murdoch children's research institute

THE UNIVERSITY OF MELBOURNE

2020

HONOURS & MASTERS PROJECTS

Department of Paediatrics

Faculty of Medicine Dentistry & Health Sciences

CONTENTS

Laboratory based Research

Cell Biology

1. Milk 4 D study: Validaiton of a novel low cost point-of-need diagnostic for the Assessment of Vitamin D Deficiency in infants

Dr Anushi Rajapaksa
T 383416497
E anushi.rajapaksa@mcri.edu.au
Professor John Wark
E jdwark@unimelb.edu.au

Associate Professor Ronda Greaves
E ronda.greaves@mcri.edu.au

Professor Kim Mulholland
E kim.mulholland@mcri.edu.au

Available as Masters Project: Yes

THE PROBLEM: Milk is an important source of vitamin D for various risk populations, including infants. Vitamin D deficiency among children is common in Australia, the Middle East, India, Africa, and South America, is often undiagnosed as symptoms may not manifest for several years and long-term deficiency has been linked to health problems including osteoporosis, diabetes and cancer. The estimated national annual incidence of vitamin D deficiency rickets among children was 4.9/100 000 Australian children. Vitamin D and calcium in the human milk is essential for the growth and the prevention of rickets in infants. The accurate measurement of vitamin D in milk is necessary to provide adequate supplementation advice for infants. Currently the majority of vitamin D testing is performed in large-scale commercial laboratories which have high operational costs and long times-to-result. Development of a low-cost point-of-need assay could be transformative to deficiency analysis in limited-resource settings. The best biomarker of vitamin D status, 25 hydroxyvitamin D3 (25(OH)D3), however, is particularly challenging to measure and a variety of techniques have been reported for the assay of vitamin D and its metabolites especially in biological fluids.

THE PROJECT: This project is for the clinical validation of a recently developed rapid diagnostic test for the accurate, quantitative assessment of 25(OH)D3 in human breast milk. This project will involve the validation of vitamin D detection system in breastmilk at high sensitivity and specificity. TECHNIQUES: The student will design and use biochemical sensing methods to quantify these biomarkers in breast milk from at risk populations. The techniques developed will be validated against gold standard methods of diagnosis using blood tests using advanced biochemical methods. This project is a collaborative effort between Engineering, Chemistry and Clinical sciences together with close collaboration with our Melbourne-based industry partner. Candidates with a strong background or interest in Biomedical Engineering, Chemical Engineering, Biochemistry, or other relevant expertise are encouraged to apply. Please submit your expression of interest (outlining your short and long-term goals) along with you CV and academic transcripts to anushi.rajapaksa@mcri.edu.au

2. Potential of stem cell therapy to treat Hirschsprung's disease

Dr Lincon Stamp
E lstamp@unimelb.edu.au
A/Prof Sebastian King
E Sebastian.King@rch.org.au

Dr Marlene Hao
E hao.m@unimelb.edu.au

Available as Masters Project: Yes

Hirschsprung's Disease arises from the failure of neural crest cells to migrate to the anal end of the colon, resulting in a lack of enteric neurons in the unpopulated region. As the enteric nervous system (ENS) is crucial for gastrointestinal function, there is no propulsive activity in the aganglionic region and there is a build-up of gut contents, which can prove fatal if left untreated. HSCR patients currently undergo "pull-through" surgery to remove the aganglionic region of bowel. Whilst this is life-saving, most patients suffer chronic, long-term complications, including constipation, faecal soiling, and associated psychosocial problems. Stem cell therapy, where missing enteric neurons are replaced, is an exciting area area of research. In this project, we are using a rat model of Hirschsprung Disease to investigate the clinical application of cell therapy for Hirschsprung patients.

3. Gut epithelial stem cell function: the influence of enteric neurons

Dr Lincon Stamp
E lstamp@unimelb.edu.au
Dr Marlene Hao
E hao.m@unimelb.edu.au

A/Prof Sebastian King
E Sebastian.King@rch.org.au

Available as Masters Project: Yes

This project aims to investigate the interaction between gut neurons and the epithelial stem cell compartment, as well as the relationship between age-related loss of enteric neurons and changes in gut epithelial stem cells. The role of epithelial stem cell-nerve communication, and the signalling pathways mediating it, are currently poorly understood. This study, which includes novel co-culturing of organoids and enteric neurospheres, will identify signalling pathways and cellular mechanisms by which nerves influence the epithelia during homeostasis and ageing. The outcome of the project will be a better understanding of the biology of the body's most highly proliferative, long-lived stem cells; intestinal epithelial stem cells

4. A gut feeling about new therapies for glioma treatment

Dr Marlene Hao
E hao.m@unimelb.edu.au
Dr Lincon Stamp
E lstamp@unimelb.edu.au
A/Prof Sebastian King
E Sebastian.King@rch.org.au

Available as Masters Project: Yes

Gliomas are a very aggressive form of brain cancer, with a very poor 5-year survival rate. Gliomas can arise from over-proliferation of glial cells or stem cells in the brain. Glial cells are a prominent part of the enteric nervous system in the gut. In this project, we will use a novel line of transgenic mice to investigate gene expression patterns between glial cells in the brain and the gut using RNA-sequencing technology and bioinformatic analysis.

5. Epigenetic programming of inflammatory memory in endothelial cells - a role in atherosclerosis

Dr Boris Novakovic
T 83416341
E boris.novakovic@mcri.edu.au
Professor Richard Saffery
T 83416341
E richard.saffery@mcri.edu.au
Professor Dave Burgner
T 99366730
E david.burgner@mcri.edu.au

Available as Masters Project: Yes

For decades it has been clear that cells of the adaptive immune system are capable of developing long term memory to specific antigens. Contrary to prevailing dogma, more recent data have shown that innate immune cells, such as monocytes and macrophages, may also develop a non-specific memory in response to inflammatory signals. This is known as 'innate immune memory' or 'inflammatory memory' and governs the cell's future response to a range of pathogens. This process can be modelled in vitro, using yeast and bacterial antigens and a range of other stimuli including metabolites and vaccines. Intriguingly, it is becoming clear that inflammatory memory may not restricted to cells of the hematopoietic lineage. Indeed, limited experiments in mouse epithelial stem cells and human endothelial cells indicate a possible widespread phenomenon in response to inflammatory antigens. The establishment and maintenance of this memory is wired in the epigenome of the cell. Epigenetics' (literally 'above DNA') refers to the study of molecular interactions that influence chromosome structure and gene activity. A key property of many epigenetic marks is that they not only indicate the state of the cell at a set point in time, but can also carry 'memories' of past exposures, with the potential influence cellular responses to future stimuli. Therefore, the epigenome (the complete epigenetic profile of a cell) contains information about the 'past, present, and future' of a cell or tissue. In this project we apply a multi-omics approach to study inflammatory memory in purified human umbilical vein endothelial cells (HUVECs) and other human endothelial cell populations. This is an advanced laboratory-based project anticipated to lead to publications. It will involve cell culture, DNA/RNA extraction, chromatin immunoprecipitation and sequencing (ChIP-seq), RNA sequencing (RNA-seq) and bioinformatic analysis.

6. The same but different: Transcriptional responses to inflammatory stimuli in phenotypically discordant monozygotic twins

Professor Richard Saffery
T 83416341
E richard.saffery@mcri.edu.au
Professor David Burgner
T 99366730
E david.burgner@mcri.edu.au
Dr Boris Novakovic
T 83416341
E boris.novakovic@mcri.edu.au
Professor Jeff Craig
T 52278655
E jeffrey.craig@deakin.edu.au

Available as Masters Project: Yes

The term 'epigenetics' literally means 'above DNA' and refers to the study of molecular interactions that influence chromosome structure and gene activity. We can think of epigenetic marks as signals that determine whether a stretch of DNA is 'open for business' and accessible for regulatory factors or 'closed' and therefore inaccessible. A key property of many epigenetic marks is that they not only indicate the state of the cell at a set point in time, but can also carry 'memories' of past exposures, with the potential influence cellular responses to future stimuli. Therefore, the epigenome (the complete epigenetic profile of a cell) contains information about the 'past, present, and future' of a cell or tissue. Understanding the relative roles of genetic and environmental influence to epigenetic variation is important in many aspects of human health, particularly the immune system. Inflammation is a key outcome of the immune response to exogenous 'foreign' stimuli and is also a feature of excessive weight in children and adults. This project will examine the transcriptional response of purified blood monocytes to inflammatory stimuli in vitro in twins discordant for weight from birth to 6 years of age. As monozygotic twins are genetically identical, any differences in response will be directly attributable to cumulative environmental exposures, allowing the relative contribution of genes and environment to this important aspect of immune cell function to be directly assessed. The project will be laboratory-based and will involve will stimulating peripheral blood monocular cells and purified monocytes, profiling cytokine release and transcriptional response via single-cell RNAseq and bulk RNAseq. It is anticipated that the results will form the basis of a future publication.

7. Maximising the utility of clinical samples collected in pregnancy for population-based microbiome analysis at scale

Richard Saffery
T 83416341
E richard.saffery@mcri.edu.au

Melissa Wake
T 83416200
E melissa.wake@mcri.edu.au

Available as Masters Project: Yes

The rising prevalence of chronic conditions (such as obesity, cardiovascular disease, allergy, mental health) threatens to overwhelm health care systems internationally in coming decades. It is now clear that such conditions may have their origins even before birth, as a result of the environment experienced in utero. A key exposure that has yet to be assessed at scale is the maternal microbiome, passed from mother to child from birth. Current approaches to pregnancy research generally involve recruitment and targeted collection of biological samples (biosamples) in pregnancy specifically for research purposes, but this is time consuming and costly. The Generation Victoria (GenV) Initiative aims to do things differently. GenV will approach all 160,000 births in 2021/2022 to build one of the largest population-based cohorts internationally. In contrast to traditional research approaches, GenV will curate and store all routinely collected clinical samples in pregnancy, for later (post consent) application of state-of-the-art research methodologies. It is envisaged that this approach will revolutionise biobanking for pregnancy research internationally. This project focuses on the Group B Streptococcus (GBS) swab, collected at 36 weeks gestation. It will involve a literature review to evaluate previous testing of these swabs for microbiome profiling (both 16S and metagenomics) and also direct testing of clinical sample handling parameters (across Victoria Pathology providers) on the downstream microbiome data generated by sequencing technologies This project will provide a strong, evidence-based summary of the utility of GBS swabs collected in pregnancy for inclusion in the GenV Biorepository. It is anticipated that findings will form the basis of a publication.

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

Associate Professor Shireen Lamande
T 8341 6465
E shireen.lamande@mcri.edu.au

Professor John Bateman
E john.bateman@mcri.edu.au

Available as Masters Project: Yes

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

9. Immune system dysfunction and epigenetic deficits underpinning the development of food allergy in children

Prof Richard Saffery
T 83416341
E richard.saffery@mcri.edu.au
Dr Melanie Neeland
T 83416200
E Melanie.neeland@mcri.edu.au

Dr Boris Novakovic
T 83416200
E boris.novakovic@mcri.edu.au

Available as Masters Project: Yes

Allergic diseases such as food allergy are among the most common chronic inflammatory disorders, arising from a complex interplay between genetic risk and early life environment. Now recognized as a major public health concern, much is still unknown about the extent of immune system disruption and underlying molecular mechanisms associated with food allergy development. This knowledge gap needs to be addressed if novel interventions are to be effectively targeted to those most at risk at the most effective time. The incidence of food allergy is increasing at a rate greater than changes to the DNA sequence could allow, demonstrating the role of the modern environment to alter the development of the immune system, most likely through epigenetic reprogramming. We have recently described deficits in monocytes, T cells and B cells in children with food allergy, with recent evidence implicating innate immune cells, such as monocytes as the primary drivers of this condition. To date, no analyses have been performed to test the hypothesis that monocytes are inherently 'programmed' in children with food allergy. This project will define the trajectory of immune system dysfunction and epigenetic deficits underlying the development of food allergy, using T cells and monocytes collected from the VITALITY childhood allergy clinical trial. Techniques include cell sorting, in vitro culture, DNA/RNA extractions, qPCR and bioinformatics analysis. The results of this study will be included in future publications.

Clinical Science

10. What role does Bax paly during gonocyte transformation into spermatogonial stem cells?

Ruili Li
T 99366757
E ruili.li@mcri.edu.au

John Hutson
T 93455808
E john.hutson@rch.org.au

Available as Masters Project: Yes

Congenital undescended testis (UDT), or cryptorchidism, affects 2-4% of newborn boys and leads to a 5-10 fold increase in testicular cancer (seminoma), and 30-60% risk of infertility. Seminomas in young men with UDT arise from immature germ cells which failed in both transformation into spermatogonial stem cells (SSC) and apoptosis. We propose that persisting neonatal germ cells (gonocytes) are the results of gonocytes that failed to transform into SCC or failed to disappear by apoptosis. This study will use mouse model to examine the role of an apoptosis regulator, Bax, in removing persisting gonocytes from the testicular tubules so that they do not mutate into CIS cells and testicular seminomas after puberty. The study will involve use mouse flow cytometry immunohistochemistry with molecular markers and confocal microscopy.

11. Effect of congenital UDT on Gonocyte development

Ruili Li
T 99366757
E ruili.li@mcri.edu.au

John Hutson
T 93455805
E john.hutson@rch.org.au

Available as Masters Project: Yes

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 or human biopsies. The study will involve the use of flow cytometry, immunohistochemistry, confocal microscopy, PCR.

12. Characterising the genetic profile of gubernacular cells derived from androgen receptor knockout mice (ARKO) during testicular descent.

Dr. Gulcan Sarila
T 403468027
E gulcan.sarila@mcri.edu.au

Prof. John Hutson
E john.hutson@mcri.edu.au

Available as Masters Project: No

In rodents, the second phrase of testicular descent also known as the androgen dependent phase is completed within the first 2 weeks of neonatal development, whereas in humans this is finalised before birth and the testes move inside the scrotum. Androgen has been demonstrated to play an important role in remodelling the gubernaculum, however the exact molecular mechanism still remains controversial. While the morphological changes that take place during testicular descent have been previously described, very little is still known about the cellular targets of hormones, genes, signalling pathways and the effects of androgen. There has been two main ways in which AR results in cryptorchidism; 1) by the persistence of the mammary gland tissue in males that were treated with the pharmacological anti-androgen inhibitor which prevented the gubernaculum outgrowth, 2) by stimulating the role of AR-signalling in the genitofemoral nerve releasing calcitonin gene-related peptide (CGRP) This project will determine the genetic characteristics of the gubernacular cell derived from the androgen receptor knockout mice during the second phase of testicular decent. By creating and maintain cell lines in culture from these mice at the age of embryonic day 17 to day 3 post birth, we will profile the extracellular matrix genes as well as characterise the growth, elongation (mitosis and differentiation) of these cells in vitro. These cells will be compared to adipocytes isolated form the inguinoscrotal fat pad as they are a target tissue for androgen receptors. In addition, by using the CGRP drug we will determine if the molecular signature of the cells can be significantly altered during testicular descent. This study will provide essential evidence between androgen receptor, CGRP, and if we can potential use this as a treatment in children to trigger testicular decent.

13. Identification of blood markers of delayed concussion in children

A/Prof Vera Ignjatovic
T 99366520
E verai@unimelb.edu.au
Prof Vicki Anderson
E vicki.anderson@mcri.edu.au

Franz Babl
E franz.babl@rch.org.au

Available as Masters Project: No

Traumatic brain injury (TBI) is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force". Mild traumatic brain injury (mTBI) is one of the most common forms of TBI and accounts for one out of every 220 paediatric patients admitted to the emergency department within the United States, totalling approximately 144,000 patients per year on a national level and 18% of all paediatric head injury patients. An audit of children who attended the Royal Children's Hospital (RCH), Melbourne, Australia in 2004 for a head injury found that 90% of the patients were classified as a mTBI. While

most children improve within one week following a mTBI, there is growing consensus that symptoms can persist for up to one month in approximately 30% of patients, with approximately 40% of individuals remaining symptomatic 2 weeks post-injury. This differs significantly from that of adults, a population which sees most individuals recover within a 2 week period. These prolonged symptoms, which may include headaches, dizziness, difficulties concentrating, irritability, cognitive/emotional impairments, and behavioural difficulties carry the potential to develop into significant cognitive, academic and emotional-behavioural difficulties if left unchecked. The last decade has seen a progressive shift to blood proteome analysis as a means of assisting the determination of clinical diagnosis, prognosis and outcome in the setting of concussion. To date, very few studies have investigated the differential plasma protein expression following paediatric mTBI, and specifically the association of blood proteins with delayed clinical outcomes post-concussion in children. We have recently utilized the SWATH-MS analysis to assess changes in expression of up to 400 plasma proteins. This allowed for an unbiased discovery of proteins not yet implicated in concussion research. This project aims to utilize the complex proteomics SWATH-MS dataset to identify plasma proteins associated with delayed clinical outcomes post-concussion in children. Validation using ELISA and/or MS approach will be required.

14. Anatomical and physiological characterisation of the Fgf10-deficient mice during embryonic development

Associate Professor Warwick Teague
E warwick.teague@rch.org.au

Dr. Gulcan Sarila
E gulcan.sarila@mcri.edu.au

Available as Masters Project: No

Fibroblast Growth Factor 10 (Fgf10) is a protein coding gene, from the FGF family, known to play an important role in the regulation of embryonic development, cell differentiation and proliferation. FGF proteins bind to four Fgf receptors to initiate signalling events that mediate various biological functions in target cells, with Fgf receptor 1 and 2 (Fgfr1, -2) appearing to be the most common. In 30-50% of mice embryos with Fgf10/Fgfr2 genetic deletion results in a congenital obstruction of the duodenum known as duodenal atresia (DA). Fgf10-deficient mice also show impaired lung/trachea development, colonic atresia, absence of limb bud formation, cranio-facial anomalies and impaired wound healing. The cause of DA in humans is not known, however these findings, in addition to the genetic association of DA to trisomy 21, support a genetic aetiology for this disease. Despite numerous studies, the molecular mechanism of this genetic link still remains unclear, highlighting its unique and complex properties within different aspects of health and disease. This study will characterise the anatomical development of the Fgf10-deficient mice during embryogenesis (embryonic day E11.5 to 18.5) using immunohistochemical staining. Embryos derived from heterozygous Fgf10 mice will be embedded into paraffin and sectioned to generate a physiological atlas of the mice and to determine the presence/type of DA. We hypothesised that Fgf10-deficient mice with DA will display distinctive changes in the developmental and apoptotic signalling pathways, as well as a physical disruption of normal duodenal morphology. The project will yield key insights into the anatomy and physiology of the Fgf10-deficient mice impacting the design of new diagnostic and therapeutic options for DA.

Genetics

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

Doctor Katie Ayers
T 83416425
E andrew.sinclair@mcri.edu.au

Professor Andrew Sinclair
T 83416425
E andrew.sinclair@mcri.edu.au

Available as Masters Project: Yes

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

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

Professor Andrew Sinclair
T 83416425
E andrew.sinclair@mcri.edu.au

Dr Katie Ayers
T 83416425
E andrew.sinclair@mcri.edu.au

Available as Masters Project: Yes

Often the first question asked when a child is born is "is it a boy or a girl". Unfortunately, a definitive answer cannot be given to the parents of a child born with severe ambiguous genitalia. These cases occur with a frequency of 1 in 4500 births and are part of a large spectrum of disorders known as Disorders/Differences of Sex Development (DSD), which are caused by mutations in the genes that regulate how the testis or ovaries develop and function. Yet, less than 50% of patients with DSD currently receive a clinical genetic diagnosis, due to a poor understanding of the genes that can cause DSDs. This project will use genomic technologies such as Whole Exome Sequencing and targeted microarrays to

find novel candidate genes that may cause DSDs. In this project, you will analyse DSD patient sequencing data for potential pathogenic gene variants in an effort to identify novel candidate genes. These genes will then be validated using lab technologies such as immunofluorescence staining on embryonic gonads and qRT-PCR. This work will uncover novel genes that contribute to DSD in humans and improve diagnosis rates for patients with these difficult disorders.

17. What are the functional consequences of CDKL5 dysregulation in patient derived neuronal cells?

Dr Nicole Van Bergen
E nicole.vanbergen@mcri.edu.au

Prof. John Christodoulou
E john.christodoulou@mcri.edu.au

Available as Masters Project: Yes

The Cyclin-Dependent Kinase-like 5 (CDKL5) protein is critical for neuronal function and differentiation. CDKL5 Deficiency Disorder (CDD) is an X-linked developmental encephalopathy that results in early onset and difficult to control seizures and severe neurodevelopmental impairment, leading to lifelong disability. The CDKL5 protein is expressed in the brain, predominantly in neurons and regulates key phosphorylation events that in turn regulate cell proliferation, neuronal maturation, synaptic activity, neuronal network function and the movement of subcellular cargo in neurons. This project will contribute to our investigations on the critical role of the mammalian CDKL5 protein in neurons. CDKL5 is a kinase that regulates key phosphorylation events on many proteins. Some recently identified targets of CDKL5 in neuronal cells include microtubule proteins, however only a few targets have been discovered, leaving many potential targets yet to be identified. The phosphorylational regulation of microtubules is very important as it will affect neuronal maturation, synaptic activity, and neuronal network function and the movement of subcellular cargo in neurons. This project will validate potential new targets regulated by CDKL5. These targets will be validated using complementary in vitro techniques. We will validate potential CDKL5 targets using a combination of standard biochemical and molecular biology techniques including, but not limited to cell culture, qPCR, SDS-PAGE immunoblotting, phospho-specific western blotting, cloning, co-immunoprecipitation, immunofluorescence and enzyme assays. We will identify key pathways regulated by CDKL5 and which will improve our understanding of how this kinase regulates synaptic activity in brain-like neural networks. This project will for the first time provide a comprehensive and detailed understanding of the CDKL5 kinase in neuronal cell biology. Our project will provide future opportunities for drug design and therapeutics targeting kinase activity.

18. NAXD deficiency: unravelling the pathological consequences, and evaluation of therapeutic opportunities

Dr Nicole Van Bergen
E nicole.vanbergen@mcri.edu.au

Prof. John Christodoulou
E john.christodoulou@mcri.edu.au

Available as Masters Project: Yes

There are major gaps in our basic understanding of the inborn error of metabolism, NAXD deficiency, and no specific treatments are available. It is likely that disruption of core metabolic processes including ATP synthesis, the Krebs cycle and other pathways could be aggravated by intercurrent illnesses and challenge an already compromised energetic state. Our research team focuses on uncovering the molecular basis of undiagnosed childhood brain disorders using genomic sequencing. We have recently identified mutations in a new gene called NAXD in young children who were born healthy and developed normally until a febrile episode or common infection triggered failure of the metabolite repair system associated with NAXD. All of these children died rapidly during such an episode. We have shown that mitochondrial energy production was severely compromised in skin cells from these children and was associated with a vast accumulation of damaged metabolites. Prior to our discovery, mutations in this gene had never been described before in humans. This work was published in Brain in January 2019. We will utilise a number of techniques to investigate mitochondrial impairment including, but not limited to cell culture, mitochondrial inhibition assays, mitochondrial enzyme activities and respiration, protein expression, gene expression, metabolite extraction and analysis and proteomics. There is scope to expand this project from an Honours to a Masters project by the inclusion of stem cell modelling for screening of potential therapeutic agents for NAXD deficiency, using patient-derived and gene-corrected iPSC for differentiation into relevant cell types for NAXD deficiency. This research proposal will enhance our understanding of this new genetic disorder by uncovering molecular pathways perturbed by loss of gene function, and may provide an understanding of therapeutic targets to protect the brain when children with gene mutations suffer febrile illnesses that would otherwise overload the repair system.

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

Associate Professor Paul Lockhart
T 03 8341 6322
E paul.lockhart@mcri.edu.au

Dr Sarah Stephenson
E sarah.stephenson@mcri.edu.au

Available as Masters Project: Yes

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

seizures of TSC originate in dysplastic lesions known as cortical tubers. Tubers are well circumscribed and are characterised by disorganised cortical lamination and abnormal cells including dysmorphic neurons and balloon or giant cells. Our recent experience with modelling tuber microstructure using ultra-high field (16.4T) ex vivo diffusion MRI acquired from the resected tuber specimens also plausibly demonstrated localisation of dyslaminated cortex and dysmorphic neurons in the tuber centre. This suggests that it is the tuber centre that is likely to contain the highest density of dysmorphic neurons. We have qualitative data from visual analysis of tubers using routine histopathological techniques to support this, however neither we nor any other group have systematically tested this hypothesis by quantitative analysis of the density of dysmorphic neurons in various regions of a tuber. In this project, the candidate will use immunostaining and stereological techniques to determine the gradient density of dysmorphic neurons in resected tuber tissues. These histology findings will be combined with our ultra-high field ex vivo diffusion MRI data to create a 3D reconstruction of tubers.

20. Using cerebral organoids for the study of tuberous sclerosis complex

Associate Professor Paul Lockhart
T 61383416322
E paul.lockhart@mcri.edu.au

Doctor Sarah Stephenson
T 61399366563
E sarah.stephenson@mcri.edu.au

Available as Masters Project: Yes

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

21. Application of multi-omic approaches to identify the genetic bases of disorders of mitochondrial oxidative phosphorylation.

Professor John Christodoulou
T 9936 6516
E john.christodoulou@mcri.edu.au
Professor David Thorburn
E david.thorburn@mcri.edu.au
Dr Alison Compton
E alison.compton@mcri.edu.au

Available as Masters Project: No

Although individually rare, as a group, the disorders of mitochondrial oxidative phosphorylation (OXPHOS) are the most common inherited metabolic disorders, with more than 300 distinct monogenic disorders now identified. Whilst genomic sequencing technologies have greatly improved the genetic diagnosis of this complex group of disorders, many cases remain unsolved, as exemplified by the Australian Genomics Health Alliance Mitochondrial Flagship patient cohort. In this group of patients, analysis of known mitochondrial disease genes has resulted in a diagnostic yield of ~ 45% so far. For some of those unsolved cases, candidate disease genes have been identified that need to be functionally validated, whereas in other cases genomic sequencing has failed to identify plausible targets. These unsolved cases will be tackled in this project. A combination of state-of-the-art technologies will be employed to identify candidate disease genes, including where appropriate whole genome sequencing, transcriptomic and quantitative proteomic studies, followed by a range of cell and/or tissue-based functional studies to validate their pathogenic significance. This combination of approaches will allow us to reach a definitive diagnosis for a significant proportion of patients who are currently missed by initial genomic sequencing approaches. For some, this may point to a targeted therapy and for all will restore reproductive confidence in their parents.

22. Modulation of toxic alpha synuclein in vivo

Paul Lockhart
T 83416322
E paul.lockhart@mcri.edu.au
Sarah Stephenson
T 99366563
E sarah.stephenson@mcri.edu.au
Yujng Gao
T 99366563
E yujing.gao@mcri.edu.au

Available as Masters Project: Yes

Parkinson's disease (PD) is a neurodegenerative disorder with a complex aetiology and progression. Mutations in the parkin gene are the most common cause of early onset-PD. Pathologically PD is characterised by loss of dopamine producing neurons and Lewy bodies composed of aggregated of alpha-synuclein. This has led to the hypothesis that reducing alpha-synuclein burden within cells may slow or halt disease progression. We have generated several novel Parkinson's disease mouse strains within our laboratory including knockout of causative disease genes parkin (with and without parkin's coregulated partner

PACRG) and Rab39b. We are interested in understanding the mechanisms by which disease associated genes modulate alpha-synuclein within the brain. We hypothesise that genes that cause Parkinson's disease by loss of functional protein play a key role in eliminating toxic proteins such as alpha-synuclein from within the brain. Failure of their function results in the accumulation of toxic proteins and results in the development of PD. We have recently aged a number of unique cohorts that are dysregulated for multiple combinations of parkin/PACRG/Rab39B/alpha-synuclein in the laboratory. These will be characterised for markers of altered neuropathology, biochemistry and correlated with behaviour data already obtained.

23. Investigating the molecular basis of Parkinson's Disease using novel stem cell models

Associate Professor Paul Lockhart
T 83416322
E paul.lockahrt@mcri.edu.au

Dr Yujing Gao
E yujing.gao@mcri.edu.au

Available as Masters Project: Yes

Parkinson's disease is a prevalent neurodegenerative disorder with largely unknown cause. However, recent advancements in genomic technologies have led to the identification of over 20 genes to be causative of around 10% of Parkinson's disease cases. The key neuropathological features of Parkinson's disease include a loss of dopamine producing neurons and the presence of alpha-synuclein containing protein aggregates in surviving neurons. We recently identified RAB39B as a novel gene for Parkinson's disease. RAB39B has a putative function in intracellular trafficking, and we hypothesise that it plays a role in the regulation of alpha-synuclein. The aim of this project is to characterise the function of RAB39B and investigate its role in the pathogenic mechanisms underlying Parkinson's disease. Studies will utilise newly developed and unique induced pluripotent stem cell models to perform preclinical studies to characterise the disease process and identify potential therapeutic targets. The primary techniques to be utilised in this project will include stem cell maintenance and differentiation into neurons, and various molecular and cell biology assays.

24. Investigating the molecular basis of Parkinson's Disease using novel mouse models

Associate Professor Paul Lockhart
T 83416322
E paul.lockhart@mcri.edu.au

Dr Yujing Gao
E yujing.gao@mcri.edu.au

Available as Masters Project: Yes

Parkinson's disease is a prevalent neurodegenerative disorder with largely unknown cause. However, recent advancements in genomic technologies have led to the identification of over 20 genes to be causative of around 10% of Parkinson's disease cases. The key

neuropathological features of Parkinson's disease include a loss of dopamine producing neurons and the presence of alpha-synuclein containing protein aggregates in surviving neurons. We recently identified RAB39B as a novel gene for Parkinson's disease. RAB39B has a putative function in intracellular trafficking, and we hypothesise that it plays a role in the regulation of alpha-synuclein. The aim of this project is to characterise the function of RAB39B and investigate its role in the pathogenic mechanisms underlying Parkinson's disease. Studies will utilise newly developed and unique mouse models with mutations in RAB39B to perform preclinical studies to characterise disease processes and identify potential therapeutic targets. The primary techniques to be utilised in this project will include mouse handling, behavioral testing and various molecular and cell biology assays.

25. Understanding the molecular basis of CANVAS, a novel neurological disorder caused by an expanded repeat

Associate Professor paul.lockhart
T 83416322
E paul.lockhart@mcri.edu.au

Professor Martin delatycki
T 83416293
E martin.delatycki@vcgs.org.au

Available as Masters Project: Yes

Repeat expansions cause over twenty neurogenetic disorders of major clinical significance which can present with heterogenous, overlapping clinical phenotypes. Discovery of novel expansions and diagnostic testing of known loci has proven extremely challenging due to the repeat sequences being refractory to standard molecular techniques. We recently determined that a novel intronic pentanucleotide repeat expansion on chromosome 4 causes the neurogenetic disorder termed cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). Our preliminary studies suggest the expansion is the most common genetic cause of ataxia in humans. This project will characterise the causal expansion repeat using short read and long read gene Next Generation sequencing technologies. It will investigate pathogenic mechanisms underlying disease utilising molecular and cell biology techniques, including primary cell and induced pluripotent stem cell generation and characterisation. The candidate will also contribute to the gene discovery component of an ongoing trial testing the diagnostic utility of expansion repeat detection in next generation sequencing data.

26. Novel molecular and clinical aspects of FMR1 in fragile X syndrome with implications for patient management

Associate Professor David Godler
E david.godler@mcri.edu.au
Dr Emma Baker
E emma.baker@mcri.edu.au

Professor David Amor
E david.amor@mcri.edu.au

Available as Masters Project: Yes

Fragile X syndrome (FXS) is a common single gene cause of intellectual disability (ID) and autism spectrum disorder (ASD) features, caused by loss of FMR1 protein (FMRP). FMRP is essential for normal synaptic function and neurodevelopment. While loss of FMRP is thought to be primarily responsible for the FXS phenotype, another gene transcribed in the opposing direction to FMR1, called antisense FMR1 (ASFMR1), may also contribute to the FXS phenotype, but to date, the role of ASFMR1 has not been thoroughly studied. Over the past 5 years an international study called FREE FX has been led by our team at MCRI. The FREE FX study aims to better characterize the molecular basis of FXS presentations and the variability between affected individuals. To date, more than 130 participants with FXS have been recruited and assessed with a number of neuropsychological assessments and novel experimental methods. Extensive behavioural and parent-reported medical history data, as well as bio-specimens including DNA, RNA and protein lysates have been collected from various tissue types for most participants. Genetic and genomic state-of-the-art technologies have also been developed to accurately detect changes at epigenetic (DNA methylation), RNA and protein levels. This honours project will utilise many of the developed technologies, the vast collection of bio-specimens and clinical data, to characterize the relationship between FMR1 mRNA, FMRP and abnormal ASFMR1 expression with epigenetic and clinical changes in FXS males and females. The primary project outcome will be characterization of the distinct and overlapping molecular pathways associated with ID and ASD features in FXS. This will result in better understanding of the molecular basis of Fragile X related disorders, and will lead to further validation of our prognostic biomarkers, with the potential to improve clinical practice through earlier diagnosis and better prognosis.

27. Peripheral UBE3A expression as a predictor of the clinical phenotype in Angelman Syndrome

Dr Emma Baker
E emma.baker@mcri.edu.au
Professor David Amor
E david.amor@mcri.edu.au

Associate Professor David Godler
E david.godler@mcri.edu.au

Available as Masters Project: Yes

Angelman Syndrome (AS) is characterised by varying degrees of intellectual disability (ID), autism ASD traits, severe seizures, motor and sleep problems. AS is caused by severe reduction in the expression of UBE3A in the brain. Despite the systemic pattern of reduction

of UBE3A in AS, much research has been focused on the central nervous system, in animal models. Until now, comprehensive analysis of UBE3A expression in peripheral tissues and different clinical phenotypes have not been performed in humans. Over the past 3 years our team at MCRI has led a study that aims to better characterise the molecular basis of AS presentations and the variability between affected individuals. Thirty participants with AS have been recruited and assessed with a number of neuropsychological assessments as well as novel experimental methods. Extensive behavioural and parent-reported medical history data, as well as bio-specimens including DNA, RNA and protein lysates have been collected from various tissue types for most participants. Genetic and genomic state-of-the-art technologies have also been developed to accurately detect changes at epigenetic, RNA and protein levels. This honours project will utilise many of the developed technologies and clinical data to characterise relationships between UBE3A expression with objective assessments of developmental functioning, autism traits, and sleep problems. Twenty new patients will be recruited and assessed as part of this project. Additionally, patients who have previously been involved in our studies will be recontacted to undertake further assessment. This additional time-point will help us to better define relationships between the neurodevelopmental and epigenetic trajectories in individuals with AS. This study will provide an indication of the associations between UBE3A molecular changes and clinical phenotypes of AS, to assist in better understanding disease natural history. The findings may also have implications for patient stratification in clinical trials aimed at improving outcomes for AS individuals.

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

Associate Professor Paul Lockhart
T 61383416322
E paul.lockhart@mcri.edu.au

Dr Kiymet Bozaoglu
E kiymet.bozaoglu@mcri.edu.au

Available as Masters Project: Yes

Autism Spectrum Disorder (ASD) is a complex and highly heritable neurodevelopmental disorder defined by deficits in social communication and repetitive behaviours with restricted interests. Over 300,000 Australians have ASD and the annual national economic cost is ~$9.7 billion. Whilst there have been many studies that have identified variants which are predicted to predispose to ASD, the challenge is to unravel which variants are truly contributing to the phenotype and the mechanisms by which they do so. Therefore a key requirement for understanding disease pathogenesis is the development of models that recapitulate the disease enabling key insights into basic underlying mechanisms. ASD has a heritability estimate of 50% which means and therefore family studies are important in understanding the mechanisms of ASD. To this effort, we collect and analyse samples from extended families that have autism. These families are multigenerational and consist of grandparents, parents, children, aunts, uncles and cousins. We perform high throughput genetic screens to identify candidate genes associated with the disorder. This project will focus on characterising the function of candidate genes identified from these families at a molecular level to understand how they contribute to ASD. Techniques will include differentiation of stem cells into brain cells (neuron and glial cells) and manipulating the cells using various drug treatments to determine ASD pathogenesis. Specific techniques that

will be used include stem cell tissue culture, real time PCR, western blot, immunofluorescence, enzyme activity assays.

29. Understanding the molecular mechanisms of autism using human NF1 stem cell derived neuronal networks

Dr Kiymet Bozaoglu
T +61 3 9936 6563
E kiymet.bozaoglu@mcri.edu.au

Associate Professor Paul Lockhart
T 61383416322
E paul.lockhart@mcri.edu.au

Available as Masters Project: Yes

Autism (or autism spectrum disorder; ASD) is a neurodevelopmental disorder characterised by debilitating impairments in social communication and restricted interests and repetitive behaviours. In most cases, the cause of autism is unknown and because of this, there are no effective treatments for autism in the general population. However, in some cases, autism occurs because of a known genetic cause. This is the case in children with neurofibromatosis type 1 (NF1), an autosomal dominant disorder caused by a loss-of-function mutation in the NF1 gene. Research estimates that 25% of individuals with NF1 have autism and many more have autism-like features that are clinically impairing. Given that the cause of autism in NF1 is known, we are in the position to understand how the genetic mutation results in changes in the way the brain develops and functions, and causes autism. This project will use human preclinical models to characterise the neuronal deficits in individuals with NF1. The proposed study will be the first to use human stem cell-derived brain cell networks (comprising neurons and glia) to examine the effects of NF1 mutations on neuronal development, determine how well they connect together in networks and whether they are able to function efficiently. Various drugs targeting specific pathways important in NF1 will also be used in the stem cell derived neuronal networks to determine whether they can reverse the biological abnormality in these cells Some of the techniques that will be used include stem cell culturing, differentiation of stem cells into brain cells, confocal microscopy, network activity assays, drug screening techniques, real time PCR and western blot analysis.

30. Pluripotent stem cell models of mitochondrial disease

Dr Ann Frazier
T 9936 6602
E ann.frazier@mcri.edu.au

Prof David Thorburn
E david.thorburn@mcri.edu.au

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 child is born with a mitochondrial disorder. Many of these children die in the first years of life and most suffer from severe disease, particularly affecting their brain and/or heart. Access to these tissues from patients is limited, making it difficult to assess the impact on mitochondrial and other pathways contributing to disease pathology. This project will involve the generation and characterization of human

pluripotent stem cell models of mitochondrial energy generation disorders. These models include human Embryonic Stem Cells (hESCs) with knockout-type mutations generated by CRISPR/Cas9 gene editing in genes known to cause mitochondrial disease, and human Induced Pluripotent Stem Cells (iPSCs) generated from mitochondrial disease patient cell lines. These pluripotent cell lines can then be differentiated into cardiac and neural cell lineages relevant to mitochondrial disease, thus enabling the study of the phenotypic rescue of novel defects, disease pathogenicity and treatment approaches. The project aims are: 1) Characterize pathogenic pathways in relevant cell lineages by assessing the impact of OXPHOS (energy generation) defects on the mitochondrial and cellular proteome of cardiomyocytes and neural cells generated from hESCs or iPSCs, as well as the impact on mitochondrial function and cellular physiology. 3) Define the impact of targeted therapeutic strategies in these models on the cellular proteome and other markers of cellular homeostasis. In this research project, the hESCs generated by CRISPR/Cas9 mediated gene disruption, or iPCs from mitochondrial disease patient fibroblasts, will be validated as mitochondrial disease models, followed by confirmation of the impact on the targeted gene and pathway. Selected cell lines will then be differentiated to cardiomyocyte and/or neural lineages to enable comparison (with control cells) of the impact of the gene knockout on various aspects of mitochondrial and cellular function. These may include respiration, ATP synthesis, reactive oxygen species, mitochondrial membrane potential, redox balance, cellular stress response and quantitative proteomics.

31. Mitochondrial disease caused by ATAD3 rearrangments: Unravelling the complexity

Dr Ann Frazier
T 03 9936 6602
E ann.frazier@mcri.edu.au

Prof David Thorburn
E david.thorburn@mcri.edu.au

Available as Masters Project: Yes

Mitochondria are our cellular power plants that burn sugars, fats and proteins to generate energy. Mutations in genes affecting mitochondrial energy generation and function can lead to mitochondrial disease. These diseases are both genetically and clinically heterogenous, with nearly 300 genes now known to cause mitochondrial disease. We and others have identified mutations in the ATAD3 gene cluster as causing mitochondrial diseases with a wide range of clinical severity. The ATAD3 gene locus encodes 3 highly homologous proteins and arose via tandem duplication events. Only hominids have three ATAD3 genes, with other multicellular organisms carrying only a single copy. Due to the high sequence homology and complexity within the locus, many of the disease causing mutations identified so far have included complicated structural genomic rearrangements, such as deletions, duplications and gene conversions. While ATAD3 is implicated in cellular cholesterol and mitochondrial DNA homeostasis, the precise molecular function of ATAD3 within mitochondria is not well resolved. Furthermore, little is known about why hominids have 3 ATAD3 genes and whether they are functionally redundant. This project will therefore utilize a range of molecular biology, cell biology and biochemical techniques to evaluate the individual ATAD3s and their contribution to cellular and mitochondrial functions. Investigations will include measurement of ATAD3 ATPase activities, generation and

characterization of knock-out cell lines using CRISPR/Cas9 gene editing and complementation with stably expressed ATAD3s, use of "Long Read" DNA Sequencing technologies and assessment of ATAD3 protein complexes.

Infection and Immunity

32. Characterisation of rotavirus strains emerging in the vaccine era

Professor Julie Bines
T 9345 4107
E jebines@unimelb.edu.au

Dr Celeste Donato
E celeste.donato@mcri.edu.au

Available as Masters Project: No

Rotaviruses are the most common cause of severe diarrhoea in young children worldwide. To reduce this burden of disease, the rotavirus vaccines, Rotarix and RotaTeq, have been introduced in the National Immunisation Programs of 100 countries. Both vaccines were included in the Australian National Immunisation Programs on 1 July 2007, and vaccine coverage of 84% has been achieved leading to a significant reduction in children ≤5 years of age hospitalised with acute gastroenteritis. The high vaccine coverage in the Australian paediatric population and resulting herd immunity may impact the diversity of rotavirus strains circulating in the community, driving the evolution of vaccine-escape strains, which may reduce the long-term effectiveness of the vaccination program. The Australian Rotavirus Surveillance Program has monitored rotavirus strains causing hospitalisation across Australia for over 20 years. We have observed several changes in the diversity of rotavirus strains in the decade following vaccine introduction; which is suggestive of a vaccine-derived effect at the population level. The Northern Territory, Western Australia, New South Wales and South Australia have experienced rotavirus outbreaks occurring in vaccinated and unvaccinated children, and the elderly, where rates of rotavirus disease approached those reported in the pre-vaccine era. The aim of this project is to characterise these emerging rotavirus strains and understand their evolution in context of global rotavirus isolates. This project will combine both laboratory experiments and bioinformatics analysis. The methods utilised in this project will include RT-PCR, generating libraries for Next Generation Sequencing, computational pipelines for genome assemblies, phylogenetic analysis, and Bayesian analysis, to describe the evolution of these emerging strains. This project will provide a unique insight into the diversity of strains circulating in the vaccine-era and support efforts to maintain an effective immunisation program.

33. Common infections in children and the risk of cardiovascular disease - a role for innate immune memory?

Professor David Burgner
T 399366730
E david.burgner@mcri.edu.au

Dr Siroon Bekkering
E siroon.bekkering@mcri.edu.au

Dr Melanie Neeland
T 383416493
E melanie.neeland@mcri.edu.au

Professor Richard Saffery
T 383416341
E richard.saffery@mcri.edu.au

Available as Masters Project: Yes

Cardiovascular disease is the leading cause of death in adults, but the underlying cause - 'hardening of the arteries' (atherosclerosis) - begins in childhood. Inflammation, a normal response to infection, may contribute to atherosclerosis. Infections are common and severe childhood infections predict adult cardiovascular disease. In a unique study (VASCular changes aFter INfectious Diseases, VASCFIND), we are currently measuring early cardiovascular changes in children with recent severe infection. We hypothesize that children will show adverse cardiovascular changes after infection compared to healthy controls. These will be correlated with changes in the innate immune response. In this project, we will measure the innate immune response of isolated and cryopreserved peripheral blood mononuclear cells samples from these children at several timepoints following infection to investigate if previous infection induces an 'immune memory' resulting in increased inflammation compared to controls. We will compare viral with bacterial infections and gram-positive vs gram-negative bacteria. This project is appropriate for students with an interest in translational science, molecular biology, infection and immunology - using techniques such as flow cytometry, monocyte isolation and culture as well as ELISA, chromatin immune-precipitation (ChIP), DNA and RNA extraction and real-time PCR. Training will be given, but some laboratory experience, interest and aptitude would be beneficial.

34. Inflammation in pregnancy and the induction of innate immune memory (as underlying mechanism of cardiovascular risk in adulthood)

Professor David Burgner
T 399366730
E david.burgner@mcri.edu.au
Dr Siroon Bekkering
E siroon.bekkering@mcri.edu.au
Dr Melanie Neeland
T 383416493
E melanie.neeland@mcri.edu.au
Professor Richard Saffery
T 383416341
E richard.saffery@mcri.edu.au

Available as Masters Project: Yes

Cardiovascular disease, the leading cause of death in adults, is associated with systemic inflammation and is primarily caused by atherosclerosis (hardening of the arteries). The process to atherosclerosis begins before birth and develops over decades into adulthood. The American Heart Association has stated that with early prevention, cardiovascular disease is "largely preventable". However, despite this, early life has been largely overlooked as an opportunity for prevention. This is particularly relevant to preterm infants, who are at increased cardiovascular risk as adults, through largely unclear mechanisms. This project investigates how inflammation in pregnancy (associated with chorioamnionitis) could contribute to the early development of atherosclerosis by activating early immune responses. We will compare cells from preterm infants whose pregnancies were complicated by chorioamnionitis with matched healthy births. The inflammatory phenotype of cryopreserved cord blood mononuclear cells (CBMCs) and 18-month peripheral blood mononuclear cells (PBMCs) will be examined by flow cytometry, ex vivo stimulation assays and RNA sequencing. In the event of differences in any of these processes, we will use Chromatin Immunoprecipitation followed by sequencing to study the long term epigenetic changes underlying the observed phenotypic differences. This project is appropriate for

students with an interest in translational science, molecular biology and immunology - using techniques such as flow cytometry, monocyte isolation and culture, ELISA, chromatin immune-precipitation (ChIP), DNA and RNA extraction and real-time PCR. Training will be given, but some laboratory experience, interest and aptitude would be beneficial.

35. Development and validation of qPCR RNA testing for E. coli, K. pneumoniae and S. epidermidis

Dr Amanda Gwee
T 9345 5522
E amanda.gwee@rch.org.au

Prof Nigel Curtis
E nigel.curtis@rch.org.au

Available as Masters Project: Yes

Bacteraemia is associated with significant morbidity and mortality in children. The gold standard diagnostic test for isolation of bacteria from blood is a blood culture. However, there are numerous limitations to blood cultures: 1. the sensitivity depends on the volume of blood taken; 2. it takes between 24 to 48 hours to identify the bacteria; 3. the amount of bacteria present cannot be quantified. We aim to develop and validate a qPCR RNA test for E. coli, K. pneumoniae and S. epidermidis that will be used to quantify the bacterial load on a small volume of blood. This test will enable us to determine the rate of decline in the bacterial load with current recommended antibiotic doses. Thus, we will be able to compare effectiveness of antibiotic treatment and whether treatment can be optimised.

36. Characterising the immune response to RSV in preterm and term infants

A/Prof Paul Licciardi
E paul.licciardi@mcri.edu.au

Dr Lien Anh Ha Do
E lienanhha.do@mcri.edu.au

Available as Masters Project: Yes

Respiratory syncytial virus (RSV) is the most common viral pathogen associated with acute lower respiratory tract infection in children. Globally, RSV affects 33 million children and causes 60,000 in-hospital deaths in children under 5 years of age each year, with severe infection more likely to occur in preterm infants. The increased susceptibility to RSV among preterm infants is thought to be due to immaturity of the immune system. Using a cohort of preterm and term infant cord blood samples, we aim to characterise their immune response profiles by using a combination of cell culture, flow cytometry and multiplex cytokine assays. This data will provide important insights into the immunological susceptibility to severe RSV during early life with the promise of developing more targeted approaches to protect this vulnerable group of infants.

37. HPV immunity as markers of protection against infection

Dr Zheng Quan Toh
E zheng,quantoh@mcri.edu.au

A/Prof Paul Licciardi
E paul.licciardi@mcri.edu.au

Available as Masters Project: Yes

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

38. Streptococcal transmission and disease

A/Prof Catherine Satzke
T 03 8341 6438
E catherine.satzke@mcri.edu.au

Prof Andrew Steer
E Andrew.Steer@rch.org.au

Dr Jonathan Jacobson
E jonathan.jacobson@mcri.edu.au

Available as Masters Project: Yes

The bacterium Streptococcus pyogenes (group A streptococcus, "Strep A") causes a range of mild to severe infections, ranging from sore throat to streptococcal toxic shock syndrome. Importantly, S. pyogenes infections can lead to serious sequelae such as rheumatic fever and rheumatic heart disease. S. pyogenes can also colonise a variety of human tissues including the upper respiratory tract and skin in healthy people. In a related bacterial species, Streptococcus pneumoniae, we have shown that viral co-infection can enhance bacterial virulence by increasing bacterial density and inflammation in the host, and by driving changes in expression of bacterial virulence genes. There is recent clinical epidemiologic evidence that viruses are also important in S. pyogenes pathogenesis, but little is known about this process. In this project, you will use a murine model of S. pyogenes colonisation to examine the effect of viruses on S. pyogenes colonisation, including for transmission (spread to co-housed littermates) and disease, and the mechanisms involved. To achieve these aims, a range of methods will be employed including animal and tissue handling, immunological assays, traditional microbiology and molecular approaches such as qPCR, and gene expression analyses. Your project will provide important novel data on key components of S. pyogenes pathogenesis, and inform a pathway towards improving strategies for preventing S. pyogenes infections.

39. Pathogenesis of pneumococcal pneumonia

A/Prof Catherine Satzke
T 03 8341 6438
E catherine.satzke@mcri.edu.au
Dr Jonathan Jacobson
E jonathan.jacobson@mcri.edu.au

Prof Sarath Ranganathan
E Sarath.Ranganathan@rch.org.au

Available as Masters Project: Yes

Streptococcus pneumoniae (the pneumococcus) is the most common cause of community-acquired pneumonia and a leading killer of children world-wide. However, it is also commonly found as an asymptomatic coloniser of the upper respiratory tract, particularly in children. We are interested in elucidating the molecular processes by which the pneumococcus can transition from the carriage to infection state, and identifying signals of pneumococcal pneumonia. Previous work in our laboratory using clinical samples collected from children in The Gambia, West Africa, hospitalised with pneumonia has identified several pneumococcal genes that were upregulated in the lung. Recently, we have collected clinical samples from children with severe pneumonia at the Royal Children's Hospital. Your project aims will be to examine pneumococcal gene expression in samples collected from pneumonia patients at the Royal Children's Hospital, and elucidate the role of several candidate genes in pneumococcal pneumonia. To do this, you will use a variety of approaches including measurement of gene and/or protein expression (using methods such as qRT-PCR, RNA-seq, western blotting, and ELISA) and analysing their importance through genetic manipulation of pneumococci and functional assays. Access to clinical samples such as pleural fluid provides the unique opportunity to examine pneumococcal gene expression during pneumonia. This project will provide exciting new data on the pathogenesis of pneumococcal pneumonia.

40. Understanding the importance of variation in the capsular polysaccharide of Streptococcus pneumoniae

Associate Professor Catherine Satzke
E catherine.satzke@mcri.edu.au

Dr Sam Manna
E sam.manna@mcri.edu.au

Available as Masters Project: Yes

Streptococcus pneumoniae (the pneumococcus) is a leading cause of morbidity and mortality worldwide. Over 90 immunologically-distinct serotypes are known, defined by their unique capsular polysaccharide. Decisions around which serotypes are included in licensed vaccines have largely been based on data from high-income countries. These vaccines have subsequently been introduced into low and middle-income countries (LMICs), where limited local information on serotype prevalence and diversity is often available. Using DNA microarray, we have identified pneumococci from LMICs with significant genetic variation in the capsule locus. Some of this variation is predicted to change the capsule structure, indicating there is potential for undiscovered serotypes and/or the misidentification of existing serotypes. This project will focus on the identification and

characterisation of these variants. This includes the molecular basis of the variation and potential for mistyping, and also the relevance of such changes to the capsule on pneumococcal pathogenesis. Key approaches to this project include: genetic manipulation of pneumococcal isolates, experiments with DNA and RNA, capsular typing of pneumococcal isolates as well as conducting functional assays in vitro. Your work in helping us uncover these novel variants (and potentially new serotypes) will allow us to improve serological and molecular tools for their detection, which will be vital for accurately assessing vaccine impact and serotype replacement globally.

41. Synergistic and antagonistic interplay between Streptococcus pneumoniae and respiratory viruses

Associate Professor Catherine Satzke
E catherine.satzke@mcri.edu.au

Dr Sam Manna
E sam.manna@mcri.edu.au

Available as Masters Project: Yes

The contribution of bacterial-viral co-infections to the onset and severity of disease is increasingly attracting interest from researchers globally. Specifically, it is well established that co-infections of Streptococcus pneumoniae with respiratory viruses (e.g. Influenza or Respiratory Syncytial Virus) impact the severity of acute respiratory infections. This is because viral replication creates a more hospitable environment for pathogenic bacteria of the respiratory tract to flourish, predisposing individuals to a bacterial superinfection. However, recent research has found that the interplay between pneumococci and viruses is more complex than previously anticipated. We and others have shown that some aspects of co-infection are synergistic (resulting in greater disease severity), while others are antagonistic, where the presence of one pathogen negatively impacts the other. In this project, you will elucidate the underlying microbiological and/or immunological mechanisms that govern the synergistic and antagonistic aspects of the interplay between pneumococci and respiratory viruses. Key approaches to this project include: working with in vivo models as well as microbiological and immunological analysis of tissues from the respiratory tract. Your work will help us understand the complexities of pneumococcal-viral co-infection, including their implications for the effectiveness of vaccines targeting these pathogens.

42. Immunological responses following pneumococcal conjugate vaccination

A/Prof Paul Licciardi
E paul.licciardi@mcri.edu.au

Prof Kim Mulholland
E kim.mulholland@lshtm.ac.uk

Dr Dan Pellicci
E dan.pellicci@mcri.edu.au

Available as Masters Project: Yes

Pneumococcal diseases such as pneumonia, meningitis and sepsis are the biggest killers of children under 5 years of age worldwide, mostly in low- and middle-income countries (LMICs). There are two currently licensed pneumococcal conjugate vaccines (PCVs), PCV10 (Synflorix®, GlaxoSmithKline) and PCV13 (Prevnar-13®, Pfizer). As these are expensive

vaccines, there has been an emphasis on PCV schedules with reduced numbers of doses that rely more on herd immunity, mediated by reduction in carriage, rather than individual protection. However, the immunological determinants of long-term protection against pneumococcal carriage are poorly understood. In Vietnam, we are currently undertaking a randomised trial of reduced dose schedules of the two licensed PCVs, and have developed approaches to measure B-cell memory (Bmem), follicular T helper cells (Tfh), Th17 cells and agglutinating antibodies to comprehensively examine the immune response following PCV. This project will measure cellular immune responses following reduced dose PCV schedules in Vietnam using flow cytometry. Results from this study will facilitate our understanding of PCV-induced immunity and will contribute to the global evidence on reduced dose PCV evaluation.

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

Professor Phil Sutton
E phil.sutton@mcri.edu.au

Professor Sarath Ranganathan
E Sarath.Ranganathan@rch.org.au

Available as Masters Project: Yes

Cystic fibrosis (CF) is an inherited disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF disease begins in early life and is characterised by a reduced lung function that is related to infection with a number of opportunistic pathogens. These infections drive a chronic airway inflammation that results in pathological structural changes in the lung. In recent years a new lung pathogenic infection, Mycobacterium abscessus, has emerged as an important global threat to individuals with CF. M. abscessus are multidrug-resistant bacteria that are associated with poor clinical outcomes and for which treatment is extremely difficult. Treatment typically involves the long-term use of toxic agents, including the injection of antibiotics that are frequently associated with major side-effects such as deafness and kidney failure. M. abscessus infection can also prevent a CF patient from receiving a life-saving lung transplantation. AIM: Given the above issues, we believe prevention through vaccination holds the best promise for these patients. The Aim of this project is therefore to identify a vaccine that has the potential to prevent infection with M. abscessus. APPROACH: This project will study vaccines in a mouse model of M. abscessus infection and determine which provides the best protection. A key aim will be to use standard immunological techniques to identify the immune response induced by these vaccinations that protects against M. abscessus infection. SIGNIFICANCE: Identifying a vaccine that protects against M. abscessus in the mouse model will guide future research aimed at developing a vaccine for protecting children with CF from this important pathogen. The project will be supervised by Prof Sutton, who is an expert on vaccine development, especially against bacteria pathogens at mucosal surfaces, and Prof Sarath Ranganathan, who is Head of Respiratory Medicine at Royal Children's Hospital and an expert on CF.

44. Developing a new treatment for stomach cancer

Professor Phil Sutton
E phil.sutton@mcri.edu.au

Dr Sohinee Sarkar
E sohinee.sarkar@mcri.edu.au

Available as Masters Project: Yes

Infection with the cancer-causing bacteria Helicobacter pylori starts in childhood and lasts for life. This infection causes a chronic inflammation (gastritis) that can result in stomach cancer, globally the 3rd leading cause of cancer-related death. We have identified a genetic variant (a polymorphism) that increases the susceptibility of some people to this cancer. Individuals who have this polymorphism are five times more likely to get stomach cancer when infected with H. pylori, and this gene is highly expressed in cancer biopsies. Drugs against this gene target are already clinically available, meaning this discovery has the potential for a completely new treatment for stomach cancer. Stomach cancers arise as a result of severe inflammation driven by H. pylori mediated activation of the immune system, so this effect is likely due to genetic regulation of the immune cell response to bacterial stimulation. AIMS: Key questions to be addressed by this project include 1) how this gene (and its polymorphism) make some people susceptible to stomach cancer and 2) the mechanism by which drugs that target the product of this gene would protect against cancer. APPROACH: Cell lines will be genetically modified with the latest genome editing technology and then stimulated with H. pylori. The immune response will then be quantified by measuring the cytokine response by ELISA. This will show how this gene affects the inflammatory response of human cells to these cancer-causing bacteria. We have already identified drugs that reduce gastritis in mouse models. This project will examine the mechanism by which these drugs work to protect against disease-causing gastritis. Such information is critical for designing improved drugs that might be used for the prevention or treatment of cancer.

45. Antibiotic resistance mechanisms in Mycoplasma

Dr Gerald Murray
T 8345 3679
E gerald.murray@mcri.edu.au

Prof Suzanne Garland
E suzanne.garland@thewomens.org.au

Available as Masters Project: Yes

Antibiotic resistance is a substantial and growing problem. Our laboratory is investigating mechanisms of antibiotic resistance in Mycoplasma genitalium, a common sexually-transmitted bacterial pathogen. Infection with M. genitalium causes urethritis in men and can lead to reproductive complications for women. M. genitalium has an unusual biology and highly reduced genome, making it susceptible to a small spectrum of antimicrobial reagents. Resistance to first line (macrolide) and second line (fluoroquinolone) treatments is high, and increasing. Dual resistance to both classes of antibiotic has increased, resulting in effectively "untreatable" infections. The project will use molecular methods including Sanger sequencing, quantitative PCR, and digital PCR, in combination with bacterial culture, to investigate the mutations that contribute to antibiotic resistance, and how these

mutations arise. Developments in this area will contribute to our understanding of treatment failure. This will lead to the development of the next generation of diagnostic assays that report the presence of antibiotic resistance mutations, thereby allowing treatment to be tailored to the individual. The long term outcome will be improved antimicrobial stewardship.

Population Health

46. Developing novel diagnosis methods for tree nut allergies

Dr Kirsten Perrett
E Kirsten.Perrett@rch.org.au

Dr Thanh Dang
E thanh.dang@mcri.edu.au

Available as Masters Project: No

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

Non-laboratory based Research

Cell Biology

47. Australian children and adults exposure to trace elements, and their association with cognition and development

Professor Richard Saffery
T 61383416341
E richard.saffery@mcri.edu.au
Associate Professor Ben Edwards
E ben.edwards@anu.edu.au

Professor Melissa Wake
T 61393455937
E melissa.wake@mcri.edu.au
Dr Susan Clifford
T 61393457620
E susan.clifford@mcri.edu.au

Available as Masters Project: Yes

Australian children and adults are potentially exposed to a range of trace elements through their food intake and physical environments. Some elements, such as iron, copper and iodine, are vial trace elements for life; with deficiency causing illness and high levels being toxic. Others, such as lead and mercury, are thought to only be toxic – these have been associated with diverse developmental outcomes, including anti-social behaviour, body mass index, depression and impulsivity. There is little known about the patterns of element exposure in Australian children and adults (e.g. does exposures to heavy metals cluster together?), and if exposure to metal mixtures amplify neurotoxicity compared to exposure to a single element.
The Longitudinal Study of Australian Children (LSAC) is a national, population-derived cohort assessing children and their families every two years since birth. These biennial assessments include interview, questionnaire and computer-based testing of cognition and physical development. In 2015-16, children (aged 11-12 years) and one of their parents completed a physical health assessment and biospecimens module, called the Child Health CheckPoint. Urine samples collected from the approximately 2000 children and 2000 parents at the CheckPoint visit are currently being analysed for 75 elements, and data are expected to be available prior to the beginning of the student project. Other physical health measures collected at the CheckPoint assessment include body composition; cardiovascular and respiratory health; musculoskeletal, renal, hearing and visual characteristics; physical activity and sleep, allergies and pain.

We propose to work with an Honours student to investigate patterns of Australian children and adults exposure to trace elements, and how beneficial and toxic elements (are associated with cognition and development. There is latitude in this project for the student to select which cognitive and development outcomes are of interest to investigate, given the broad range of outcome data available.

Children can be exposed throughout childhood to beneficial and toxic elements (trace metals and non-metals) through their food intake and physical environments, although at lower levels than children in less developed nations. Lead and mercury exposure are associated with diverse developmental outcomes, including anti-social behaviour, body mass index, depression and impulsivity. Recent research has implicated cadmium and

manganese in poorer cognition and behaviour. There is little known about the interactive effect of metal mixtures, and if the work together to amplify neurotoxicity compared to exposure to a single element. The Longitudinal Study of Australian Children (LSAC) is a national, population-derived cohort assessing children and their families every two years since birth. Child cognition and physical development are measured every two years. At age 11-12 years, study participants completed a physical health assessment and biospecimens module, called the Child Health CheckPoint. Urine samples collected from the approximately 2000 study children at the CheckPoint visit are currently being analysed for 75 elements, and data are expected to be available prior to the beginning of the student project. Other physical health measures collected at child age 11-12 years include body composition; cardiovascular and respiratory health; musculoskeletal, renal, hearing and visual characteristics; physical activity and sleep, allergies and pain. We propose to work with an Honours student to investigate how beneficial and toxic elements (trace metals and non-metals) are associated with children's cognition and development. There is latitude in this project for the student to select which cognitive and development outcomes are of interest to investigate, given the broad range of outcome data available.

Clinical Science

48. Validation of automated blood pressure devices in children

Dr Jonathan Mynard
T 9936 6038
E jonathan.mynard@mcri.edu.au

A/Prof Michael Cheung
E michael.cheung@rch.org.au

Available as Masters Project: Yes

As the leading risk factor for global disease burden, high blood pressure is one of the greatest health challenges of our time. Of particular concern, high blood pressure is detected in the doctor's office in ~15% of children and adolescents and at 7 years of age has been associated with higher and steeper blood pressure trajectories into adulthood and elevated cardiovascular disease risk in mid-adulthood. Annual screening for high blood pressure is recommended in children from 3 years of age or at every health care encounter in children with obesity, renal disease, diabetes or aortic coarctation history, in whom blood pressure is both a key diagnostic indicator and therapeutic target. Due to convenience and ease-of-use, automated blood pressure measurement devices have now largely supplanted the manual (auscultatory) method. However, few automated devices have been validated in children and the paucity of validated paediatric devices is recognised as a major gap with real-world implications for diagnosis and therapy. The aims of this project are 1) to perform a formal validation study of an automated blood pressure monitor that is commonly used in children, and 2) to investigate the utility of an electronic stethoscope and offline auscultatory analysis for improving the efficiency and robustness of validation studies. The project will involve recruitment and data collection in 100 children and adolescents attending the Royal Children's Hospital day clinics.

49. Measuring pain in children with cerebral palsy who are unable to self-report

Dr Adrienne Harvey
T 9345 5522 ext 57540
E adrienne.harvey@mcri.edu.au

Prof David Amor
T 99366404
E david.amor@mcri.edu.au

Available as Masters Project: Yes

Pain is a common comorbidity in children with cerebral palsy (CP) but is poorly identified and therefore under treated in this population. Pain is difficult to identify and measure in this group because many children are unable to self-report their pain due to communication and/or cognitive impairments. The tools currently available to measure pain in children with CP rely on observation or parent report and therefore may not be an accurate representation of a child's pain presence or severity. This project aims to explore the use of technology for measuring pain in children with CP. It involves trialing an App that incorporates facial coding as well as other observations to score pain levels in adolescents with CP. The App is currently being used in adults with dementia and we are exploring its potential for use in children with CP. A pilot sample of 10-20 adolescents with CP will be

recruited and their pain rated using the App as well as other behavioural pain scales commonly used in clinical practice. If found to be useful, this study will be the first step in potentially developing a CP specific App for measuring pain.

50. A new muscle endurance test for the arms

Dr Kate Carroll
T x 9345 4287
E kate.carroll@mcri.edu.au
Katy de Valle
E katy.devalle@mcri.edu.au

Dr Rachel Kennedy
E rachel.kennedy@mcri.edu.au

Available as Masters Project: Yes

Children with neuromuscular disorders have muscle weakness affecting their ability to stand up, walk, climb stairs and perform everyday activities including dressing and self-care tasks such as washing hair and brushing teeth. Some are unable to walk and use a wheelchair for mobility. Muscle strength and endurance impacts everyday function and needs to be measured accurately to guide clinical care, plan treatments and assist with equipment prescription. The only robust measure of muscle endurance tested in this population in the 6 minute walk test that cannot be used when a child is non-ambulant. Reliable measures of arm muscle endurance are lacking. This project focuses on the measurement of muscle endurance in the arms. The primary aim of this project is to test a new measure of arm muscle endurance in a group of typically developing children. These normative data will contribute to understanding arm endurance and establishing reliability and validity of this new outcome measure.

Infection and Immunity

51. How do early-life exposures shape childhood metabolomic profile?

Prof Richard Saffery
T 83416341
E richard.saffery@mcri.edu.au
Prof David Burgner
T 83416200
E david.burgner@mcri.edu.au

Dr Toby Mansell
T 83416200
E toby.mansell@mcri.edu.au

Available as Masters Project: Yes

Modern techniques such as nuclear magnetic resonance (NMR) have allowed for simultaneous measurement of a large number of metabolites in a wide range of bodily fluids and tissues, leading to rapid advances in studies of the human 'metabolome'. While specific metabolites have been linked to a range of diseases in adults, it remains unclear what influences shape metabolomic profile in children from birth. In utero, the developing foetus is sensitive to wide range of environmental exposures, with the potential to impact growth and development. Key maternal factors are implicated in this process, including BMI, metabolic profile, health and lifestyle factors (diet, smoking, alcohol consumption etc.), all of which have been linked to specific aspects of childhood health and development. We hypothesise that altered infant metabolic profile from birth mediates the relationship between early life exposures and various aspects of childhood development. To test this, we will examine the relationship between specific maternal factors, including metabolomic measures of maternal blood during pregnancy (28 weeks gestation), and offspring metabolome (birth, 12 months, and 4 years of age). We will also test the association between childhood metabolome (from birth) with growth and cardiovascular measures at 4 years of age and how infant genetic variation influences these relationships. This project is appropriate for students with an interest in population molecular epidemiology and biostatistics and is anticipated to contribute to at least one publication.

Population Health

52. Understanding family preferences for accessing mental healthcare for children with chronic physical health problems

Dr Jemimah Ride
E jemimah.ride@unimelb.edu.au

Prof. Harriet Hiscock
E harriet.hiscock@mcri.edu.au

Available as Masters Project: Yes

This project is a discrete choice experiment - a survey-based method that helps us to understand people's choices or decisions. The context is unmet need for mental healthcare among children with chronic physical health problems attending RCH outpatient clinics. The aims are: to understand what pathways to mental healthcare would fit best with the preferences of families attending outpatient clinics at RCH; and to identify strategies to achieve optimal uptake of pathways to mental healthcare in this group, and thereby inform efficient resource allocation by RCH to address this unmet service need. Families engaged with outpatient clinics seek or expect mental healthcare from the hospital rather than community-based alternatives and this contributes to the level of perceived and reported unmet need among these children. There are a range of factors that may contribute to this situation, including: the absence of alternatives that are free or bulk billed at the point of care; viewing the hospital as their child's 'usual' place of care; belief that the hospital will provide better quality care than alternatives; or lack of knowledge of alternatives. Addressing each of these requires different actions and resources, so that understanding which are the main drivers of family help-seeking behaviour and unmet need will inform the efficient allocation of resources to this problem. The work will include literature review and qualitative methods to identify the relevant factors that are important to families' choices and the contexts within which they may seek help for their child's mental health problems. The student will work with the health services group, including health economists and clinicians. It will suit someone interested in qualitative research, mental health, health services research and/or health economics.

53. What role does the built environment play in the development of allergic diseases?

Dr Rachel Peters
E rachel.peters@mcri.edu.au

Dr. Suzanne Mavoa
E suzanne.mavoa@unimelb.edu.au

Available as Masters Project: No

Melbourne has the highest prevalence of food allergy internationally and 40-50% of children in Melbourne have experienced symptoms of an allergic disease in their preschool years. The rise in allergic diseases is a relatively recent phenomena and may be related to modern lifestyle factors. According to the hygiene hypothesis, lack of exposure to microbes in early life influences the development of the immune system, potentially skewing it towards the allergic phenotype. Studies have shown that children growing up in farm environments have lower risk of allergic diseases than children who grow up in cities. However, few studies

have examined the role between the urban built environment, and the development of food allergy and other allergic diseases. The HealthNuts study presents a unique opportunity to address this research question. HealthNuts is a population-based, longitudinal study of allergic diseases. The cohort consists of 5300 infants recruited at 12-months of age and has been followed-up at ages 4 and 6. Objective measures of allergic diseases including food allergy, eczema and asthma have been collected. The cohort is also linked to derived measures of urban environment characteristics created using geographic information systems (GIS). A research project is available for a student to assess whether urban characteristics such as urban density and backyard features, are associated with the risk of food allergy and other allergic diseases. This project would suit a student with an interest in epidemiology, allergy or the use of GIS data in health research. The student will work with supervisors to undertake statistical analysis and potentially some additional GIS analysis and mapping.

54. The relationship between diet and mental health in children and young adults

Dr Sharon Lewis
T 9936 6558
E sharon.lewis@mcri.edu.au

Dr Katherine Lange
E katherine.lange@mcri.edu.au

Available as Masters Project: No

Mental illness confers up to 60% higher risk of cardiovascular disease and premature death, with the majority of common mental illnesses predicted to begin prior to 14 years of age. This highlights the need to understand what impacts mental health from early childhood, in order to most effectively apply preventative measures at the right time. Numerous studies have demonstrated a relationship between diet quality and mental health, although the specific factors driving this relationship are largely unclear. This project will investigate the association between specific components of dietary intake and mental health, and the potential blood metabolites mediating this relationship. This project utilises two large independent population-based cohorts of Australian children and adults - (1) the Longitudinal Study of Australian Children (LSAC) with the nested Child Health CheckPoint physical health and biospecimens module, and (2) the Clinical review of the Health in adults conceived with Assisted Reproductive Technologies (CHART) study. Potential students will use linear regression to investigate the association between dietary intake (such as fresh fruit, raw and cooked vegetables, fatty foods, dairy, meat and fish) and mental health in mid-childhood. Time permitting, key intermediate blood metabolites will be explored as potential mediators in the relationship in children and young adults. The results may inform potential areas for early intervention to improve long-term mental health. This project will suit a student with an interest in population-based health, developing statistical experience and Stata skills. Some prior experience in basic statistical techniques or analytical packages (such as Stata, R, MPlus or MATLAB) would be an advantage. The broader research team includes expertise in longitudinal and high-throughput metabolomic data analyses, statistical support, and access to Stata software and expertise to conduct the project. Given the large, high quality data available, findings are likely to be published in a quality journal.

55. Metabolic profiles of mental health trajectories in childhood and early adulthood

Dr Sharon Lewis
T 9936 6558
E sharon.lewis@mcri.edu.au

Dr Katherine Lange
E katherine.lange@mcri.edu.au

Available as Masters Project: No

Mental illness confers up to 60% higher risk of cardiovascular disease and premature death, with the majority of common mental illnesses predicted to begin prior to 14 years old. This highlights the need to identify mental health difficulties from early childhood, in order to most effectively apply preventative measures to the right people at the right time. We have preliminary evidence for an association between mental health and a number of blood metabolites in children, including unsaturated fatty acids, triglycerides and some amino acids. However, it is unclear if these metabolic profiles differ for short-term and long-term mental health difficulties. This project will investigate the association between mental health trajectories and blood metabolite profiles. This project utilises two large independent population-based cohorts of Australian children and adults - (1) the Longitudinal Study of Australian Children (LSAC) with the nested Child Health CheckPoint physical health and biospecimens module, and (2) the Clinical review of the Health in adults conceived with Assisted Reproductive Technologies (CHART) study. Potential students will classify participants according to mental health trajectories, and then use regression models to investigate the association between these trajectory groups and blood metabolite concentrations in mid-childhood and young adults. The results could provide novel insights into objective biomarkers classifying mental health trajectories. This project will suit a student with an interest in population-based health, developing statistical experience and Stata skills. Some prior experience in basic statistical techniques or analytical packages (such as Stata, R, MPlus or MATLAB) would be an advantage. The broader research team includes expertise in longitudinal and high-throughput metabolomic data analyses, statistical support, and access to Stata software and expertise to conduct the project. Given the large, high quality data available, findings are likely to be published in a quality journal.

56. 'Beating the odds': Early life experiences influencing the association between genetic prediction and language development in mid-childhood

Dr Anneke Grobler
T 9936 6450
E anneke.grobler@mcri.edu.au
Dr Katherine Lange
E katherine.lange@mcri.edu.au

A/Prof Ben Edwards
E ben.edwards@anu.edu.au

Available as Masters Project: No

Language skills are important determinants of daily functioning and health, and are closely linked to academic and employment outcomes. Recent evidence has identified a range of genetic factors that influence educational attainment, but genetics is clearly only one part of

a complex interplay of factors. This project aims to investigate the interaction between genetic predisposition for educational attainment, and early life exposures, in determining childhood language development in a large cohort of Australian 11-12 year old children. The Longitudinal Study of Australian Children (LSAC), is a national, population-derived cohort of Australian children, collecting data every two years since birth. We recently undertook the Child Health CheckPoint study, a cross sectional physical and biospecimens module of LSAC at 11-12 years of age. We are currently applying an adult-derived polygenic score for educational attainment to the CheckPoint cohort. This project will (1) investigate the association between this polygenic score and language development (vocabulary) at 11-12 years, and (2) investigate the mediation of this genetic-outcome correlation by a range of early-life exposures, including home environment, extra-curricular activities, parental involvement, social support and family demographics. The results may help to identify key lifestyle factors that contribute to resilience for language development in children with poorer genetic prediction. This in turn may inform future targeted policy development and intervention strategies. This project will suit a student with an interest in population-based health, developing statistical experience and Stata skills. Some prior experience in basic statistical techniques or analytical packages (such as Stata, R, MPlus or MATLAB) would be an advantage. The broader research team includes expertise in longitudinal and high-throughput genetic data analyses, statistical support, and access to Stata software and expertise to conduct the project. Given the large, high quality data available, findings are likely to be published in a quality journal.

57. Understanding hospital, GP, and family factors associated with paediatric asthma re-admissions

Dr Katherine Chen
T 99366582
E katherine.chen@rch.org.au

Professor Harriet Hiscock
T 93456910
E harriet.hiscock@rch.org.au

Available as Masters Project: No

Asthma is the most common chronic childhood illness affecting approximately 10% of Australian children. Asthma hospitalisations are associated with serious outcomes including worse lung function, functional limitations, future admissions and increased risk of mortality. In addition, hospitalisation poses a significant burden on hospitals with asthma accounting for approximately 3% of all hospitalisations for Australian children aged 5-14 years in 2015-6. Approximately 1 in 5 children admitted to hospital for the treatment of asthma will be re-admitted within 1 year. The overall aim of this project is to identify modifiable and translatable factors associated with asthma re-admissions in order to inform new models of care to keep children out of hospitals. The recruitment for this project is underway at 3 hospitals (The Royal Children's Hospital, The Northern Hospital and University Hospital Geelong) with a rich data set including medical record data extraction, GP survey, parent interviews, and data linkage to the Victorian Admitted Episode Dataset and the Victorian Emergency Minimum Dataset in order to understand health service utilisation. The student will assist with data collection, analysis and exploring a specific angle of interest in more detail within this broader project.

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 Murdoch 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 2018, 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: Online application: Register for the Honours Application Tracking System (SONIA) before making your application in SONIA. Lodge an online application by Thursday 31 October 2019 (Round 1), Friday 17 January 2020(Round 2), and Friday 7 February 2020 (Round 3). http://mdhs-study.unimelb.edu.au/degrees/honours/apply-now#apply-now

STEP 3: Project preference

Once you have submitted an online course application, you will receive an email within 3 working days with your personal login details to access the Honours Project Preference System - SONIA. Please follow the instruction in the email to set up your password and select your preferences for projects offered within MDHS departments. You may select up to 4 project preferences in Round 1 or 3 project preferences in Round 2, 3 and mid year. You must only preference projects after contacting with the relevant supervisor(s) and at least reaching a verbal agreement. You are allowed to log into Sonia to change your preferences any time by the closing date.

Start year intake round 1 - Monday 12 August 2019 – Friday 15 November 2019

Start year intake round 2 - Friday 20 December 2019 – Friday 17 January 2020
Start year intake round 3 - Thursday 23 January 2020 – Friday 7 February 2020

STEP 4: Offers: Round one offers for entry into 2020 will be made by Friday 13 December 2019. 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 or Round 3 under specific circumstances, but that is not guaranteed.

UNIVERSITY OF MELBOURNE MASTER OF BIOMEDICAL SCIENCE

The Master of Biomedical Science is a coursework program (Course code **MC-BMEDSC**) offered through the Department of Paediatrics. This program offers graduates a pathway into research or other science based careers, and can lead on to PhD studies. Students may consider undertaking a Masters as an alternative to the Honours Program.

Students undertake a major research project and discipline-specific coursework subjects offered by MDHS. A range of professional development subjects are offered to complement and enhance the research undertaken and to progress students' career opportunities.

MDHS website: http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/overview

MASTERS RESEARCH PROJECT

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

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

The research subject is completed as a project under the supervision of experienced senior scientific researcher/s within a research group at the Murdoch 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 2020

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

For commencement in semester one 2020, applications close: 30 November 2019

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