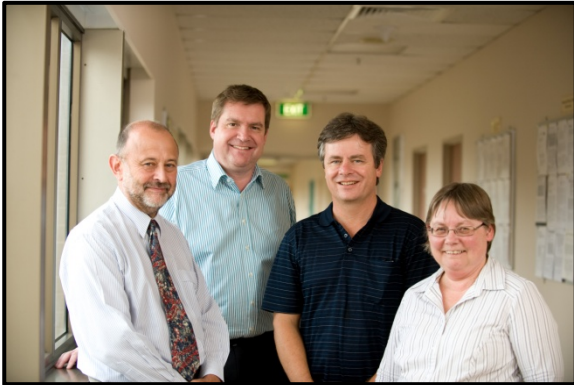


# Research Centres and Projects

## The Ritchie Centre



### Centre Director Professor Euan Wallace

The Ritchie Centre is affiliated with the university departments of Obstetrics and Gynaecology, and Paediatrics. It has a world leading reputation in scientific and medical research relating to women's health; fetal, infant and child health; sleep medicine; and stem cell biology. The Ritchie Centre is one of the few research units that have world-class laboratories and access to clinical patients (women and babies) in a major teaching hospital, allowing seamless translation of experimental work to clinical trials and healthcare.

The Ritchie Centre brings together scientists, clinicians and engineers in major research programs in urogynaecology, endometrial biology and cancer, fetal and perinatal medicine, maternal health, stem cell biology and paediatric cardio-respiratory function, including:

- novel treatments for ectopic pregnancy
- understanding endometrial regeneration and regulation
- the use of stem cells in regenerative medicine in lung disease, pelvic floor prolapse and spinal surgery
- development of the lungs, heart, brain and kidney during fetal and neonatal life
- transition of the cardio-respiratory system at birth
- the mechanisms involved with the Sudden Infant Death Syndrome

- novel bed-side tests of brain function in extremely low birth weight babies,
- physiological and mathematical models of the control of breathing in the newborn
- causes of apnoea and its consequences on heart and brain function
- causes and treatment of obstructive sleep apnoea in infants, children and adults
- disorders of the heart, circulation and breathing during sleep in preterm infants
- mechanisms leading to chronic lung disease in the preterm infant and potential therapies
- mechanisms of vessel dysfunction in preeclampsia and the development of new therapies
- prevention of perinatal brain injury (cerebral palsy)

### Spectroscopic imaging of stem cells and tissues

**Project Leaders:** Prof. Graham Jenkin, Prof. Euan Wallace & Prof. Rob Lewis (Director, Monash Centre for Synchrotron Science)

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**Phone:** 9594 7447

#### Project Description:

The project uses state of the art Infra Red and Rahman spectroscopic imaging technologies and light from the Australian Synchrotron to achieve physiological, histological and biochemical measurements in human stem cells and tissues, including lung and spinal disks. An exciting new project has recently commenced where the use of the new Medical Beamline at the Australian Synchrotron is being used to track the movement and fate of amnion epithelial stem cells in live animals and tissues after they have been administered to animals in preclinical trials for the treatment of adult, fetal and neonatal lung and brain damage.

## The Ritchie Centre

### Reparative effects of human amnion epithelial cells in hyperoxia induced lung injury

**Project Leaders:** Prof. Euan Wallace & Dr. Rebecca Lim  
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**Project Description:**

Our research focuses on the wellbeing of mother and child with particular interest in pulmonary distress. Regenerative medicine is a relatively new field of medicine with aims to help natural healing processes work faster, or use special materials to replace damaged tissue. Recently, human amnion epithelial cells (hAEC) have attracted a lot of attention as a cell source for regenerative therapies. Amnion-derived cells have the considerable advantage in that they do not require the sacrifice of human embryos for isolation, as the amnion is usually discarded as medical waste along with the placenta following birth. This project will investigate the therapeutic benefits of hAEC in reducing lung inflammation and fibrosis in a neonatal mouse model of bronchopulmonary dysplasia. Various techniques will be employed such as small animal surgery, stem cell culture, immunohistochemistry, FACS, real-time PCR and western blotting. This project will provide valuable pre-clinical data to support future human clinical trials of hAEC therapy.

### Human amnion cells: a new therapy for preterm lung disease

**Project Leaders:** Prof. Euan Wallace, Dr. Rebecca Lim & Prof. Graham Jenkin  
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**Project Description:**

The overall aim of our research is to study the utility of human amnion epithelial cells (hAECs) in repairing preterm lung injury. To do this, we will use two sheep models of in utero lung injury namely in utero ventilation and in utero infection (LPS). We will induce lung injury with these models separately and use our well characterised hAECs to explore whether the cells can ameliorate the induced lung injury in the fetal sheep. If successful, we will be well placed to readily apply this technology to very preterm human babies. Our previous research has shown that hAECs are capable of reducing inflammation and preventing fibrosis formation in an adult model of lung fibrosis, differentiating in vivo into alveolar type I and type II cells within the injured lung. We are now studying the effects of hAECs on preterm lung damage and have early pilot data showing that in the preterm fetal lung hAECs will reduce inflammation, reverse scarring and repair the lung exactly as they do with adult lung scarring.

These projects will include whole animal physiology, surgical techniques as well as histological, genomic and proteomic technologies including a novel technique that will allow us to identify a number of early response genes within the fetal and maternal blood that indicate that the fetal lung is being damaged, and that with hAEC administration, this damage is prevented.

## The Ritchie Centre

### Tracking human amnion epithelial cells in vivo in regenerative medicine

**Project Leaders:** Dr. Rebecca Lim, Prof. Euan Wallace & Prof. Graham Jenkin  
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#### **Project Description:**

We are exploring the use of human amnion epithelial cells (hAECs) as a cellular regenerative therapy for a variety of diseases including bronchopulmonary dysplasia and chronic lung disease of the preterm infant. In our previous studies, using an adult mouse model of pulmonary fibrosis, we have been able to identify these hAECs at post-mortem using human specific antibodies, in the lung, up to 4 wk after injection. We have also shown that these cells differentiate into alveolar type I and type II cells within the injured lung. This project will utilise novel labelling techniques, including gold nanoparticles that will allow us to track the migration profile of these hAECs in real-time. These studies will provide important information regarding cell fate, migration patterns and engraftment and differentiation efficiency. There are a number of techniques that will be utilised to monitor the migration, location and differentiation of hAECs in vivo such as colloidal gold nanoparticles which can be incorporated into the cells, injected into an animal model and the cells tracked in real-time using the Synchrotron and MRI. The same technology allows post-mortem validation.

### New treatment targets in preeclampsia

**Project Leaders:** Dr. Rebecca Lim & Prof. Euan Wallace  
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#### **Project Description:**

Preeclampsia is a condition of high blood pressure and multi-organ failure that affects 1 in 20 women in pregnancy. It remains a major cause of maternal mortality and perinatal mortality worldwide and is a leading cause of premature birth in Australia. Current treatment is centred solely around the control of maternal blood pressure. Over recent years, our work has identified the likely cause of the high blood pressure and multi-organ failure – namely disturbed endothelial function induced by massive increases in placental production of activin. Most recently, we have shown that activin induces its endothelial effects via the NADPH oxidases (NOX 2) and that these effects may be modulated by NOX inhibitors and/or activin inhibitors. In this project, we will take our in vitro studies into a mouse model of preeclampsia, inducing hypertension in pregnant mice with activin and “treating” those mice with NOX inhibitors and activin antagonists. We expect that this work will lead to highly novel clinical therapies in the future. The project will involve mouse studies, histology, basic molecular techniques and immunoassays. While an animal-based, this project would particularly suit students with clinical interests.

## The Ritchie Centre

### Regenerative medicine and placental stem cells

**Project Leader:** Prof. Graham Jenkin  
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#### **Project Description:**

The innate capacity of the fetus to repair and regenerate tissues is being used to develop unique new models of organ and tissue regeneration using stem cells. Our research group has developed models of fetal compromise (intrauterine growth restriction), hypoxia induced brain injury and infection in pregnancy and respiratory compromise associated with premature delivery. This research will enable potential new therapies using novel stem cells, including adult stem cells, placental mesenchymal stem cells and amnion epithelial cells and their derivatives to be tested in appropriate animal models. Of particular interest are human amnion derived epithelial stem cells which have many of the characteristics of embryonic stem cells, but which can be obtained without the ethical issues associated with embryonic derived stem cells. In collaboration with Professor Euan Wallace and Dr. Suzie Miller, we are studying the properties of these cells, both in vitro and in vivo, their derivation, their characteristics including plasticity and their potential therapeutic use in repair of respiratory epithelium, cardiac tissue and neural tissues, as well as in spinal disk repair. The latter involves development of biomatrices using stem cells and tissue scaffolds in preclinical research projects on bone and cartilage repair. We are currently undertaking clinical trials, using adult mesenchymal progenitor cells, on spinal disk repair.

### Stem cells and tissue scaffolds

**Project Leaders:** Prof. Graham Jenkin & Dr. Tony Goldschlager  
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#### **Project Description:**

In these studies, we are investigating the suitability of novel new biomimetic matrices to form tissue structures. Our aims are to produce biomimetic spinal discs for repair of discs damaged by trauma or degenerative processes. The use of stem cells to produce cartilage for the repair of knee joints is also a major focus. The advent of tissue engineering in the last few decades, together with stem cell developments, has given researchers the potential ability to suitably engineer cellular constructs for replacement of damaged tissues. We will study the characteristics of biomatrices both in vitro and in vivo in collaboration with commercial companies. We will determine the appropriateness of our cellular scaffolds for the production of engineered tissues. We will determine the most appropriate polymer compositions and stem cell combinations that can be developed into the most viable scaffold for therapeutic use.

## The Ritchie Centre

### Novel approaches to assessing cerebral circulation and oxygenation in preterm human infants

**Project Leaders:** Dr. Flora Wong, A/Prof. Rosemary Horne & Prof. Adrian Walker  
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**Phone:** 9594 5700

#### Project Description:

This project seeks to establish simple, yet reliable, methods based upon NIRS of measuring brain blood flow and brain oxygenation that will be suitable for use in the critically ill newborn. By greater understanding of the basic mechanisms that determine the NIRS measurements, and their correlation with brain blood flow, our project will provide essential information that can be used to enhance the treatment of the more than 5000 babies born each year in Australia that require intensive care for cardio-respiratory dysfunction. By inducing (in newborn lambs) fluctuations in blood pressure, hypoxic-ischaemia and simulated septic shock, we create a model of the most common clinical disturbances in newborn human infants undergoing intensive care. We are then able to evaluate the usefulness of NIRS measurements in these clinical situations of disturbed blood flow and oxygen balance.

### Postnatal consequences of intrauterine growth restriction on cardiovascular control during sleep in infants

**Project Leader:** A/Prof. Rosemary Horne & Dr. Stephanie Yiallourou  
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#### Project Description:

Intrauterine growth restriction (IUGR) has been associated with increased risk of cardiovascular disease, high blood pressure, obesity and insulin resistant diabetes later in life. The causes of this increased susceptibility remain unclear. Cardiovascular control undergoes dramatic maturation changes within the first 6 months of life. In the newborn period infants spend approximately 70% of their time asleep and it is during sleep that infants are at increased risk of cardiovascular instabilities. To date there has been no description of the consequences of IUGR on the maturation of cardiovascular control during sleep in human infants. We have previously described normal maturation of both blood pressure (BP) and heart rate (HR) control in both healthy full-term infants and infants born preterm. In these novel studies we will expand our previous studies to examine the effects IUGR on the maturation of BP and HR control during sleep within the first 6 mo of life. This study will provide information on the postnatal consequences of IUGR and aid in understanding any contributing factors that may contribute to increase blood pressure and cardiovascular complications later in life.

## The Ritchie Centre

### Development of cerebrovascular control during sleep in infants: effects of prone sleeping and implications for SIDS

**Project Leaders:** A/Prof. Rosemary Horne & Dr. Flora Wong  
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#### Project Description:

It has been suggested that Sudden Infant Death Syndrome (SIDS) may be due to an inadequate compensatory response to a hypotensive challenge resulting from either a cardiovascular or respiratory event during sleep. Sleeping in the prone position is still a major risk factor for SIDS, and as yet the reason for this is unknown. We, and others, have previously identified that infant autonomic cardiovascular control and arousability from sleep are impaired in the prone position and this is most marked at 2-3 months of age when SIDS risk is highest. Furthermore, preterm infants are at increased risk for SIDS and we have previously identified impaired autonomic cardiovascular control and arousability in preterm infants compared with age matched term infants. The impaired arousability in SIDS may be related to poor regulation of brain blood flow and oxygen level during sleep. In these novel studies we will expand our previous studies to examine the effects of sleeping position and prematurity on blood pressure (BP) and heart rate (HR) control and cerebral oxygenation using Near Infra Red Spectroscopy (NIRO).

### Novel approaches to bedside monitoring of cerebral oxygenation in infants with HIE undergoing therapeutic hypothermia

**Project Leaders:** Dr. Flora Wong, Dr. Alex Veldman & Prof. Adrian Walker  
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#### Project Description:

Hypoxic ischaemic encephalopathy (HIE) is major problem worldwide with significant mortality and morbidity. Based on recent evidence that therapeutic hypothermia is beneficial to term newborns with HIE, neonatal units now offer cooling as recommended therapy. Yet, there are significant unresolved issues in the application of cooling, including uncertainty of appropriate cerebral monitoring during cooling and re-warming, potential side effects with impact on cerebral circulation and oxygenation, and long-term neurodevelopmental outcome. This project aims to improve and refine the cooling therapy, by using the Tissue Oxygenation Index measured by Near Infrared Spectroscopy (NIRS). We plan to continuously monitor the cerebral oxygenation of HIE infants by NIRS, and relate the measurements to neurodevelopmental outcome. The study will provide bedside information to aid clinical assessments with the potential to guide therapeutic interventions in these critically ill infants.

## The Ritchie Centre

### Impact of dopamine in the immature brain

**Project Leaders:** Dr. Flora Wong, Prof. Adrian & A/Prof. David Walker  
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#### **Project Description:**

Dopamine is commonly prescribed to preterm babies to raise their blood pressure, but its effect in the immature brain is uncertain. This project aims to define the effects of dopamine in the immature brain using a preterm lamb model, in order to evaluate the therapeutic potential of dopamine in improving brain oxygenation and reducing brain injury in preterm babies. Our proposal is based on our preliminary findings in preterm babies that dopamine might promote brain oxygenation to meet metabolic requirement of the brain, thus offering protection against hypoxic-ischaemic injury. We plan to use complementary human-lamb studies: in preterm human infants receiving dopamine therapy, we will monitor their cerebral oxygenation over 3 days using Near Infrared Spectroscopy (NIRS). In preterm fetal lambs receiving dopamine infusion, we plan to correlate changes in cerebral blood flow and metabolism with dopamine dosage and level of dopamine in cerebrospinal fluid.

### Protection against Sudden Infant Death Syndrome: is dummy-sucking the answer?

**Project Leader:** A/Prof. Rosemary Horne  
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#### **Project Description:**

Epidemiological studies consistently show a protective effect of dummy/pacifier use against Sudden Infant Death Syndrome (SIDS); however the promotion of dummies has been controversial, particularly as the mechanisms responsible for this protection remain unknown. It has been proposed that SIDS may involve an impaired ability to mount an appropriate cardiorespiratory and/or arousal response, to compensate for a threatening situation during sleep. Our laboratory and others have previously demonstrated that both autonomic control and arousability from sleep are impaired by exposure to known risk factors for SIDS, such as the prone position and maternal smoking. In this project, we will investigate the effects of dummy-sucking, a SIDS protective factor, on infants' sleep patterns, baseline physiology (heart rate, blood pressure, respiration) and arousal processes throughout the first six months of life.

## The Ritchie Centre

### Postnatal maturation of infant sleep physiology

**Project Leader:** A/Prof. Rosemary Horne  
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**Phone:** 9594 5100

#### **Project Description:**

It has been suggested that despite appearing well and physiologically normal prior to their deaths, victims of Sudden Infant Death Syndrome (SIDS) may have had a pre-existing abnormality which impaired their ability to arouse from sleep. In support of this hypothesis, we have previously shown that arousal processes are modified by major SIDS risk factors, prone sleeping and maternal smoking. An incomplete progression of sub-cortical to full cortical arousal may provide a marker to identify "at risk" infants with an increased likelihood of succumbing to SIDS. This may have the potential to minimise the incidence of SIDS by increasing awareness of both parents and medical staff, in association with close monitoring and early intervention; however this would be impossible without normative values for comparison. This study will examine recordings of undisturbed nocturnal sleep in healthy infants throughout the first 12 months of life. We will compare changes in baseline cardiorespiratory variables and spontaneous arousal processes both between infants and within individual infants across development. In addition, using spectral analysis techniques, we will investigate maturational changes in EEG activity, and on heart rate variability (as a measure of autonomic control).

### Blood pressure changes in preschool children with sleep disordered breathing

**Project Leader:** A/Prof. Rosemary Horne  
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#### **Project Description:**

Sleep disordered breathing (SDB) affects up to 34% of children and symptoms can range from primary snoring without obstructed breathing to obstructive sleep apnoea syndrome (OSAS). OSAS is common in childhood occurring in about 2% of the population, with the peak occurrence between 2-8 years of age and the vast majority of cases are associated with adenotonsillar hypertrophy. Frequent arousal from sleep in response to apnoea, results in sleep fragmentation have serious neurobehavioural consequences such as aggressive behaviour, learning disabilities, excessive daytime sleepiness and attention deficit/hyperactivity. In children apnoea is frequently terminated without any changes on the electroencephalograph and so it is difficult to measure the exact severity of sleep fragmentation. In this study of pre-school children with SDB referred to the Melbourne Children's Sleep Unit for investigation we will measure blood pressure and heart rate during sleep to examine if SDB is associated with increased BP as it is in adults and whether or not this is associated with changes in cardiovascular control.

## The Ritchie Centre

### Behaviour and neurocognition in pre-school children with sleep disordered breathing

**Project Leader:** A/Prof. Rosemary Horne  
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**Project Description:**

Frequent arousal from sleep in response to apnoea, results in sleep fragmentation have serious neurobehavioural consequences such as aggressive behaviour, learning disabilities, excessive daytime sleepiness and attention deficit/hyperactivity. However, few studies have examined a range of severities of clinically defined SDB and how this association is linked with the repeated hypoxic events that occur during sleep and the resultant sleep disruption. This study will examine the effects of a range of severities of SDB on behaviour and neurocognition in 3-5 year old children referred to the Melbourne Children's Sleep Unit for assessment of SDB.

### Effectiveness of treatment for the resolution of Sleep Disordered Breathing, cardiovascular, behavioural and neurocognitive symptoms in primary school children

**Project Leader:** A/Prof. Rosemary Horne  
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**Project Description:**

Our previous studies have identified that sleep disordered breathing (SDB) is associated with increased blood pressure and heart rate and also with impaired neurocognition and behaviour. In current clinical practice, only those children with more severe SDB are treated, primarily with adenotonsillectomy (A/T). A/T has been shown to improve sleep quality and neurobehavioural outcomes, however to date there have been no studies on the effects of treatment on the cardiovascular system. Perhaps more importantly, there have been no studies to assess what happens in untreated children with milder symptoms as currently it is believed that children "will grow out of" their SDB. In this study we will follow up the children previously studied to determine the effects of SDB treatment and non treatment on both the cardiovascular system and neurobehavioural outcomes.

## The Ritchie Centre

### A clinical tool for the detection of children at high risk of obstructive sleep apnoea

**Project Leaders:** Dr. Gillian Nixon & A/Prof. Rosemary Horne  
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#### **Project Description:**

Obstructive sleep apnoea (OSA) affects 1-3% of children and is a major health issue in childhood, with significant impacts on cognition, behaviour and cardiovascular health. The cardinal symptom of OSA is snoring. Approximately 35% of children snore-over one million children in Australia- but only about 10% of snoring children (1-3% of the population) will have OSA. Formally defining the presence of OSA in a snoring child requires polysomnography, a technically challenging and expensive (about \$1000 each) test only available in paediatric tertiary referral hospitals. Such facilities could never meet the demand if all snoring children were referred. We are developing a clinical scoring tool that will help predict children at highest risk of OSA without the need for polysomnography. The tool involves clinical evaluation of the patient including features such as age, body mass index (BMI), symptoms of OSA (snoring, restless sleep) and clinical findings, plus simple sleep tests that can occur in a patient's home.

### The impact of obstructive sleep apnoea on cardiovascular function: are children with Down syndrome at higher risk

**Project Leaders:** Dr. Denise O'Driscoll, Dr. Sarah Hope & Dr. Gillian Nixon  
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#### **Project Description:**

Surges in blood pressure and heart rate and increased activation of the sympathetic nervous system occur as a result of obstructive sleep apnoea (OSA) in adults. These responses are part of the protective arousal response to obstructive apnoeas and hypopnoeas, but are also partially responsible for the adverse cardiovascular effects of OSA. Children with Down Syndrome (DS) have reduced autonomic responses during wakefulness and may therefore have a diminished response to obstructive events during sleep, making them more at risk of hypoxia for a given severity of OSA than otherwise healthy children. Children with DS are at greatly increased risk of pulmonary hypertension, and unrecognised hypoxia due to OSA may contribute to this disorder. In this study we will measure cardiovascular activity and levels of sympathetic activity during sleep in children with DS and otherwise healthy children referred to the Melbourne Children's Sleep Unit for investigation for sleep disordered breathing.

## The Ritchie Centre

### Investigating the effects of prenatal stress in cardiovascular and respiratory responses to stress in the newborn

**Project Leaders:** Dr. Elaine Stockx, Dr. Philip Berger & Dr. Mandar Joshi  
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**Phone:** 9594 5395

#### **Project Description:**

Prenatal stress disrupts normal development and results in susceptibility to further complications later in life and to substantial health care costs throughout life. We hypothesise that increased inflammation and reactive oxygen species are implicated in the mechanistic outcomes of stress.

In this study, we will assess the developmental outcomes of prenatal stress in the newborn using a mouse model. Pregnant mice will be exposed to prenatal stress and the pups will be evaluated for their resting cardiovascular and respiratory function. Additionally, their cardiorespiratory responses to physiological challenges will also be evaluated. Small animal echocardiography will be used to assess the cardiovascular function. Respiratory chamber measurements will be used to assess the lung function. Pups will be subjected to stress by pharmacological agents for cardiovascular studies or hypercapnic challenges for respiratory measurements. Various immunohistochemical, biochemical and molecular biology techniques will be used.

We predict that animals born to mothers who were exposed to stress will have poor responses to challenges in the newborn period. Additionally we expect to see increased inflammation and oxidants in these pups. Defining these mechanisms will enable us to identify therapeutic targets and to develop novel therapies in the future.

### Control of breathing in the Newborn

**Project Leaders:** Dr. Philip Berger, Dr. Andrew Ramsden & Mal Wilkinson  
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#### **Project Description:**

Artificial surfactant therapy is highly effective in controlling lung disease in the newborn. Nevertheless, many preterm infants develop breathing difficulties that require long periods of costly intensive care. Of major concern to clinicians, and a puzzle to explain in terms of current ideas on the control of breathing, is the appearance of breathing pauses (apneas) lasting up to 30 seconds or more. Long apneas are often associated with profound decreases in blood oxygenation and are therefore life-threatening. This project examines the physiology of respiratory control with the goal of understanding the genesis of these pauses. The study will also examine the mechanisms underlying the rapid desaturation that occurs during apnea in the newborn infant.

## The Ritchie Centre

### Oxygen therapy for the preterm infant – optimising delivery

**Project Leaders:** Dr Kenneth Tan, Dr Philip Berger  
& Dr Andrew Ramsden  
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Oxygen therapy is life-saving for preterm infants with respiratory distress syndrome. However, excessive amount of oxygen is potentially harmful, leading to conditions such as bronchopulmonary dysplasia and retinopathy of prematurity (ROP). Excessive fluctuation in oxygen level is also implicated in the pathogenesis of ROP. The task of regulating the amount of oxygen delivered to the infant is still totally reliant on manual adjustments to the inspired oxygen and requires extraordinary vigilance by the bedside nurse. Despite great care, considerable variations in oxygen levels are known to occur frequently. Although evidence indicates that manual control of oxygen delivery can be much improved by assigning one nurse to each infant with sole responsibility for oxygen control/delivery, such a solution is impractical both in terms of economics and work satisfaction.

Several small studies have demonstrated vast improvements in oxygen control and marked reduction in variations in oxygen levels with the automated delivery of oxygen. Automatic oxygen delivery has the advantages of saving staff time as well. The project will involve clinical measurements and data collection from infants receiving intensive care in the NICU at Monash Newborn, the development of mathematical models relating changes in oxygen to underlying disturbance to physiological systems and the development of a novel automatic oxygen controller for premature infants using a range of techniques including neural networks and fuzzy logic.

### Development of serotonergic innervation of the spinal cord of the fetal sheep

**Project Leaders:** Dr. Elaine Stockx &  
Dr. Philip Berger  
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**Phone:** 9594 5477

#### **Project Description:**

The development of motor activity in the fetus is critically dependent upon the establishment of functional inputs from the brain. A key brainstem input that is known to have a major impact on spinal function in the mature animal derives from the neurons of the raphe complex, most of which have serotonin as their principal neurotransmitter. As part of a larger study this project will adopt two approaches to assessing the physiological roles of the serotonergic innervation of the spinal cord. The first approach will determine, using immunohistochemical techniques, when serotonergic terminals are first found in the gray matter of the spinal cord, to quantify the density of the serotonergic innervation of the spinal cord with gestational age, and to examine the timing of appearance of postsynaptic serotonergic receptors in the spinal cord. The second will involve examining the effect on fetal behaviour of selectively destroying the serotonergic innervation of the spinal cord using pharmacological agents.

## The Ritchie Centre

### Analysing inflammatory profiles in preterm newborns developing chronic lung disease

**Project Leaders:** Dr. Alex Veldman, Dr. Andrew Ramsden & Dr. Philip Berger  
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#### Project Description:

Chronic lung disease (CLD) is the most common disease of the preterm infant, with a prevalence that has changed little over the past 30 years despite enormous research efforts. This program will probe the molecular causes, and identify therapeutic strategies, for this major disease. Inflammation is increasingly recognised as the mainstay in the development of CLD. With observations on blood taken from preterm infants on the first day of life, and weekly thereafter until term equivalent age, we will for the first time systematically map the "biochemical fingerprint" of the causative inflammatory process during the postnatal period over which CLD develops. In a prospective, case control observational human study of preterm infants born between 24 and 28 weeks gestation, we will determine the expression profile and the dynamic changes across a comprehensive spectrum of 36 pro- and anti-inflammatory cytokines and proteins in 50 babies. Blood samples will be taken from the cord, in the first 24 hours of life, on days 7 and 14, and at 36 weeks corrected gestational age and analysed using a cytokine profiler to provide semi-quantitative information on the levels of all the candidate cytokines and inflammatory mediators. Total RNA will also be isolated to analyse proteins of the PC pathway not covered by the profiler.

### Testing the anti-inflammatory action of Protein C and IL1Ra in an animal model of chronic lung disease of the preterm infant

**Project Leaders:** Dr. Alex Veldman, Dr. Andrew Ramsden & Dr. Philip Berger  
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#### Project Description:

Severe chronic lung disease (CLD) of the preterm newborn causes considerable suffering for affected children and families and contributes substantially to health care costs in childhood, being second only to the costs for treating asthma and by far exceeding the cost of treating cystic fibrosis. Inflammation is increasingly being recognised as the mainstay in the development of CLD. In this study, we will assess the therapeutic potential of PC and IL1Ra in a well-established animal model of neonatal CLD. Newborn mice pups of C57BL/6J mice will be exposed to room air or to a hyperoxic environment (FiO<sub>2</sub> 0.85). Hyperoxia results in an arrest of alveolarisation, increased pro-inflammatory signalling with subsequent apoptosis of pneumocytes and increased alveolar PAI1 and MMP9 concentrations, mimicking the clinical and biochemical profile of human CLD. We predict that animals receiving PC or IL1Ra will show less biochemical markers of lung inflammation, less histological evidence of CLD, improved alveolarisation and vascularisation, and improved respiratory and clinical performance compared to controls.

## The Ritchie Centre

### Novel therapy for inflammation and microvessel loss in Diabetic Cardiomyopathy

**Project Leader:** Dr. Mandar Joshi  
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#### Project Description:

According to the International Diabetes federation it is estimated that annually some 76,000 children aged less than 15 years develop Type-1 diabetes worldwide. Hence there is an urgent need to define the mechanisms of cardiac complication during diabetes and also develop effective, safe and low-cost therapies. Coronary heart disease is the leading cause of death in the diabetic population and the mechanisms involved are not fully understood. Recently it has been demonstrated that loss of coronary microvessels (microvessel rarefaction) contributes to diabetic cardiomyopathy. However, the dynamic regulation of coronary microvessel prevalence has not been investigated in this setting.

Our study is designed to better understand how loss of microvessels in heart muscle (a phenomenon known as rarefaction) occurs in diabetes, and how this loss may contribute to heart dysfunction and coronary heart disease. Inflammatory pathways play an important role in many cardiovascular diseases and may cause loss of coronary microvessels. Diabetic patients have elevated levels of inflammatory factors (cytokines) in the circulation and the heart. *Hence understanding the mechanistic role of increased inflammation in the progression of diabetic cardiomyopathy is critical for the development of novel therapeutic strategies in the future.* We will use a relevant animal model to study this phenomenon. Additionally, this project will test the therapeutic value of a chemical (resveratrol); commonly found in grapes, peanuts and red-wine in this setting. The long-term goal of this project is to rationally design new ways to prevent this problem or even reverse the process.

### Molecular characterisation of reproductive stem cells for tissue engineering

**Project Leaders:** Dr. Gayathri Rajaraman & Dr. Caroline Gargett  
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#### Project Description:

Mesenchymal stem cells (MSC) are rare populations of undifferentiated cells found in many tissues that are capable of self renewal and differentiating into multiple mesodermal lineages. We first discovered a novel MSC population in the endometrium, the highly regenerative lining of the uterus, (eMSC) and can isolate them using two specific markers. We have also isolated a population of MSC from the human placenta decidua basalis (dbMSC) using eMSC markers. Potential use of reproductive stem cells for tissue engineering and cell-based therapies is attractive as it may be possible to use a patient's own stem cells to repair reproductive organs. However, the molecular characterisation of eMSC/dbMSC has not been done and is necessary prior to their application in regenerative medicine. This study will identify candidate genes that may control eMSC/dbMSC function.

#### Techniques:

Gene array, Real-time PCR, Western immunoblotting

## The Ritchie Centre

### The Effect of CPAP on energy expenditure in obstructive sleep apnoea

**Project Leaders:** Dr. Denise O'Driscoll & Dr. Garun Hamilton  
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**Phone:** 9594 5479

#### **Project Description:**

Obstructive sleep apnoea (OSA) in adults is strongly associated with obesity and the metabolic syndrome. OSA may have variable effects on energy expenditure. Features of OSA that have been shown to cause an *increase* in energy expenditure include: arousal from sleep with secondary body movement, and increased work of breathing during upper airway obstruction. Counterbalancing this, energy expenditure may be *decreased* in OSA due to reduced physical activity (mediated via hypersomnolence) or nocturnal hypoxia (with subsequent reduction in resting energy expenditure).

In this study we will measure energy expenditure (corrected for lean body mass) during sleep and wake in obese subjects with and without OSA, and also assess the effect of continuous positive airway pressure (CPAP) treatment. This study aims to determine the pattern of physical activity and energy expenditure (total and resting) in free-living individuals with severe OSA, and the subsequent effect of treatment with CPAP using a portable, combined physical activity and energy expenditure monitor.

### Preventing prenatal brain injury in the growth restricted fetus

**Project Leaders:** Dr. Suzie Miller & Prof. Euan Wallace  
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#### **Project Description:**

The developing fetus requires an adequate supply of oxygen and nutrients, derived from the mother via the placenta, to meet its metabolic demands for optimum growth and maturation. In pregnancies complicated by intrauterine fetal growth restriction (IUGR) where impaired placental function causes suboptimal transfer of gases and nutrients to the fetus, the fetus is at increased risk of significant morbidities, such as brain injury, and intrauterine death. We have previously shown that IUGR is associated with significant fetal oxidative stress. We believe that it is this oxidative stress, rather than a shortage of oxygen and/ or nutrients per se that may have detrimental effects on the developing fetus leading to brain injury and other poor outcomes. We hypothesise that antioxidant treatment will reduce oxidative stress and improve fetal and neonatal wellbeing in IUGR fetuses. To address this we have designed a project using melatonin, which is safe for pregnant women and their babies, as an antioxidant. We have shown previously that melatonin is protective in the fetal brain in response to a short period of severe hypoxia. In this project we will induce IUGR in fetal sheep; half of the ewes will be treated with melatonin and half with a placebo. We will then let the ewes deliver and monitor a range of outcome measures in the lamb to assess whether melatonin improves outcome. We will also study brain structure in the newborn lambs. This project will combine whole animal physiology, surgical techniques and postnatal animal monitoring with studies of cardiac structure and function, brain histology and immunohistochemistry. Ultimately, we hope that this project may lead to new treatment options for obstetricians to offer in the management of human IUGR.

## The Ritchie Centre

### IGF-1 as a novel fetal neuroprotectant

**Project Leaders:** Dr. Suzie Miller & Prof. Euan Wallace  
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#### **Project Description:**

Cerebral palsy (CP) is the most frequent cause of childhood disability. Presently, there is no cure. While the origins of CP are not fully understood periventricular leukomalacia (PVL), a form of cerebral white matter damage, is the most common brain pathology associated with it. There is a strong association between intrauterine infection, PVL and CP. We have been studying the pathways that link infection, PVL and subsequent CP and have shown that if the fetal inflammatory response is modified, it may be possible to prevent brain injury, despite the infection. In this study, we will test the use of insulin-like growth factor I (IGF-1) as a neuroprotectant. IGF-1 both modifies the adverse effects of the inflammatory cytokine, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and may protect oligodendrocytes – the cells that produce myelin, forming the basis of the fetal brain white matter. This research will provide important insights into the contribution of inflammation in fetal brain injury and to neonatal morbidity. We hope that this study may direct future clinical studies in this area. During the project the student will acquire skills in fetal sheep surgery and animal maintenance, immunohistochemistry, immunoassays and basic molecular techniques.

### Does antioxidant treatment during late-pregnancy improve neonatal outcome in an ovine model of intrauterine growth restriction (IUGR)?

**Project Leaders:** Dr. Suzie Miller, Prof. Graham Jenkin, Prof. Euan Wallace, Dr. Marianne Tare & A/Prof. David Walker  
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#### **Project Description:**

Intrauterine growth restriction (IUGR) affects up to 10% of the population and is associated with an increased risk of perinatal mortality and increased risks of short and long-term morbidity. It has been shown in human IUGR that markers of oxidative stress are significantly upregulated in the placenta and fetus. Oxidative stress, and elevated levels of reactive oxygen species, may have detrimental effects on the developing fetus, and may be responsible for some of the poor outcomes which are observed in IUGR infants. We hypothesise that treatment with the antioxidant melatonin will reduce oxidative stress and improve fetal and neonatal wellbeing and that administration of insulin-like growth factor-1 (IGF-1) will protect the fetal brain in the face of infection and hypoxia. In this project we will induce IUGR in fetal sheep; the ewes' fetuses or neonates will be treated with melatonin or IGF-1 or placebo. We will monitor a range of outcome measures in the lambs to assess whether melatonin or IGF-1 improves outcome. This project will combine whole animal physiology, surgical techniques and postnatal animal monitoring with studies of cardiac structure and function and brain histology and immunohistochemistry. This project may impact on the treatment options available to obstetricians treating human IUGR or Cerebral Palsy.

## The Ritchie Centre

### The effects of steroid administration on the cardiovascular system of IUGR fetuses

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#### **Project Description:**

Glucocorticoids are routinely administered to pregnant women at risk of preterm delivery in an effort to mature the fetal lungs for birth. There is no question that this treatment saves the lives of many newborns. However, glucocorticoids are powerful regulators of vascular function and as such glucocorticoid treatment may place the growth restricted fetus at risk, since they already demonstrate cardiovascular impairment. Using our ovine model of intrauterine growth restriction (IUGR) we have shown that blood flow responses to betamethasone (a synthetic glucocorticoid) are quite different in IUGR fetuses when compared to normally grown fetuses which may have consequences that persist into adulthood. The effects of these changes in blood flow and subsequent impact on development of specific organs remains entirely unexplored and therefore in this project we will look closely at the brain, heart and lungs to examine possible differences between IUGR and normal fetuses administered betamethasone, as well as perinatal outcomes.

This project will combine whole animal physiology, surgical techniques and animal monitoring and experimentation with studies of cardiac and lung structure and function. We hope that this project will provide an important insight into the mechanisms occurring, and possible management strategies, in human IUGR pregnancies.

### The metabolic cost of pregnancy

**Project Leaders:** A/Prof. David Walker & Dr. Hayley Dickinson

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#### **Project Description:**

During pregnancy both the mother and developing fetus go through a range of well-defined endocrine changes; however very little information is known about the metabolic changes that occur during pregnancy or labour. When the pregnant mother is sick or exposed to chronic stress, the metabolic changes of the mother may have detrimental consequences for the developing fetus. The project will focus on characterising the metabolic changes of the mother and the developing fetus throughout pregnancy and during labour, as well as the specific metabolic-regulating neurotransmitter systems within the brain.

Techniques utilised include; fetal surgery, monitoring of maternal and fetal physiology (heart rate, blood pressure, brain electrical activity, brain blood flow, and oxygen consumption), immunohistochemistry, real-time PCR and other molecular biological techniques, and an understanding of neuroanatomy.

## The Ritchie Centre

### Can maternal creatine and/or melatonin supplementation protect the fetus against hypoxic injury?

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**Project Description:**

Fetal oxygen deprivation is a common denominator in many difficult pregnancies. When severe or prolonged, this can result in energy failure and damage to fetal tissues.

Using our established model of birth asphyxia in the spiny mouse (*Acomys cahirinus*), we have previously shown that this insult at day 37 or 38 of gestation results in a reduced survival rate of the pups (~60%), and significant damage to the brain, but also severe functional and structural damage to the diaphragm. We have explored possible treatments to prevent these injuries arising from birth asphyxia; for example, (1), administration of creatine (an energy buffer utilised as an energy source in the absence of oxygen) to the mothers prior to birth asphyxia at day 38 resulted in improvements in pup survival rate as well as reductions in the damage observed in the brain and diaphragm and amelioration of behavioural deficits; and (2), administration of melatonin (an anti-inflammatory agent) to these dams prior to birth asphyxia at day 37 resulted in a reduced occurrence of abnormal cells and levels of inflammatory cytokines in the neonatal brain.

We now wish to extend these observations to determine, by examining juvenile and young adult animals, if the brain and muscle injury seen in our models of birth asphyxia persist beyond the immediate postnatal period. In particular, we will examine the heart, skeletal muscle, kidneys and lung for evidence of physical and functional damage arising from the birth asphyxia. If injury does occur and persist in the heart, skeletal muscles, kidneys and lung, we will determine if this can also be prevented with the creatine or melatonin treatments we have already shown, separately, to have

protective benefits for the neonatal brain. Finally, we will determine if combined treatment with creatine and melatonin offers greater protection to the fetus during periods of asphyxia at birth

### Pregnancy, parturition and conception in the spiny mouse – A busy 24h!

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**Project Description:**

The spiny mouse is a precocial rodent species with a relatively long gestation that exhibits a postpartum estrus within 24h of parturition. The mechanism of delivery (labor) is not known in the spiny mouse, but we have recently discovered that the ovary, via an active corpus luteum, is essential for the maintenance of pregnancy to term.

This project will explore the mechanism of luteolysis in this species and determine the sequence of events leading to the delivery of 1 litter and ovulation and conception of the next litter, all within a 24h period

## The Ritchie Centre

### In vivo and in vitro embryo development in the spiny mouse

**Project Leaders:** Dr. Hayley Dickinson & A/Prof. David W Walker  
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#### **Project Description:**

A central focus of our research group is to better understand the mechanisms that determine the length of pregnancy. We are undertaking a series of experiments to explore whether gestation length is under the control of the mother, fetus or placenta. In order to complete these experiments it is necessary for us to understand the development of the spiny mouse embryo. This project will compare the in vivo and in vitro development of spiny mouse embryos, optimize a technique for storing these embryos for our later embryo transfer experiments and provide a description of the metabolic needs of the embryo as it develops.

Embryos will be collected on days 1, 2, 3, 4 and 5 of gestation. Two cohorts of embryos will be used. The first cohort will be collected, their stage of development noted and they will then be used to optimise a vitrification (freezing) protocol before being stored for later use. The second cohort of embryos will be collected, their stage of development noted and they will then be cultured to hatching stage (either individually or in groups). Samples of media will be taken regularly from cohort 2 embryos cultured individually, and frozen for later metabolic profiling experiments.

### Critical Windows of organ development susceptible to maternal stress

**Project Leaders:** Dr. Hayley Dickinson & A/Prof. David Walker  
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#### **Project Description:**

In this study we propose to identify the times during pregnancy when organ systems such as the lung, heart, pancreas, liver, brain, adrenal and placenta are susceptible to the effects of excess maternal stress hormones. Knowledge of when particular fetal organ systems are most vulnerable to maternal stress, illness and malnutrition would give a rational basis for knowing more about how to handle and /treat such illnesses during pregnancy. In these studies we will use a most appropriate rodent species, the spiny mouse. The spiny mouse produces the same 'stress' hormone as the human (cortisol), and gives birth to offspring at a similar stage of maturation as the human at birth.

We will administer dexamethasone, cortisol or saline to pregnant spiny mice for 60h on days 15, 25, 30 or 35 of gestation (term is 39 days) and determine the fetal, newborn and adult consequences for the offspring. Fetal growth and blood flow will be monitored throughout pregnancy using our established ultrasound technique. Fetal, neonatal and adult tissue will be processed for histological, genomic, proteomic and hormone analysis. Offspring will be exposed to a battery of behavioural, physiological and body composition tests to thoroughly assess their developmental outcome.

## The Ritchie Centre

### Creatine synthesis and transport in the human placenta

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**Project Description:**

There is evidence to suggest that the fetal kidney and liver do not support creatine synthesis until late in pregnancy. Until this time, the fetus presumably relies on transfer of creatine from the mother across the placenta. We will use a dual perfusion apparatus to study the transfer of creatine from the maternal to fetal side of placentas collected from the Labor Ward, MMC. Techniques that will be learnt include vascular perfusion, biochemical measurement of creatine, creatinine and other amino acid derivatives. We also want to establish if placental tissue can actually synthesize creatine, and we will use methods to identify the mRNA and protein for the creatine transporter – CrT1.

Students taking on this project should be prepared to be available at most hours of the day and night, including weekends, during semester 1 & 2 because we cannot predict when samples will be available.

### Transition to life after birth

**Project Leaders:** Prof. Stuart Hooper, Dr. Tim Moss, Dr. Graeme Polglase & Dr. Kelly Crossley  
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**Project Description:**

The transition to air-breathing after birth is one of the greatest physiological challenges that we will ever face during our lives. Within moments of birth, the airways must be cleared of liquid, to allow the entry of air, which greatly increases blood flow through the lungs and closes shunts that allow blood to by-pass the lungs during fetal life. When the umbilical cord is cut the infant loses ~1/3 of its blood volume and venous return to the heart is reduced by ~50%. It is truly amazing that most infants transition smoothly from fetal to newborn life: however, many don't and these huge physiological changes provide life threatening challenges for these infants, which can have life-long repercussions. To reduce the risks for newborn infants during this challenging period, we need to better understand these changes and the factors controlling them. The aim of this project is to study the changes that occur at birth and to identify factors that both facilitate and impede these changes.

## The Ritchie Centre

### Imaging the entry of air into the lungs at birth

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**Project Description:**

Surviving the transition to air-breathing at birth is dependent upon the clearance of liquid from the airways to allow the entry of air into the gas exchange regions of the lung. This process occurs very smoothly in most infants, but preterm infants have difficulty in clearing their lungs of liquid and allowing air to enter the regions where gas exchange can occur. We have developed a unique imaging technique, using a synchrotron, which allows us to observe the entry of air into the lungs at birth. Using this technique we can study and identify the factors that facilitate air entry into the lungs at birth. The aim of this project is to use our imaging technique to identify factors that promote and impede the entry of air into the lungs at birth in animals born preterm. These experiments will provide important information for doctors caring for very preterm infants and will be conducted at a synchrotron in Japan.

### Ventilation-induced lung injury in very preterm infants

**Project Leaders:** Prof. Stuart Hooper & Dr. Megan Wallace  
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**Project Description:**

Preterm birth is the greatest cause of death and disease in newborn infants because their lungs are too immature to take over the role of gas exchange at birth. As a result, very preterm infants must be artificially ventilated from birth, but this usually damages their lungs and causes the lung to develop abnormally. Little is known of the mechanisms by which artificial ventilation causes lung injury or how this injury causes abnormal lung development because it is so difficult to study. However, we have recently developed an animal model of *in utero* ventilation which allows us to specifically identify types of ventilation that injure the immature lung and how injury causes abnormal development. Several projects are possible including; determining the types of ventilation that injure the lung, identifying the genes that are activated by injury and cause abnormal development and identifying treatments that may prevent injury and the resulting abnormal development. These projects can involve fetal surgery, *in utero* ventilation experiments and the analysis of lung tissue for injury using histological and molecular approaches.

## The Ritchie Centre

### Factors regulating fetal lung growth

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**Project Description:**

The transition to extra-uterine life is largely dependent upon the ability of the fetal lungs to take over the role of gas exchange. Infants born preterm, before the lungs have had sufficient time to develop, or with lungs that have not developed properly (lung hypoplasia), are at high risk of death or disease. To improve the outcome for these infants it is important to develop new therapeutic treatments. To do this, we must first understand the mechanisms that regulate normal lung development, so that we can find new ways to accelerate it. The fetal lung doesn't grow or develop properly unless it is distended during fetal life by a liquid that is produced by the lungs. Increased fetal lung distension accelerates fetal lung growth whereas deflation of the lung causes fetal lung growth to cease. Lung deflation is the major cause of lung hypoplasia in humans. However, the mechanisms involved are largely unknown. We have recently identified a group of candidate genes that may mediate the effect of lung distension and this project will examine the role of these genes in regulating lung growth.

### Factors regulating alveolar epithelial cell differentiation

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**Project Description:**

Survival at birth is dependent on the ability of the lung to take over the role of gas exchange. In particular, the lungs must have developed a complex airway structure and the terminal airsacs (alveoli) must contain mature alveolar epithelial cells (AECs). There are two types of AECs and both are vital for normal lung function. Type-I AECs are large flat cells that facilitate gas diffusion between alveoli and capillaries, whereas type-II AECs produce surfactant which reduces surface tension and prevents lung collapse at end-expiration. Preterm babies are born before these cell types develop and so have lungs lined with immature, undifferentiated cells that lack the ability to facilitate gas exchange or prevent lung collapse. Despite the critical importance of type-I and type-II cells, little is known of the factors that regulate their development. This project will investigate the factors responsible for determining the formation of mature AECs during fetal life.

## The Ritchie Centre

### Effects of the prenatal environment on the fetal immune system

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**Project Description:**

Very low birth weight preterm babies have a very high risk of potentially life threatening infections. One of the reasons for this high risk is the immaturity of the preterm infant's immune system but the risk is likely altered by other factors associated with preterm birth. The aim of this project is to measure cellular immune function in fetal sheep exposed to 2 factors that are common in cases of human preterm birth: inflammation and synthetic glucocorticoid exposure. Many preterm births occur as a result of infection or inflammation within the uterus but we know very little about how these early life exposures affect the developing immune system. Women at risk of preterm birth routinely receive injections of synthetic glucocorticoids to induce fetal maturation. Glucocorticoids are potent inhibitors of inflammation but also are critical regulators of prenatal development; their effects on the developing immune system are poorly defined. These experiments will provide information important for understanding how early life events influence individuals' risk of lifelong immune diseases such as asthma and allergy.

### Can ultrasound measurements of fetal growth provide information about exposure to infection/inflammation before birth

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**Project Description:**

In recent years we have become aware that infection or inflammation within the pregnant uterus increases the risk of preterm birth and the risk of brain and lung disease in babies. Detection of intrauterine infection/inflammation is critical for tailored management of these pregnancies. There are currently no non-invasive tests that allow detection of infection/inflammation within the uterus. Data from animal experiments suggest that the pattern of fetal growth may be altered in the presence of intrauterine inflammation/infection. The aim of this project is to examine whether routine measurements of fetal growth, obtained using ultrasound, can be used to predict adverse pregnancy outcomes due to intrauterine infection/inflammation

### How does inflammation before birth alter fetal lung development?

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**Project Description:**

Inflammation within the uterus is common in human pregnancies that end in preterm birth and influences the risk of lung disease in preterm babies. The means by which inflammation before birth alters fetal lung development is unknown. The aim of this project is to identify the mechanisms that mediate the effects on fetal lung development of inflammation within the uterus before birth. These studies will use sheep or mouse models of intrauterine inflammation.