the CRE-CP core values is to involve parents, carers and persons with cerebral palsy in all aspects of the program to ensure outcomes are meaningful and relevant to the end-users. Community engagement is a widely embraced concept, however strategies that have proved effective remain under-explored. The CRE-CP has an opportunity for an honours or masters student to work alongside researchers, community representatives and the CRE-CP Community Coordinator to explore what factors contribute to successful community engagement, and to make recommendations that can be adopted by other research groups.

The student will work closely with leading researchers, clinicians and our experienced team of community representatives to review current literature, and then hold interviews and focus groups to gather data on barriers and how these can be overcome. The student will document the lessons learned and contribute to the literature on meaningful community engagement across the disability research field.

51. Measuring movement variability with inertial measurement units

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Available as Masters Project: Yes

The purpose of this project is to develop and validate an algorithm to determine movement variability from one inertial measurement unit. The algorithm will be validated against a state of the art motion capture system available at The Royal Children's Hospital. We will use the algorithm to study the movement variability of a range of simple grasping task in typically developing children. The longer term objective is to compare the movement variability of typically developing children with that of children with cerebral palsy.

52. Impact of pregnancy on women with Fontan circulation.

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Background.

THE EXTRAORDINARY FONTAN CIRCULATION. Babies born with a single pumping heart chamber can survive if they undergo a series of operations, culminating in the Fontan procedure after which the desaturated blood goes directly to the lungs without being pumped by the heart. The results of this operation have been far better than expected. It is estimated that between 50-70 000 such patients are alive in the world, 40% of them aged above 18. Many of these young women seek to become mothers, but with half a heart, this may be a real challenge both for their foetuses and themselves. The possible longer term effects of pregnancy in this population are unknown.

We have created the Australia and New Zealand Fontan Registry, the largest database of such patients in the world and are leading the research in this field. Women with a Fontan circulation have a much higher risk of miscarriages, prematurity and maternal morbidity. WE STILL DO NOT KNOW IF THEIR HEARTS WILL SUFFER LONG-TERM DAMAGE FROM SUPPORTING PREGNANCIES.

The project.

We have information on 20 women who reported a total of 40 pregnancies. We want to collect very detailed analysis of their heart including echocardiography and exercise capacity. We will analyse the evolution of their cardiac function over time from before to several years after the pregnancy. We will then find very similar patients with a Fontan but no pregnancy and compare these groups to understand the later impact of pregnancy on Fontan hearts.

The team.

We expect this Honours student to get two publications from this work. We have a high track record of successful supervision of Honours students, Masters, and PhD. We have been supporting students in their subsequent careers and expect them to be an integral part of our team.
53. Educational and training needs assessment of health professionals to inform implementation of genomic medicine

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**Available as Masters Project:** Yes

The successful implementation of genomics in healthcare will depend on the availability of a workforce to deliver genomic medicine and its acceptance on both clinical and ethical grounds by health professionals, patients, their families and society.

It is widely accepted that the Australian health system workforce is not sufficiently literate in genomics to optimally incorporate it into their current roles. The limited number of genetic and other expert health professionals cannot meet demand. Australia needs an integrated approach to workforce development in genomic medicine to minimise duplication of effort, leverage existing resources, and support good clinical and ethical practice.

Program 4 of the Australian Genomics Health Alliance (funded by the NHMRC) is focused on understanding the needs of health professionals who would contribute to the genomic workforce or be impacted by genomics.

The aim of this project is to develop a survey to inform strategies around education and training of health professionals to enable them to incorporate genomic medicine into their future practice.

This project (suitable for Honours or Masters) would involve creating a needs assessment survey, based on existing literature and other data obtained by Program 4, which would ultimately be disseminated to health professionals. Health professional groups could include non-genetics medical specialists, general practitioners, nursing and allied health professionals. In the first instance the student/s would design 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) and piloted with a small group of health professionals. In the case of a Masters project, the survey would then be disseminated to a large group of relevant health professionals and the responses/data analysed.

Non-Laboratory based research  
**Theme: Genetics**

54. ‘Genomic wellness’ - exploring experiences and expectations of personal genomic testing in alternative medicine

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This project is embedded in the GeNIOZ study (Genomics: National Insights of Australians), funded by the Australian Research Council. Overall, GeNIOZ seeks to understand Australians’ experiences and expectations of personal genomics, with the aim of developing education support for informed decision-making by the general public.

In the last year, there has been a surge of personal genomic testing offered in Australia through naturopath and other alternative medicine practitioners, with limited (if any) genetic counselling support/training. Many of the claims of the marketing around these tests have little grounding in evidence-based research or practice.

This Honours project will involve analysing the relevant content of ‘genomic wellness’ websites for accuracy and claims of personal and clinical utility, and exploring the experiences and attitudes of people who have had, or considered having, a ‘genomic wellness’ test offered through an alternative medicine practitioner. Participants will be identified through their responses to a current online survey, and then contacted for telephone interviews. This involves undertaking qualitative analytical methods and the student will be trained and supported in this methodology by the supervisors.

The outcomes from this research will inform the overall GeNIOZ study, specifically around how personal genomic testing for ‘genomic wellness’ is being offered in Australia, and how best to develop unbiased educational material to support people when making decisions about this type of DNA testing.

Non-Laboratory based research  
**Theme: Infection & Immunity**

55. Risk factors for severe childhood pneumonia in Lao PDR

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Pneumonia is the commonest infectious disease causing childhood death worldwide. Pneumococci are responsible for about 1/3 of all pneumonia deaths.

We have a number of studies in Laos documenting the impact of pneumococcal vaccine on pneumococcal disease in Laos, including a prospective study of all childhood pneumonia admissions to determine how carriage surveillance can be used to document herd immunity. In this study we will be using that data to describe the risk factors of severe pneumonia.
56. Linking early life environment with child health: a longitudinal twin study

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What happens in the womb can last a lifetime. Factors such as maternal diet and lifestyle during pregnancy are linked with a lifetime risk for chronic diseases, ranging from cardiometabolic to neurodevelopmental. Twin studies are ideal for studying such diseases because of their ability to resolve genetic, shared (maternal and early life) and individual environments. For example, comparing twins within a pair enables regression of within-pair differences in pre- and perinatal factors on within-pair differences in health outcomes, controlling for genetics and shared environment.

This project takes advantage of the unique data collected in the Peri/postnatal epigenetic Twin Study (PETS) of Drs. Craig and Saffery. In this study, women pregnant with twins were recruited in mid gestation, extensive data were collected on maternal diet and lifestyle and on the twins themselves multiple times in utero, at birth, 18 months and 6 years of age. This rich dataset enables a number of potential projects based on the student’s interests and is ideal for a wide range of disciplines from genetics to medicine. Our main outcomes of interest are cardiometabolic (weight, height, skin fold thickness, blood pressure) and infectious and other illnesses. Specific research questions include, but are not limited to:

1. Are shared maternal factors such as smoking, gestational weight gain, diet and stress associated with health outcomes in 6 year-olds?
2. Are twin-specific prenatal factors such as intrauterine growth rate, placenta weight, and location of cord insertion into the placenta associated with within-pair differences in health outcomes in 6 year-olds?
3. Do factors such as maternal smoking in pregnancy predict within-pair discordance in child health outcomes?
4. Are twin zyosity, sex and chorionicity associated with child health outcomes?

Each specific research project will be supported by experts in specific domains of child health.

57. 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, remain largely unknown. This includes whether the new wave of infant food allergy will persist into later childhood, and the role of food allergy in the development of other allergic diseases e.g. 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 challenge to test for food allergy. The cohort has been followed up at ages 4 and 6 years. By the end of 2016, all the HealthNuts children will have turned 6 and completed follow-up. 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 food allergy plays in the development of other allergic diseases in the first 6 years
- To describe the natural history of infantile eczema, including identifying predictors of persistence and resolution
- Which children with early-life wheezing will developing asthma at age 6 years?
58. Habitual dietary intake, snacking behaviour and oral health in 11-12 year old children and their parents

**AIMS:**
- To examine the association between habitual dietary intake and snacking behaviour with oral health in children aged 11-12 years and their midlife parents (N = 1200).

**OBJECTIVES:**
- To understand the epidemiology of oral health in these age groups.
- To examine the influence of dietary habits and snacking behaviour on oral health outcomes.

**OVERVIEW:**
Children and adults with unhealthy eating patterns are at risk for poor oral health, but the literature is limited in two ways. First, previous studies have had small samples making it difficult to draw population-level conclusions that might influence intervention strategies. Second, no research has been able to study how naturalistic food choices, habitual dietary intake and/or dietary trajectories relate to oral health at a population level. This is because, until now, it has been technically too challenging to comprehensively measure diet, eating behaviour and oral health profiles in community samples.

Working within the Longitudinal Study of Australian Children's Child Health CheckPoint, this project will address these current limitations, while also providing a rare opportunity to work within one of Australia's most important and exciting national research projects.

**OBJECTIVES:**
- The Child Health CheckPoint provides a snapshot of oral health and eating behaviour in children 11-12 years and their midlife parents (N = 1200). Children and parents participate in Tooth Booth where a series of 2D dental photographs were taken and stored for later analyses.
- AIM 1: To describe the cross-sectional epidemiology of oral health in a population representative cohort of:
  - Australian 11-12 year olds
  - One parent/caregiver of each child
- AIM 2: To examine parent-child concordance in oral health.

59. Parent-child concordance in oral health

**AIMS:**
- To examine parent-child concordance in oral health.

**OBJECTIVES:**
- To understand the epidemiology of oral health in these age groups.
- To examine the influence of dietary habits and snacking behaviour on oral health outcomes.

**OVERVIEW:**
The concordance between child and parent oral health is poorly understood - the literature is limited in two ways. First, previous community studies have had small samples making it difficult to understand the epidemiology of oral health in these age groups. Second, no research has conducted the same assessment of child and parent oral health at the same time point at a population level. This is because, until now, it has been technically too challenging to comprehensively measure oral health profiles in large community samples.

Working within the Longitudinal Study of Australian Children's Child Health CheckPoint, this project will address these current limitations, while also providing a rare opportunity to work within one of Australia's most important and exciting national research projects.

60. Delving into adolescents' dispositional optimism/pessimism and exploring its association with cardiovascular health in 11-12 year olds: a population-based study

**AIMS:**
- To examine (1) Australian adolescents' dispositional optimism/pessimism and its association with cardiovascular health.
- To examine (2) the extent to which it cross-sectionally predicts cardiovascular health (macro- and micro-vascular structure, vascular function and adiposity) at age 11-12 years.

**METHODS:**
- Data will be drawn from The Child Health CheckPoint's (n=1864) Life@25 data (ie handwriting sample where children were asked to write about their life at age 25) and its rich physical measures of cardiovascular health. The student will make a major contribution to scoring Life@25 data and work closely with a strong interdisciplinary team.

**IMPACT OF RESEARCH:**
- The study will likely draw international attention given the large, high quality data available. Findings are likely to inform the genesis of cardiovascular disease and be disseminated in a high quality journal.
61. Delving into adolescents’ dispositional optimism/pessimism and exploring its association with health-related quality of life in 11-12 year olds: a population-based study

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Dispositional optimism or pessimism refers to an individual's tendency to generally expect positive or negative outcomes. It is thought to be reasonably stable over time and to be influenced by interactions between environment and genetics. High levels of optimism have been shown to be associated with a range of positive outcomes (eg physically, psychologically and academically), while high levels of pessimism have been shown to be linked to poorer outcomes. However, much of this research has focused on individuals with chronic illnesses. Understanding whether optimism/pessimism effect health-related quality of life (HRQL) in the population could offer novel insights into interventions to improve general health and wellbeing. This seems particularly important in adolescence, as the recent Lancet Commission into adolescent health argues that a broader 'lens' on their lives is required that goes beyond traditional 'health problems'. Using rich qualitative data paired with standardised utility and profile measures of HRQL, we have a unique opportunity to gain insights into Australian adolescents' dispositional optimism/pessimism and its association with HRQL.

RESEARCH AIMS:
To examine (1) Australian adolescents' dispositional optimism or pessimism, and (2) the extent to which it cross-sectionally predicts HRQL at age 11-12 years.

METHODS:
Data will be drawn from Child Health CheckPoint's (n=1864) Life@25 data (ie handwriting sample where children were asked to write about their life at age 25) and the self-reported questionnaire that assessed adolescents' HRQL (CHU-9D, PedsQL). The student will make a major contribution to scoring Life@25 data and work closely with a strong interdisciplinary team.

IMPACT OF RESEARCH:
The study will likely draw international attention given the large, high quality data available. Findings are likely to be disseminated in a high quality journal and will inform our understanding of HRQL.

62. Delving into adolescents’ dispositional optimism/pessimism and exploring its social determinants in 11-12 year olds: a population-based study.

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INTRODUCTION:
Dispositional optimism or pessimism refers to an individual's tendency to generally expect positive or negative outcomes. It is thought to be reasonably stable overtime and is also influenced by interactions between environment and genetics. High levels of optimism have been shown to be associated with a range of positive outcomes (eg physically, psychologically and academically), while high levels of pessimism have been shown to be linked to poorer outcomes. Understanding the extent to which adverse or positive life events, social circumstances and strength of family and peer relationships impact on one's mindset as an optimist or pessimist would offer insights into how modifiable these mindsets are and could help guide programs to build more optimistic life views. Using rich qualitative data paired with lifetime data children from birth, collected across six waves, we have a unique opportunity to gain insights into the social determinants of Australian adolescents' dispositional optimism/pessimism.

RESEARCH AIMS:
To examine the social determinants of dispositional optimism or pessimism in Australian 11-12 year olds.

METHODS:
Using nationally representative data from 1,864 children, this project will draw on six waves of data collected biennially from the Longitudinal Study of Australian Children (eg adverse life events, number and quality of relationships, socioeconomic status) and its recent Child Health CheckPoint where children completed Life@25 (ie handwriting sample where children were asked to write about their life at age 25) at age 11-12 years. The student will make a major contribution to scoring Life@25 data and work closely with a strong interdisciplinary team.

IMPACT OF RESEARCH:
The study will likely draw international attention given the large, high quality data available. Findings are likely to be disseminated in a high quality journal and will inform our understanding of dispositional optimism/pessimism.
63. Changes in adolescents’ time use over the past decade

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INTRODUCTION:  
How we spend our time has a major impact on our health and wellbeing. However, studying time use is inherently difficult as it relies on 24-hour recall in order to consider all activities, as one activity naturally displaces the other. Novel measures, such as the Multimedia Activity Recall for Children and Adolescents (MARCA), which collects information on 259 activities, now make this possible. Over the past decade there have been major shifts in adolescent time use, with social media and screen time playing a much larger role in the lives of young children and adolescents, and possible declines in levels of physical activity. We have a unique opportunity to examine changes in time use across three cohorts that all used the MARCA to assess changes in adolescents' time use over the past decade. Changes in time use patterns are often anecdotally discussed, however, few studies offer rich 24-hour time use data to quantify these changes.

RESEARCH AIMS: To examine changes in time use over the past decade in Australian age 11-12 year olds.

METHODS:  
Using MARCA data from the Health Young Victorian Study (HOYVS; 2005), The National Survey (2007) and Australia’s recent Child Health CheckPoint (2015) we can compare changes in time use in 11-12 year old children over the past decade. The student will work closely with a strong interdisciplinary team to conduct these analyses.

IMPACT OF RESEARCH:  
The study will likely draw international attention given the large, high quality data available. Findings are likely to be disseminated in a high quality journal and will inform our understanding of time use.

64. How early life factors influence cardiovascular function at age 11-12 years: a population-based longitudinal study

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INTRODUCTION:  
Cardiovascular disease is the number one killer worldwide. Although overt disease usually presents later in life, there are strong grounds for believing that it has its origins in early life. Early life factors, such as birth weight and adverse life events, have been shown to predict adverse cardiovascular events in adulthood. However, few studies have considered whether early life factors predict cardiovascular health in childhood. This is an important limitation as studies focusing on adverse cardiovascular events are unable to account for a lifetime of confounding (eg smoking, stress and adiposity). Establishing whether early life factors predict cardiovascular health would offer novel insights into the genesis of disease. Using new technology, we have a unique opportunity to assess early life factors influence on arterial stiffness via a measure of pulse wave velocity, at age 11-12 years.

RESEARCH AIMS: In a large population study, we aim to quantify to the extent to which pulse wave velocity (as a measure of arterial stiffness) at age 11-12 years is predicted by early life factors.

METHODS:  
Using nationally representative data from 1,500 children, this project will draw on six waves of data collected biennially from the Longitudinal Study of Australian Children (eg anthropometrics, birth weight, gestational age mode of delivery, diabetes in pregnancy, gestational age, and preecampsia, growth trajectory, parental hypertension) and its recent physical and biomarkers module, the Child Health CheckPoint (pulse wave velocity) at child age 11-12 years. The project will suit someone with a strong interest in health and epidemiology who will work closely with a strong interdisciplinary team to generate appropriate analytic models.

IMPACT OF RESEARCH:  
The study will quantify key environmental factors influences on cardiovascular health. Given the large, high quality data available, findings are likely to be disseminated in a high quality journal and inform policy.
INTRODUCTION:
Osteoporosis and osteopenia (low bone density) affect over two-thirds of Australians over the age of 50 and contribute to a large burden of disease. Poor bone health has been described as a paediatric disease with geriatric consequences, because peak bone mass occurs in the early 20s and then gradually declines throughout the life course. How to optimise bone accrual in childhood and minimise bone attrition throughout adulthood are vital public health unknowns. Modifiable environmental factors such as diet and body composition could be important to both. In an era where dietary patterns have changed rapidly and overweight and obesity have reached record highs, understanding how and when diet and body composition patterns over time influence bone health at two stages of the life course - early adolescence and mid-life - is essential to optimise bone health.

RESEARCH AIMS:
In two parallel national cohorts (parent-child dyads), to examine the extent to which bone health, at both stages of the life course, is predicted by:
1) Trajectories of body composition and diet spanning the preceding 10 years, and
2) The combination of these factors using a model causal logic framework.

METHODS:
Using nationally representative data from 1,200 children and their parents, this project will draw on six waves of data collected biennially from the Longitudinal Study of Australian Children (diet, body composition, puberty) and its recent physical and biomarkers module, the Child Health CheckPoint (bone) at child age 11-12 years. The project will suit someone with a strong interest in health and epidemiology who will work closely with a strong interdisciplinary team to generate appropriate analytic models.

IMPACT OF RESEARCH:
The study will quantify key environmental factors influences on bone health. Given the large, high quality data available, findings are likely to be disseminated in a high quality journal and inform policy.

INTRODUCTION:
Respiratory diseases are the second leading cause of mortality and morbidity globally. While they typically present in late adulthood, susceptibility to respiratory diseases may be first established in childhood when the lungs are still developing, with potential for further modification throughout the life-course. Lung function has a strong genetic predisposition, but modifiable environmental factors such as diet and body composition are also thought to play a major role in optimising lung function, although their contribution is yet to be quantified. In an era where dietary patterns have changed rapidly and overweight and obesity have reached record highs, understanding how and when diet and body composition patterns influence lung function at two important stages of the life course could point the way to optimising lung function throughout life.

RESEARCH AIMS:
In two parallel national cohorts (parent-child dyads), to examine the extent to which lung function, at both stages of the life course, is predicted by:
1) Trajectories of body composition and diet spanning the preceding 10 years, and
2) The combination of these factors using a model causal logic framework.

METHODS:
Using nationally representative data from 1,800 children and their parents, this project will draw on six waves of data collected biennially from the Longitudinal Study of Australian Children (dietary patterns, body composition) and its recent physical and biomarkers module, the Child Health CheckPoint (state-of-the-art lung function data) at child age 11-12 years. The project will suit someone with a strong interest in health and epidemiology and will involve working closely with a strong interdisciplinary team to generate appropriate analytic models.

IMPACT OF RESEARCH:
The study will quantify key environmental factors influences on lung function. Given the large, high quality data available, findings are likely to inform policy to optimise respiratory health and be disseminated in a high quality journal.
**67. Unnecessary use of pathology testing in hospital admissions.**

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**IMPACT OF RESEARCH:**  
Across the developed world, there is growing interest in identifying and reducing unnecessary medical tests. For children, these tests can include blood tests that do little to change management but may cause harm to the child (pain) and healthcare system (increased costs). Hypotheses: In a sample of children admitted for unplanned, short stays at the RCH, the proportion of unnecessary pathology testing will be high for common conditions and factors associated with unnecessary testing will include child age (younger child), presence of IV cannula, and admission type (medical > surgical).

**METHODS:**  
3-month prospective audit drawing upon inpatient admission data recorded in Epic. Patients with planned admissions for chronic illnesses (eg chemotherapy) will be excluded. Bivariate analysis to determine child (eg age, gender, family SES), clinician and other factors (seasonality, IV cannula presence) associated with increase ordering of unnecessary pathology testing. Logistic regression to determine significant factors associated with unnecessary pathology 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 pathology testing.

**OUTCOMES/SIGNIFICANCE:**  
Before trialling interventions to reduce unnecessary pathology testing, we first need to identify which children and which conditions are associated with unnecessary testing and any potentially modifiable risk factors associated with unnecessary testing. Results will inform a peer-reviewed publication and a planned randomised controlled trial of an intervention to reduce unnecessary testing.

**68. Insights into the conundrums of managing mild congenital hearing loss**

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**INTRODUCTION:**  
Congenital hearing loss (CHL) affects 1-3 in 1000 children. Over the last decade, universal newborn hearing screening has enabled early diagnosis of CHL, including mild CHL, in infants as young as a few weeks old. This has transformed the life chances of infants with moderate to profound CHL by improving language outcomes through early aiding and cochlear implantation. However, there has not been the same positive shift in outcomes for children with mild bilateral CHL despite earlier diagnosis, and it is unclear whether early fitting of hearing aids offer long-term benefits or unintended negative effects. This is despite clinical practice shifting towards offering hearing aids to these infants without established evidence of benefits or lack of harm, possibly contributing towards unnecessary health care costs.

**RESEARCH AIMS:**  
To explore and describe, in infants with bilateral mild CHL, the a) Factors influencing audiologists’ decisions to offer/not offer hearing aids; and b) Parental experiences of management options offered and associated positive/negative impacts.

**METHODS:**  
Qualitative study. Structured focus groups (audiologists)/telephone interviews (parents/carers). Audiologists are invited to participate through email correspondences through Australian Hearing. Carers of infants

**IMPACT OF RESEARCH:**  
The study will give unique insights into why audiologists do/do not offer hearing aid fitting to infants with bilateral mild CHL, and explore carer experiences of the pros and cons of being offered hearing aids. The results will inform the piloting of a randomised controlled trial of offering/not offering hearing aid fitting to infants with bilateral mild CHL, to ultimately answer the question of whether hearing aid fitting will improve outcomes for children with bilateral mild CHL.

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Bowel and/or bladder dysfunction (BBD) affects up to 6% of children. These children can have constipation, soiling or wetting problems that often occur together and cause a great deal of distress for families. A large number of children with BBD are referred to the Royal Children's Hospital (RCH), Melbourne. They may be seen in one (or more) of the following clinics: Gastroenterology, Renal, Paediatric Surgery, Urology, General Medicine, or Encopresis. Waitlists range from seven months (Enuresis clinic) to 12 months (Renal clinic) and there are few guidelines to work out where patients should go and how they should be managed.

The project aims to evaluate a new model of care implemented to streamline referral and care pathways for children who are referred to RCH specialist clinics for bowel and bladder dysfunction. The prospective student will undertake an audit of hospital records to evaluate wait times and care pathways post implementation of the new model. Patient experience will further be explored through clinic surveys used to capture satisfaction rates from wait list to receiving the service and quality of life.

70. Trends in additional health and developmental needs over time: Evidence from three cohorts of the Australian Early Development Census

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The Australian Early Development Census (AEDC; www.aedc.gov.au) is a population measure of children's development - including their language and cognitive skills, social competence, emotional maturity, physical health and wellbeing, and communication skills and general knowledge - completed by teachers for all children in their first year of school across Australia. It also includes information about children's additional health and developmental needs (AHDN), including children's special needs status, the impact of health problems on their school functioning, and whether they require further assessment. The AEDC is completed every three years, and data is now available from 2009, 2012, and 2015, with over 250,000 children in each cohort. This provides a rare opportunity to examine trends in AHDN over time across these cohorts, including areas of difficulty like language and behavioural issues and actual diagnoses as reported by teachers, for both the full population and vulnerable groups such as those living in disadvantaged communities. The results will contribute to understanding the support needs of Australian children starting school.

This project involves quantitative analysis of existing data using Stata software. Ethics approval for this project has been granted by the Royal Children's Hospital HREC.
**UNIVERSITY OF MELBOURNE 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;
- and 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: www.paediatrics.unimelb.edu.au
Murchison Childrens Honours Website: www.mcri.edu.au/students/honours-students
MDHS website: http://sc.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 – 25 points (semester 1)
**PAED40005** Paediatrics Research Project – 50 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 Childrens 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 (13.3%)
3. Supervisor’s report on the student's overall research ability (6.7%)

**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 2017, and you would like to undertake your project and coursework with the Murdoch Childrens 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**

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 2017 are also listed on the Murdoch Childrens Research Institute and Department of Paediatrics websites.
STEP 2: Lodge an online application

Register for the Honours Application Tracking System (HATS) before making your application in HATS. Lodge an online application between Friday 26 August and Friday 11 November 2016:

http://sc.mdhs.unimelb.edu.au/how-apply

STEP 3: Honours Application and Tracking System (HATS): Applications for specific projects are entered into HATS in order of preference, however you can change or re-order your project preferences at any time, up until Friday 25 November 2016.

STEP 4: Offers - Round one offers for entry into 2017 will be made from Monday 19 December 2016. 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.

For further details see the Murdoch Childrens Masters Website: www.mcrl.edu.au/students/masters-students

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 Childrens 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 2017 are also listed on the Murdoch Childrens Research Institute and Department of Paediatrics websites.

For commencement in semester one 2017, applications close: 30 November 2016

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

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