The University of Melbourne, Department of Paediatrics and Murdoch Childrens Research Institute

Faculty of Medicine, Dentistry & Health Sciences

HONOURS & MASTERS PROJECTS 2024

Honours and Master of Biomedical Science

Honours and Masters Information Evening in person, **Tuesday 29 August, 4.30pm onwards**

Online webinar will be held on **Monday 4 September at 5pm**

Register here

Contents

Laboratory based

Cell Biology

1. Using iPSC derived skeletal muscle cultures to study muscle disease

Using iPSC derived skeletal muscle cultures to study muscle disease   This project aims to use skeletal muscle derived from induced pluripotent stem cells (iPSCs) collected from patients with rare inherited muscle disorders, like Duchenne muscular dystrophy (DMD) and Nemaline myopathy.   The protocols needed to complete this work have been developed in our laboratory and we are now using these methods to study muscle grown in a dish in both 2 and 3 dimensional models.   Cell culture-based models of muscle diseases will greatly enhance our ability to assess disease and develop novel therapeutic approaches to treat these debilitating conditions.   The projects will use stem cells from patients with various muscle diseases including Nemaline myopathy, Collagen VI myopathy and mitochondrial disease.   We will teach you all that is required to grown skeletal muscles from iPSCs and how to phenotype the relevant condition in vitro.   The skills you will learn include aseptic tissue culture techniques as well as laboratory-based methods such as, immunocytochemistry, flow cytometry, western blotting and quantitative real-time PCR (RT-qPCR).

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Available as Masters Project: Yes

2.   Characterising the distribution of human cells in the mouse tissues

Humanised mouse models, generated by transplanting human HSCs into mice, have made significant contributions to our understanding of haematopoiesis, immune responses, and the development of novel therapeutic strategies for blood-related disorders. This study aims to assess the presence and distribution of human-derived IPS HCS cells within the immunocompromised mouse (NSGWB strain) tissues through histological analysis. Various staining techniques will be employed to visualise the engrafted human cells within the mouse tissues, followed by examination of the tissue under a light microscope or a fluorescence microscope, depending on the staining technique used. This will allow us to observe the distribution, localisation, and morphology of the engrafted human cells within the mouse tissues and facilitate the identification of specific tissue compartments where the engrafted cells reside and their interaction with the mouse cellular components. Overall, this project will provide valuable tool for studying the behaviour of human HSCs in mouse models and will offer insights into their engraftment and contribution to the hematopoietic system.

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3.   Investigating M. abcessus infection in the lung epithelium

The incidence of non-tuberculous mycobacteria infections has been steadily increasing worldwide. Mycobacterium abscessus (M. abscessus) can cause lung infections in both seemingly healthy individuals and patients with chronic lung diseases, such as cystic fibrosis, bronchiectasis and emphysema. This is of concern, as treatment of these infections is difficult due to antibiotic resistance. Understanding the pathogenesis of M. abscessus infection in the lung is urgently needed. The lung epithelium is the first line of defense against inhaled pathogens; however, to date little is understood about how M. abscessus infects these cells. This project will use novel induced-pluripotent stem cell (iPSC)-derived lung epithelial cell platforms to address this knowledge gap. This project will establish for the first time an M. abcessus-infection model of iPSC-derived lung epithelial cells and characterize the cellular response to infection. This will include determining bacterial load (e.g., colony forming assays, imaging of immunofluorescent bacteria), and elucidating the host's innate response to infection (e.g., cytokine arrays, single-cell RNA-seq) to identify novel therapeutic targets to M. abscessus in the lung.

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4.   Creating a new iPSC-based platform to understand pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease, characterized by scarring of the lung tissue, leading to difficulty breathing. Treatment options for patients with IPF are limited, likely in part because the pathogenesis of IPF is not entirely understood. This project will develop a novel human platform using induced-pluripotent stem cells (iPSC) to study pulmonary fibrosis. Using established directed differentiation protocols iPSC-derived alveolar epithelial cells and fibroblasts will be derived. This project will functionally characterize this platform to study pulmonary fibrosis, using techniques such as immunofluorescence and histology, RNA sequencing, and Western blotting. This novel human iPSC-based platform will be vital in future research studying pulmonary fibrosis and identifying novel therapeutic targets.

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5. **Developing a somatic brain organoid model to study developmental mechanisms underlying epilepsies.**

The development of the human cortex relies on coordinated genetic and cellular cues for proliferation, differentiation, migration, and neural circuit formation. Molecular analysis of abnormal human brain tissue reveals unique spatiotemporal norms and pathogenic consequences specific to the human brain. The main causes of lesional pediatric epilepsy requiring surgery are malformations of cortical development (MCD) and low-grade epilepsy-associated brain tumors (LEAT). Somatic mutations occurring early in brain development, leading to genetic mosaicism, are emerging as major contributors to the development of MCD and LEAT. We have observed that brain-specific somatic variants affecting genes within the mTOR pathway or SLC35A2 are significant causes of MCD. Recent discoveries have also identified somatic variants in RAS pathways that span subtypes of both MCD and LEAT. The interplay between the origin of pathogenic variants, spatiotemporal timing, cell type, and dysregulated molecular pathways dictates the specific brain regions affected. Somatic mutations provide an opportunity for lineage tracing and a better understanding of human brain development, as well as clarifying the influence of abnormal cortical architecture and ongoing cellular dysfunction on epilepsy resulting from dysregulated molecular pathways. Brain organoids serve as a model system, replicating aspects of early brain development and enabling the study of cell division, differentiation, and migration mechanisms that cannot be ascertained from human brain biopsies. This project aims to establish a protocol using human brain organoids to investigate how the type and timing of somatic mutations impact the development and function of these organoids. Additionally, the project aims to determine the relevance of these findings to known clinical phenotypes associated with epilepsy.

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Available as Masters Project: Yes

6. **Role of glia maturation factor beta (GMFb) and the actin cytoskeleton in neuronal differentiation during development and in the childhood cancer neuroblastoma**

Neuroblastoma is the most common solid tumour of childhood excluding brain tumours. Children with this malignancy can present with disseminated disease. Of interest, infants with neuroblastoma occasionally demonstrate spontaneous disease regression, especially those without MYCN amplification, but the mechanism to explain this phenomenon is poorly understood. Glia maturation factor beta (GMFb) was initially considered as an exogenous growth factor. However, in silico modelling and subsequent in vitro studies demonstrate that GMFb is a member of the actin depolymerizing family and is a cofilin homologue. Transient overexpression of GMFb leads to significant neurite outgrowth in neuroblastoma cells and may promote tumour differentiation in vitro. Moreover, GMFb is a phosphoprotein. Preliminary data shows GMFb is expressed in the tumour stroma around undifferentiated tumour cells and in differentiated ganglioneuroblastoma cells. The student will perform GMFb gain and loss of function studies in neuroblastoma cell lines in vitro using CRISPR gene editing methods, including spinning disc confocal microscopy, assessment of actin cytoskeleton dynamics, and invasion, migration and colony forming assays. Identification of upstream cell signalling pathways that phosphorylate GMFb during development will potentiate the development of novel therapeutics for this complex and often fatal childhood cancer.

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Infection and Immunity

7. Anti-inflammatory effects of sulforaphane

Sulforaphane is a dietary compound with a diverse range of biological effects, including anti-oxidant, anti-inflammatory and chemoprevention. The biological effects of sulforaphane against infectious pathogens are less well understood, although some effects have been described for specific bacteria and viruses. Identification of novel anti-viral compounds with activity against SARS-CoV-2 is a priority research area. This project will involve undertaking some in vitro assays to assess the anti-inflammatory effects of sulforaphane against SARS-CoV-2. A combination of flow cytometry and cytokine assays will be performed.

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8. Systems serology analysis of single dose HPV vaccination in Mongolia

A single dose of human papillomavirus (HPV) vaccine appears to be as efficacious against HPV infection, the prerequisite of cervical cancer, as two or three doses, despite inducing lower antibody titers. Neutralizing antibodies are thought to be the primary mediator of protection, but the threshold for protection is unknown. Antibody functions beyond neutralization have not been explored for HPV vaccines. This project aims to examine antibody profiles (isotypes, subclasses) and features (Fc receptors) in the serum of girls vaccinated with a single dose of HPV vaccine in Mongolia. This study will involve multiplex fluorescent assays to several HPV types as well as methods for production and validation of HPV pseudovirus.

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9. Examining the role of low affinity Fc receptor binding following HPV vaccination

The antibody response to microbial infection is diverse. The functional repertoire of an antibody is dictated by a combination of the Fab region, which determines antigen specificity, and the Fc region, which binds Fc receptors (FcR) found on immune cells throughout the body. Crosslinking of FcRs on effector cells allows a range of protective immune responses apart from neutralization to be directed against pathogens. Fc-mediated antibody effector functions have been shown to be essential for multiple infectious pathogens including malaria, Ebola, HIV and SARS-CoV-2. Similarly, Fc-mediated effector functions might also be able to prevent HPV infection through a variety a effector mechanisms. There are a number of Fc receptors which have both high and low affinity for antibody and both may be important in preventing infection. High affinity Fc receptors have been studied in more detail than low affinity Fc receptors despite the fact that low affinity Fc receptors are known to be important in modulating adaptive immune responses. This project will measure low affinity Fc receptor responses in the context of single dose HPV vaccination using our clinical cohorts to provide a greater understanding of the mechanisms of action.

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10. Effect of booster vaccination on the immune response to serotype 1 bacteria

Serotype 1 pneumococcal bacteria is a highly virulent strain causing serious invasive pneumococcal diseases such as meningitis and sepsis. Current vaccines contain serotype 1 but the protective immunity that these vaccines produce largely depends on the vaccine schedule used. The WHO recommends three doses of

pneumococcal conjugate vaccine (PCV) to be given to infants either as three primary doses with no booster (so called 3+0 schedule) or as two primary doses plus a booster (so called 2+1 schedule). Evidence to date suggests that the administration of a booster dose provide much more functional immunity to serotype 1 compared with if no booster is given. The reason(s) for this are poorly understood. Using samples collected from our randomised controlled trials in Vietnam, we are interested in examining serotype 1 immunity in more detail using a combination of approaches including IgG binding assays, opsonophagocytic assays and Fc receptor binding assays. This project will measure serotype 1 immunity following different vaccine schedules to understand the role of booster vaccination for this important serotype.

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11. New drug discovery pipeline for the cystic fibrosis superbug, Mycobacteroides abscessus

M. abscessus is responsible for causing a wide clinical spectrum of disease in the complex microenvironment of the CF airways. Current treatment regimens span months and involve cocktails of 3-5 different parenteral antibiotics with wide-ranging toxicities. The presence of M. abscessus also excludes patients from life-saving lung transplants in certain healthcare systems. Thus, there is an enhanced focus on M. abscessus infections in the context of the CF lung by clinicians and researchers alike. Our unique drug discovery pipeline combines physiologically relevant stem cell-based infection modelling with high throughput drug screening to identify new treatment options for this CF superbug. This project will include extensive validation of identified compounds in pre-clinical models of infection including cell-based assays, mouse infection model and biofilm assays.

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12. Beyond the clinical outcomes of the BRACE randomised controlled trial

Interested in being part of the largest BCG vaccine trial of its kind worldwide?   The BRACE trial is our international RCT of 6828 healthcare workers across 36 sites in five countries. This trial is working to determine if BCG vaccination reduces the impact of COVID-19 and other respiratory diseases. In addition to data on symptoms during respiratory illness including COVID-19, participants provided information on COVID-19 risk factors, vaccinations and vaccine reactions, as well as blood samples for assessment of immune responses.   Using data collected from participants in the BRACE trial and existing immunological data we have a range of projects available investigating the interplay between COVID-19 symptoms, risk factors, vaccine responses and vaccine reactions. In addition, we have several projects involving immunological analysis of samples from the BRACE trial to investigate the how BCG changes the immune system and the associations between immune markers and clinical outcomes (e.g. COVID-19 risk and vaccine reactions).   The Infectious Diseases Laboratory is located at the Murdoch Children's Research Institute, part of the Melbourne Children's Campus, which also includes the Royal Children's Hospital and the University of Melbourne.   Projects may be laboratory or non-laboratory based.

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13. Does epigenetics predict cell response to exposures?

The term "epigenetics" literally means "above DNA" and refers to the study of molecular interactions that influence chromosome structure and gene activity. We can think of epigenetic marks as signals that say whether a stretch of DNA is "open for business" and accessible for regulatory factors to bind and exert their function or "closed" and therefore inaccessible. A key property of epigenetic marks, which are valuable in understanding the interaction between DNA and the environment, is that they do not simply indicate the state of the cell at time of collection but can carry the memory of past exposure and influence the potential of a cell to respond to future stimuli. Therefore, the epigenome (the complete epigenetic profile of a cell) can be said to contain information about the "past, present, and future" of a cell. One such epigenetic mark is DNA methylation, which when present at the promoter of a gene is (mostly) associated with gene silencing. Mounting evidence linking environmental exposures in early life to later risk of cardiovascular disease has led to intense interest in the process of vasculature development in utero. The placenta is home to three specific types of endothelial cells, which line the placental arteries: placental artery endothelial cells (PAEC), placental vein endothelial cells (PVEC) and umbilical cord vein endothelial cells (HUVEC). These cells play important roles in foetal development, and have very different DNA methylation patterns (Joo et al. BMC Genomics 2013; Cvitic et al. Diabetalogia 2018). Interestingly, all major genes involved in vitamin D signalling and metabolism are differently methylated in PVECs compared to PAECs and HUVECs. In this project we want to follow this finding with functional analysis. We will stimulate primary cultures of PVECs, PAECs, and HUVECs with active vitamin D in vitro. Expression of key downstream genes will be evaluated using quantitative PCR at several time-points. Based on these data we will determine the time-point at which vitamin D responses are the strongest, and subject it to RNA sequencing and epigenomic analysis. We want to ask: how does DNA methylation regulate the response to vitamin D? Does vitamin D induce different gene pathways in different cells? Using computational approaches, we want to identify other pathways that similarly show differences in DNA methylation between these cells.

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14. Does our innate immune system remember pregnancy?

We all know that the adaptive immune system develops memory following specific antigen exposure, but is the same true for the innate immune system? An emerging field of research tells us exactly this, with epigenetic remodelling as the underlying mechanism. Innate immune cells, such as monocytes and macrophages, form this non-specific memory in response to a variety of exogenous signals. Exposure-induced epigenetic remodelling governs their future response to a range of pathogens. This process can be modelled in vitro, using both yeast and bacterial antigens and metabolites (Novakovic et al. Cell 2016), metabolites (Bekkering et al. Cell 2018), vaccines (Arts at el. Cell Host Microbe 2018) and a range of other stimuli. During pregnancy, both maternal and foetal monocytes show attenuated pro-inflammatory responses correlated with pregnancy-associated hormones. Additionally, foetal monocytes are exposed to a range of environmental factors. We hypothesise that monocytes remodel their chromatin in response to early life environments, which explains their altered function during pregnancy. To test this hypothesis, we will isolate pure monocytes from human blood, and treat them with various stimuli in vitro. After treatment we will measure cytokine release, RNA expression and epigenetic (histone modification) changes. This project is appropriate for students with an interest in molecular biology and immunology and will utilise monocyte isolation and culture, ELISA, chromatin immune-precipitation (ChIP), DNA and RNA extraction and real-time PCR.

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

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

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Available as Masters Project: Yes

16. Epigenetic reprogramming of immune cells in response to gender-affirming hormone therapy

Introduction   Transgender people, whose gender identity is markedly and persistently incongruent with their biological sex, almost always experience gender dysphoria. Characterised by severe distress and discomfort, and the feeling of 'having been born in the wrong body', gender dysphoria compels transgender individuals to seek cross-sex hormone treatment. While there is clear sexual dimorphism (differences between sexes) in immune function and response to infection, it is not known how hormone therapy influences these at the functional or molecular level. In this project we will study immune cells from individuals that underwent cross-sex hormone therapy to answer these questions. A key aim is to understand what proportion of sexual-dimorphism is due to genetics and how much is due to sex hormones alone.   The Project   Two clinical trials of cross-sex therapy were completed, for which we have biological samples: 1. Whole blood genome-wide DNA methylation data is available for 12 individuals who underwent female-to-male hormone treatment and 12 underwent male-to-female hormone treatment (baseline, 6 months and 12 months after treatment). These data need to be analysed using bioinformatics tools. 2.   Live frozen peripheral blood mononuclear cells are available at baseline and 6 months after cross-sex estrogen hormone treatment in male-to-female transition (n = 60). These live frozen cells will be used for immune-phenotyping, epigenetic (DNA methylation, histone modifications) and transcriptomic profiling of specific innate (monocytes) and adaptive (naïve T and B) cell types. This will evaluate the changes in immune function during sex hormone administration.   Methods involved Molecular Biology: RNA/DNA extraction, chromatin preparation and pulldown, sequencing library preparation. Cellular Immunology: Cell sorting and analysis of immune-phenotyping data. Cell culture to elicit inflammatory responses in immune cells. Bioinformatics: R and linux to analyse DNA methylation, ChIP-seq and RNA-seq data (no prior knowledge of coding is required).

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17. High Dimensional Immune and Epigenetic Profiling of Children with Juvenile Idiopathic Arthritis (JIA)

Autoimmune Disease is a condition arising from an abnormal immune response to a functioning body part. There are about 80 Autoimmune Diseases, which affect 5-10% of the population of the Western world. Around 70% of those affected are female, owing to a combination of genetic and hormonal factors. Juvenile idiopathic arthritis (JIA) is an autoimmune rheumatic disease that is one of the leading causes of childhood disability and affects around 6000 Australian children. It typically causes joint pain and inflammation in the hands, knees, ankles, elbows and/or wrists. But, it may affect other body parts too. We hypothesise that blood cells (e.g. T cells, monocytes and B cells) from JIA patients will show different responses to activation, will circulate in different numbers and have a distinct molecular profile compared to control children. To test this, You will apply immunology and molecular genomic sequencing techniques to circulating blood cells from JIA patients and matched controls. Our CLARITY (Childhood Arthritis Risk factor Identification Study) JIA biobank has grown to be one of the largest, most biospecimen- and information-dense collections in the world. We will combine samples from this cohort with state-of-the-art transcriptome and epigenetic profiling. Techniques include cell culture, cell sorting, high dimensional flow cytometry, DNA/RNA extraction, a range of epigenetic approaches, RNA sequencing (RNA-seq) and bioinformatic analysis.

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18. Exploring the relationship between Assisted Reproductive Technology (ART) and DNA methylation at birth

More than 7 million individuals have been conceived by Assisted Reproductive Technologies (ART) and there is clear evidence that ART is associated with a range of adverse early life outcomes, including rare imprinting disorders. The periconception period and early embryogenesis are associated with widespread epigenetic remodelling, which can be influenced by ART, with effects on the developmental trajectory in utero, and potentially on health throughout life. DNA methylation is an epigenetic mark that is sensitive to the environment and plays a role in regulating gene expression (for example it has been extensively studied at imprinted genes). We previously used a cohort of ART conceived individuals (CHART) and identified regions of the genome where DNA methylation levels were associated with ART at birth. This finding has now been replicated in several cohorts and meta-analyses and represents the first evidence of epigenetic variation in those conceived by ART. This is a combination 'dry' and 'wet' laboratory-based project based in the Molecular Immunity group at the Murdoch Children's Research Institute. It will involve bioinformatics and statistical analysis of available methylation data from various birth cohorts to confirm previously published ART-associated DNA methylation. Additional locus-specific DNA methylation and data analysis will also be performed on a range of biological samples (varied age, tissues; restrictions permitting) in order to further characterise the tissue distribution, stability and sensitivity to genetic variation, of ART-associated epigenetic variation. This project will address additional questions surrounding the extent of ART-associated epigenetic variation across tissues, the stability of ART-associated epigenetic variation over time, the role of genetics in modifying this effect, and the component processes of ART that induce this epigenetic change (for example

culture in a dish or superovulation hormones). The ultimate aims of this research are to identify (i) biological pathways impacted by, and (ii) the factors that contribute to, ART-induced epigenetic variation to inform future optimisation of ART processes.

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Available as Masters Project: No

19. Investigating novel antimicrobial resistance determinants in Streptococcus pneumoniae

Streptococcus pneumoniae (the pneumococcus) is an important global pathogen and is one of the top six pathogens causing deaths attributable to antimicrobial resistance (AMR). Within our pneumococcal vaccine impact projects across the Asia-Pacific we are interested in exploring changes in AMR and AMR determinants. In this project you will investigate AMR determinants in pneumococci from the Asia-Pacific through a combination of microbial genomics and laboratory experiments. Key approaches include: bacterial culture, phenotypic AMR testing, bacterial mutagenesis and bioinformatics analyses (including using R). Your research will provide new insight into AMR determinants in pneumococci.

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20. Understanding streptococcal pathogenesis

Streptococcus pyogenes ('Strep A', group A streptococcus) is an important global pathogen. In a related bacterial species, Streptococcus pneumoniae, we and others have shown that viral co-infection can enhance bacterial virulence, by increasing bacterial density and inflammation in the host, and by driving changes in bacterial virulence gene expression. 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 murine and cell-culture models to examine the effect of viruses on S. pyogenes colonisation, transmission (spread to co-housed littermates) and disease, and the mechanisms involved. To achieve these aims, you will employ a range of methods such as bacterial transcriptomics, working with in vitro and/or in vivo models such respiratory cells from patients grown as air-liquid interface, genetic manipulation, as well as microbiological and immunological analysis of local and systemic samples.   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.

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21. Optimising the use of narrow spectrum antibiotics in children

Optimising the use of antibiotics with a narrow spectrum range of activity is important for preserving first line antibiotics for resistant infections. NSAIDs are commonly used in children to treat pain and inflammation but known to reduce glomerular filtration rate and renal blood flow. This effect on the kidneys can decrease the

elimination rate of particular medication, extending the half-life. This honours project aims to determine whether administering NSAIDs in combination with a narrow spectrum antibiotic will alter the pharmacokinetics-pharmacodynamics and allow reduced dosing frequency. The results of this study may expand treatment options such as Hospital in the Home, for children with serious infections.

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Genetics

22. Improving outcomes of mitochondrial diseases using human stem cell models

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 severe 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 involves the characterization of human pluripotent stem cell models of mitochondrial energy generation disorders that can be differentiated into clinically relevant cell types. The aims include: 1) Developing cellular models of mitochondrial disease using human Embryonic Stem Cells (hESCs) and human Induced Pluripotent Stem Cells (iPSCs) to study phenotypic rescue of novel defects, pathogenicity and treatment approaches. 2) Characterize pathogenic pathways by assessing the impact of these energy generation defects on cardiomyocytes generated from hESCs or iPSCs, as well as their impact on mitochondrial function and cellular physiology. 3) Define the impact of targeted therapeutic strategies in these models on the cellular proteome and other markers of cellular homeostasis. We have established a mitochondrial disease panel of hESCs using CRISPR/Cas9 mediated gene disruption, and iPCs from mitochondrial disease patient fibroblasts. This project will validate selected cell lines from this panel and differentiate them to cardiomyocytes to assess the impact of the gene knockout on various aspects of mitochondrial and cellular function. Molecular and cellular characterizations may include generation of correction lines, mitochondrial and cellular functional assays (e.g. ATP synthesis, fluorescence microscopy, FACS, multi-electrode arrays), quantitative proteomics and RNAseq. Students will develop skills in cell culture, molecular biology and biochemistry.

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23. A human stem cell-based model of the fetal testis to study Differences of Sex Development

The testis has three functions. First, it provides the environment for the development of the spermatozoa, the male gametes, from the germ cells. Second, it synthesizes testosterone, a male sex hormone. Third, it works with the hypothalamus-pituitary unit to regulate reproductive function. During embryonic development several key somatic cell lineages arise in the testis including the Leydig cells which make the hormones, the peritubular myoid cells which help form the testis cord structures, and the Sertoli cells which support the germ cells. When processes are disrupted it can lead to Differences of Sex Development (DSD). These conditions, in which sex is atypical, affect almost 1% of babies. They present serious challenges for patients, families and clinicians. Currently, there are very few tools to study these conditions. Specifically, we lack cell lines for human fetal Leydig, peritubular myoid or Sertoli cells. This means that we have a very poor understanding of their biology, and cannot study how genetic changes in patients might disrupt this. Recently several groups including our own have applied pluripotent stem cell technologies to this problem - developing new protocols

to differentiate gonadal-like cells.   The aim of this project is to optimise and further develop these protocols, to create a world first complete testis organoid. This includes optimising our own organoid protocol by differentiating and adding the hormone-producing Leydig cells. Once developed, these stem cell protocols will be applied to disease modelling for DSD, allowing us to understand the pathogenic mechanisms of patient genetic variants. They will also provide an exciting new platform for investigating the action of gonad disrupting chemicals such as BPA plastics. This project will include stem cell culture, RNA expression technologies and advanced imaging aspects. There will also be a human genetics component, which will underlie the important disease modelling aspect of the study.

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Available as Masters Project: Yes

24. Discovering novel genes and pathways to ataxia

Ataxia is the term for a group of neurological diseases that affect movement and coordination, impacting ~1:15,000 individuals. While there is considerable evidence that gene mutations cause ataxia, currently only ~30% of affected individuals receive a genetic diagnosis. A focus of our research is to identify novel genes that cause ataxia.   We have recently identified several novel genetic causes of ataxia, caused by pathogenic repeat expansions. This is when a segment of repetitive DNA, termed a short tandem repeat, is significantly expanded in size compared to the general population. This project will utilise modern genomic technologies, including exome and genome sequencing and transcriptomics to characterise the size and structure of these novel repeat expansions. Subsequently, the genes will be characterised in patient-derived cells to study disease-specific mechanisms and identify potential therapeutic treatments. The successful candidate will have the opportunity to learn a range of laboratory techniques including generating and analysing Next Generation Sequence data, cell culture, immunocytochemistry, microscopy, real-time qPCR and western blot analysis. In addition, they will work closely with clinicians and bioinformaticians within a large multidisciplinary team.

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Available as Masters Project: Yes

25. Human stem cell-derived neuronal models of brain development disorders linked to epigenetic regulator genes.

Studies into human cortical development (or corticogenesis) have identified unique cellular processes during embryogenesis which further our understanding of how the human cortex is formed. However, primary human neuronal tissue can be difficult to source and is less amenable to genetic and cellular manipulation for experimental purposes. Therefore, researchers have turned to human pluripotent stem cells (hPSC's) to model human cortical development in culture. hPSC's are highly expandable which allows for scaled up experimentation and established cortical differentiation protocols mimic key cellular hallmarks of corticogenesis such as neural stem cell proliferation, synaptic maturity, neurite morphology and activity. More recently, the ability to generate gene knockouts with CRISPR/Cas9 technology has allowed researchers to scrutinise the role of specific genes in the development of their tissue of interest. Our interest is focused on a subset of epigenetic regulators - proteins which modify histones and DNA to regulate transcription of underlying genes - and how these genes regulate aspects of neurodevelopment. A growing body of genetic evidence has identified a large number of epigenetic regulator genes to be associated with

neurodevelopmental disorders resulting in intellectual disability, suggesting that neurodevelopment is susceptible to epigenetic changes as neurons develop and mature. How these genes affect neuron-specific functions at the cellular level is largely unexplored.   The aim of this Honours project is to generate a CRISPR/Cas9-mediated knockouts of epigenetic regulator genes associated with intellectual disability and characterise their role in corticogenesis using a stem cell-based model of cortical development. This will involve designing and cloning of CRISPR/Cas9 constructs, clonal generation of knockout stem cell lines, live-cell imaging of stem cell-derived neurons using virally delivered fluorescent reporters and calcium indicators to assess cell proliferation, synaptogenesis, maturation, neurite extension and activity, and biochemical assays to assess changes in histone modifications during neuronal development in the knockout neurons.

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Available as Masters Project: Yes

26. Improving Mitochondrial Disease Diagnosis via the Mitochondrial Diagnostic Network for Genomics and Omics

Mitochondrial diseases (Mito) are the most common group of inherited metabolic disorders and are highly complex since they comprise more than 350 different genetic disorders, affect any or all organ systems and can present with a wide range of clinical phenotypes and inheritance types. Genomic (DNA) sequencing technologies have increased our ability to diagnose Mito patients from <25% to ~50% however this still leaves many patients without a diagnosis.   The Mitochondrial Diagnostic Network for Genomics and Omics, led by MCRI, comprises clinicians, researchers and diagnostic scientists around Australia. It combines genome testing with additional Omic technologies (RNAseq, quantitative proteomics and metabolomics) to improve diagnostic rates for Mitochondrial disease to over 70% and will identify novel genes, mechanisms and phenotypes. Recruitment of suspected Mito patients into this study commenced in 2022, with 150 patients to undergo genome sequencing over a 4 year period. An additional 100 patients who have remained undiagnosed after prior clinical genome sequencing are also to be enrolled for additional Omics testing along with extended computational reanalyses of genomic data, mitochondrial DNA and long-read sequencing plus targeted functional testing.   This project will focus on patients where novel sequence variants are identified in known disease genes or in candidate disease genes not previously linked to disease and will use a range of bioinformatic, molecular, biochemical, immunochemical and cell biology approaches to investigate causality of these novel variants. This will generate definitive diagnoses in previously unsolvable cases, aid understanding of pathogenic mechanisms and develop methods that can be applied to understanding the genetics of a wide range of other rare diseases.

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Available as Masters Project: Yes

27. A better brain in a dish: improved models of human cortical development

Studies into human cortical development (or corticogenesis) have identified unique cellular processes during embryogenesis which further our understanding of how the human cortex is formed. During corticogenesis, excitatory neurons expand and mature from local neural precursor cells, whilst inhibitory interneurons migrate into the developing cortex from ventral structures. In the third trimester a neuron-to-glia switch occurs where

neural precursors in the cortex begin to generate astrocytes - the support cells within the brain necessary for proper brain function.   Researchers have established human pluripotent stem cells (hPSC's) to model human cortical development. However, these models require over 6 months to obtain mature cultures that can then be used for investigating cortical development and function.   Recent studies have established more rapid and robust models that are able to generate mature cortical neurons within 4 weeks. With these models, we are now able to generate different types of neurons and co-culture them together to model human brain development more closely.   This project will use 3 newly developed transgenic hPSC that are able to differentiate into the 3 main cell types (cortical neurons, astrocytes and interneurons) that are important for brain development and function. The aims of this project are to characterise the fidelity of these lines at faithfully generating 3 cortical cell types and whether co-culturing of these three cell-types together influences the maturity and complexity of neuronal networks and connections over-time. These important neuronal effects will be assayed using various molecular biology techniques such as immunofluorescence and advanced microscopy to assess structural changes to neuronal morphology and synaptic connections, calcium imaging and electrophysiology to assess neural activity, as well as qPCR to assess gene expression changes.

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28. A high throughput drug screen to identify candidate targets for the treatment of Neurofibromatosis Type 1.

NF1 is a single-gene disorder caused by a loss-of-function mutation in the NF1 gene resulting in a reduction of the protein neurofibromin. Cognitive deficits occur in approximately 80% of children with the genetic syndrome, neurofibromatosis type 1 (NF1), making them the greatest cause of disability for individuals with this lifelong genetic condition. These manifest as academic failure due to learning disabilities (70%), attention deficit-hyperactivity disorder (ADHD; 40%) and a significantly increased risk for autism spectrum disorder (ASD; 25%).   Current therapies, whether medication or behavioural interventions, are often ineffective because they use 'trial and error' approaches targeting symptoms, rather than the cause. Therefore is an urgent need to discover new therapeutics for the impairing neurodevelopmental symptoms experienced by children with NF1.   This drug screening project aims to identify compounds that may modulate neurofibromin expression using patient derived stem cell lines. Cells will be differentiated into neuronal cells and then used to perform a high throughput drug screen. Functional readouts from the screen will include assessment of neurofibromin steady state levels as well as structural readouts including neurite development, length and number of neurons in the cultures. Once candidate compounds have been identified, validation assays will be performed in NF1-patient derived stem cell models to determine whether the compound treatment/s can ameliorate neuronal deficits. Extensive functional analyses will be performed including the assessment of neuron growth and maturation (using immunofluorescence assays), neuron function (using multi electrode arrays and calcium imaging) as well as biochemical assays such western blotting, real time PCR and ELISAs to determine biological changes in our patient lines versus control lines.

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Available as Masters Project: Yes

29. Understanding the neurobiology of autism in NF1 using patient derived stem cell models

Neurofibromatosis Type 1 (NF1) is an inherited neurological syndrome, with a prevalence of 1:3000 that affects major organs including the brain, spinal cord, peripheral nerves and skin. Approximately 80% of children with NF1 suffer lifelong cognitive deficits. We and others have shown that NF1 mutations confer additional risk for common neurodevelopmental disorders (NDD) including autism spectrum disorder. There are currently no evidence-based treatments for the NDDs in NF1. Research to date is based on mouse models which are limited in modelling higher cognitive functions and have not led to any useful targeted therapies. Increased understanding of how NF1 mutations affect brain development in a human setting will allow for the advancement of therapeutic strategies that rescue neurodevelopmental deficits and will significantly improve the quality of life of individuals with NF1.   This project will investigate how and why 80% of children with the genetic syndrome NF1 develop neurodevelopmental disorders. To answer this, we will use our established unique NF1 patient-derived stem cell models to characterise the neuronal deficits in individuals with NF1. Specifically, human stem cell-derived brain cell networks will be generated 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 in this project 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. This project will help us understand the molecular mechanisms underpinning neurodevelopmental deficits associated with NF1 and identify effective treatments for the neurodevelopmental aspects of NF1.

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30. Genetic causes of ataxia: investigating the role of altered dna methylation

Ataxia is the term for a group of neurological diseases that affect movement and coordination, impacting ~1:15,000 individuals. While there is considerable evidence that gene mutations cause ataxia, currently only ~30% of affected individuals receive a genetic diagnosis. A focus of our research is to investigate novel ways of identifying genes causing ataxia.   Using cutting edge platforms like ONT long-read sequencing and Illumina whole-genome sequencing to assess patient DNA, we can identify complex mutations called repeat expansions, similar to the CAG expansion causing Huntington's disease or CGG expansion of fragile X syndrome. When non-expanded, these sequences appear to have a fundamental biological purpose that helps facilitate gene expression and protein function. However, mutations that cause expansion beyond a locus-specific threshold and/or altered sequence composition can have pathogenic consequences. This project aims to investigate ataxia causing mechanisms, like gene methylation, by utilising advanced genomic technologies. Novel repeat expansions causing ataxia are regularly being discovered in this dynamic research landscape however, the unstable and unpredictable nature of these regions make it difficult to determine pathogenicity. One method for assessing potential disease mechanism is by detecting changes in methylation, a process that can lead to gene silencing by reduced RNA polymerase binding. Gene promoter regions are C-G rich and largely unmethylated however, repeat expansions can interfere with this sequence, introducing non-GC nucleotides or increasing cytosine methylation, leading to a decrease in transcription. A focal point of this project will be to assess methylation patterns within genes associated with ataxia to determine the changes caused by a repeat expansion. In addition, the candidate will work as part of a multidisciplinary team that includes clinicians and bioinformaticians, to determine patient specific disease outcomes.

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31. Beyond biopsies-Can we rely on a new mouse model or in vitro organoids to understand the ACTN3 polymorphism during development?

The project aims to characterize the metabolic and functional changes that occur in a-actinin-3 (ACTN3) deficient skeletal muscle. ACTN3 deficiency occurs in approximately 1.5 billion people worldwide. Our published data indicates that a-actinin-3 plays a critical role in skeletal muscle function and development, with key changes occurring in early muscle development that result in reduced skeletal muscle mass, function, and sprint/power performance.   To further assess the impact of ACTN3 deficiency during development we developed a novel CRISPR/Cas9 "humanized" mouse model which reproduces the nonsense mutation seen in humans. In addition we have established novel human induced pluripotent stem cell (iPSC) lines that we will use to grow 3D skeletal muscle organoids in a dish. These models will enable us to study the impact of ACTN3 in human tissue without the need of a muscle biopsy. In this project the student will use a range of techniques including animal handling, muscle physiology (ex vivo & in vitro), immunohistochemistry, western blotting and iPSC 3D cell culture techniques.

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Available as Masters Project: Yes

32. Validation of a novel ASO-based therapeutic for TRAPPC4-related disorder

We identified a new severe childhood neurological disorder where all affected children are homozygous for the exact same mutation in a well-conserved splice site of TRAPPC4 [1]. There are no treatments. We have designed and refined antisense oligonucleotides (ASOs) to modify aberrant splicing processes. Our lead ASOs increase protein levels and normalise the mis-splicing events.

To our knowledge no stem cell models exist for this disease. In the proposed studies we will achieve the following:

1: Utilise existing patient-derived stem cells and characterise neuronal phenotypes due to TRAPPC4 deficiency.

2: Undertake functional validation of lead ASOs in patient stem cell derived neurons.

By the end of this study, we anticipate identifying top safe ASO for future human trials.

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33. A human stem cell-based model of the fetal testis to study Differences of Sex Development A human stem cell-based model of the fetal testis to study Differences of Sex Development

The testis has three functions. First, it provides the environment for the development of the spermatozoa, the male gametes, from the germ cells. Second, it synthesizes testosterone, a male sex hormone. Third, it works with the hypothalamus-pituitary unit to regulate reproductive function.   During embryonic development several key somatic cell lineages arise in the testis including the Leydig cells which make the hormones, the peritubular myoid cells which help form the testis cord structures, and the Sertoli cells which support the germ

cells. When processes are disrupted it can lead to Differences of Sex Development (DSD). These conditions, in which sex is atypical, affect almost 1% of babies. They present serious challenges for patients, families and clinicians.   Currently, there are very few tools to study these conditions. Specifically, we lack cell lines for human fetal Leydig, peritubular myoid or Sertoli cells. This means that we have a very poor understanding of their biology, and cannot study how genetic changes in patients might disrupt this. Recently several groups including our own have applied pluripotent stem cell technologies to this problem - developing new protocols to differentiate gonadal-like cells.   The aim of this project is to optimise and further develop these protocols, to create a world first complete testis organoid. This includes optimising our own organoid protocol by differentiating and adding the hormone-producing Leydig cells. Once developed, these stem cell protocols will be applied to disease modelling for DSD, allowing us to understand the pathogenic mechanisms of patient genetic variants. They will also provide an exciting new platform for investigating the action of gonad disrupting chemicals such as BPA plastics. This project will include stem cell culture, RNA expression technologies and advanced imaging aspects. There will also be a human genetics component, which will underlie the important disease modelling aspect of the study.

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Available as Masters Project: No

34 Understanding the role of Histone deacetylase 6 (HDAC6) inhibitors in KIF1A-Associated Neurological Disorders

Histone deacetylase 6 (HDAC6) is an enzyme that plays a crucial role in the regulation of cellular processes through its involvement in epigenetic modifications and protein quality control mechanisms. HDAC6 primarily functions as a cytoplasmic deacetylase, targeting non-histone proteins for deacetylation, rather than histones. One of its most well-known roles is its involvement in regulating microtubule dynamics. Microtubules are important components of the cell's cytoskeleton and play a critical role in various cellular processes, including cell division, maintaining cell structure and co-ordinating intracellular transport through motor proteins including kinesins. The Kinesin family member 1A (KIF1A) is a neuron-specific microtubule plus end-directed motor protein that is involved in ATP-dependent fast anterograde transport of specific synaptic vesicle precursors such as Brain Derived Neurotrophic Factor (BDNF) to the tips of neurons. In children, defective trafficking by dysfunctional KIF1A due to mutations in the KIF1A gene triggers a devastating spectrum of rare progressive brain disorders collectively referred to as KIF1A-Associated Neurological Disorders (KAND). The symptoms appear at birth or early childhood and has variable severity including death within 5 years of life. There is no cure or treatment for this condition and there is an enormous unmet therapeutic need to alleviate cellular impairments caused by pathogenic mutations in the KIF1A molecular motor. Given HDAC6's role in regulating microtubules and influencing cellular processes that are crucial for neuronal function and health, it has been studied in the context of various neurological disorders, including neurodegenerative disorders. However, its role in KAND remains largely unknown. This project will enhance our understanding of the effects of HDAC6 inhibitors on the microtubule dynamics in the cellular models of KAND, providing valuable insights into the underlying mechanisms of these disorders and potentially opening new avenues for therapeutic interventions.

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Clinical Sciences

35. Adjunct Cord Blood Cell Therapy for Paediatric Heart Failure

A high risk of heart failure complications and death is faced by children with severe congenital heart disease such as hypoplastic left heart syndrome (HLHS), and by children with dilated cardiomyopathy or severe myocarditis requiring ventricular assist device implantation and support. HLHS requires extensive complex surgical reorganisation of the neonatal heart, however metabolic supply-demand insufficiencies limit postoperative recovery at a time when neonatal myocardial growth and increased myocardial performance is required. For cardiomyopathy patients, workload-dependent energy demand, pressure and volume load in excess of capacity drives progressive worsening of myocardial dysfunction, cardiac remodelling and heart failure. Their survival requires mechanical assist device implantation to permit ventricular unloading and increased cardiac output. In both patient cohorts cardiopulmonary bypass surgery is a first step in initiating respective treatments. Despite advances in surgical intervention, further advances are required to target myocardial remodelling directly at a cellular level. Our work examines how cord blood immune and stem cells influence adaptive processes involved in muscle growth and metabolism, inflammation and fibrosis by promoting growth and limiting adverse myocardial remodelling in the paediatric heart at risk of failure. Recently, we demonstrated a new method of delivering cord blood stem cells to the heart using an experimental animal model of paediatric cardiopulmonary bypass surgery and have completed a preliminary safety trial in neonates with HLHS. Project opportunities may involve studies of immune cell metabolism, paracrine cell-cell interactions between cord blood cells and heart cells in models of inflammation, fibrosis and angiogenesis. More than one project is available according to student qualifications and interests.

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Available as Masters Project: Yes

36. SPILLOVER2.0: What is the impact of preterm respiratory support outside of the lung?

70% of all preterm infants within the Neonatal Intensive Care unit (NICU) require assisted respiratory support. However, whilst life-saving, we have shown that even brief periods of mechanical ventilation when applied to the immature lung may not only initiate lung injury, but may also result in hepatic alterations such as changes in morphology or protein composition . In this follow-up study, we will extend the initial findings by assessing the impact of longer ventilation periods and different mechanical ventilation modalities on the liver in a large animal model of preterm birth.
In this project, the student will use a range of techniques, including histology, cutting-edge proteomics and bioinformatics to assess the impact of different ventilation strategies on liver and plasma protein expression.

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37. Assessing the impact of mechanical ventilation on the preterm diaphragm

70% of all preterm infants within the Neonatal Intensive Care unit (NICU) are unable to breathe at birth and therefore require assisted respiratory support such as mechanical ventilation. The role of mechanical ventilation in initiation of preterm lung injury has been extensively documented, however, the extrapulmonary impact of mechanical ventilation remains largely unknown. Despite

evidence that mechanical ventilation induces diaphragm dysfunction,　there is limited data detailing its mechanism and impact on the immature diaphragm of preterm infants. To therefore improve how preterm infants breathe at birth, it is imperative that we understand the impact of mechanical ventilation on diaphragm pathophysiology. In this project, the student will use a range of techniques, including histology, cutting-edge proteomics and bioinformatics to assess the impact of different ventilation modalities on diaphragm composition using a large animal model of preterm birth.

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Non-Laboratory based

Infection and Immunity

38. Auto-titrating positive airway pressure in Paediatric patients for the treatment of obstructive sleep apnoea.

Introduction: Obstructive sleep apnea (OSA) is a sleep breathing disorder associated with multiple neurobehavioral &medical problems in children. The first-line treatment of OSA in children is adenotonsillectomy however many have residual symptoms of OSA postoperatively &require continuous positive airway pressure (CPAP). CPAP therapy involves the provision of pressure via a face mask to treat upper airway obstruction. Currently the gold-standard for determining appropriate treatment pressure is a manual pressure titration by a sleep scientist during attended in-laboratory sleep study. This method of in-laboratory titration is labour intensive, costly &subject to hospital waitlists. Auto-titrating positive airway pressure (APAP) devices provide variable pressure delivery by constantly monitoring the patient's airflow using algorithms developed by each company. APAP for the treatment of OSA has been widely used in adult patients, particularly during the initiation phase of therapy, however there is a paucity of data in children.　Aims: To assess the efficacy of APAP in treating OSA in children.　Methods: All children with OSA requiring an in-laboratory CPAP titration study at the Royal Children's Hospital (RCH), February -July 2021 will undergo an unattended titration study using the ResMed Airsense 10 APAP device with portable sleep monitoring equipment to determine their appropriate treatment pressure.　The sleep studies will be set-up &data collated &analysed by the student.　The titration study will be analysed by Sleep Scientists to determine efficacy of APAP for treatment of paediatric OSA.　Clinical Implications: CPAP therapy is an effective &safe treatment for OSA in children. In-laboratory titration PSG is standard to determine optimal therapeutic pressure in children with OSA treated with CPAP. The use of APAP devices as an alternative is not well studied in children however has the potential to provide therapeutic pressures in the home without the need for in-hospital titration sleep studies.

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39. Sleep quality in children and adolescents with Cystic Fibrosis in hospital versus Hospital in the Home (HITH)

Children and adolescents with Cystic Fibrosis have more sleep disturbance than healthy children. Poor sleep quality has a negative effect on immune function and pain tolerance, both critical to recovery from illness. Additionally, sleep disturbance during hospital admission may negatively impact on the coping skills of children and their co-sleeping caregivers. Whilst sleep is fundamental to a child's health, previous studies have shown that children have shorter sleep duration and more sleep disturbance in hospital than at home. To date no studies have investigated sleep quality in children and adolescents with CF in the inpatient setting. This study will compare their sleep quality whilst an inpatient in hospital and at home. The aims of this study are to evaluate objective and subjective measures of sleep quality in children and adolescents with Cystic Fibrosis (CF) during hospital admissions and Hospital in the Home (HITH) admissions. Also, to assess perspectives (child, caregiver, nurse, doctor) on the most frequent disruptors of sleep during inpatient admissions. Objective measures of sleep patterns and quality include actigraphy (a wrist-worn device that quantifies sleep using a movement algorithm) together with a sleep diary. Subjective measures of sleep patterns and quality include standardised questionnaires and a medical record review from each admission. We hypothesise that children with CF admitted to hospital are exposed to factors which reduce the duration and quality of their sleep in addition to the sleep disruption associated with a disease exacerbation. These extrinsic factors are potentially modifiable through behaviour change and reconfiguration of the clinical environment. The results of this study will inform the design of an intervention study that targets modifiable, child-centred alterations to night-time ward culture, focusing on measurable child and parental outcomes. This quality improvement project has the potential to improve sleep quality for all children and parents during hospitalisation at both the RCH.

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Genetics

40. Characterising the Sleep Phenotypes of Genetic Neurodevelopmental Disorders

Genetic neurodevelopmental disorders (NDDs) are characterised by varying intellectual functioning, sleep problems, and anxiety symptoms. They are life-long conditions requiring ongoing management and treatment. Parents of children with these conditions report that anxiety and sleep are the most challenging behaviours to address and remain ineffectively treated. For sleep, this is likely due to poor characterisation of the sleep problem and hence poorly targeted treatments. There are core challenges for children with NDDs in complying with gold standard sleep assessment measures. The success of clinical trials aimed at developing new treatments targeting these symptoms relies on practical and robust outcome measures that are also sensitive to change, and currently these are critically lacking. This project aims to characterise the sleep phenotypes of children with a neurodevelopmental disorder (Prader-Willi syndrome, Angelman syndrome, or Childhood Apraxia of Speech; the student can select the condition that they are most interested in). This project will use both subjective (parent reports) and objective (a wearable sleep tracking device) measures of sleep to comprehensively assess and characterise sleep disorders in the chosen condition. The project can also examine correlates of sleep problems in the chosen condition (e.g., anxiety, speech and language). The student will join the Speech and Language group at the Murdoch Children's Research Institute. The group examines genetic, neural, and social-environmental predictors of speech, language, and literacy development, as well as understanding other co-occurring conditions that these individuals may experience. We aim to develop intervention strategies based on research evidence so children with neurodevelopmental disorders can reach their full potential.

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Available as Masters Project: No

41. Using new technology to characterise the developmental trajectory of motor coordination in children. Ataxia is associated with many neurological disorders and manifests as disordered movement resulting from cerebellar dysfunction. Ataxia is usually quantified by a clinical rating of performance of specific tasks that accentuate incoordination. Most clinical rating scales are yet to be validated in children. Specifically maturation of the cerebellum (peaking around 12 years) and rapidly changing body morphology impact on the use of these scales in children.   This study aims to understand age-effects on development of movement skills. This will be examined in terms of developmental effects to upper limb and stance measures that are targeted by the Ataxia Instrumented Measurement (AIM) system. The AIM system, an innovation of a team including biomedical engineers and clinicians (Professor Pubudu Pathirana, Professor Malcolm Horne, Associate Professor Louise Corben, Associate Professor David Szmulewicz) consists of data loggers equipped with an inertial measurement unit (IMU) to capture signals, algorithms that use machine learning to analyse these signals, and a mechanism to export to a smartphone a score. This system has been validated for use in measuring ataxia in individuals with Friedreich ataxia, an inherited ataxia.   The student will collect AIM data from children across the following age ranges: 6-7; 8-9; 10-11; 12-13, and 14-16 years (20 children in each age bracket; 50% female). These data will be used to build growth curves that reflect normal developmental changes in motor coordination. Results will provide new knowledge about cerebellar maturation in typically developing children and the normal developmental trajectory of motor coordination.   In this project the student will join the Bruce Lefroy Centre at the Murdoch Children's Research Institute. The group comprises a dynamic team of researchers and diagnostic staff that interact to solve problems of both genetic and clinical nature. This project is cross-disciplinary, spanning fields of neuroscience, outcome measure development, allied health, and digital health.

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42. Increasing diversity in Australian genomic databases
The current lack of diversity in genomic databases means that patients from underrepresented populations are less likely to receive an accurate genetic diagnosis, leading to poorer health outcomes. This honours project will tie into a large Medical Research Futures Fund (MRFF) project led by Prof Daniel MacArthur at the Centre for Population Genomics (a collaboration between the Garvan Institute of Medical Research and the Murdoch Children's Research Institute), which is developing a more representative genomic database for the Australian population. The honours project will use empirical data to explore ethical issues relating to the use of incentives to encourage participation in genomic database research.

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Available as Masters Project: No

Clinical Sciences

43. Changing respiratory admissions for children with neurodisability across the pandemic

Children with neurolodisability, for example cerebral palsy, are at increased risk of serious respiratory infection due to a number of factors related to their neuromuscular status, and have a high burden of repeated and lengthy hospitalisations. There is growing evidence of the decrease in respiratory infections during periods of social restrictions employed to reduce Covid-19 transmission across the population. However, since children with NI have different causes to their respiratory risk compared to the broader population, it is hard to know how relevant population data is. This study aims to investigate patterns in hospitalisation for lower respiratory tract infections among children with neurodisability relative to Covid era - three periods will be investigated, prior to Covid (<2020), during periods of Covid social restrictions (2020-2021), and in a period of Covid exposure without restrictions (2022). Patient and hospitalisation data will be collected from the electronic medical record and categorised by number of admissions, length of stay, reasons for admissions, clinical markers and pathogen if known. Additionally, a survey will be used to examine patient and family factors that might influence respiratory risk across these periods. Among other factors, the survey will explore whether families practiced measures over and above government restrictions to reduce Covid-19 risk and whether their children with neurodisability attended school when able.

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Available as Masters Project: Yes

44. The effect of anti-epileptic drugs on bone health

This project builds on pilot data from our group, in taking the next steps to set up a longitudinal cohort of young people taking AEDs with sibling controls. Subjects will undergo assessments of bone density and muscle function, along with biochemical testing and questionnaires to establish risk factors for bone health outcomes. The cohort will be followed for 3-5 yrs but a higher degree student will gain invaluable experience in setting up the cohort, establishing baseline data, undertaking analysis of these data including advanced analysis techniques such as finite element modelling.

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Available as Masters Project: Yes

45. Optimal parent-recorded videos of spontaneous infant movements for computer analysis

Infants who are born 3-4 months preterm or who are unwell at birth are at risk of developmental delays including movement impairment which can affect a child's ability to fully participate in daily living. Not all infants who are unwell at birth will go on to develop movement impairment. Using the General Movements Assessment (GMA), where human assessors observe a pattern of movements in early infancy from video recordings, can be used to detect which infants will go on to have movement problems, in particular, cerebral palsy. The Baby Moves app has been used by parents in research settings to record and send videos of infant movements for remote assessment to improve the timeliness and ease of data capture. There is keen interest in computer automation of the GMA from Baby Moves videos. However, parents are not always able to record videos that satisfy quality requirements for computer analysis. The aim of the project will be to compare the quality of video recordings from an older version of the Baby Moves app with recordings obtained from the latest updated version of the Baby Moves app, as well as an adapted version through the GenV project. The

latter two versions are supported by more family-friendly instruction and images to assist parents to record optimal videos.

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Available as Masters Project: No

46. Exploration of children's and parents' perspectives about content and delivery of digital platforms for chronic pain management in cerebral palsy.

Chronic pain is common in children with cerebral palsy, yet it is poorly identified and managed in this vulnerable population. Recent research has improved the identification and assessment of pain in children and young people with cerebral palsy, however management practices remain sub-optimal for this group. Digital technologies are increasingly seen as a way to connect young people with health services and resources that support their self-care and platforms are being developed for children and young people with chronic pain who do not have cerebral palsy. More research is required to ensure such platforms can be adapted so they are accessible and meaningful for children and young people with cerebral palsy, who may have a range of cognitive, communication and movement limitations. The aim of this project is to examine what people with lived experience think is needed to ensure digital platforms targeting chronic pain education and management are tailored and responsive to the specific health needs of children and young people with cerebral palsy. This mixed-methods study will use both qualitative (interviews) and quantitative (survey) methods. Participants will be children and young people with cerebral palsy and parents of children with cerebral palsy, recruited from established consumer networks. The study will have two phases: Phase 1. Interviews with up to 10 participants exploring what content to include, what requires adapting, mode of delivery, features etc., for online platforms for children and young people with cerebral palsy and chronic pain. Phase 2. An online survey incorporating the results from Phase 1 with up to 100 participants. The results will be instrumental in future research co-designing accessible digital platforms for chronic pain management in cerebral palsy.

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Available as Masters Project: No

47. The Gait Outcomes Assessment List, Responsiveness to change in gait function for children with CP

Gait function in children with CP is assessed using a variety of outcome measures. While these measures provide a great deal of objective information, they tend to focus on body structure and function or activity domains of the WHO's ICF framework. It is important to evaluate all domains of the ICF. The Gait Outcomes Assessment List or GOAL is a new 48 item questionnaire developed by a multidisciplinary team at the Hospital for Sick Children, Toronto, Canada. It can be completed by parents or children. It includes seven domains, which reflect gross motor function across all the ICF domains. GOAL total and domain scores are scored out of 100, with a higher score indicating better function. The GOAL was developed with the direct input of children and families. Items are rated according to difficulty and amount of assistance required or frequency of symptoms. Concerns and expectations are measured by indicating the importance of each item as a current goal. In the context of the gait laboratory a measure like the GOAL is extremely useful to assist with recommendations, planning of interventions and measurement of outcome. Using the GOAL as part of the assessment tool matrix in the gait laboratory is essential. We introduced the GOAL to the raft of assessment tools used in the Hugh Williamson Gait Laboratory in 2014. The validity and reliability of the GOAL has been established but it's responsiveness to change has yet to be evaluated. The aim of this study is to investigate

whether the magnitude and direction of changes in the GOAL scores reflected those of valid measures of gait and function.

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Available as Masters Project: No

48. What do physiotherapist know about their patients with variations of sex characteristics

Variations of sex characteristics(VSC), also known as differences of sex development or intersex conditions are a diverse cluster of congenital conditions that result in atypical chromosomal, hormonal or anatomical features impacting on sexual development. They include conditions such as uterovaginal agenesis, hypospadias, Turner syndrome, androgen insensitivity syndrome and bladder exstrophy. Children, adolescents and adults with VSC quite frequently require the clinical input and support from physiotherapists. People with lived experience often voice their concern that the health professionals they see have little or no knowledge of their diagnoses, and dislike having to explain their diagnosis to their health professionals. The aim of this project is to understand what physiotherapists and physiotherapy students are currently taught about the wide range of diagnoses that are encompassed by VSC. By incorporating a co-design process the initial stage of this project would aim to involve physiotherapists and physiotherapy students in face to face interviews or focus groups, to gain an understanding of the current education and the pathways of physiotherapists in achieving an understanding of their patients with variations of sex characteristics. This process would enable the identification of the gaps in their learning and knowledge, and to clarify their potential learning needs. Then using a discrete choice experiment, the key issues identified would be presented to a larger cohort of physiotherapists and physiotherapy students to qualitatively assess their priorities and preferred learning approaches.

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Available as Masters Project: Yes

49. What do pharmacists know about their patients with variations of sex characteristics

Variations of sex characteristics(VSC), also known as differences of sex development or intersex conditions are a diverse cluster of congenital conditions that result in atypical chromosomal, hormonal or anatomical features impacting on sexual development. They include conditions such as congenital adrenal hyperplasia, Turner syndrome, androgen insensitivity syndrome and premature ovarian insufficiency. Children, adolescents and adults with some of these VSC require the use of medications which may not typically be used by people in their age group (eg hormone replacement therapy) or may have significant side effects (eg steroids) if used inappropriately by people without their diagnosis.   Never the less people with these VSC attend their local pharmacy for their prescriptions to be filled and may be asked questions that they find embarrassing, challenging or counter to what they have been instructed. People with lived experience often voice their concern that pharmacists have little or no knowledge of their diagnoses, why they might be on their medications and dislike having to explain this to their pharmacist. The aim of this project is to understand what pharmacists and pharmacy students are currently taught about the range of diagnoses that may require specific yet atypical hormonal interventions that are encompassed by VSC. By incorporating a co-design process the initial stage of this project would aim to involve pharmacists and pharmacy students in face to face interviews or focus groups, to gain an understanding of the current education and the pathways of pharmacists in achieving an understanding of their patients with variations of sex characteristics who require these medications and prescriptions. This process would enable the identification of the gaps in their learning

and knowledge, and to clarify their potential learning needs. Then using a discrete choice experiment, the key issues identified would be presented to a larger cohort of pharmacists and pharmacy students to qualitatively assess their priorities and preferred learning approaches.

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Available as Masters Project: Yes

50. What do teachers and student teachers know about their students who may have variations of sex characteristics?

Variations of sex characteristics(VSC), also known as differences of sex development or intersex conditions are a diverse cluster of congenital conditions that result in atypical chromosomal, hormonal or anatomical features impacting on sexual development. They include conditions such as uterovaginal agenesis, hypospadias, Turner syndrome, androgen insensitivity syndrome and bladder exstrophy. Adolescents and young adults with VSC who are students in classes on biology, human health and development, or relevant science or psychology subjects at university quite frequently are confronted by information that is presented in a manner that makes their body, their variation of sex characteristic feel 'abnormal ' or 'like a freak', or that their body is talked about as a textbook example. People with lived experience often voice their concern that their teachers/ lecturers have little or no knowledge of the breadth of potential diagnoses, and that they may have students in their class or lecture theatre who have these diagnoses. As clinicians we often forewarn patients that these subjects might be challenging and to consider warning their welfare or year coordinator to give them permission to leave a class if the topic is too confronting. The aim of this project is to understand what teachers and student teachers are currently taught about the wide range of diagnoses, their awareness of the frequency of these diagnoses, their language used to describe and teach about these conditions and thus the potential impact that they may have on students with these diagnoses in their classes. By incorporating a co-design process the initial stage of this project would aim to involve teachers and student teachers in face to face interviews or focus groups, to gain an understanding of the current education and the pathways of teachers and student teachers in achieving an understanding of their potential students with variations of sex characteristics. This process would enable the identification of the gaps in their learning and knowledge, and to clarify their potential learning needs. Then using a discrete choice experiment, the key issues identified would be presented to a larger cohort of teachers and student teachers to qualitatively assess their priorities and preferred learning approaches.

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Available as Masters Project: Yes

51. Knowledge production and synthesis: Infant pain management

Two opportunities exist to lead nation-wide surveys relating to neonatal and paediatric pain.   1. Nationwide survey of neonatal pain guidelines in maternal/newborn care hospital settings. This will include guidelines

from neonatal intensive care units caring for sick newborns requiring repeated painful procedures and postnatal units caring for healthy newborns requiring heel lances for newborn screening, bilirubin and blood glucose monitoring. The survey will focus on procedural pain management.   2.   Nation-wide survey of vaccination pain management practices and guidelines for early childhood vaccination. Target sample will be maternal and child health and primary care settings.

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Available as Masters Project: Yes

52. Informing the psychological care needs of children with an anorectal malformation and their families

The project is offered within a cilnical team, in paediatric surgery - the colorectal pelvic reconstructive service. Ethics has already been passed. The project involves identification, recruitment and interviewing 10 families of a child with an ARM using an established interview schedule. This project involves asking highly sensitive questions to vulnerable families and is supervised by the team clinical psychologist.   The applicant will have the chance to be mentored by many team members of the service, and to experience clinics and meetings to maximise their experience.

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Available as Masters Project: No

53. Surveillance of developmental outcomes in infants with HD and ARM

Infants with Hirschsprung disease and Anorectal Malformations are admitted to NICU within 48 hours of birth. They experience significant medical intervention that may impact their developmental outcomes. This project forms part of a collaboration between the colorectal pelvic reconstruction service and neonatology. The aims of the candidate would be to examine developmental data collected at the 2 year mark of children with HD and ARM.

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Available as Masters Project: No

54. Establishing a human iPSC-model of alveolar RSV infection

Respiratory syncytial virus (RSV) infection is the most common cause of bronchiolitis and pneumonia in infants. Severe and/or frequent RSV infections are often followed by episodes of wheezing and subsequent diagnosis of asthma. The current dearth of treatments for RSV infections, can be traced to the lack of tractable human relevant models to examine responses to viral infections. While the response of the upper airway to RSV

infection is well characterized, how the alveolar regions of the lung respond to RSV (where bronchiolitis and pneumonia occur) has been less studied in humans. This project will use novel induced-pluripotent stem cell (iPSC)-derived alveolar epithelial cell platforms to address this knowledge gap. This project will establish for the first time an RSV-infection model of iPSC-derived alveolar epithelial cells and characterize the cellular response to infection. This will include determining viral load (e.g., viral shedding, immunofluorescence staining for virus), and elucidating the host's innate response to infection (e.g., cytokine arrays, single-cell RNA-seq) to identify novel therapeutic targets to accelerate RSV clearance in the distal lung.

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Available as Masters Project: Yes

Population Health

55. The impact of government policies on maternity and newborn outcomes

The impacts of policy - federal, state, local - on the life chances of individuals and communities can be profound but hard to pin down.   GenV is a whole-of-Victoria cohort of nearly 50,000 children and their parents recruited Oct 2021-Oct 2023. Its unique features could shed light on policy cause and effect - notably, the cohort's very large size and diversity (with all Victorian population groups represented) and inclusion of all localities and services (with areas varying in when and what policy is implemented). Additionally, many natural experiments arose from its establishment during the COVID-19 pandemic, with its seismic policy changes during preconception, pregnancy and early childhood and parenthood life stages.   This Honours student will create a temporal and spatial map of major policy changes across Victoria from 2018 to 2023, and use causal and area-variation analytic techniques to study their likely impacts for new parents and babies at GenV recruitment.

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Available as Masters Project: Yes

56. A statewide clinical biobank to augment Australia's largest child research cohort (GenV) and EMR-based phenotyping

Generation Victoria (GenV) is Australia's largest longitudinal cohort of children and their parents, commencing prior to birth. All Victorian children born from Oct 2021 to Oct 2023 and their parents are eligible, with over 100, 000 participants joining to date. Designed as a multi-purpose, Open Science platform for observational and interventional research, GenV has also established one of the largest ante/perinatal universal biobanks internationally, working in partnership with pathology providers statewide to store excess clinical biosamples at research quality for later consented research use.   This PhD will lead similar partnerships to explore and develop consented prospective retention of excess clinical samples (whether collected in hospitals or community pathology laboratories) for in-age children throughout childhood. Bringing together (1) the rich consented GenV lifecourse cohort with (2) biosamples and (3) EMR-based digital phenotyping would create a resource at the cutting edge of science capable of advancing the health and wellbeing of all children. Supervised by leading researchers in children's biobanking, health informatics and population paediatrics, this PhD offers immense opportunities to establish a career and leadership in transformative childhood biosciences at scale within the GenV initiative and beyond.

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Available as Masters Project: Yes

57. What are the global determinants driving the adolescent obesity epidemic?

The problem: The world's obesity crisis continues to escalate. High body mass index (BMI) has become one of the top five global risk factors for mortality. Recently, the Global Burden of Disease Study estimated that high BMI increased by 127% between 1990 and 2019, with 37% of that rise occurring in the last decade. In 2019, overweight and obesity accounted for just over 5 million global deaths and 160 million disability-adjusted life years. It is now a major cause of non-communicable disease burden in both high-income countries and in low-income and middle-income countries. Children and adolescents are the population most impacted by this epidemic, with 324 million adolescents globally (18%) overweight or obese - this equates to an increase in 177 million since 1990 (increased by 120%).

What is needed: Because adolescent obesity rarely resolves and has intergenerational consequences, urgent monitoring of trends is needed to effectively plan prevention and intervention strategies. To understand past and future global trends, there is a need to review the global literature to identify high-level universal structural determinants driving adolescent obesity (e.g., food insecurity, wealth inequality) that are modifiable at the population level via public health policy or intervention.

This project: Based within the Centre for Adolescent Health, we are seeking a student to lead a systematic scoping review/s to gather information about modifiable structural determinants of adolescent obesity, and potentially to scope the existence and availability of global-level surveillance data on the identified structural determinants (e.g., school health surveys, census data, surveillance surveys). The applicant will have an interest in, or be eager to learn about, global health, adolescent health, obesity, systematic and scoping reviews, life course cohort research, epidemiology, and biostatistics.

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Available as Masters Project: Yes

UNIVERSITY OF MELBOURNE HONOURS ENTRY REQUIREMENTS

To be eligible to enter the Bachelor of Biomedicine (Degree with Honours) or the Bachelor of Science (Degree with Honours), applicants must satisfy both:

- the Faculty of Medicine, Dentistry and Health Sciences (MDHS) or Faculty of Science entry requirements.
- and the requirements of the department offering the Honours program.

Please note demonstrated eligibility does not guarantee a place in the Honours program. All successful applicants will also need to be selected for admission by the Department. The University of Melbourne handbook contains detailed information about the subjects available and entry requirements for departments offering Honours. https://handbook.unimelb.edu.au

For further details please visit;

Department of Paediatrics:
www.paediatrics.unimelb.edu.au

MCRI: https://www.mcri.edu.au/students/honours-students

MDHS: http://sc.mdhs.unimelb.edu.au/entry-requirements

HOW TO APPLY - MDHS HONOURS

Course Codes:

Bachelor of Biomedicine (Honours) – **BH-BMED**

Bachelor of Science (Honours) – **BH-SCI**

RCH Academic Centre Enrolling Unit is: **Department of Paediatrics**

If you wish to be considered for Honours in 2024, and you would like to undertake your project and coursework with the Murdoch Childrens Research Institute, Royal Children's Hospital, Academic Centre, Faculty of Medicine and Dentistry Sciences with the enrolling unit being Department of Paediatrics, you will need to carry out a FOUR STEP PROCESS.

STEP 1: Look for Projects and Contact Potential Supervisor (Note: 2024 Start Year Intake projects will be available in Sonia by mid-August.) You will need to decide which Supervisor(s) and Project(s) that you wish to apply for. To do this, contact potential supervisors listed in this Handbook, you should speak to them and organise a meeting to discuss the project further. Projects available for 2024 are also listed on the Murdoch Childrens Research Institute and Department of Paediatrics websites.

STEP 2: Submit Online Application: Register for the Honours Application Tracking System (SONIA) before making your application in SONIA. Lodge an online application by Tuesday 31 October 2023 (Round 1), and Friday 19 January 2024 (Round 2).

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

STEP 3: Submit Project preference in Sonia: For Round 1 applicants, once you have submitted an online course application and met the minimum entry requirements, you will receive an email within 3 working days with your personal login to access the Honours Project Preference System – Sonia. Please follow the instructions to set up your login and submit your project preferences. If you have applied for Round 2, you will be contacted in early January about project preference submission in Sonia. You may select up to 4 project preferences in Round 1 or 3 project preferences in Round 2 and mid-year. You **MUST** contact the relevant supervisor(s) and reach an agreement before selecting their projects. You can log into Sonia to change your preferences any time by the preference submission closing dates.

STEP 4: Respond to Your Offer: Round one offers for entry into 2024 will be issued around mid-December 2023. Students must accept their offer by the Offer Lapse Date notes in their offer letter. Students who meet the minimum entry requirements but are not made a Round 1 offer may be considered for Round 2 under specific circumstances, but that is not guaranteed.

UNIVERSITY OF MELBOURNE MASTER OF BIOMEDICAL SCIENCE

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

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

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

MASTERS RESEARCH PROJECT

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

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

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

To organise the research project, students must speak to the prospective supervisor/s listed in this Handbook for projects marked as available for Masters. Students should meet with the supervisor/s to discuss the project further. Projects available for 2020 are also listed on the Murdoch Childrens Research Institute and Department of Paediatrics websites.

For commencement in semester one 2024
Applications closing dates
Semester 1 (February) entry - 30 November
Semester 2 (July) entry - 31 May

Late application closing dates
Semester 1 (February) entry - 15 January
Semester 2 (July) entry - 15 June

*late applications may be accepted based on the availability of places. Only timely applications will be considered for Commonwealth Supported Places (CSP).
http://futurestudents.unimelb.edu.au/admissions/applications/grad-dom