MCRI PhD Projects for 2020

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Lab-based Projects

Cell Biology

Modelling human cartilage and bone disorders using pluripotent stem cells

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

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

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.

Clinical Sciences

The role of apoptosis in gonocyte transformation and testicular malignancy

Dr Ruili Li
ruili.li@mcri.edu.au
9936 6757

Professor John Hutson
john.hutson@rch.org.au

Congenital undescended testis (UDT), or cryptorchidism, affects 2-4% of newborn boys and leads to a 5 fold increase in testicular cancer (seminoma), and 30-60% risk of infertility. Seminomas in young men with UDT arise from persisting immature germ cells. We propose that persisting neonatal germ cells (gonocytes) that cause cancer are the gonocytes that failed to transform into into spermatogonial stem cells (SSC) or failed to disappear by apoptosis. The PhD project will use rodent models and human biopsies from patient with undescended testis to study the role of apoptosis in the fate of germ cells during postnatal development and the molecular and cellular mechanism of gonocyte transformation into SSC. This will provide clues for both the basic knowledge on germ cell development as well as novel ways to prevent testicular cancer, such as supplementary hormonal treatment or a different timing for surgery in male infants with UDT.

Cord Blood Stem Cell Therapy in Paediatric Cardiac Surgical Interventions

Associate Professor Salvatore Pepe
salvatore.pepe@mcri.edu.au
9345 4114
Associate Professor Christian Brizard
christian.brizard@mcri.edu.au
9345 5200

Associate Professor Joe Smolich
joe.smolich@mcri.edu.au
9345 4571

The surgical innovation of recent decades has enabled a remarkable increase in survival outcomes after surgical operations in neonates and older children for congenital heart disease (CHD). However subsequent development of cardiac dysfunction and failure remains a high risk in those with more severe forms of CHD, thus contributing to persistent morbidity and reduced survival. Cord blood, obtained from the placenta and umbilical cord, contains haematopoeitic stem cells and other pluripotent cells. Our custom utilisation of these cells harnesses the paracrine and exosomal properties of these cells when applied with our unique methodology to the heart. By promoting physiological growth for increased myocardial mass, maturation and improved contractile performance we seek to limit post-operative low cardiac output syndrome and heart failure. Studies will employ large animal and cellular models, imaging and laboratory analyses. Students ideally should have a background in areas such as immunology, haematology, genetics, biochemistry and physiology. The project is also suitable for students with large animal veterinary skills and surgical interests. We also have opportunities for medical graduates interested in cardiology or cardiac surgery based projects related to our current clinical trial work.

Genetics

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

Professor John Christodoulou
john.christodoulou@mcri.edu.au
9936 6515

Professor David Thorburn
david.thorburn@mcri.edu.au
8341 6235

Dr Alison Compton
alison.compton@mcri.edu.au
8341 6287

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.

Pluripotent stem cell models of mitochondrial disease

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

Professor David Thorburn
david.thorburn@mcri.edu.au
8341 6235

Dr Alison Compton
alison.compton@mcri.edu.au
8341 6287

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.
2) 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.

Mitochondrial disease caused by ATAD3 rearrangements: Unravelling the complexity

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

Professor David Thorburn
david.thorburn@mcri.edu.au
8341 6235

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 heterogeneous, 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" Sequencing technologies and assessment of ATAD3 protein complexes.

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

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

Dr Emma Baker
emma.baker@mcri.edu.au

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

Dr Minh Bui

Fragile X syndrome (FXS) is a common single gene cause of intellectual disability (ID) and autism 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, >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 PhD project will utilise 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 autism 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. This project is suitable for students interested in clinical and/or laboratory research, as well as bio-statistics.

Applying new genomic technologies to understand the genetic basis of Autism Spectrum Disorder

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

Dr Kiymet Bozaoglu
kiymet.bozaoglu@mcri.edu.au
9936 6563

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 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.

Using cerebral organoids for the study of tuberous sclerosis complex

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

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

Associate Professor Richard Leventer

richard.leventer@mcri.edu.au
9345 5661

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. In this project the candidate will developing iPSC-derived cerebral organoid models to investigate the aetiology of tuber formation and resultant epilepsy. They will utilise molecular and cellular techniques including stem cell culturing, differentiation, immunostaining and advanced microscopy to analyse organoid models of TSC. There is considerable scope for collaborative interaction with clinicians and bioinformaticians involved in the program.

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

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

Dr Yujing Gao
yujing.gao@mcri.edu.au
9936 6563

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.

Identifying the genetic causes of brain malformation in children

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

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

Associate Professor Richard Leventer
richard.leventer@mcri.edu.au
9345 5661

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 as part of a large multidisciplinary team.

Understanding the molecular mechanisms of Autism using human NF1 stem cell derived neuronal networks

Dr Kiymet Bozaoglu
kiymet.bozaoglu@mcri.edu.au
9936 6563

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

Dr Jonathan Payne
jonathan.payne@mcri.edu.au

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.

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

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

Professor Martin Delatycki
martin.delatycki@vcgs.org.au
83416293

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). Preliminary studies suggest the expansion is the most common genetic cause of ataxia. 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.

Infection and Immunity

Vive La Resistance: Mapping Antimicrobial Resistance in Children

Associate Professor Penelope Bryant
penelope.bryant@rch.org.au

Professor Nigel Curtis
nigel.curtis@rch.org.au

Dr Amanda Gwee
amanda.gwee@rch.og.au

Antimicrobial resistance (AMR) is a major threat because antibiotics underpin modern healthcare. Half of all Australian children receive at least one prescription by their first birthday, one of the highest rates in the world. How antibiotic use relates to AMR is unknown in children, however if we continue to use antibiotics at this rate resistance will increase. This is an unsolved problem in children because we do not know i) the prevalence or location of AMR, ii) how antibiotic use relates to AMR and iii) how other factors impact AMR.
This project aims to address these gaps by mapping AMR in RCH patient populations from across greater Melbourne, validating AMR screening methodologies and exploring the links with risk factors (e.g. socio-economic status, hospitalisation). Ultimately, the aim is to scale-up this project across Victoria and Australia. The results of this project will provide critical information on who, what and where AMR is, the associated risk factors and allow the design of targeted interventions to reduce AMR. There has never been a study of AMR

prevalence in children in all-comers to any hospital worldwide, so this is the first of its kind.
The successful candidate will be based in the Infection & Immunity theme at MCRI and will be supported by a multidisciplinary team of researchers on the Melbourne Children's Campus. There is some flexibility regarding the direction the project takes, and the successful candidate will have some room to design their own aspects of the project. A PhD scholarship is available for the successful candidate to pursue this project. Candidates will be expected to apply for other competitive external scholarships. All applicants will be considered, however this project is best suited to clinicians.

What is the microbiological effect of a single dose of azithromycin given in labour?

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

Professor Fiona Russell
fmruss@unimelb.edu.au

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

Administration of azithromycin during labour can reduce maternal pathogen carriage, and lower infection risk in both mother and infant, and has considerable potential impact in resource-limited settings. Bulabula MaPei is a randomised controlled trial in Fiji, to examine the effect of a single oral dose of azithromycin given to women in labour.

In this PhD, you will use microbiological approaches to understand the benefits of this approach by determining the effect of antibiotic (compared with placebo) on bacterial carriage in both the mother and the infant. It is also important to determine whether the use of broad-spectrum antibiotics in this way might have an adverse impact, and so you will determine this by measuring antibiotic resistance in the bacterial isolates.

You will be based at the Murdoch Children's Research Institute in the microbiology laboratory headed by A/Prof Satzke. You will also be supported through supervision by Prof Fiona Russell who is the overall lead of Bulabula MaPei, and Dr Jonathan Jacobson who is a post-doctoral scientist in microbiology. This project is based in Melbourne, and you will also have the opportunity to travel to present findings to project partners in Fiji and/or conferences.

Streptococcal transmission and disease

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

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

Professor Andrew Steer
andrew.steer@rch.org.au

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 respiratory viruses (e.g. Influenza) 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.

Synergistic and antagonistic interplay between Streptococcus pneumoniae and respiratory viruses

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

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

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.

Population Health

Improving the diagnosis of tree nut allergy using novel methods

Dr Kirsten Perrett
kirsten.perrett@mcri.edu.au

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

Dr Melanie Neeland
melanie.neeland@mcri.edu.au

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-Lab Projects

Clinical Sciences

Modelling cardiovascular dynamics during the birth transition in normal and at-risk babies

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

Associate Professor Joe Smolich
joe.smolich@mcri.edu.au

As soon as a baby is born, the locus of respiration must shift from the placenta to the lungs. This transition involves profound and rapid changes in the cardiovascular system, which are still not fully understood given the ethical and practical challenges of measuring and manipulating key physiological parameters. This means that current medical practices for delivering at-risk babies may not be optimised, with birth-related complications associated with prematurity, birth asphyxia and congenital heart disease frequently leading to brain haemorrhage, life-long health/neurodevelopmental problems and death. The Heart Research group at the Murdoch Childrens Research Institute is at the forefront of research into birth transition dynamics. A PhD project is available for an outstanding student to develop a state-of-the-art computational model of cardiovascular transitions at birth. This project will benefit from our established expertise in fetal and post-birth cardiovascular modelling and a large database of high quality experimental data of birth transition dynamics. The student will incorporate new components into an established modelling framework and will use the model to investigate how the delivery and/or resuscitation of at-risk babies may be optimised.
Students will be enrolled through the University of Melbourne and will work within the Heart Research group at the Murdoch Childrens Research Institute. Applicants will be required to apply for a competitive scholarship such as the Graduate Research Scholarship from the University of Melbourne.
Applicants will need qualifications in engineering, mathematics or physics (preferably with a biomedical major). Experience with computer programming (e.g. Matlab, python), physiological modelling and numerical methods is preferred. Excellent written communication skills are required.

Using technology to measure pain in children with developmental disabilities

Dr Adrienne Harvey
adrienne.harvey@mcri.edu.au
03 9345 5522

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

Chronic pain is common in children with cerebral palsy and other developmental disabilities, yet it is not well understood, is under-identified and poorly managed in this population. One contributing factor is the underutilisation of tools that can adequately identify and measure pain in this medically complex and heterogeneous group. In the typically developing population, self-report is the "gold-standard" for measuring pain. The selection and administration of pain tools in cerebral palsy and other disabilities is complicated by varying abilities of children and adolescents to self-report pain across a spectrum of disability and ages. Many are unable to self-report due to cognitive and/or

communication limitations. Consequently, no "gold standard" exists.
This PhD project aims to use technology to develop and validate innovative methods for identifying and measuring pain in children with cerebral palsy and other developmental disabilities. It will involve; 1) developing the methods and 2) validating the methods in children across a range of ages and impairment levels.

Evaluating health outcomes of transgender children and adolescents

Dr Ken Pang
ken.pang@mcri.edu.au
93455986

Dr Michelle Tollit
michelle.tollit@mcri.edu.au

Referrals of young transgender individuals to clinical services are rising exponentially across the western world. Consistent with this, recent population-based estimates suggest that the prevalence of young people identifying as transgender is ~1%, which is much higher than previously thought. Providing optimal clinical care for transgender young people is critical. A recent community-based survey of 859 Australian trans youth found a significant proportion had been diagnosed with depression (74.6%) and anxiety (72.2%), with 79.7% of respondents reported having self-harmed and 48.1% having attempted suicide. Many of these young people had never accessed gender-affirming health care, and there is increasing evidence that providing supportive clinical care to transgender youth significantly improves mental health and wellbeing.
The Royal Children's Hospital Gender Service (RCHGS) provides care to transgender children and adolescents, and is one of the largest multidisciplinary clinics of its kind in the world. While our team recently released the first ever clinical guidelines specific for transgender children and adolescents - as highlighted by a recent editorial in The Lancet - there is still a lack of good research data to inform clinical practice in this nascent field. To address this gap in knowledge, the RCHGS commenced a longitudinal cohort study known as Trans20 at the start of 2017. Trans20 aims to evaluate the clinical outcomes of individuals receiving care through the service, and is currently on track to enrol >600 patients into the study during 2017-20. Data is collected annually across multiple domains, including gender identity, mental health, physical health, quality of life and family functioning. This rich dataset offers a tremendous opportunity for interested PhD students to address important questions in the field of transgender health. In particular, candidates with an interest in transgender health, and a background in psychology, paediatrics, psychiatry, or endocrinology are encouraged to apply.

Resilience and coping in children with chronic conditions affecting their physical appearance

Dr Louise Crowe
louise.crowe@mcri.edu.au
9936 6762

Associate Professor Cathy Catroppa
cathy.catroppa@mcri.edu.au

Children coping with chronic illness need strong resilience skills, however, children whose condition alters their physical appearance may have increased difficulties with resilience and coping skills. This project will look at how resilience and coping are measured in children. Following this, children with a chronic illness that alters their physical appearance will be compared to children with chronic illness and typically developing children. Groups will be compared on factors such as self-esteem, coping strategies and mental health. Children with chronic illness will be patients of the Royal Children's

Hospital. Children will be of school-age. This is an under researched topic and the findings have valuable clinical implications.

Infection and Immunity

MIND the Vax Gap: Measuring Immunisation in NeuroDiverse populations and developing an intervention to improve uptake

Associate Prof Margie Danchin
margie.danchin@rch.org.au

Dr Alexandra Ure
alexandra.ure@unimelb.edu.au

Dr Jessica Kaufman
jess.kaufman@mcri.edu.au

We are seeking a high-quality clinical graduate (ie doctor, nursing, psychologist or allied health) to contribute to a mixed methods study focused on vaccine hesitancy and uptake among children with Autism Spectrum Disorder (ASD) and their siblings. The preferred candidate will have an interest in social science, behavioural research and/or mixed methods research and intervention development and clinical trials.
This is the first study in Australia to 1) assess vaccine hesitancy and vaccine uptake among children with ASD and their siblings; 2) identify barriers and facilitators to uptake; and 3) design and pilot a tailored intervention to reduce hesitancy and increase uptake in this vulnerable population. Overview: ASD is a neurodevelopmental condition of unclear aetiology, with a genetic explanation identified in only 15-20% of cases. It is common in Australia, affecting approximately 164,000 or 4% of the population, and is generally diagnosed in the pre-school years. While studies have repeatedly refuted an association between ASD and vaccines, particularly MMR, up to 10% of Australian parents or expectant mothers are still concerned about an ASD-MMR link. Recent research from the US has shown that children with ASD and their younger siblings have lower rates of vaccine uptake than children without ASD, leaving them vulnerable to vaccine-preventable diseases (VPDs). However, little is known about current levels of vaccine hesitancy and uptake among children with ASD and their siblings in Australia. Furthermore, it is unclear whether the perceived ASD-MMR link is the primary factor influencing uptake and hesitancy in this population, or whether other factors, such as behavioural challenges or anxiety, may be implicated. By comparing data for families with ASD and with Down Syndrome (DS), a neurodevelopmental condition with no perceived link and a clear genetic cause, we are aiming to develop and pilot an intervention that specifically targets identified barriers and influencing factors unique to ASD to improve vaccine uptake.
The candidate will work with an experienced team of researchers from RCH, MMC, Macquarie University and Baylor College of Medicine and Texas Children's Hospital, USA. This study will involve several phases and methods including quantitative surveys, a qualitative intervention development process and a pilot study to assess acceptability, feasibility and preliminary impact of the intervention. Larger funding will be sought to test effectiveness of the intervention through an RCT.

Determining the early life influences of childhood disease

Professor Nigel Curtis
nigel.curtis@rch.org.au

Dr Nicole Messina
nicole.messina@mcri.edu.au

9345 6366

The Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR) study is a randomised controlled trial (RCT) to assess the effect of neonatal BCG (tuberculosis) vaccination on clinical allergy and infection outcomes over the first five years of life. For more information see https://lifecourse.melbournechildrens.com/cohorts/mis-bair/

This PhD project will leverage the existing extensive MIS BAIR databank to investigate the contributing factors to the development of asthma, infections, eczema and/or allergy. In addition, they will have the opportunity to contribute to the analysis of the primary outcomes of the clinical trial.

Short course treatment of acute septic arthritis and osteomyelitis in children

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

Professor Nigel Curtis
nigel.curtis@rch.org.au
9345 6366

Antibiotic treatment of septic arthritis and osteomyelitis in children traditionally requires a minimum of 2-4 days of IV therapy followed by oral therapy for 3 weeks. However, a previous studies in children with bone and joint infections found that there was no difference in cure between 2 and 3 weeks of oral therapy. This is a randomised factoral design non-inferiority trial of short course antibiotic therapy for children with acute septic arthritis and osteomyelitis.

Inclusion criteria: Children 1-9 years with acute haematogenous septic arthritis or osteomyelitis. Primary end points: Proportion of children with complete recovery at 6 weeks defined by no symptoms or signs of acute haematogenous osteomyelitis or septic arthritis.

Population Health

Biostatistical methods for causal inference in the presence of missing data

Dr Margarita Moreno-Betancur
margarita.moreno@mcri.edu.au

Professor John Carlin
john.carlin@mcri.edu.au

Associate Professor Katherine
katherine.lee@mcri.edu.au Lee

Causal inference constitutes an exciting and very active field of biostatistical research that has great impact potential given its relevance to health research. The proposed project seeks to investigate methods for causal inference in the context of missing data, which is a very common problem in longitudinal studies. This will involve evaluation and extension of methods, such as multiple imputation, within the context of modern causal methods such as inverse probability weighting. This is a very topical area of research. The research will be motivated by case studies from the Murdoch Children's Research Institute LifeCourse initiative, which comprises over 40 cohort studies in child and adolescent 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 within a very active team of missing data methods research. The candidate will be supported within the broad

research environment of the Victorian Centre for Biostatistics (ViCBiostat). Graduates with strong background in biostatistics or statistics are encouraged to apply.

Racism and adolescent health in the school context: Investigating data from the Speak Out Against Racism (SOAR) student survey

Associate Professor Naomi Priest
naomi.priest@mcri.edu.au

Dr Meredith O'Connor
meredith.oconnor@mcri.edu.au
9345 6539

Racism is a system that stratifies, devalues and disempowers groups considered inferior and differentially allocates opportunities and resources within society. Considerable evidence documents racism's harmful effects on health, including for children and adolescents. One of the important contexts in which racism can arise for young people is school, which is a critical setting for the development of self-esteem and identity. This project will use data from the Speak Out Against Racism (SOAR) student survey, a large-scale, population representative cross-sectional study of 4,664 government school students in Years 5-9 in New South Wales and Victoria. Responses were collected across 23 schools in metropolitan and regional areas in 2017. This data provides an opportunity for a PhD student to explore a range of themes relating to racism and adolescent health using quantitative analytic techniques such as mediation analysis and multi-level modelling. Potential themes that can be explored in this data include, for example: the health effects of experiencing and witnessing racism; skills and competencies that allow young people to thrive as 'global citizens' including responding to racism; and characteristics of schools that promote inclusive communities.

Key readings:

- Priest N, Paradies Y, Trenerry B, Truong M, Karlsen S, Kelly Y. A systematic review of studies examining the relationship between reported racism and health and wellbeing for children and young people. Social Science and Medicine. 2013;95:115-127
- Priest N, Chong S, Truong M, et al. Findings from the 2017 Speak Out Against Racism (SOAR) student and staff surveys. Canberra: Centre for Social Research and Methods, Australian National University;2019.
- Priest N, King T, Bécares L, Kavanagh AM. Bullying Victimization and Racial Discrimination Among Australian Children. American Journal of Public Health. 2016;106(10):1882-1884.

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

Dr Valerie Sung
valerie.sung@rch.org.au
9345 4363

Dr Lisa Mundy
lisa.mundy@mcri.edu.au
9345 7978

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.