

Murdoch Children's Research Institute

PhD Projects available for 2021



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Lab-based projects

Cell Biology

1. Developing high content screens of novel treatments for congenital nephrotic syndrome

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Congenital nephrotic syndrome presents early in life and results in kidney failure and resulting severe proteinuria which can be life threatening. No treatments are available for this condition other than renal transplantation and dialysis. The genetically inherited forms of this condition most commonly result from mutation in genes expressed in the podocytes of the glomerulus. We have developed a method for generating human kidney tissue from pluripotent stem cells that represent good models of the human kidney. We have also established patient stem cell lines and gene edited stem cell lines with specific point mutations in genes known to result in congenital nephrotic syndrome. This project would characterise these mutant kidney tissues and develop a high content screen to identify compounds that may be able to treat this disease. In this way, the objective would be to develop personalised treatments for congenital nephrotic syndrome.

2. Controlling nephron patterning and segmentation in kidney organoids

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The human kidney contains approximately 1 million nephrons that are responsible for filtration of the blood, active secretion of waste products and the reabsorption of water and critical molecules back into the body. To do this, the final nephron need around 25 distinct cell types each with specific functions. We have developed a method for recreating human developing kidney tissue from pluripotent stem cells. These tissues, referred to as kidney organoids, contain patterning and segmenting nephrons beginning to form each of the many required cell types. However, these remain immature and some cell types are not present. It is also clear that different culture conditions favour one end of the nephron over another. The aim of this project would be to dissect what pathways are driving the patterning of different nephron segments and cell types to improve the model and/or generate cell types that are currently missing or immature.

3. Regulating the vascularisation of the human glomerulus in vitro.

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The human kidney contains approximately 1 million nephrons each of which is comprised of a glomerulus into which a capillary bed grows and through which the blood is subsequently filtered to form the urine. We have developed a model of the developing human kidney generated from human pluripotent stem cells that contains forming nephrons with maturing glomeruli as well as endothelial cells. However, the efficiency with which capillary loops form within these glomeruli is low. This project will investigate molecular approaches to induce growth factor secretion from the glomerulus to improve capillary formation in vitro. This will allow the modelling of glomerular kidney disease and potentially improve tissue survival post transplantation.

4. Nephrotoxicity screening using stem cell-derived proximal tubules

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The human kidney contains approximately 1 million nephrons each of which is comprised of a glomerulus into which a capillary bed grows and through which the blood is subsequently filtered to form the urine. We have developed a model of the developing human kidney generated from human pluripotent stem cells that contains forming nephrons with maturing glomeruli as well as endothelial cells. However, the efficiency with which capillary loops form within these glomeruli is low. This project will investigate molecular approaches to induce growth factor secretion from the glomerulus to improve capillary formation in vitro. This will allow the modelling of glomerular kidney disease and potentially improve tissue survival post transplantation.

5. Developing computational approaches to analyse development and disease

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The use of complex 3D tissues derived from stem cells affords many significant advantages for the study of development and disease. The analysis of the resulting tissue is, however, complex given their size and cellular complexity. Advances in imaging technology, transcriptional profiling resolution and machine learning provide the tools that should allow high throughput characterisation of such complex structures. This project aims to develop novel computational approaches to handle high content image datasets for the interrogation of disease mechanism. The applicant should have some basic understanding of computational biology and/or imaging.

Clinical Sciences

6. Towards treatment of intellectual disability caused by errors in the chromatin machinery

Prof David Amor

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Intellectual disability occurs in 2-3% of newborns, for a variety of reasons, including environmental factors, chromosomal abnormalities and mutations in single genes. Intellectual disability results in lifetime dependency on family and societal support, yet traditionally, it has been viewed as an untreatable condition. However, recently it has been recognised that intellectual disability resulting from inborn errors in the chromatin machinery may be treatable. More than 40 genetic syndromes have so far been identified in this category, including Kabuki syndrome, KAT6A syndrome and Kleefstra syndrome. This project will focus on mutations in chromatin factors and chromatin-modifying enzymes found in patients with intellectual disability, because chromatin changes are reversible, and because these classes of molecules are well established as therapeutic targets in other disorders. The project will identify and characterize mutations in the chromatin machinery in infants and children with brain development disorders, delineate human phenotypes associated with these mutations, and characterize the phenotypic, cell biological, molecular and biochemical consequences of the patient-specific mutations in model systems. The longer term objective is to test potential therapeutic interventions in genetic models in vitro and in vivo. We anticipate that the investigation of the role of individual chromatin modifiers will go well beyond a specific syndrome and will provide an understanding of the regulation of gene expression in brain development and plasticity, potentially highlighting therapeutics for patients without mutations in these factors. We hope to recruit a high quality student wishing to undertake research into genetics and neurodevelopmental disorders.

7. Neuropsychological profile of children with childhood apraxia of speech

Prof Angela Morgan

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Childhood speech disorders are common, affecting 1 in 20 preschool children in the general population. Yet these children present with mild articulation or phonological disorders that typically resolve with or without intervention. By contrast, approximately 1 in 1,000 patients present with a persistent and less tractable speech disorder known as childhood apraxia of speech (CAS). Three core symptoms support a CAS diagnosis: including inconsistent errors on consonants and vowels; lengthened and disrupted coarticulatory transitions between sounds and syllables; and inappropriate prosody (ASHA 2007). Lifelong impairment is seen, with psychosocial impact, literacy deficits, and restricted educational and employment outcomes. Why is CAS so much more persistent than other speech conditions? Increasing evidence has shown a genetic basis for up to 1 in 3 children with CAS. Novel molecular pathways have also been revealed, indicating a role for transcriptional dysregulation. This mechanism is associated with altered brain development which results in the CAS

symptomatology, along with other commonly shared deficits such as impaired motor skill development. To date, few studies have examined neuropsychological strengths and challenges in children with CAS. A greater understanding of cognitive contributions to the condition, combined with new genomic data, will lead to more targeted therapeutic interventions and help to explain the mechanisms which lead to this symptom profile. Our team has an exciting PhD opportunity for a project examining cognitive contributions in CAS associated with our speech genetics clinic at the Royal Children's Hospital.
3 year stipend offered.

Essential criteria: Degree in Clinical Psychology or Neuropsychology; High academic marks that would meet eligibility for enrolment at the University of Melbourne.

Desirable: Experience in testing children with neurodevelopmental disorders or equivalent clinical experience.

8. Pain in children with cerebral palsy and other developmental disabilities

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Pain is increasingly being recognised as a significant issue for children with cerebral palsy (CP) and other developmental disabilities, yet is under identified and consequently managed sub optimally in this population. In addition, there are limitations with current methods of measuring pain in children who are unable to self-report due to cognitive and/or communication limitations. This PhD project will focus on tools that identify and measure pain and validating these in children with cerebral palsy as well as developing innovative methods using technology to measure pain in children who are unable to self-report. We hope to recruit a high quality allied health, nursing or medical professional into this PhD position and experience in disability is desirable.

9. Placental Cord Blood Cell Therapy in Children at High Risk of Heart Failure

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Our work seeks to reduce the high risk of heart failure and death faced by children with severe and complex heart diseases. Babies born with severely malformed heart and blood vessels that are inadequate for normal blood circulation undergo a series of complex heart operations, the first is performed on day 2 or 3 of life (Norwood procedure). Even after surgery, the heart is under great metabolic and mechanical stress as excessive demands do not allow normal heart muscle growth to sufficiently support blood circulation leading to high mortality in the first year of life. In other children with heart failure due to heart muscle damage (cardiomyopathy), surgical implantation of a ventricular assist device (VAD, mechanical pump) supports heart function, alleviating pressure and volume overload to allow potential adaptive repair, muscle growth, improved muscle function and weaning from the pump. However many still require a heart transplant or die within 2 years of diagnosis. From our previous research and that of others, cord blood stem cells (CBSC) have

been found to stimulate normal heart muscle growth, increase pumping capacity, and reduce inflammation, fibrosis and metabolic stress after surgery. In order to apply this, we have designed a safe way to directly treat the heart with CBSC during the cardiopulmonary bypass surgery that is employed in the Norwood and VAD implantation procedures. Depending on the qualifications and interests, a number of research projects are available at honours, Masters or PhD level, involving laboratory or clinical based work. Student background and research interests are ideally in one or more areas such as: physiology, immunology, haematology, genetics, biochemistry, pharmacology, surgery, veterinary medicine or medicine.

Genetics

10. Investigating the molecular basis of Parkinson's disease using novel genetic models

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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 and mouse models with mutations in RAB39B. In this project, the candidate will characterise these novel disease models and perform various functional studies. They will be able to develop skills and expertise in a wide range of techniques including stem cell culture, stem cell differentiation, mouse handling, and mouse behavioural testing. They will also utilise a range of standard molecular and cellular techniques such as real time PCR, western blotting, immunostaining and microscopy. Overall, this project will involve performing preclinical studies on novel disease models to improve our understanding of the molecular basis of Parkinson's disease and identify potential therapeutic targets.

11. Identifying the genetic causes of brain malformation in children

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The human cortex is the surface of the brain that enables advanced intellectual function. It forms through a series of overlapping steps involving neuronal proliferation, migration and differentiation. Abnormal formation of the cortex causes a group of disorders known as

malformations of cortical development (MCD), which can result in epilepsy, intellectual disability and cerebral palsy. There is considerable evidence that gene mutations cause MCD, but to date few of the genes involved have been identified. This project will utilise modern genomic technologies, including whole exome and genome sequencing, to identify the genetic basis of MCD. Close collaboration with neurosurgeons and neurologists at the Royal Children's Hospital enables unique access to tissue to investigate relevant disease mechanisms. Methodology will include single cell transcriptomics and proteomic analyses of resected brain tissue. Newly identified genes will be investigated in model systems, including pluripotent stem cells to determine underlying disease pathogenesis. The successful applicant will work closely with clinicians and bioinformaticians within a large multidisciplinary team.

12. Understanding the molecular basis of CANVAS - a novel neurological disorder caused by an expanded DNA repeat

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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 be a component of a larger study that aims to characterise the CANVAS repeat mutation 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.

13. Development of novel human stem cell derived models of beta-propeller protein-associated neurodegeneration for disease modelling and drug screening

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Beta-propeller Protein-Associated Neurodegeneration (BPAN) is a rare, X-linked neurological disorder characterised by intellectual disability, seizures and ataxia in early childhood. The condition progresses rapidly leading to development of Parkinsonism, dystonia and cognitive impairment in adolescence/early adulthood. Children affected by BPAN display brain iron accumulation at an early age, leading to classification of BPAN under a group of

disorders known as neurodegeneration with brain iron accumulation (NBIA5). BPAN is caused by pathogenic variants in the WDR45 gene which encodes the WD repeat-containing protein 45. The protein plays an important role in autophagy, a biochemical mechanism that regulates degradation and recycling of cellular components. However, very little is known about the cellular effects of variants in WDR45 on the nervous system and how it causes BPAN. Hence, there are no drugs available that can cure or slow the progression of BPAN. In this project we will use patient-derived induced pluripotent stem cells (iPSC) to generate brain cell cultures in order to study disease-specific mechanisms and test potential drug treatments. The first step will be to examine the effects of pathogenic variants on electrophysiological, biochemical and morphological properties of differentiated cells, with a focus on neurons. Drugs targeting relevant pathways (e.g. autophagy, iron metabolism, etc.) will be used to determine their effectiveness in modulating disease phenotype in the neuron. This will help establish the validity of our culture model as a vital preclinical tool for BPAN drug screening. The prospective candidate will get the opportunity to learn a range of laboratory techniques including stem cell culturing, differentiation of stem cells into neurons, electrophysiology, immunocytochemistry, microscopy, drug screening assays, real-time qPCR and western blot analysis.

14. Discovery of new treatments for brain development disorders linked to epigenetic regulatory genes

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The cerebral cortex - the outer layer of the brain - is highly expanded in humans compared to other mammals, and it is this unique human characteristic which is thought to account for our species' increased intellectual capacity. Impaired cognition, as observed in people with intellectual disabilities, is often associated with defects during brain development. Due to advances in human genetic sequencing, a large number of developmental disorders associated with intellectual disabilities have been linked to genetic mutations in specific genes. Interestingly, a large number of these genes are involved in epigenetic regulation - a cellular process which regulates which genes are expressed or silenced through reversible modification of histones or DNA. Cortical development is a highly complex process which requires tight and timely control over transcriptional programmes orchestrating expression and silencing of a multitude of genes which govern various cellular processes including proliferation, migration and neuronal differentiation. Therefore, misfunction of epigenetic genes which regulate these transcriptional programmes results in failures in one or more of these cellular processes during cortical development and lead to long-term intellectual disability. The broad aims of this project are to: 1. Model human cortical development in vitro using human embryonic stem cell (hESC) and induced pluripotent stem cells (iPSC) derived from intellectually disabled patients harbouring deleterious mutations 2. Identify gene-dependent deficits during cortical development 3. Run a small-scale drug screen for treatment of these genetic disorders. Successful candidates will generate a battery of genetically modified hESCs using CRISPR-Cas9 mediated gene disruption, perform in vitro cortical differentiation, conduct neuronal phenotype analysis using live cell confocal imaging of genetically encoded fluorescent reporters, assess electrophysiological properties of

neurons using MEA assays, conduct biochemical analyses of epigenetic markers along with performing basic molecular biology techniques such as cloning, genotyping PCR, western blot and immunocytochemistry.

Infection and Immunity

15. Understanding the cause of Human papillomavirus (HPV)-negative cervical cancers in Australian women.

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Background: Cervical cancer is listed as the fourth most common tumour in women worldwide. With the vast majority of these cancers attributed to HPV infection, many countries are using prophylactic HPV vaccines to prevent infection, as well as HPV DNA detection assays as the primary screening tool replacing Pap cytology. However, this screening method may miss a small percentage of cervical cancer cases seemingly not caused by HPV. Identification of specific DNA based targets are needed to capture this small percentage of cervical cancer cases.

The Project: Currently HPV negative cervical cancers are attributed to approx. 7% of all cervical cancers with the aetiological agent currently unknown. Previous studies have identified that a proportion of these HPV negative cancers do contain HPV sequences of either genotypes not commonly tested for or known genotypes that contain DNA mutations in the L1/L2 and E6/E7 genes, commonly used as PCR targets. The project is part of a collaboration with research institutes and hospitals across the Eastern coast of Australia and involves the use of laboratory based molecular techniques and bioinformatic analysis of next generation sequencing data, to identify the aetiological agent for these HPV negative cancers.

Project Outcomes: The project aims to identify HPV negative cancers among all recently diagnosed cervical cancers in Australia. Uncover the unknown causes for the underlying neoplasia and use this to aid in the expansion of current molecular targets.

Financial support An initial first year PhD scholarship is available for the successful applicant to the value of \$33,092. The successful applicant will also be encouraged to apply for an Australian Research Training Scholarship for the remainder of their project.

16. Immune mechanisms of peanut allergy remission

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Food allergies are a major health burden globally, and Australia has the highest reported rates of food allergy in the world. There is currently no cure so research has focused on identifying approaches to redirect allergen-specific immune responses away from allergy towards a tolerant state, which can support clinical remission of allergy. Several therapies under investigation can induce remission, which may be transient or long lasting. The immune changes of long-lasting remission are unknown; understanding the key factors that

lead to long-lasting remission will enable development of effective long-term treatments for food allergy. We have been investigating a combination treatment, Probiotic and Peanut Oral Immunotherapy (PPOIT), which has been shown to induce long-lasting remission that persists to 4 years post-treatment. By contrast, published reports of peanut oral immunotherapy (OIT) without immunological adjuvant suggest that OIT-induced remission may be short-lived, with two thirds (67%) of treatment responders losing their remission state by 12 months post treatment. The aim of this project is to use a combination of gene expression and flow cytometry approaches to understand the immune mechanisms involved in retraining the allergic response towards long-lasting remission of peanut allergy. Gene expression and flow cytometry data will be generated on immune cells before and after intervention in 1) patients who achieve remission of peanut allergy remission following PPOIT treatment 2) patients who achieve remission of peanut allergy following standard OIT 3) patients who remain allergic to peanut following placebo treatment. Findings will provide clues of key immune factors that drive lasting remission of allergy compared to remission that is lost over time, which may in turn lead to development of more effective long-term treatments for food allergy.

17. The cardiometabolic legacy of SARS-CoV-2 in longitudinal adolescents

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Summary: SARS-CoV-2 is a respiratory virus that hasn't read the textbook on how it should behave; acute COVID-19 appears to be a disease of blood vessels as much as of the respiratory tract. There is also concern regarding the long-term effects of acute SARS-CoV-2 infection, with increasing reports of protracted symptoms ('long COVID') and increased risk of cardiovascular disease (CVD). This project will address the effects of COVID-19 on the cardiovascular and metabolic (cardiometabolic) health of adolescents. This exciting innovative project will focus on the newly established YoungLives cohort of over 1000 population-representative adolescents, who will have a detailed non-invasive assessments and extensive metabolomic profiling at recruitment and again 12 months later. The findings will have immediate translational importance and will inform prevention, interventions and policy.

Project Description: The successful applicant will join a friendly, dynamic multidisciplinary team (including other PhD students working on the immunological and psychosocial aspects of the YoungLives cohort, who are academic paediatricians, research scientists, and epidemiologists. The candidate will analyse cardiometabolic and laboratory data collected at recruitment, and undertake training to participate in the ongoing assessment of the participants. The project combines hands-on clinical research, laboratory work, and data analysis and interpretation. The project would suit a clinician (e.g. paediatrician, infectious diseases, cardiologist, endocrinologist) or a scientist with an interest and some content knowledge in these areas. Full training of cardiometabolic assessments and other key skills will be given. Excellent people skills are essential and some experience of data management and statistical analysis would be beneficial. The successful candidate is expected to be competitive for own scholarship funding (APA or similar). Top-up funding may be available.

18. Defining the mechanisms that underpin the beneficial off-target effects of BCG

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In addition to protecting against its target disease, tuberculosis, the Bacillus Calmette-Guérin (BCG) has beneficial off-target ('heterologous' or 'non-specific') effects on human health including reducing all cause infant mortality, likely by protecting against non-mycobacterial infectious diseases. This protection is proposed to result from the immunomodulatory effects of BCG. Our team has established two randomised controlled trials (RCTs) investigating whether BCG protects against non-mycobacterial diseases: - Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR): our RCT of neonatal BCG vaccination in >1200 children in Melbourne to determine if BCG protects against allergic disease, eczema, asthma and infections. The BRACE trial: our international RCT of >10,000 healthcare workers to determine if BCG vaccination reduces the impact of COVID-19 and other respiratory diseases. This project will use samples from participants in one or both of these RCTs to characterise BCG-induced changes in the immune system. This project will use a combination of in vitro stimulation, flow cytometry, multiplex cytokine assays, epigenetic analysis and gene expression. The findings of this project will provide important insights into the immunomodulatory effects of BCG and the associations between these changes and the beneficial clinical effects of this vaccine.

19. Unravelling the Inflammatory Signatures of Paediatric Respiratory Disease

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Inflammation is a key aspect of the pathophysiology of many common paediatric respiratory diseases, but very little is known about the exact inflammatory pathways that define different diseases. A better understanding of the inflammatory signature of different paediatric respiratory diseases would help to identify novel therapeutic targets and predictive biomarkers. In this PhD you will have the opportunity to work as part of a larger study that is aiming to define the inflammatory signatures of common diseases such as asthma/wheeze, acute lower respiratory tract infections, lung disease of prematurity and bronchiectasis. What is unique and world leading about this project is the use of tissue specific samples (bronchoalveolar lavage and bronchial brushings). The exact focus of the PhD can be determined, but broadly speaking your PhD would involve laboratory experience with techniques such as flow cytometry and single cell RNA sequencing, and bioinformatic analysis using multi-omic data sets. The ideal candidate would have laboratory experience, ideally with flow cytometry or RNA sequencing, and be keen to undertake research that has a strong clinical component.

Population Health

20. Predictors of infection and clinical severity with SARS-CoV-2 in extant longitudinal LifeCourse population cohorts of children and their household/family contacts

A/Prof Kirsten Perrett
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Summary: This project will use data from the COVID-Immune and YoungLives cohort studies which harness the MCRI's unique population cohorts of children to investigate whether pre-COVID immune phenotypes and biomarkers predict susceptibility to and severity of SARS-CoV-2 infection. In addition, this project offers the opportunity to further understand the clinical features, natural history, transmission dynamics and long-term effects/legacy of SARS-CoV-2 infection in children, adolescents and young adults. The findings will have immediate translational importance and will inform prevention, interventions and policy. Project Description: COVID-19 epidemiology and pathophysiology are unprecedented but poorly understood, hampering short- and long-term management. Infection-related, dysregulated immune responses are central and likely underpin the increasingly recognised long-term impacts. A striking feature of the current COVID-19 pandemic is the relatively low incidence of symptomatic infection and milder disease in children. This is markedly different to almost every other infectious disease, particularly those due to viruses. Key scientific questions are therefore, why children are less susceptible to infection and, if infected, why the clinical severity is much less than in adults, who is at risk and what is the immunological legacy of infection. This project will investigate pre-pandemic immune data and biosamples from up to 3500 children, adolescents and young adults from 4 of MCRI's unique population cohorts and follow them for symptoms/signs of COVID-19 and seroconversion. In addition, comprehensive immune phenotyping will be done at baseline and 12 months in the adolescent/young adult YoungLives cohort (n=1000) to investigate the immunological legacy of COVID-19 infection to understand early evidence of adverse changes in immune responses and inflammation.

21. Predictors of infection and clinical severity with SARS-CoV-2 in extant longitudinal LifeCourse population cohorts of children and their household/family contacts

Prof Melissa Wake
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The placenta regulates a healthy pregnancy. The population burden of disordered placentation and function is unquantified but potentially immense. This highly novel PhD takes placental research to scale, developing innovative high-throughput placental imaging and sampling within the 'Generation Victoria' cohort, targeting all 160,000 Victorian births over two years and all 70 birthing hospitals. Initially focusing on the placental pathophysiology of the great obstetric syndromes, the resource once established can later quantify placental roles in maternal, fetal, childhood, adult and transgenerational health. The landmark GenV thus offers immense opportunities to establish a career and leadership in transformative pregnancy and newborn research.

Non Lab-based projects

Cell Biology

22. Metabolic reprogramming of the failing heart

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After a heart attack the heart muscle undergoes major cellular changes in order to preserve function and remain viable. These changes are believed to be an 'adaptive' mechanism to allow the heart muscle to continue to pump enough blood to the rest of the body. In the short term, these cellular changes successfully maintain function but failure to return to normal physiology leads to cellular dysfunction. Most of these physiological changes affect the mitochondria's capacity to produce energy and regenerate. Accumulation of dysfunctional mitochondria becomes a source of toxic subproducts that significantly contributes to cell death. The mitochondrion has been termed the powerhouse of the cell, considering it generates large quantities of energy. Due to its role, it is imperative that mitochondrial homeostasis is maintained to guarantee adequate energy generation for cardiac function and to reduce the production of toxic cellular subproducts. Mitochondrial quality control and recycling is orchestrated by a multiprotein complex that allows identification and degradation of damaged mitochondria. Modulation of one or multiple members of this complex could enhance mitochondrial regeneration and have potential for the treatment of diseased cardiomyocytes. To date, mitochondrial regeneration has not been explored as a therapy for heart failure. In this proposal, we will take advantage of our "heart attack" model from human pluripotent stem cells to validate factors for mitochondrial regeneration and improve cell survival, reduce cardiac muscle loss and increase contractility. This project will involve the generation of human heart cells from stem cells, cell culture, immunohistochemistry and confocal imaging.

Clinical Sciences

23. Long-term impact of moderate and late preterm birth: effects on neurodevelopment, brain development and respiratory health at school age

Prof Jeanie Cheong
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The Victorian Infant Brain Studies group at The Murdoch Children's Research Institute is seeking a PhD student to join their team on a project investigating the impact of moderate-late preterm (MLP; 32 to <37 weeks' gestation) birth on neurodevelopment, brain development, and respiratory health at 9 years of age. The majority of preterm births are attributed to MLP births, and there is a growing evidence-base demonstrating that children

born MLP experience more adverse outcomes in early childhood than their term-born peers. Specifically, children born MLP experience increased respiratory morbidity in infancy and early childhood than their term-born peers. Our previous research has also found that infants born MLP have smaller and less mature brains than term-born infants at term-equivalent age, although less is known about brain changes over time in this population. Within the larger project, children in the study are wearing a tri-axial accelerometer to measure physical activity, sedentary behaviour and sleep patterns for one week, as well as completing a self-reported physical activity questionnaire. The PhD student will investigate one of the following areas in relation to these activity data: 1) The association between physical activity levels and brain function in 9-year-old children born MLP compared with term-born controls. Children are undergoing brain MRI, and the PhD student will be supported by experts in the area of neuroimaging. 2) The association between physical activity levels and respiratory function in 9-year-old children born MLP compared with term-born controls. The project contains rich data concerning respiratory health, as children are completing lung function tests and we are collecting data on respiratory symptoms and diagnoses. 3) The associations between sleep duration and quality and cognitive/behavioural outcomes in 9-year-old children born MLP compared with term-born controls. We are collecting detailed neuropsychological data, such as IQ, memory and academic achievement, alongside data concerning behavioural problems.

24. Neuropsychological profile of children with speech disorder

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Childhood speech disorders are common, affecting 1 in 20 preschool children in the general population. Yet most of these children present with mild articulation or phonological disorders that typically resolve with or without intervention. By contrast, approximately 1 in 1,000 patients present with a persistent and less tractable speech disorder known as childhood apraxia of speech (CAS). Three core symptoms support a CAS diagnosis: including inconsistent errors on consonants and vowels; lengthened and disrupted coarticulatory transitions between sounds and syllables; and inappropriate prosody. Lifelong impairment is seen, with psychosocial impact, literacy deficits, and restricted educational and employment outcomes. Why is CAS so much more persistent than other speech conditions? Increasing evidence has shown a genetic basis for up to 1 in 3 children with CAS. Novel molecular pathways have also been revealed, indicating a role for transcriptional dysregulation. This mechanism is associated with altered brain development which results in the CAS symptomatology, along with other commonly shared deficits such as impaired motor skill development. To date, few studies have examined neuropsychological strengths and challenges in children with CAS. A greater understanding of cognitive contributions to the condition, combined with new genomic data, will lead to more targeted therapeutic interventions and help to explain the mechanisms which lead to this symptom profile. Our team has an exciting PhD opportunity for a project examining cognitive contributions in CAS associated with our speech genetics clinic at the Royal Children's Hospital.

25. Measuring child and family centred outcomes following spinal surgery for children with neuromuscular scoliosis

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Scoliosis is common in children with cerebral palsy and other developmental disabilities who have significant gross motor impairment and impacts significantly on the child's wellbeing, quality of life and participation. Spinal surgery is the definitive treatment for progressive scoliosis, however it comes with a moderately high complication rate. There is some evidence that surgery is effective for reducing the deformity, but insufficient evidence that it improves functional outcomes, caregiver outcomes, and quality of life. This project focuses on developing robust methods to measure child and family-centred outcomes following spinal surgery for children with neuromuscular scoliosis. The project will involve both quantitative and qualitative methodologies. We hope to recruit a high quality allied health, nursing or medical professional into this PhD position and experience in disability is desirable.

26. Comprehensive clinical phenotyping of individuals with stuttering

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Stuttering is characterized by dysfluent speech, which may have a profound effect on an individual's social and mental wellbeing. Up to 11% of children begin stuttering by 4 years of age. Approximately one-third of affected preschoolers will go on to develop a persistent stutter. Stuttering interventions are effective for some children in the preschool years; yet there are less effective treatments for older children, adolescents and adults. Further, it is not possible to predict who will develop persistent stuttering. Understanding the genetic bases of stuttering will provide insights into the underlying biology, potentially leading to stratification of stuttering into clinically relevant subtypes and more targeted therapies. Estimates for the heritability of stuttering range from 0.4-0.8, indicating a strong genetic influence. Family-based studies have implicated rare variants in 4 genes, however it is not clear whether these genes are also relevant to stuttering in the general population. We hypothesize that common genetic variation makes a substantial contribution to the risk of stuttering and propose that this is most effectively investigated by undertaking a genome-wide association study (GWAS), using a large population-based sample of people with stuttering. Our Australian team at the WEHI, MCRI, QIMR and University of Melbourne are leading an international GWAS consortium to identify genetic loci and molecular pathways important to stuttering. As part of this effort, we have already collected speech data on almost 1000 individuals with stuttering, the largest cohort of its nature to date, with data collection ongoing. Despite decades of interest in the symptomatology of stuttering, existing deep phenotyping studies are largely limited to small highly biased clinical samples. This PhD project will focus on comprehensive clinical phenotyping of individuals with stuttering recruited to our GWAS study. Our genotype-phenotype approach will allow us to begin to

disentangle the biological pathways and gene networks that underlie stuttering, the most common speech disorder.

27. Mental health and participation outcomes for children and youth with cerebral palsy

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Mental health problems and participation restrictions are frequently reported for children with disabilities. There is little information on the long-term relationships between mental health and participation in the presence of child-onset disability, or about how mental health is affected by rehabilitation services provided for these children and families. This collaborative program of research is being led by a Swedish research team (Prof. Mats Granlund) and will investigate relations between participation and factors affecting participation with a focus on mental health and services provided to children with disabilities who have mental health problems. The program is in two parts: (i) children will be followed for 5 years to collect long-term outcome data on participation and mental health; and (ii) children, parents and professionals will collaborate to develop and evaluate methods for involving children and parents in the (re)habilitation intervention process. There is an opportunity for an Australian doctoral scholarship (with stipend) within this program of work with a particular focus on outcomes for adolescents and young adults with cerebral palsy. We hope to recruit a high-quality allied health, psychology or medical professional into this PhD position and experience in disability is desirable.

28. Supporting young people with complex disability to participate in important life situations

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Being able to attend and be involved in a variety of activities and meaningful life situations is a strong contributor to long-term health and wellbeing. Young people who have intellectual impairments, with or without associated physical impairments, often experience restrictions in their participation in community life, including employment and recreation. Programs are being designed that aim to support the learning of skills needed to effectively navigate the environments in which community activities occur. Development of participation-supporting skills (e.g. setting participatory goals, determining relevant barriers and supports, gaining self-advocacy skills) is critical to enabling increased participation. This work sits within the NHMRC funded Centre for Research Excellence CP Achieve program, and is targeted towards investigating the feasibility, effect and potential for up-scaling of a participation-focused intervention, suitable for those with intellectual impairments. There is an opportunity for a doctoral student within this program of work. We hope to recruit a high-quality allied health, psychology or educational professional into this PhD position and experience in disability is desirable.

29. Understanding and defining supportive health/NDIS service environments

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As young people with long term health conditions transition through adolescence and into adulthood they become more responsible for how they navigate their environments to gain access to, and to participate in, a range of important activities. One environment known to be of great importance and a significant challenge, is the navigation of health and disability service provision in the adult service provision sector. Currently we have limited knowledge about how parents and young people with cerebral palsy in Australia work together to navigate this aspect of the young person's transition to adulthood. We know that some young adults with cerebral palsy will transition successfully with their usual supports, some will always need significant assistance, and we anticipate a third group who have the capacity to develop self-management skills but who struggle to do so. The goal of this program of work is to explore the impact of the health and disability service environments, the quality of the individuals' support networks on their access and use of services across settings. This work sits within the NHMRC funded Centre for Research Excellence CP Achieve program, and aims to identify modifiable barriers for more effective health and disability services transition for young adults with cerebral palsy. There is an opportunity for a doctoral student within this program of work. We hope to recruit a high-quality allied health, nursing, psychology or medical professional into this PhD position and experience in disability is desirable.

30. Adapt an evidence-based healthy lifestyle program to an Australian context

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Young people with developmental disability may experience long term social, physical and mental health issues that impact on their life participation and ability to live a healthy life. The transition period from childhood to adulthood provides an opportunity to develop self-management skills and assume greater independence, with or without some assistance. However, we don't know how best to support the development of self-efficacy, health literacy and participation skills in young people with cerebral palsy in Australia, to enable them to make good choices and live a healthy life. There are some 'lifestyle programs' available in other countries, but we don't know if they will meet the needs of young people with cerebral palsy living in Australia. The goal of this program of research is to identify what information young people with cerebral palsy need, and how best to provide this education in order for them to live a healthy and happy life. This work sits within the NHMRC funded Centre for Research Excellence 'CP-Achieve' program, and aims to develop and test a consumer-informed evidence-based healthy lifestyle program. There is an opportunity for a doctoral student within this program of work. We hope to recruit a high-quality allied health, nursing, psychology or medical professional into this PhD position and experience in disability is desirable.

31. Optimising use of everyday technology for children and adolescents with acquired brain injury

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Acquired brain injury (ABI) is a common cause of childhood disability. In children and adolescents, among the most common causes of ABI are traumatic brain injury, stroke, infection, tumour, hypoxia, and encephalitis. Many children with ABI experience long-term cognitive, communication, physical and social difficulties that are associated with reduced independence, participation and overall quality of life. Everyday technologies, such as smartphones and tablets, have great potential as popular, multifunction tools to support independence and participation following acquired brain injury (ABI). Almost all Australian adolescents and two-thirds of primary school aged children now own their own tablet or smartphone. However, there is evidence that everyday technologies such as these are under-utilised in rehabilitation contexts despite growing evidence to support their use as effective assistive devices across a range of disabilities. There is a distinct need to better understand current patterns of use, as well as health professional and caregiver familiarity, skill, knowledge and confidence in supporting children and adolescents with ABI to use technology to optimise independence and participation in everyday life.

This project will use a mixed methods approach to: (1) better understand how children and adolescents with ABI use everyday technologies, (2) identify the facilitators and barriers to supporting the use of everyday technologies in a rehabilitation context, and (3) examine if and how rehabilitation professionals and caregivers support and teach children to use of everyday technology in their home, school and community as part of their rehabilitation. This data will be used in the co-design of a health professional and family training package to optimise the use of everyday technology for children and adolescents with ABI. This project will fit under the broader umbrella of the MCRI ABI integrated knowledge translation program. Students would need a strong academic track record and interest in rehabilitation and technology is desirable.

32. Assessment and management of fatigue following paediatric acquired brain injury

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Acquired brain injury (ABI) is defined as any brain insult that occurs after birth. In children and adolescents, among the most common causes of ABI are traumatic brain injury, stroke, infection, tumour, hypoxia, and encephalitis. Fatigue is a frequently reported sequelae of acquired brain injury (ABI), and can negatively impact on a child's participation in everyday life. In childhood ABI, fatigue is associated with poor academic achievement, limited physical activity, and social and emotional problems. The effective management of fatigue is a clinical priority for paediatric rehabilitation services. However, there is minimal research that focuses on understanding the best approach to supporting children and families to

manage fatigue. This study will use a mixed methods design to examine existing approaches to the assessment and management of fatigue in children with ABI from the perspectives of children, families and paediatric rehabilitation professionals. This data will be used in the co-design of a fatigue management program for children with ABI. This project will fit under the broader umbrella of the MCRI ABI integrated knowledge translation program. Students would need a strong academic track record and interests in rehabilitation. This project will be based within the Neurodisability and Rehabilitation group at the Murdoch Children's Research Institute and the Victorian Paediatric Rehabilitation Service where the successful candidate will be supported by a highly experienced clinical research team.

Genetics

33. Rare Diseases Now - Great care for rare

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Rare diseases individually affect fewer than 1 in 2,000 births, but collectively they are common - over 5,000 patients are seen on the Melbourne Children's campus for rare disease diagnosis each year. Nationally, more than 15,000 Australian children born each year will have a shortened lifespan or experience disability due to a rare disease. About 80% of rare diseases are of genetic origin and they are estimated to cause 35% of deaths in children before one year of age, and up to 20% of paediatric hospital admissions worldwide. Despite genomic testing, the majority of children with a rare disease do not receive a genomic diagnosis and even fewer receive impactful interventions. At the beginning of 2020, the MCRI Rare Disease Flagship received almost \$2M over three years from the Royal Children's Hospital Foundation for Rare Diseases Now (RDNow), an exciting initiative to deliver genomic diagnoses and precise, personalised care to RCH families. Drawing on the research and clinical expertise at the MCRI and VCGS, RDNow will engage with non-genetics specialists within RCH to establish a campus-wide framework for undiagnosed children to have the best chance of receiving a diagnosis and to access the latest clinical trials and treatments. RDNow seeks an enthusiastic PhD student passionate about rare diseases for a project examining a key question in the rare disease field. Scope of potential projects includes novel genomic testing methods and analysis strategies, developing pathways for registries to study the natural history of a rare disease and linking to clinical trials and therapies. The student will address these challenges by being a member of the RDNow team to develop systems to improve access to rare disease diagnosis, linking new discoveries to natural history studies and clinical trials, and facilitate the broadening of genomic expertise into multiple RCH Departments. This project would suit an individual with a paediatric clinical background or undergraduate, postgraduate, or vocational genetics/genomics experience. A keen interest in rare diseases is essential. A publication track record in rare diseases or genomics is highly desirable. The successful applicant will develop collaborative relationships with RCH clinicians, MCRI scientists, the VCGS laboratory team and bioinformaticians.

34. Implementation considerations for a national program for expanded reproductive carrier screening

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Background: Publicly-funded genetic carrier screening in Australia is currently limited to individuals with a family history of a genetic condition, and particular ethnic groups. Most Australian couples who have children affected by severe recessive genetic conditions are not aware of their high chance of having an affected child. In May 2018, Federal Health Minister Greg Hunt announced \$20M funding from the Medical Research Future Fund (MRFF) for Mackenzie's Mission (MM), a research study to investigate how best to deliver a free, easily accessible RGCS program in Australia for all couples who wish to use it. MM will screen 10,000 couples for their chance of having a child with a condition due to mutation(s) in about 1300 genes. The aims of the MM carrier screening project are to:

- Develop and test processes for RGCS as provided by MM
- Evaluate the uptake of RGCS, frequency of increased-risk couples and their reproductive decisions
- Evaluate the implementation of RGCS
- Evaluate the screening experience of couples including
 - psychosocial impacts,
 - implementation challenges,
 - ethical issues and
 - health economic implications

PhD project design : The PhD student will take responsibility for a mixed-methods, longitudinal analysis of the MM program with a focus on implementation from the perspective of couples who participate in the study. This will include intrinsic and extrinsic influences on couples' decision-making about screening and about future reproductive choices. The candidate will work collaboratively across the MM research streams gathering data to support their PhD. Quantitative data (drawing on implementation and evaluation frameworks and existing scales including the multi-dimensional measure of informed choice, deliberation, decisional conflict and regret) will be collected and analysed to assess congruence of knowledge, attitude and behaviour to evaluate informed decision-making. The student will analyse relevant quantitative data collected in surveys from couples completed before and after screening provided through the MM program. The student will collect and analyse qualitative data in interviews with purposively selected individuals before and after screening to explore and explain decision-making. The outcomes of this PhD will include an evaluation of the MM program from the perspective of participating couples, recommendations to address barriers and enablers identified and participation in development of an implementation plan for a nationwide screening program. The project may include an evaluation of a delivered implementation plan.

Stipend: The candidate will be expected to apply for competitive PhD scholarships (NHMRC, University, etc.) although a 3-year PhD stipend is available for an excellent candidate.

Location The research will be undertaken at the Murdoch Children's Research Institute and MM is coordinated through the Australian Genomics Health Alliance. The PhD candidate will enrol with the Department of Paediatrics, University of Melbourne.

Infection and Immunity

35. Dose optimisation of antibiotics in children with cystic fibrosis using pharmacokinetic-pharmacodynamic modelling

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The aim of this project is to optimise antibiotic dosing in children with cystic fibrosis. The project involves: (i) leading a multicentre prospective audit to collect blood samples in children with cystic fibrosis (ii) using modelling to determine the pharmacokinetics (what happens to the drug in the body) and pharmacodynamics (the effect of the drug in the body) of antibiotics in children with CF. The model will then be used to simulate the antibiotic dose required to improve care for children with cystic fibrosis.

36. Application of intra-oral 3-Dimensional Scanning to monitor oral health in children

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The COVID-19 pandemic has highlighted the urgent need for improved options for tele-health, including tele-dentistry. Three-dimensional scanning promises considerable potential for recording and monitoring oral health. Although traditionally restricted clinically to orthodontics and prosthodontics, recent rapid developments in 3D technologies will expand its application to a much broader range of clinical and research settings including remote oral health assessment and automatized diagnostics. This PhD project will evaluate the validity of an intra-oral scanner to measure the presence and severity of dental caries and developmental defects in children of different ages in both primary and secondary dentition. The project will be nested within a number of large population-based and clinical high-risk cohorts at the Melbourne Children's Campus. The PhD involves performing clinical assessments, including dental examinations and 3D intra oral scanning, on children, with a substantial analytical component to validate the intra oral scanner for population health research and as a diagnostic and patient management tool. The successful applicant will join a dynamic, supportive and productive research team based in Melbourne, Australia and Copenhagen, Denmark. The candidate will be based at the MCRI but will work closely with the product development team at 3Shape (Denmark). The PhD program will include a full-time PhD stipend, and potential funding for international travel, including part of the candidature to be based in Denmark. Part-time candidature may be considered.

37. Cluster RCT of a multi-component intervention package to improve maternal and childhood vaccination in Victoria

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Maternal and childhood vaccination is vital to ensure the health of women and children, but concern regarding vaccine safety and effectiveness remains a pressing issue. Uptake of both influenza and pertussis vaccines in pregnancy is poor, despite being strongly recommended. This leaves many pregnant women and their infants needlessly vulnerable. Childhood vaccine coverage and timeliness, including birth Hepatitis B vaccine, are also an ongoing challenge. Pregnancy is a critical time for vaccine decision-making, when expectant parents must consider both maternal vaccines and childhood vaccines for their baby. To date, there have been no evidenced-based interventions to optimise maternal and childhood vaccine uptake. To address this important gap, we have developed an innovative, evidence-based, multi-component intervention package tailored for midwives at the Practice, Provider and Parent (P3) levels to meet the diverse and complex information needs of pregnant women. Our pilot study found the P3 intervention to be acceptable and feasible for use by midwives and parents and informed updating and development of the next iteration of the P3-MumBubVax intervention. Now, with a multi-disciplinary team of researchers we need to assess the impact and cost-effectiveness of this approach to support rapid translation into practice. We are seeking a PhD student to lead the conduct of a cluster randomised controlled trial in Victoria to evaluate the P3-MumBubVax intervention package using a factorial design for improving uptake of influenza and pertussis vaccination among pregnant women, timely uptake of routine infant vaccines, maternal vaccine knowledge, attitudes and beliefs and midwife confidence in discussing vaccination. We will also assess the implementation barriers and facilitators to inform adaptability and scalability and evaluate the expected cost-effectiveness of P3-MumBubVax compared to usual care. The trial will be conducted in antenatal centres in Victoria alongside Generation Victoria (GenV), a whole-of-state Australian birth cohort for discovery and interventional research.

Population Health

38. Genetics of childhood hearing loss

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Congenital hearing loss affects 1-3 per 1000 children. Over the last quarter century, remarkable advances have transformed these children's life chances: universal newborn hearing screening, early access to technology, intervention and cochlear implantation. Yet, early diagnosis and intervention do not guarantee improved outcomes. The Victorian Childhood Hearing Impairment Longitudinal Databank (VicCHILD) is a statewide databank (with more than 950 hearing-impaired children to date) designed to discover the hidden factors that predict language and quality of life outcomes. One of the possible factors may be the underlying genetic aetiology, poorly understood to date due to the lack of comprehensive diagnostic testing. Recent years have seen great advances in genetic testing. In 2017-2018, exome sequencing was offered to newborns in VicCHILD with moderate to profound hearing loss, leading to monogenic diagnoses for 59 of 106

newborns, raising diagnostic rates from 22% to 56% of the eligible VicCHILD cohort and changing management for 51%. Translation of exome sequencing into routine clinical care now demands evidence as to its prognostic prediction of long-term child outcomes, cost-utility and cost-consequence benefits. We seek an outstanding clinician doctoral researcher to complete exome sequencing for the rest of the 2017-2108 VicCHILD cohort with mild and unilateral hearing loss, and to complete collection of the 5-7 year old longitudinal outcomes of the whole 2 year VicCHILD cohort.

39. Associations between COVID-19 psychosocial stressors and immune and cardiometabolic markers among adolescents

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Adolescents are at high risk of infection by the SARS-CoV-2 virus. Adolescents have also been disproportionately impacted by the pandemic via educational disruption, isolation, employment loss, financial and housing stress, substantially increasing the risk of population mental ill health and death by suicide. COVID-19 has also been accompanied by 'a second pandemic' of racism that has impacted many adolescents from Indigenous and from ethnic minority backgrounds. Racism, including media exposure to racism, has profound negative impacts on adolescent mental health including suicidality, depression, anxiety, substance use as well as physiological changes such as high blood pressure and raised markers of inflammation. Associations between psychosocial stressors, mental health and immune and cardiometabolic markers are also increasingly documented among adolescents and young people. Exploring associations between COVID-19 related psychosocial stressors and immune and cardiometabolic markers among adolescents is required to inform evidence based responses to address health inequities in cardiometabolic disease and mental health. The project will use secondary data from the Young Lives cohort study of ~1000 adolescents to investigate how psychosocial stressors related to the COVID-19 pandemic are associated with immune and cardiometabolic markers among adolescents. Evidence generated will be used to inform policy decision making and action to reduce adolescent health inequities in cardiometabolic disease and mental health.

40. Longitudinal and secular trends in outcomes for adolescents with hearing impairment in Victoria

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The last 25 years have seen significant changes to methods of detection, intervention and services available to children born in Victoria with a hearing impairment. Universal newborn hearing screening, early intervention and cochlear implantation have revolutionised the opportunities for hearing-impaired children, but their language and learning still lag behind their hearing peers. Several longitudinal cohort studies in Victoria have followed children through childhood to examine language, psychosocial, mental health and quality of life outcomes. The CHIVOS study (Children with Hearing Impairment in Victoria Outcome Study)

followed children born in 1991 to 1993 (when detection was largely opportunistic) with follow up waves taking place at ages 7 to 8, 12 to 14 and 17 to 19. The SCOUT study (Statewide Comparison of Outcomes Study) followed children born a decade later between March 2003-February 2005 (when detection was via risk factor screening) and this cohort have been followed up at ages 5 to 6, 10 to 12 and will be aged 17 to 18 at next proposed follow up in 2021. The VicCHILD (Victorian Childhood Hearing Impairment Longitudinal Databank) study began in 2011/12, incorporating the SCOUT cohort (via informed consent) and inviting all children born in Victoria with a permanent hearing impairment from 2005 onwards into the study, with continuous follow ups of children aged 5-7 years and 10-12 years and proposed future follow up at ages 17-18 years. We seek an outstanding doctoral researcher to examine longitudinal outcomes of the SCOUT cohort and secular trends in outcomes for adolescents born in Victoria with a hearing impairment over the last 25 years. This will involve assessment of the SCOUT cohort at age 17-18 years including parent- and child-reported outcomes, direct assessments, accessing academic (NAPLAN) results, and biological sampling. Examining secular trends will incorporate data already collected from the CHIVOS cohort.

41. Inequities in children's mental health: evidence to inform precision policy responses

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Inequities in children's health and development refer to differential outcomes that are unjust and preventable. Australian children exposed to disadvantage from infancy are at higher risk of poor mental, physical and academic outcomes by late childhood. These inequities track forward into adulthood, where they carry high costs for individuals and society. Reducing child inequities is a public health priority. While Australian governments are committed to reducing inequities, the translation of currently available evidence into effective action continues to be challenging. The Changing Children's Chances project works collaboratively with policymakers to generate evidence that identifies clear and actionable policy pathways to reduce inequities in children's health and development. A Changing Children's Chances scholarship is available for a PhD candidate to contribute a mixed-methods study. The project will investigate how evidence related to the modifiable social determinants of child mental and developmental health inequities can inform policy decision making and action. The project will involve quantitative analysis of existing data (e.g. the Longitudinal Study of Australian Children) and interviews with stakeholders. The outcomes will help to inform how researchers can better deliver evidence to meaningfully inform policy, and are expected to be of high relevance to efforts to address the impacts of COVID-19 on children's mental and developmental health. The PhD will be conducted through the University of Melbourne and the successful candidate will be based at the Murdoch Children's Research Institute. The candidate will be supported by the Changing Children's Chances team and the broader research environment of the Centre for Community Child Health. Key reading: Goldfeld S, Gray S, Azpitarte F, et al. Driving precision policy responses to child health and developmental inequities. *Health Equity*. 2019; 3(1): 489-494.

42. The impact of positive and adverse experiences on children's cardiovascular disease risk and mental health outcomes

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Non-communicable diseases and mental illness account for a substantial portion of the global burden of disease. These diseases often have their origins in childhood. A key challenge facing governments internationally is understanding how to effectively prevent NCDs and reduce inequities in health outcomes at the earliest possible stage. Children are growing up in a social environment that includes both adverse and positive experiences. Exposure to childhood adversity (e.g. household mental illness) has harmful effects on physical and mental health throughout the life course. Similarly, exposure to positive experiences (e.g. a stimulating learning environment) contribute to optimal health and developmental outcomes. However, positive childhood experiences remain under-explored in relation to later health outcomes, including how they buffer against adversity. The project will use quantitative analysis of existing data (e.g. the Longitudinal Study of Australian Children) to generate evidence about the impact of positive and adverse experiences on children's cardiovascular disease risk and mental health outcomes. Findings can be used to inform policy decision making and action to reduce inequities in children's physical and mental health. This PhD project is not a funded project, so the candidate will need to apply for a PhD scholarship or other types of funding. The PhD will be conducted through The University of Melbourne and the successful candidate will be based at the Murdoch Children's Research Institute. The candidate will also be supported by the Changing Children's Chances team and the broader research environment of the Centre for Community Child Health. The Changing Children's Chances project works collaboratively with policymakers to generate evidence that can inform how existing policy interventions can be optimised to reduce inequities in children's health and development. Key reading: O'Connor M, Slopen N, Becares L, et al. Inequalities in the distribution of childhood adversity from birth to 11 years. *Academic Pediatrics*. 2020;20(5):609-618.

43. Improving lifetime outcomes for babies in special care nurseries

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More than 10% of newborns are admitted to special care nurseries (SCN), many experiencing lifelong adverse outcomes. Within the 'Generation Victoria' cohort, targeting all 160,000 Victorian births over two years from 2021 and encompassing all 28 SCNs, this PhD will assist in setting up a new statewide SCN registry. It will overcome research challenges of dispersed care and difficulties in long-term outcomes measurement to build an evidence base for better physical, mental and developmental outcomes. GenV's linked datasets, digital 'ePhenome' will support exploration of the impacts of variations in care and comparisons with the general population. It offers immense opportunities to establish a career and leadership in transformative newborn and child health services research.

44. Precision prediction of maternal and child outcomes from routine fetal ultrasounds

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Prediction of the great obstetric and newborn syndromes remains frustratingly impossible, resulting in avoidable burden to maternal and child health and health care services. Artificial intelligence could transform the predictive value of routine fetal ultrasounds - if a mega-repository existed combining ultrasounds with well-phenotyped outcomes. This PhD will help develop and capitalise on an internationally-unique statewide consented repository of fetal ultrasounds for Victorian babies born 2021-22 and their mothers, working within the 'Generation Victoria' cohort, its linked datasets and digital 'ePhenome'. The landmark GenV offers immense opportunities to establish a career and leadership in the digital transformation of pregnancy and/or childhood health.