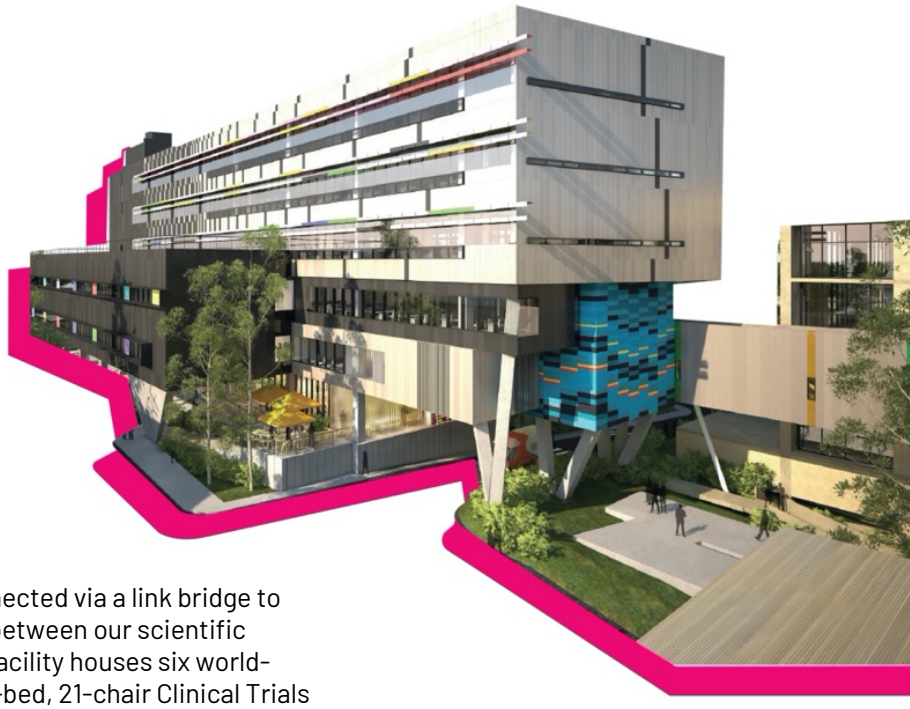
HUDSON
INSTITUTE OF MEDICAL RESEARCH

THE RITCHIE CENTRE

2023 Student Research Projects

MHTP Monash Health Translation Precinct | MONASH University | HUDSON INSTITUTE OF MEDICAL RESEARCH | Monash Health

Contents



The Translational Research Facility is connected via a link bridge to Monash Health and provides a crucial link between our scientific discoveries and medical treatments. The facility houses six world-leading technology platforms and an eight-bed, 21-chair Clinical Trials Centre that support the transition of discoveries from initial Phase I testing through to Phase IV primary health trials.

Welcome to Hudson Institute

Hudson Institute specialises in discoveries in five areas of medical need

- **Inflammation**
- **Reproductive health and pregnancy**
- **Infant and child health**
- **Cancer**
- **Hormones and health**

Our 443 scientists and students focus on laboratory discovery science and translational research – taking discoveries to patients and industry for real-world impact.

267 STAFF

176 STUDENTS

45 RESEARCH GROUPS

257 RESEARCH PUBLICATIONS

Students at a glance 2021

68 POSTGRADUATE AND HONOURS STUDENTS COMPLETED

176 STUDENTS
125 PhD
1 MASTERS
50 HONOURS

26 STUDENTS WITH MEDICAL TRAINING

We educate and train more than 170 students through our academic affiliation with Monash University. Our postgraduate training is predominantly through the School of Clinical Sciences at Monash Health, part of the Faculty of Medicine, Nursing and Health Sciences at Monash University.

Our students

- Are exposed to university, institute, and hospital research
- Attend national and international conferences
- Publish their research in high impact journals
- Are mentored by leading supervisors and their teams
- Win prestigious prizes and awards
- Join regular networking and learning and development programs, including the off-site Institute student retreat
- Learn a range of dynamic and transferable skills for careers in the biomedical and clinical research sectors including commercialisation

All work and no play ...

Our students can join in a range of student networking and social events organised by Hudson Institute Student Society (HISS), including being part of the management committee.

Our precinct

Hudson Institute is a leading Australian medical research institute recognised internationally for discovery science and translational research into inflammation, reproductive health and pregnancy, infant and child health, cancer, hormones and health.

Our Institute is home to 443 world-class scientists, who push the boundaries of scientific knowledge to answer complex questions about human disease, including prevention and treatment.

We are a founding member of the Monash Health Translation Precinct (MHTP) with partners Monash Health and Monash University. Our close ties with clinicians and industry enable us to translate our discoveries into new preventative approaches, therapies and devices for patients.

Our location at Monash Medical Centre means our research is informed by patient need and our discoveries are transitioned into practical treatments.

Working alongside clinicians in Melbourne hospitals for more than 50 years, our scientists pioneered IVF and stem cell discoveries and are now leading developments in cell therapies, paediatric cancer and the human microbiome. Our worldwide scientific and medical collaborations provide a foundation for transformative healthcare programs across the globe.

The Ritchie Centre

Location

Hudson Institute of Medical Research
27–31 Wright Street
Clayton VIC 3168

t: >+61 3 8572 2877

e: >caroline.menara@hudson.org.au

w: >hudson.org.au/research-centre/the-ritchie-centre/

Centre Head

Professor Stuart Hooper

The Ritchie Centre is Australia's premier clinical and research Centre for women, babies, and children. The Ritchie Centre offers a unique setting where research advances can be rapidly applied for the benefit of women, seriously ill infants, and children. This has led to rapid translation of its basic research into clinical trials and clinical practice.

The Ritchie Centre is strategically located within the Monash Medical Centre. Integration into the daily life of the hospital means that its researchers are able to develop research in response to the complications that present in the clinical setting and demonstrated the value of bringing together a critical mass of dedicated scientists and clinicians to undertake translational research.

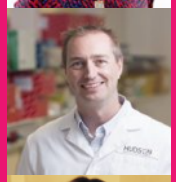
The Centre's mission to improve the health of women, infants and children through innovative research is achieved through its unique associations as the principal research Centre of the **Monash University Department of Obstetrics and Gynaecology and the Department of Paediatrics**, Monash Women's Services, Monash Newborn and Melbourne Children's Sleep Centre. It is also a major research partner of the Monash Children's Hospital.

Ritchie Centre Research Themes:

- Women's Health
- Fetal and Neonatal Health: Respiratory and Cardiovascular
- Fetal and Neonatal Health: Brain Injury and Neurodevelopment
- Infant and Child Health
- Infection, Inflammation, and Immunity
- Cell Therapy and Regenerative Medicine

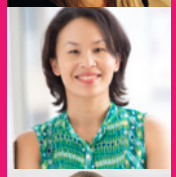
Research Group Heads

Endometrial Stem Cell Biology
Prof Caroline Gargett

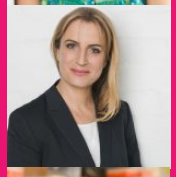


Perinatal Transition
Prof Graeme Polglase

Neurodevelopment & Neuroprotection
Prof Suzie Miller

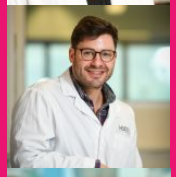


Amnion Cell Biology
A/Prof Rebecca Lim

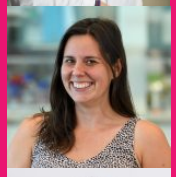


Interventional Immunology in Early Life Diseases
Prof Claudia Nold
Prof Marcel Nold

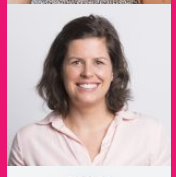
Translational Tissue Engineering
Dr Shayanti Mukherjee



Perinatal Inflammation and Neurophysiology
Dr Robert Galinsky



Epidemiology and Clinical Trials
Dr Miranda Davies-Tuck



Perinatal Cardiovascular Physiology
Dr Beth Allison

Lung Development
A/Prof Megan Wallace

Neonatal Brain Protection
A/Prof Flora Wong

Women's Health

Characterising novel targets for the treatment of endometriosis

Suitability: Honours, Masters
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Fiona Cousins, Prof Caroline Gargett
Email: *fiona.cousins@hudson.org.au*

Project description: Endometriosis is a chronic disorder that has a major impact on quality of life. Despite its high prevalence, there is a lack of understanding of its pathogenesis, there is no cure, and current treatment options are limited to medicines with side effects or invasive surgery. We are aiming to develop new therapeutic strategies that focus on the immune system and not a woman's menstrual cycle, like most current treatments. Interferons are a family of cytokines that have anti-pathogen and anti-tumour actions. They work by controlling cell growth, survival, migration and activation in immune cells that cause inflammation.

Interferon epsilon (IFNε) is a novel cytokine and immunomodulator that is constitutively expressed and only in the female reproductive tract (FRT) epithelium. IFNε exerts its protective effects in the FRT to prevent bacterial/viral infections and cancers. IFNε exerts a protective effect against the development of ovarian cancer in pre-clinical mouse models and can also reduce cancer metastases when given as a therapeutic in these mice. Given the similarities between ovarian cancer and endometriosis; increased cell growth and adaptation to an inflamed environment, we are interested to see whether IFNε may play a role in endometriosis pathogenesis and whether it can be used as a new therapeutic for the disease.

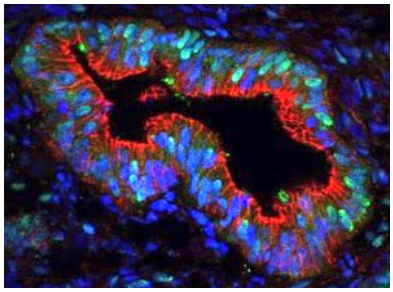
Keywords: endometriosis; immune system; immunomodulation; endometrium; women's health; disease;

A novel non-invasive diagnostic for endometriosis/adenomyosis

Suitability: PhD/Honours/Masters
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leader: Prof Caroline Gargett, Dr Caitlin Filby
Email: *caroline.gargett@hudson.org.au*

Project description: Women with endometriosis and adenomyosis suffer for up to 10 years in pain before a diagnosis is made. This is in part due to lack of a non-invasive diagnostic test. Endometriosis affects 10% of girls and women and is characterised by lesions of endometrial tissue form throughout the pelvic cavity, causing pain, disease and infertility. Adenomyosis is a related condition where lesions form within the myometrial layer of the uterus. This project will build upon our novel findings that menstrual fluid may serve as a novel non-invasive diagnostic for endometriosis and adenomyosis. The project involves quantitation and functional characterisation of endometrial stem/progenitor cells and plasma proteins. Techniques include tissue culture, flow cytometry, ELISA, and immunofluorescence. Techniques employed can be tailored to suit the interests of the student. This project has international funding

Keywords: Endometriosis, flow cytometry, stem cells, diagnostics\

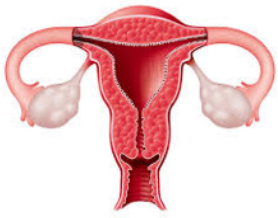


Vaginal Stem Cells: the missing link to vaginal reconstruction

Suitability: Masters/Honours/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Caroline Gargett. Dr Shanti Gurung
Email: *caroline.gargett@hudson.org.au*

Project description: The vagina is central to a woman's sexuality, her sexual health, body image and sense of wellbeing. Vaginal epithelial stem cells and mesenchymal stem cells are likely responsible for maintaining vaginal tissue and could be harnessed for use as cell therapies for women who have lost a significant proportion of their vagina due to cancer, radiation treatment or chemotherapy. This project will identify these stem cell populations in human vagina using in vitro stem cell assays: clonogenicity, self-renewal and differentiation into 3D organoids. Techniques include primary tissue culture, FACS, immunofluorescence.

Keywords: Vagina, human, epithelial stem cells, mesenchymal stem cells, organoids, flow cytometry



Deciphering Immune Response to Bioengineered Meshes

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Shayanti Mukherjee, Prof Caroline Gargett, Dr Saeedeh Darzi
Email: *shayanti.mukherjee@hudson.org.au*

Project description: Pelvic organ Prolapse (POP) is a debilitating urogynecological disorder arising from vaginal birth trauma that goes unrecognised, and culminates as a chronic diagnosis, decades later. POP affects 50% of post-menopausal parous women, and detrimentally impacts their physical, sexual, psychological, and social well-being. Until recently, non-degradable meshes made of polypropylene were commonly used to mitigate the high failure rates of native tissue repair. However, such meshes were banned in Australia in 2017 owing to the unacceptable rates of complications such as mesh erosion, exposure, and pain. It is now understood that such adversities arise from disruption of microenvironment after meshes implantation, lack of biocompatibility and inferior mesh designs that trigger undesirable foreign body immune responses which ultimately lead to implant failure. However, the key mediators of the immunomodulatory response remain elusive. Thus, in order to develop the next generation of surgical meshes and cellular therapies for POP treatment, it is critical to understand the immunological considerations after implantation.

This project aims to determine the key molecular players enabling foreign body response modulation to implanted biomaterials and regenerative stem cells. The study utilizes our established in vitro cell culture models, pre-clinical models, medical genomics and advanced imaging to understand how innovative bioengineering strategies can be harnessed to mitigate the undesirable post-surgical immune response in order to overcome the current hurdles in pelvic reconstructive surgery. Our team involves engineers, biomedical scientists, and surgeons. We welcome students from diverse academic backgrounds with an interest in immunology and women's health to contribute to this multi-disciplinary project.

Keywords: women's health, surgery, maternal health, immunology, stem cells, nanotechnology, animal model, pelvic organ prolapse, birth trauma

Combating Maternal Childbirth Injury with Cellular Therapies

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Shayanti Mukherjee, Prof Caroline Gargett
Email: *shayanti.mukherjee@hudson.org.au*

Project description: Maternal birth injury can have a devastating impact on women's quality of lives. Injuries incurred during vaginal childbirth are the leading risk factor for chronic debilitating pelvic floor disorders such as pelvic organ prolapse (POP). Evidence shows that acute pelvic tissue injury from forceps delivery, prolonged second stage labour, large infant birth weight, anal sphincter laceration and episiotomy lead to POP. In Australia, forceps use has risen by 70% since 2006 and 2 out of 3 births now result in pelvic tissue trauma. Although arising from vaginal birth, untreated tissue injury gradually culminates into a chronic diagnosis, years or decades later. Chronic pelvic floor disorders resulting from maternal birth injuries 50% of post-menopausal parous women, and detrimentally impacts their physical, sexual, psychological, and social well-being and yet, lacks a safe and effective treatment. Alarmingly, there is no therapeutic cure for POP, let alone a way of predicting and preventing the eventual onset. We are developing innovative secondary prophylactic post-partum therapies to repair birth injury and thus, prevent development of POP.

This project will look into the design and application of hydrogels to deliver highly regenerative and therapeutic Mesenchymal Stem cells from maternal tissues and evaluate its suitability in the form of a injectable therapy for maternal birth injury using pre-clinical ovine models, medical genomics and advanced imaging technologies. Our team involves engineers, biomedical scientists, surgeons, chemists, and biophysicists. We welcome students from diverse academic backgrounds to participate and contribute to the project in aspects which interests them the most.

Keywords: birth, birth injury, maternal health, women's health, hydrogel, stem cell, tissue engineering, pelvic floor

Next Generation 3D Cellular Bio printed Surgical Devices for Pelvic Reconstructive Surgery

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Shayanti Mukherjee, Prof Anna Rosamilia, Dr Kallyanashis Paul
Email: *shayanti.mukherjee@hudson.org.au*

Project description: POP is the herniation of pelvic organs, specifically the uterus, bladder and bowel into the vagina and outside the body. This biomechanical failure primarily arises from birth injuries, such as overstretching or tearing of the main pelvic support structures: suspensory ligaments, pelvic floor muscles and vaginal wall. Symptoms include a vaginal bulge and obstruction of pelvic organs leading to urinary, faecal, and sexual dysfunction. The problem is profound yet largely hidden: POP affects 1 in 2 parous women aged 50+ years and 1 in 4 women across all ages who often suffer in silence due to social stigma and

embarrassment. Acute pelvic tissue injury from instrumental delivery such as forceps, prolonged second stage labour, large infant birth weight, anal sphincter laceration and episiotomy lead to POP. About 1 in 5 women suffering from POP require pelvic reconstructive surgery. Until recently, non-degradable meshes made of polypropylene were commonly used to mitigate the high failure rates of native tissue repair. However, these led to adverse effects and complications. Therefore, such transvaginal meshes are now completely banned in many countries including Australia. At present, there is no optimal strategy or therapy to cure POP. There is a clear unmet need. To address this critical issue, we are developing the next generation of surgical devices using nanotechnology and 3D printing that involve highly regenerative therapeutic cells with the goal of advancing women's urogynaecological health.

This project will look into the design of 3D printing of cells and polymers to achieve a surgical construct and evaluate its suitability using pre-clinical ovine models, medical genomics and advanced imaging technologies. Our team involves engineers, biomedical scientists, surgeons, chemists, and biophysicists. We welcome students from diverse academic backgrounds to participate and contribute to the project in aspects which interests them the most.

Keywords: women's health, surgery, pelvic floor, maternal health, immunology, stem cells, nanotechnology, ovine model, pelvic organ prolapse, birth

Endometrial organoids: novel tools for precision gynaecological medicine

Suitability: **Honours/PhD/Masters**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Caroline Gargett, Dr Caitlin Filby
Email: *caroline.gargett@hudson.org.au*

Project description: Organoids are miniature organs cultured in a dish that enable disease modelling and development of precision medicine. This project will utilize this exciting tool to generate organoids from human and mice to study endometrial stem cell biology and its role in the formation of endometriosis. Endometriosis is a disease affecting 10% of women, whereby endometrial cells form lesions in pelvic cavity, causing pain, disease and infertility.

This project will generate a new system for investigating the causes of endometriosis and a patient-derived biobank for disease phenotypic profiling, drug discovery and precision medicine. Techniques include tissue culture, organoids, fluorescence activated cell sorting, in vitro assays, immuno-fluorescence, and mouse models. Techniques employed can be tailored to suit the interests of the student.

Keywords: Endometriosis, flow cytometry, stem cells, diagnostics, organoids, precision medicine

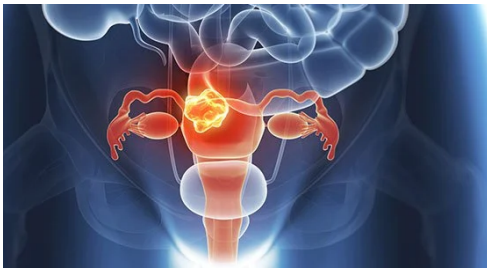
Decoding the significance of endometriosis risk

Suitability: **Honours/PhD/Masters**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Caroline Gargett, Dr Caitlin Filby
Email: *caroline.gargett@hudson.org.au*

Project description: Endometriosis is a devastating chronic disease affecting 10% of girls and women, where cells of endometrial histology form lesions throughout the pelvic cavity, causing pain, disease and infertility. The causes are unknown, although genetic risk plays a role. Current treatments are often ineffective with side effects. Recent work by us and our collaborator Prof Grant Montgomery at UQ (Sapkota, 2017) indicate that endometrial stem/progenitor cells may cause lesion formation, and this may be due to single nucleotide polymorphisms (SNPs) in over 14 regions of the genome that are associated with increased risk of endometriosis.

This project aims to decode the biological significance of these SNPs in endometriosis by isolating stem/progenitor cell populations in women with endometriosis. The study will use tissue culture, fluorescent activated cell sorting, organoid culture and single cell RNA sequencing, mouse models. Techniques employed can be tailored to suit the interests of the student. This project has international funding.

Keywords: Endometriosis, organoids, single cell sequencing, stem cells, genetics



Exosome population concordance within sample species

Suitability: Honours/Masters/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Thomas Tapmeier, Dr Shanti Gurung, Prof Caroline Gargett
Email: thomas.tapmeier@monash.edu

Project description: Exosomes are small, nanosized vesicles produced by most cells and readily found in bodily fluids which carry surface markers and genetic material from their cell of origin (Colombo 2014). This makes exosomes an attractive candidate diagnostic and therapeutic tool, and they have recently seen increased attention as potential biomarkers for diseases such as obesity and diabetes, pre-eclampsia, and cancer.

Endometriosis is a disease affecting up to 10% of women of reproductive age and characterized by menstrual and non-menstrual pain, often aggravated during and after coitus. Additionally, up to half of women with endometriosis experience a degree of infertility, as well as mental health issues and fatigue (Zondervan 2018). No clinically relevant biomarker is available. We recently isolated exosomes from peritoneal fluid with a view to investigating these as potential biomarkers (Nazri 2020). Peritoneal fluid is not readily available as a sample, and peripheral or menstrual blood would be easier to obtain. However, it remains unclear how the exosome populations within different sample fluids relate, and whether there is an exchange between exosomes within the peritoneum and peripheral and menstrual blood.

This project will investigate exosomes in peritoneal fluid and peripheral and menstrual blood within the same patients in order to determine the potential of exosomes isolated from one or the other fluid as biomarkers. A mouse model of endometriosis will be set up to test our hypotheses *in vivo*.

Methods: Cell culture, exosome isolation, ultracentrifugation, nanosight tracking analysis, Exoview immunocapture analysis, immunoblotting, RNA extraction, proteomics, microarrays. For PhD candidates: mouse model of endometriosis.

Keywords: Exosomes, endometriosis, biomarkers.

Tissue clearing microscopy in endometrium and uterine fibroids

Suitability: **Honours/Masters/PhD**
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Thomas Tapmeier, Prof Caroline Gargett
Email: thomas.tapmeier@monash.edu

Project description: Immunohistochemistry is an established method to identify cell types in Pathology. However, the sectioning of tissues means that the three-dimensional context is lost and has to be reconstructed painstakingly from individual sections.
New microscopy techniques such as tissue clearing microscopy (Susaki 2015) allow for the preparation of tissue blocks and imaging in three dimensions, thus delivering a comprehensive picture of the arrangement of cells of various type within the tissue. In addition, tissue architecture, often an important feature of pathophysiology, is preserved. However, the constituent parts of different tissues demand differential treatment before tissue clearing microscopy is possible. Fatty tissues for example are easily cleared by removing the lipid compartment of the tissue constituents, whereas collagen-rich tissues are proving challenging to clear so far. We have carried out initial experiments on imaging in uterine fibroids, collagen-rich benign tumours of the myometrium, and this project will optimise buffer conditions and identify cell types within the cleared tissue blocks by immunofluorescence staining.

Methods: tissue preparation, two photon microscopy, light sheet microscopy, immunostainings (immunofluorescence), image analysis.

Keywords: Imaging, tissue clearing microscopy, light sheet microscopy, immunofluorescence

The effect of maternal obesity on placental morphology and function

Suitability: **Honours/PhD/BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Dr Emily Camm, Prof Suzie Miller
Email: *Emily.camm@hudson.org.au*

Projects description: Obesity is one of today's most blatantly visible – yet most neglected – public health issues. In Australia, overweight and obesity impacts 63% of Australian adults and 30% of children and adolescents and is the fastest-growing cause of chronic disease. Currently, over 50% of women are entering pregnancy either overweight or obese. Alongside pregnancy complications, such as gestational diabetes mellitus (GDM) and pre-eclampsia, increasing evidence implicates maternal obesity as a major determinant of health during both childhood and later adult life with an increased risk of future obesity, cardiometabolic disease, and poor neurodevelopmental outcomes.

These inter-generational effects of obese pregnancy have profound public health implications and highlight the urgency of establishing the mechanisms involved. As the interface between the mother and fetus, the placenta may be an important mechanistic link between maternal obesity and offspring outcomes. It provides oxygen, nutrients, hormones, and growth factors essential for intrauterine growth and development. Mitochondria produce the energy for these processes in the form of adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOS). To date, little is known about the actual OXPHOS capacity of the placenta in obese women, or its association with child health.

This project will examine the effect of maternal pre-pregnancy obesity on placental morphology and mitochondrial function. This project will utilise human placentae collected from term caesarean-section deliveries.

Keywords: Obesity, placenta, mitochondria

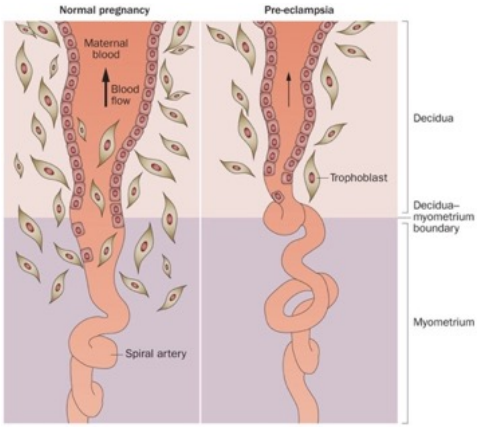
Assessing the Beneficial effects of Antioxidants

Suitability: Honours/PhD/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project leaders: Dr Sarah Marshall
Email: *sarah.marshall@monash.edu*

Project description: Early in pregnancy, the maternal vasculature undergoes dramatic adaptations to help support both the mother and the developing baby throughout pregnancy. However, failure of the maternal vasculature to fully adapt can result in the pregnancy disease known as pre-eclampsia (PE). PE affects approximately 1/20 pregnancies and is a leading cause of maternal and fetal morbidity and mortality worldwide. Unfortunately, disease severity often results in premature babies. Recently, it has become apparent how important the maternal vasculature is for disease development, making it a target to alleviate the clinical symptoms of PE and prolong pregnancy. Cruciferous vegetables, such as broccoli, provide a variety of beneficial health effects. So far, evidence suggests that novel compounds found in green leafy vegetables may have beneficial affects throughout the body, including the vasculature.

Therefore, this project aims to identify whether these extracts can promote systemic health and be potential novel treatments for women with pre-eclampsia. This project will specifically explore the placental and vascular effects.

Keywords: pregnancy; pre-eclampsia; placenta, vascular dysfunction; wire myography; vascular reactivity



Quality of care for cervical and ovarian cancers in Australia

Suitability: **Honours**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Prof Ben Mol, Dr Wentao Li
Email: *ben.mol@monash.edu*

Project description: Cervical and ovarian cancers are the most common gynaecological cancers locally and globally. Despite the large number of patients, the quality of care for these cancers has remained unexamined in Australia. Quality of care or efficiency and effectiveness of care could help minimize disease aggravation, thus improving treatment outcome as well as quality of life for patients. There have been guidelines regarding the management of gynaecological cancers to promote standardized high-quality care. To ensure that all patients receive high-quality care, it is thus imperative to evaluate the adherence of treatment centres to the recommendations outlined in these clinical guidelines.

We are going to use a registry quality dataset which recorded treatment information of all patients who underwent consultation and anti-cancer treatment in Monash Health between 2012 and 2017 to evaluate the adherence to clinical guidelines. We aim to propose a set of quality indicators based on the clinical guidelines for cervical and ovarian cancer treatment and to assess adherence to standard-of-care as an index of the quality of care in Monash Health.

This study requires a basic understanding of gynaecological cancers and evidence-based medicine. After completing this project, the student(s) is expected to have an in-depth knowledge of data analysis and the management of gynaecological cancers

Keywords: gynaecology, cervical and ovarian cancer, oncology, quality of care

Quality and integrity of randomized controlled trials: systematic review of a sample of studies

Suitability: **Honours**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Prof Ben Mol, Dr Wentao Li
Email: *ben.mol@monash.edu*

description
Randomized controlled trials (RCTs) provide the most reliable information to guide clinical practice. We regrettably came across several RCTs concerning important clinical topics published in top rank journals having critical issues with respect to randomization, analysis, reporting, and feasibility.

In the view of the rapidly growing number of RCTs and a high proportion of RCTs yielding positive findings, it is critical to ensure the quality and data integrity of RCTs. However, little attempts have been made to systematically evaluate the quality of published RCTs.

Research aims: We aim to systematically review the quality and data integrity of a sample of RCTs published in top journals of Obstetrics and Gynaecology in the last five years.

Keywords: Randomised controlled trials, systematic review, data integrity, quality assessment

Metformin for ovulation induction in women with polycystic ovarian syndrome

Suitability: **Honours, BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Dr Rui Wang Prof Ben Mol
Email: *rui.wang@monash.edu*

Project description: Polycystic ovary syndrome is one of the most common conditions in women of reproductive age. Insulin resistance is common in PCOS, and can augment excess local ovarian androgen production, resulting in premature follicular atresia and anovulation. Therefore, metformin, an insulin-sensitising medication, has been proposed treating in ovulation induction. While metformin has been most widely studied in PCOS with a reassuring safety profile, its effectiveness in improving reproductive outcomes has been controversial for decades. Existing randomised controlled trials (RCTs) comparing metformin versus clomiphene have shown conflicting results. The conclusion of the latest Cochrane systematic review based on aggregate data was inconclusive due to high heterogeneity between these trials.

Given the heterogeneous nature of the study population as well as the variations in reporting, it is impossible to undertake reliable subgroup analysis to identify who benefits most from metformin or clomiphene. In addition, subgroup analysis based on aggregate data is prone to ecological bias. Individual participant data meta-analysis (IPDMA) has the potential to overcome the above-mentioned problems by standardising the inclusion/ exclusion criteria and harmonising the subgroup choice and statistical analysis (14). It has been considered the gold standard for evidence synthesis. The project is based upon our previous work with the International Ovulation Induction IPDMA Collaboration.

In this project, the candidate will perform an IPDMA, compare the effectiveness of metformin versus clomiphene via a personalized approach.

Keywords: polycystic ovary syndrome, infertility, ovulation induction, metformin, clomiphene, Individual participant data, meta-analysis

PhD in Clinical Epidemiology in women's health

Suitability: **PhD**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Prof Ben Mol, Dr Wentao Li
Email: *ben.mol@monash.edu*

Project description: The overall PhD program will focus on addressing undetermined evidence for clinical practice in women's health. This aim will be achieved through clinical research on major questions with appropriate design and robust methodology. The candidate will identify knowledge gaps and opportunities to promote evidence that guides practice. These gaps will be identified through comprehensive reviews of the quality and credibility of current clinical research on major topics. These gaps will be addressed through the application of new research with state-of-the-art methodology, informed by stakeholder engagement.

Keywords: clinical epidemiology, evidence-based clinical practice, quality review of clinical research, public health

Usefulness of clinical research in Obstetrics and Gynaecology

Suitability: **PhD**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Prof Ben Mol
Email: *ben.mol@monash.edu*

Project description: Blue-sky research cannot be easily judged on the basis of practical impact, but clinical research is different and should be useful. It should make a difference for health and disease outcomes or should be undertaken with that as a realistic prospect. Ioannides showed that many studies, even in the major general medical journals, do not satisfy these features, and very few studies satisfy most or all of them. Most clinical research therefore fails to be useful not because of its findings but because of its design.

In this project, we will assess the usefulness of clinical research in Women's health. We will study the problem base, context placement, information gain, pragmatism, patient centeredness, value for money, feasibility, and transparency of papers published in high ranked journals. This information could fuel an altered approach which could easily produce more clinical research that is useful, at the same or even at a massively reduced cost. Ioannidis JPA (2016) Why Most Clinical Research Is Not Useful. PLoS Med 13(6): e1002049. doi:10.1371/journal.pmed.1002049

Keywords: Obstetrics, Gynaecology, Women's Health

Exploring the mechanisms behind the reduction in preterm birth observed during lockdown in Victoria

Suitability: **Honours, BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Dr David Rolnik, Prof Ben Mol, A/Prof Atul Malhotra
Email: *David.rolnik@monash.edu*

Project description: The coronavirus 2019 (COVID-19) pandemic has had important implications for health care and significant impact on peoples' lives around the World. A significant proportion of the antenatal consultations in Melbourne have moved to a Telehealth model, with reduced face-to-face interactions. Our group and others around the world have reported significant reductions in preterm births during lockdowns that aimed to reduce SARS-CoV-2 transmission (Rolnik et al, Ultrasound in Obstetrics and Gynaecology, 2021).

Melbourne is the ideal location to explore the effects of lockdowns on pregnancy outcomes, since the restrictions were strict and the number of infections during the first two years of the pandemic was relatively small. Such reduction could be beneficial if mainly driven by less spontaneous preterm births (through lower rates of infections by other common pathogens or reduced physical activity) but may also reflect a harmful delay in care if mainly driven by delays in diagnosis of pregnancy complications and timely delivery of babies that should in fact be delivered early.

We now aim to better characterise the phenotype of preterm births and the subgroups of women in whom the effect was greater, in order to explore the mechanism and lifestyle changes behind these observations.

Keywords: COVID-19, Coronavirus disease, lockdown, restrictions, preterm birth, pregnancy outcomes, stillbirth, pandemic.

LOETUS: Long Term Observation of Endometriosis with Transvaginal Ultrasound Surveillance

Suitability: **BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leader: Prof Ben Mol, Dr Nyasha Gwatha Prof Jim Tsaltas
Email: *ben.mol@monash.edu*

Project description: Endometriosis is a disease that affects up to 11% of the population of women in Australia during their lifetime with the disease process starting as early as adolescence (Endometriosis Australia, 2021). The natural course of the disease is unpredictable. The aim of this study will be to look at the progression of endometriosis as detected by TVUS. The COVID-19 pandemic has seen a significant delay in time to surgery for women with symptomatic endometriosis. It therefore provides a unique opportunity to study the natural course of the disease. In this project, as a student you will compare in women with endometriosis the course of the disease without surgery (cohort 2020-2021) to the course of the disease in women who had surgery (cohort 2018-2019).

This study will evaluate the impact of surgery versus conservative management in women with endometriosis including the progression of their disease. You will work in a stimulating environment, be able to observe clinical practice and have the possibility to present your results on scientific meetings and publish them in peer reviewed journals.

Keywords: Endometriosis, transvaginal ultrasound, COVID-19, pandemic, QOL, symptoms, pain, dyspareunia, dysmenorrhoea, dyschezia

Find the right ueterotronics for preventing postpartum haemorrhage

Suitability: **PhD, Masters, BMedSc (Hons), Honours**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Dr Wentao Li, Prof Ben Mol,
Email: *wentao.li@monash.edu*

Project description: Postpartum haemorrhage is heavy bleeding after the birth of a baby. It causes serious medical conditions, sometimes requires blood transfusion and can even lead to the death of the mother if bleeding is severe and uncontrollable. About half of the cases of severe maternal medical conditions and a quarter of maternal deaths are attributable to postpartum haemorrhage. As treatment of postpartum haemorrhage is often too late for many women, prevention is important.

Uterotonics, a family of medications that induce contraction of the uterus, are widely used in clinical practice to prevent postpartum haemorrhage. However, existing evidence regarding the optimal choice of uterotonics is controversial. Major concerns in many of the trials on uterotonics have been identified, which weaken the confidence in the current evidence. Study aim To generate robust and personalised evidence for women with different characteristics, which will be translated into tools to aid in decisions on the choice of uterotonics by tailoring to individual circumstances. Methods and techniques Individual participant data (IPD) meta-analysis and network meta-analysis using IPD. Why us? We are an internationally recognised clinical research team in obstetrics and gynaecology with impactful outputs that change and define modern practice. Students who work with us apply cutting-edge methods to address important questions and have the opportunities to interact and collaborate with eminent researchers in this field around the world. Experts in epidemiology and statistics offer critical methodological support to research projects in our team. Why this project?

This is a large-scale clinical research project that involves multiple comparisons. Students could lead parts of the project. The infrastructure of the project is well-established including the IPD international collaboration, statistical expertise, and administrative support. This research may improve the well-being of millions of women and babies around the world each year. Previous students who worked with us, being first authors, have successfully published original papers in leading journals. Join us to perform research that changes the world.

Keywords: clinical research; obstetrics; meta-analysis; evidence-based practice; labour; birth; haemorrhage; personalised medicine; precision medicine; individual participant data; randomised controlled trial

Virtual Reality Analgesia for Post Laparoscopic Pain

Suitability: **BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Prof Beverley Vollenhoven, Assoc Prof Jim Tsaltas, Dr Lima Wetherell (External), Mr Ritesh Warty
Email: *Beverley.vollenhoven@monash.edu*

Project description: Post-operative pain following surgery remains an area of concern for patients and clinicians alike and can affect between 20-40% of patients. Available evidence shows that even in the context of modern pain management strategies, it is an area which causes significant morbidity to many patients and is a parameter which is frequently underestimated by clinicians as well. The immediate concerns relating to poor analgesia control in these patients include decreased patient satisfaction, delayed postoperative ambulation, delayed discharge from the hospital and the propensity for the development of chronic pain syndromes.

Laparoscopy is a commonly performed gynaecological procedure. The studies surrounding post-operative pain in these women are sparse and conflicting. However, they suggest the frequency of post-operative pain sits between 35 – 65%. The primary mechanisms of pain are theorised to be related to diaphragmatic irritation and peritoneal inflammation and stretching. Ekstein et al. demonstrated that in the acute postoperative period (4-hours post-surgery), nearly 46% of patients post laparoscopy were in severe pain [≥ 6 on the visual analogue scale (VAS)] and they required significantly greater amounts of analgesia in comparison to patients undergoing laparotomy. Gerbershagen et al. further outlined the underestimation and reduced treatment of pain in these patients by demonstrating that patients with high post laparoscopy pain scores were administered lower level of opioid analgesia in comparison to other surgical procedures with equivalent pain scores.

Considering this, it is vital that alternative and adjunct analgesics are developed to bridge the current gap in pain management, particularly, post-laparoscopy. Virtual reality (VR) is one such burgeoning technology which has the potential to address the shortcomings of current post-operative pain management. Through the application of a head mounted device, VR allows for users to be immersed in and interact with a three-dimensional virtual environment through multisensorial stimulation. As it stands, VR has demonstrated clinical efficacy in pain reduction whilst also being well tolerated by patients. Importantly, a recent controlled trial by Tashijan et al. demonstrated a 24% drop in pain scores in patients utilising VR for acute pain of various pathologies. At present, there are several theories behind the mechanism of action on how VR facilitates analgesia. Although the primary mechanism is unknown, it is theorised to cause an effect through both distraction

and neurophysiological changes to the pain matrix of the brain. As such, there remains a significant clinical gap in judging the utility of VR in providing analgesia post-operatively. This fact prompted us to design a pilot study to evaluate the efficacy of VR in this context. Despite being conducted in a small sample size, the results of this pilot study were promising. Notably, we demonstrated a reduction in pain scores over time and a high degree of patient satisfaction for the device. The pilot study demonstrated the potential of VR to facilitate analgesia in a small sample size, however, this does not entail that similar results will be found in a larger population.

As a result, the following randomised controlled trial (RCT) was designed to further investigate the effect of VR analgesia on pain scores and opiate treatment post-laparoscopy. Positive results from this trial will greatly benefit the healthcare system. Decreased post-operative pain has the positives of increased rates of patient satisfaction and decreased requirement for opiate analgesia. Importantly, for day case laparoscopies, it does give the advantage of immediate discharge from the hospital thereby enacting cost saving benefits to the healthcare system as well. It is hoped that this study can be used as a platform for implementation of VR analgesia post laparoscopy as well as a basis for further testing of the device in a variety of post-operative settings.

We're looking for an enthusiastic student who would be involved in running the trial, data collection, and analysis. You will be based at Monash Medical Centre, Moorabbin and have an opportunity to work with the patients during their post-operative period.

Keywords: Virtual reality, analgesia, post-operative pain, laparoscopic

Evidence-based fertility care (including assisted reproduction)

Suitability: **PhD**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Dr Rui Wang Prof Ben Mol,
Email: *rui.wang@monash.edu*

description: About the projects: Current available projects include: - Personalised fertility care Couples with infertility refer to a heterogeneous population. The conventional "one-size-fits-all" approach may not be applicable to interventions in infertility. We are working with international trialists to collect de-identified individual participant data (IPD) of completed randomised controlled trials to evaluate treatment effects of interventions during assisted reproduction on different groups of couples with infertility, aiming to provide a personalised treatment pathway to guide clinical practice. - Diagnostic and prognostic tests in reproductive medicine There are new diagnostic and prognostic tests emerging in recent years, aiming to improve diagnostic accuracy and prediction of reproduction-related conditions. We are systematically evaluating the performance of these tests (diagnostic accuracy or prognostic value) in diagnostic accuracy test and prognostic factor meta-analyses. We are also working with large fertility clinics to evaluate the prognostic value of biomarkers or validate prediction models.

Evidence-based tools to improve fertility care Evidence end-users, especially consumers often find scientific evidence from evidence synthesis too technical and difficult to understand. Based on the findings of our previous and ongoing large collaborative evidence synthesis projects, we are developing and evaluating evidence-based online tools to make the evidence more accessible to consumers. - Improving reporting and transparency in reproductive research Clinical research in reproductive medicine has its unique features in terms of design, conduct and outcome choices. The reporting of clinical research in this area is not always optimal. Therefore, it is important to assess existing clinical research in this area, and to identify the key limitations, so that effective improvement strategy could be provided to improve reporting and transparency.

About the research environment: Monash University is a top 40 University in the world for Medicine. Faculty of Medicine, Nursing and Health Sciences is the University's largest research faculty and has established a reputation for the quality and impact of its research in health care and the biosciences. The School of Clinical Sciences at Monash Health is a vibrant hub of teaching and translational research in collaboration with Monash Health, Victoria's largest hospital network.

Evidence-based Women's Health Care research group within the Department of Obstetrics and Gynaecology is an international renowned research group in women's health research. The candidate will be supported by leading experts in Obstetrics and Gynaecology, reproductive medicine, epidemiology, biostatistics, and meta-analysis during their candidature. Candidate Requirements: - Highly motivated in evidence-based research; - A first class Honours degree or equivalent in a relevant field (e.g., health sciences, reproductive sciences, medicine, epidemiology, biostatistics, or public health); - At least a first-author publication indexed in PubMed. How to apply: Please email your CV, a cover letter indicating your research area of interest, as well as a copy of your academic transcript to r.wang@monash.edu

Keywords: infertility, assisted production, IVF, reproductive medicine, epidemiology, biostatistics, meta-analysis, diagnosis, prognosis, treatment, personalised medicine, evidence-based medicine, embryology, transparency

Effect of aspirin on the rates of pre-eclampsia and other adverse pregnancy outcomes: a systematic review and individual-participant data meta-analysis of randomised clinical trials

Suitability: **PhD, Honours, BMedSc (Hons)**
Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton
Project Leaders: Dr Daniel Rolnik, Prof Ben Mol, Dr Wentao Li
Email: *wentao.li@monash.edu*

Project description: Pre-eclampsia is a common pregnancy complication that affects 3-5% of all pregnant women and represents a significant cause of maternal and perinatal morbidity and mortality. More than 70,000 mothers and 500,000 babies die each year due to complications of pre-eclampsia. Prediction of pre-eclampsia using checklists that consider maternal characteristics and medical history alone perform poorly, identifying only 30% of women who are destined to develop pre-eclampsia. A multimarker algorithm that considers maternal characteristics and history combined with biophysical (mean arterial pressure and uterine artery Doppler) and biochemical (placental growth factor) markers at 11 to 14 weeks of gestation, on the other hand, can identify 75% of women who will develop preterm pre-eclampsia (before 37 weeks) and 90% of those who will develop pre-eclampsia before 34 weeks.

Our group has recently conducted a large multicentre randomised controlled trial on aspirin prophylaxis for high-risk women identified using this combined predictive algorithm (ASPRE trial - Rolnik et al, New England Journal of Medicine, 2017), and showed that aspirin reduces the rates of preterm pre-eclampsia by more than 60%. Randomised trials on aspirin prophylaxis, however, are often underpowered to detect differences in other placental-mediated disorders, such as fetal growth restriction, stillbirth, and perinatal death.

We now aim to conduct a systematic review and individual-participant data meta-analysis (IPD-MA) of the effect of aspirin on pre-eclampsia, fetal growth restriction, stillbirth, and perinatal death, as well as to investigate the effect of dose and timing of initiation of aspirin on such adverse outcomes.

We will build on an existing IPD-MA (Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA; PARIS Collaborative Group. Lancet. 2007 May 26;369(9575):1791-1798.) and add the new RCTs performed since.

Keywords: Pre-eclampsia, Aspirin, Pregnancy complications, IPD meta-analysis

Fetal and Neonatal Health: Respiratory and Cardiovascular

Transition to Life After Birth

Suitability: Honours/PhD/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Stuart Hooper, Dr Kelly Crossley
Email: *Kelly.crossley@hudson.org.au*

Project description: The transition to life after birth is one of the greatest physiological challenges that humans face. At birth, the airways are cleared of liquid, to allow the entry of air, which increases pulmonary blood flow and closes vascular shunts that by-pass the lungs during fetal life. Most infants smoothly make this transition, but many don't which can be life threatening and cause life-long problems. 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 to reduce the risks that newborn infants face.

Keywords: fetal to neonatal transition, pulmonary blood flow, lungs, breathing,

Imaging the Entry of Air into The Lungs at Birth

Suitability: Honours/PhD/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Stuart Hooper, Dr Kelly Crossley
Email: *Kelly.crossley@hudson.org.au*

Project description: The transition to air-breathing at birth is dependent upon airway liquid clearance which allows gas exchange to commence. This occurs smoothly in most infants, but preterm infants have difficulty in clearing their lungs of liquid. Using a synchrotron, we can image the entry of air into the lungs at birth and the simultaneous changes in blood flow to the lungs. The aim of this project is to identify factors that promote air entry into the lungs and the increase in pulmonary blood flow at birth in premature animals.

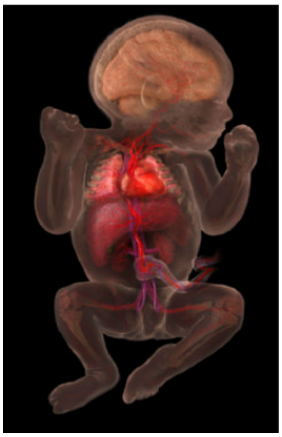
Keywords: birth, newborn, lung aeration

Trialling novel glucocorticoids to reduce lung disease in preterm birth

Suitability: Honours/PhD/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: A/Prof Megan Wallace, Prof Tim Cole
Email: megan.wallace@monash.edu

Projects description: Women who are at risk of delivering a preterm baby are given antenatal glucocorticoids to mature the lungs of the fetus before birth. However, this life-saving therapy can also impair the development of the brain and other organs After birth, glucocorticoids are also used as anti-inflammatory agents to help wean preterm babies off ventilatory support, with similar adverse effects on the brain and other organs. This project will trial exciting new steroids in animal models of preterm birth to determine if they mature fetal lungs and reduce postnatal lung inflammation without adverse impacts on other organs.

Keywords: preterm birth, preterm babies, glucocorticoids, corticosteroids, respiratory distress, bronchopulmonary dysplasia, ventilation, brain injury



Improving breathing of preterm newborns exposed to inflammation during pregnancy

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Graeme Polglase
Email: graeme.polglase@monash.edu
Phone: 03 8572 2822 (Prof Polglase)

Project description: Preterm babies exposed to inflammation during pregnancy have a high incidence of breathing difficulties and brain injury, which often lead to cerebral palsy. Many of these babies will require invasive respiratory support at birth, and whilst this is lifesaving, it can exacerbate the already ongoing inflammation, and worsen brain injury.

Our current research focuses on how intrauterine infection and inflammation (chorioamnionitis) affects the neural control of respiration, and whether anti-inflammatory treatments can protect these nerves and improve fetal and neonatal breathing. This project involves work with small and large animal models, fetal/neonatal physiology, protein and

molecular techniques, histology, immunohistochemistry, and microscopy.

Keywords: chorioamnionitis, neural control of respiration

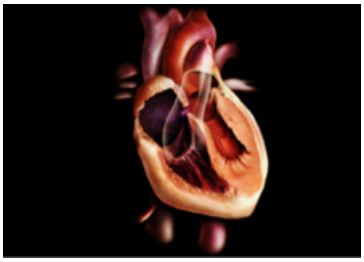
Improving the transition at birth in asphyxiated infants

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Graeme Polglase, Prof Stuart Hooper
Email: *graeme.polglase@monash.edu*
Phone: 03 8572 2822 (Prof Polglase)

Project description: Approximately 9000 newborns die in developing countries every day because of asphyxia – 30-50% die on their birthday. Approximately 13% of infants that require resuscitation at birth actually have access to the appropriate facilities to receive this life-saving intervention. There is therefore a critical need to develop simple and translatable strategies that improve the transition at birth for asphyxiated infants.

Our current research is focused on improving the transition at birth for asphyxiated preterm and term infants. This involves investigating the utility of delayed cord clamping, cord milking and improving resuscitation strategies including chest compressions delivery, with the ultimate aim of identifying strategies directly translatable to the developing world, which significantly reduces death and disability in this population. The experiments include whole-animal physiology, molecular biology, and immunohistochemistry.

Keywords: delayed cord clamping, neonatal resuscitation, transition at birth



Reducing the risk of pulmonary hypertension in infants with a congenital diaphragmatic hernia

Suitability: Honours/PhD/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Kelly Crossley, Prof Stuart Hooper
Email: *Kelly.crossley@hudson.org.au*

Project description: This project focuses on congenital diaphragmatic hernia (CDH), a birth defect characterised by a failed closure of the diaphragm, creating a continuity between the thoracic and abdominal cavities. As a result, there is displacement of abdominal organs into the chest, and this limits the space for the lungs to develop in the fetus. This leads to small lungs with abnormal airways and vessels, a condition called lung hypoplasia.

Whilst in utero, lung hypoplasia is not a problem as the fetus receives oxygen via the placenta, but immediately after birth is potentially lethal. It often results in respiratory insufficiency requiring respiratory support with invasive mechanical ventilation and is complicated by persistent pulmonary hypertension of the newborn (PPHN). The latter is caused by a smaller cross-sectional area of the lung vasculature combined with raised vascular tone due to increased muscularisation of the vessels. Overall, postnatal mortality of CDH is high (30-40%) and is significantly worse when complicated with severe PPHN (up to 56%).

There is an urgent need to mitigate the effects of PPHN and improve outcomes for infants born with CDH. We believe that by optimising the transition period immediately after birth we could significantly reduce the risk of pulmonary hypertension. We propose further pre-clinical studies that will answer fundamental questions about the management of the transition period for these challenging infants.

Keywords: congenital diaphragmatic hernia, pulmonary hypertension, fetal to neonatal transition, lung hypoplasia, mechanical ventilation

NICU emergency frequency, risk factors, causes and potential treatments

Suitability: BMedSci (Hons)
Location: The Ritchie Centre, Department of Paediatrics, Monash Medical Centre, Clayton
Project Leaders: Dr Doug Blank, Dr Calum Roberts
Email: doug.blank@hudson.org.au, calum.roberts@monash.edu

Project: description: There is no appropriate algorithm for neonatal emergencies that occur in the neonatal intensive care unit (NICU). NeoResus, and other neonatal resuscitation guidelines, cover management at birth, as the newborn initiates breathing air. However, this is only relevant for the first minutes after birth and there is little data and

guidance of what are the common emergencies in the NICU and how we should respond. The paediatric advanced lifesaving algorithms are not likely relevant to the hospitalised neonate, either.

We propose a prospective observational study and documentation of all emergency events in the NICU and special care nursery at Monash-Clayton. We will video record all buzzer events and examine the video and data from the patient's monitor. We will review the causes, responses, and solutions to the emergency. The first goal of the project is to characterise when, who, and what are the nature of the emergencies. Subsequently, we aim to develop and test protocols to address NICU emergencies.

Keywords: neonatal resuscitation, NICU emergencies

Fetal and Neonatal Health: Brain Injury and Neurodevelopment

Creatine: a novel treatment strategy for hypoxia-related injury

Suitability: Honours
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Robert Galinsky, Dr Stacey Ellery, Dr Nhi Tran
Email: robert.galinsky@hudson.org.au, stacey.ellery@hudson.org.au, nhi.tran@hudson.org.au

Project description: Fetal hypoxia is a leading cause of brain damage around the time of birth. In utero hypoxic events can be unpredictable in nature and therefore administering treatment at the correct time can be difficult and even ineffective. Creatine is a novel prophylactic treatment strategy for hypoxia-related injury during the perinatal period. Creatine is an endogenous phosphagen that functions predominantly to rapidly regenerate ATP in times of high energy demand and is thereby able to prolong the availability of intracellular energy for normal cellular function. Intracellular creatine levels can be increased with supplementation.

We hypothesise that supplementation of creatine during pregnancy, prior to an hypoxic event, will decrease the impact of hypoxia on fetal organs by preventing ATP depletion and prolonging cellular homeostasis. Given that brain function is one of the most important attributes to preserve, the overall aim of this study is to investigate the neuroprotective capacity of fetal creatine supplementation following acute fetal hypoxia. We have previously shown that creatine supplementation improves cerebral metabolism during and following brief hypoxia induced by umbilical cord occlusion. We now sought to investigate whether these improvements in cerebral metabolism also translate to an improvement in brain function using in vivo real-time electroencephalography measurements.

For this project we will use our preclinical near-term fetal sheep model of umbilical cord occlusion to investigate and assess the protective capacity of creatine pre-treatment on brain injury. The results of this preclinical project will inform future studies and may potentially inform clinical translation. The project will use techniques such as immunohistochemistry, histology, microscopy, molecular analysis, and analysis of fetal electronic monitoring measurements.

Using heart rate variability to predict clinical disease in preterm babies

Suitability: Honours/PhD
Location: Level 5, Monash Medical Centre, Clayton
Project Leaders: A/Prof Flora Wong, Prof Rosemary Horne
Email: flora.wong@monash.edu
Phone: 03 85723655 (A/Prof Wong)

Project description: The early clinical signs of diseases in the preterm baby in the neonatal intensive care unit (NICU) are often very subtle and difficult to detect. However, once the infection or disease is developed, the preterm baby often deteriorates and becomes sick very rapidly. We aim to develop a new method using heart rate variability (HRV) to detect early clinical diseases. HRV is a measure of the beat-to-beat variation in time between each heartbeat. This variation is controlled by an important part of the nervous system called the autonomic nervous system (ANS). Our project will assess HRV as a non-invasive way to identify changes in the clinical condition of the preterm baby. We have recently acquired a clinical research software known as ICM+, developed at Cambridge University. The ICM+ software offers data collection and real-time analysis, facilitating personalised medicine. ICM+ can be connected to our bedside monitors in the NICU and perform continuous analyses of the HRV in real-time, on multiple babies simultaneously.

We propose that continuous HRV can be used to assess well-being of the preterm babies in NICU, detect early infections and predict bleeding in the brain.

RESEARCH PLAN: In preterm babies born at ≤28 weeks of gestation, the ECG recording from the NICU cot side monitor will be continuously analysed for HRV in the first 4 weeks of life, using the ICM+ software. Clinical records of the babies will be examined to determine periods of when the baby was clinically stable and when the baby suffered from infection and/or developed bleeding in the brain.

Keywords: Prematurity, heart rate variability, infection, brain injury

Nanomedicine for preterm brain injury

Suitability: Honours/Masters/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Tamara Yawno, A/Prof Rebecca Lim, Prof Rod Hunt, Dr Ishmael Inocencio
Email : *tamara.yawno@hudson.org.au*

Project description: The overall objective is to offer a safer, affordable, and more targeted form of regenerative medicine specifically designed for the treatment of Cerebral Palsy (CP), which is a physical disability that affects movement and posture. Currently, there is no known cure for CP, interventions are limited to early detection and symptomatic treatments. There is now encouraging

evidence that regenerative medicine can restore healthy brain function. We propose a world class nanomedicine that will determine the efficacy of exosomes, derived from placental cells (amniotic epithelial cells) called amniotic exosomes, in a clinically relevant model of preterm perinatal brain injury. Our current research is focused on understanding how exosomes work (in vitro and in vivo) to elicit repair following injury.

We are offering several projects which will focus on exosome isolation and characterisation and understanding their mechanisms of actions; as well as efficacy, therapeutic dosing, and route of administration in reducing preterm brain injury caused by fetal inflammation in sheep. Research techniques: Aseptic tissue culture techniques, exosome isolation and characterisation. Fetal sheep surgery, fetal monitoring of brain activity and cardiovascular function. Neuropathological assessment using immunohistochemistry and molecular biology.

Keywords: preterm brain injury, brain injury, exosomes, nanomedicine, fetal brain, white matter injury

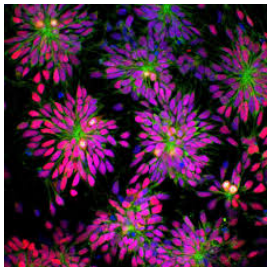
Is Neural stem cell therapy safe and feasible in a neonate?

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Courtney McDonald, Prof Suzie Miller, Prof Michael Fahey
Email: courtney.mcdonald@monash.edu
Phone: 03 8572 2799 (Dr McDonald)

Project description: Neural stem cells (NSCs) offer great promise as a neuroprotective therapy against a range of neurological conditions, like cerebral palsy. NSCs are currently being investigated in clinical trials for adult neurological conditions and these studies have shown that for NSCs to be effective they need to be injected directly to the brain and immune suppression must also be administered. These procedures carry increased risk and the detrimental effect these procedures may have on the neonate are currently unknown.

This project is aimed to test the long-term safety and feasibility of transplanting high doses of NSCs into the neonatal brain and co-administering immunosuppression. These experiments will be performed in lambs, and we will perform neurodevelopmental follow-up until 3 months of age to determine the safety of these procedures.

As part of this project, you will learn large animal surgery, neonatal sheep monitoring, behavioural testing, brain immunohistochemistry and cell culture techniques.



Improving functional deficits associated with fetal growth restriction

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Suzie Miller, Dr Amy Sutherland
Email: *suzie.miller@monash.edu*
Phone: 03 8572 2796 (Prof Miller)

Project description: Fetal growth restriction (FGR) is a serious, but common pregnancy complication, describing the infant that is born very small due to failure to achieve normal growth. FGR is present in up to 9% of pregnancies in Australia, and is strongly associated with complications after birth, including brain injury that underlies the motor deficits associated with cerebral palsy or, more subtle but no less significant cognitive dysfunctions. There are currently no antenatal or postnatal treatments that can improve outcomes for FGR infants, but this is an area of strong research interest. For obvious reasons we cannot test interventions or treatments in human pregnancies or infants, and therefore animal models of FGR are required to examine whether neuroprotective treatments are safe, feasible, and can significantly improve functional outcomes.

In the current study we will examine treatment strategies to improve the structure and function of the FGR lamb brain. A number of different neuroprotective strategies are of interest that could potentially be applied either during pregnancy (antenatally) or after birth (postnatally) that aim to optimise brain development.

Treatments of interest include antioxidants, anti-inflammatory compounds, and cord blood stem cells. We will apply complimentary assessments of brain structure and function to test the efficacy of our neuroprotective treatments of interest.

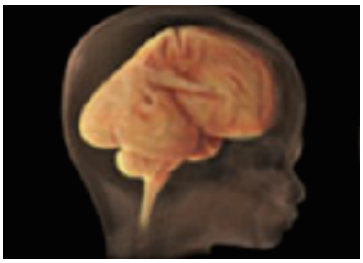
Keywords: brain development, neuroprotection, fetal growth restriction, FGR, IUGR

Developing 3D brain organoids to model perinatal brain injury

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Courtney McDonald, Prof Michael Fahey
Email: courtney.mcdonald@monash.edu
Phone: 03 8572 2799

Project description: We are developing 3-dimensional human brain organoids using induced pluripotent stem cells (iPSCs). We can model the effect of neuroinflammation in our brain organoids, thereby creating an in vitro model of perinatal brain injury. We will use this in vitro 3D model to test the mechanism of action of umbilical cord blood and mesenchymal stem cells, specifically assessing the paracrine and direct effects and determine the optimum stem cell type for reducing neuroinflammation.

This project will involve extensive cell culturing with both iPSCs and perinatal stem cells, multicolour flow cytometry and molecular analysis using PCR and protein assays.

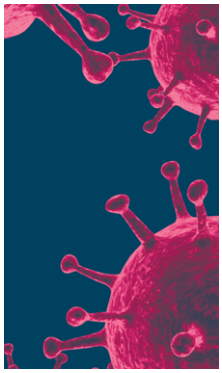


Optimising a model of preterm brain injury in the neonatal rat

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Courtney McDonald, Dr Tayla Penny
Email: courtney.mcdonald@monash.edu
Phone: 03 8572 2799 (Dr McDonald)

Project description: Babies that are born preterm are at risk of experiencing injury to the white matter of the brain, and as such developing neurodevelopmental disorders such as cerebral palsy. Cerebral palsy is the most common childhood motor disability and is associated with both motor and cognitive deficits. This project aims to develop and optimise a small animal model of preterm brain injury using neonatal rat pups. The effectiveness of this model can be tested by utilising a suite of behavioural tests previously determined by our group, as well as through analysis of brain tissue using immunohistochemistry, flow cytometry and PCR. This model will also be used to test potential therapies for preterm brain injury, including umbilical cord blood (UCB) stem cell therapies.

This project will involve small animal work including long-term monitoring and behavioural testing. You will also learn techniques involving immunohistochemistry, histology, microscopy, and molecular analysis.



Neural stem cell therapy for preterm brain injury

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr Courtney McDonald, Prof Suzie Miller, Prof Michael Fahey
Email: courtney.mcdonald@monash.edu
Phone: 03 8572 2799

Project description: Neural stem cells (NSCs) offer great promise as a neuroprotective therapy against a range of neurological conditions, like cerebral palsy. NSC therapy has been shown in small animal models to reduce brain injury. However, NSCs have never been tested in a large animal model of preterm brain injury. In this project we will assess whether NSC transplanted directly into the preterm brain can engraft and regenerate damaged brain tissue.

For this project we will use our in-utero sheep model of umbilical cord occlusion to induce preterm brain injury and test early and late treatment with NSCs to determine the optimal time of NSC therapy. As part of this project, you will learn large animal surgery, fetal monitoring, brain immunohistochemistry, protein analysis and cell culture techniques.

Infant and Child Health

Evaluation of innovative digital monitoring devices in neonates

Suitability: BMedSc (Hons)
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: A/Prof Atul Malhotra. Dr Faezeh Marzbanrad
Email: *atul.malhotra@monash.edu*

Project description: Opportunities exist to be involved in this exciting project on innovative digital monitoring devices for neonates. The project will involve evaluation of new devices being developed for neonatal cardiorespiratory and other monitoring. Project will include patient recruitment, data recording, collection, and analysis. Computer assisted analysis with follow acquisition of electronic signals. This project is in collaboration with Monash Engineers.

Keywords: Newborn, digital, electronic device

Ensuring integrity in neonatal evidence-based medicine

Suitability: BMedSc (Hons)
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: A/Prof Atul Malhotra. Prof Ben Mol
Email: *atul.malhotra@monash.edu*

Project description: Randomised controlled trials are the most important way in which evidence is collected for new therapies or re-purposed therapies or management strategies in medicine. These contribute to systematic reviews and practice changing guidelines if done well. We rely on research integrity, quality, and transparency of data. In this project, students will systematically review, collect data on doubtful or spurious studies and learn methods to analyse, report and ensure integrity in literature.

Keywords: RCTs, neonate, integrity, fake, fraudulent research

Are Sleep Spindles Associated with Neurocognitive Deficits in Children with Sleep Disordered Breathing?

Suitability: Honours/PhD/Masters
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne
Email: *rosemary.horne@monash.edu*
Phone: 8572 2827

Project description: A particular phenomenon of the electroencephalography (EEG) wave form is the sleep spindle, believed to function as mechanism through which long-term changes are made in the neocortex and as a mechanism for maintaining sleep. Sleep spindles have also been associated with different aspects of cognitive performance in healthy children.

Sleep disordered breathing (SDB), is a very common condition in children, and has been associated with neurocognitive deficits. To date, it is not known whether the poor neurocognition in children with SDB is related to a loss of sleep spindles. This study will investigate sleep spindles in children with SDB and determine if there is an association between sleep spindle numbers and neurocognitive deficits. The student will be involved in conducting sleep studies (polysomnography) and analysis of electroencephalography data.

Bad sleep is bad for your cardiovascular health

Suitability: Honours/PhD/Masters
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne, Dr Lisa Walter
Email: *rosemary.horne@monash.edu*
Phone: 8572 2827

Project description: The research of my group focuses on sleep in infants and children. This is of the utmost importance to the health of every baby and child. Sleep is the primary activity of the brain during early development. By the age of 2 years a child has spent a total of 13 months sleeping! Between 2 and 5 years of age children spend equal amounts of time asleep as awake. A common cause of sleep disruption in childhood is partial or complete upper airway obstruction, termed sleep disordered breathing, with the hallmark feature being snoring. The repetitive airway obstruction leads to intermittent periods of hypoxia, with perhaps even more damaging rapid re-oxygenation after release of the obstruction, which is known to lead to brain injury. Repetitive events also cause surges in blood pressure, which leads to hypertension. In this project we will examine the effects of sleep disordered breathing on vascular stiffness. Vascular stiffness reflects the compliance of the large conductance vessels and is an important contributor to increased cardiac stress and a risk factor for adverse cardiovascular events. It is a non-invasive method of assessing vascular dysfunction.

Students will be involved in analysing the physiological data collected during overnight clinical sleep studies and will have the opportunity to participate in these in the brand-new Melbourne

Children's Sleep Centre, Monash Children's Hospital to understand how the data are collected.

Keywords: Sleep, Children, Obstructive Sleep Apnoea

Long-term consequences of respiratory instability on neurodevelopmental and cardiovascular outcomes in preterm infants

Suitability: Honours/PhD/Masters
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne, A/Prof Flora Wong
Email: *rosemary.horne@monash.edu*
Phone: 8572 2827

Project description: In Australia about 26,873 infants are born preterm each year. Despite an increase in survival, developmental morbidity has not improved, with more than half of surviving infants born < 28 weeks of gestation growing up with significant neurodevelopmental impairment. Even infants born moderately or late preterm (> 32 weeks of gestation) are at double the risk for neurodevelopmental disability at 2 years of age compared to term born peers, with impairments being mainly in the cognitive domain. With the rising rate of preterm birth world-wide, focus on hitherto unrecognised and untreated central apnoea and periodic breathing will determine if this common problem contributes to adverse outcomes.

This study will answer important clinical questions: How do the falls in cerebral oxygenation associated with these immature breathing patterns affect neurodevelopmental outcomes? Which infants should be screened? Which infants may need treatment? Such a study would make a significant contribution to improving outcomes and reducing the long-term consequences of preterm birth.

Keywords: preterm infants, developmental outcomes, apnoea, sleep

Cerebral oxygenation in preterm babies in the neonatal intensive care unit

Suitability: Honours/BMedSc (Hons)/Joint PhD/Exchange Program
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: A/Prof Flora Wong
Email: *flora.wong@monash.edu, rosemary.horne@monash.edu*
Phone: 03 85723655

Project description: Preterm infants are at high risk of brain injury, mainly due to low blood flow and oxygenation in the brain. With this project we aim to assess the impact of various physiological and environmental factors on brain oxygenation level in the very preterm infants undergoing intensive care. The various factors to be investigated include blood pressure fluctuations, cardiac output, apnoea's, oxygen desaturations, ventilation changes and blood sampling procedures. We will use Near Infrared Spectroscopy to measure cerebral oxygenation non-invasively by the cot side of preterm infants and correlate the changes with the various factors being investigated.

The project will provide important knowledge on the effects of common physiological events, and interventional therapies on brain oxygen levels in these very small infants. The information may provide the basis on which brain protection strategies can then devised. Large amount of data has been collected on infants studied whilst receiving care in the Neonatal Intensive Care Unit at Monash Medical Centre (MMC). Cerebral oxygenation is measured at the cot side using Near Infrared Spectroscopy (NIRS) and expressed as tissue oxygenation index (TOI, %).

The infants are studied weekly, for 2-3 hours at each study. During the study, the infant spends half of the time sleeping prone (on the belly) and half of the time sleeping supine (on the back). Effects of physiological changes and clinical events will be correlated with changes in TOI in the preterm infants. We are currently analysing the effects of apnoea's and periodic breathing on the brain oxygenation in these preterm infants, and how these change during different sleeping positions.

Keywords: Preterm brain, brain oxygenation, infant sleep, periodic breathing, apnoea

Obstructive sleep apnoea in children with Down syndrome

Suitability: Honours/Masters by Research, PhD
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne, A/Prof Gillian Nixon
Email: *rosemary.horne@monash.edu*
Phone: 03 8572 2827 (Prof Horne)

Project description: Obstructive sleep apnoea (OSA) affects 30%-80% of children with Down Syndrome (DS). Different countries have proposed different guidelines to clinicians for screening for the condition, with American guidelines recommending routine sleep studies at 4 years of age and British guidelines recommending simpler overnight oximetry at home. As OSA can occur at any age, a single sleep study at a given age is an expensive and poorly targeted intervention. In addition, the benefits of treatment for OSA are poorly defined in children with DS, raising questions about the value of aggressive screening. We have recently shown that normally developing children benefit from treatment of OSA in terms of IQ, particularly in tasks associated with spatial visualisation, visual-motor coordination, abstract thought, and nonverbal fluid reasoning, and that elevated blood pressure returns to control levels. We now postulate that improvements in similar domains in children with DS might make substantial differences to their health and well-being. In this study we will quantify the impact of OSA on children with DS, especially in terms of adaptive functioning, quality of life and cardiovascular functioning, and determine the effect of treatment of OSA on these parameters. This will provide crucial information to guide clinical recommendations for screening and treatment of OSA in DS. Collection of relevant clinical data will secondarily allow us to develop screening tools for OSA in this population

Can treatment of sleep disordered breathing in children normalise alterations to brain regions associated with adverse behavioural, neurocognitive, and cardiovascular effects?

Suitability: Honours/Masters by Research, PhD
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne, Dr Lisa Walter
Email: *rosemary.horne@monash.edu*
Phone: 03 8572 2827 (Prof Horne)

Project description: The most common sleep disorder in children, affecting over 1.5 million Australian children, is that of sleep disordered breathing, with the hallmark symptom of snoring. In children sleep disordered breathing is primarily due to enlarged tonsil and adenoid tissue. Sleep disordered breathing forms a spectrum of severity from simple or primary snoring, which is not associated with clinically significant oxygen desaturation or sleep fragmentation (using current techniques) to obstructive sleep apnoea.

The apnoea's which are a feature of sleep disordered breathing are associated with repetitive falls in peripheral and cerebral oxygen saturation and the arousals which occur to terminate these events disrupt sleep. These two features are thought to underpin both the cardiovascular and neurocognitive consequences of the disorder. Our recent studies have examined the integrity of brain tissue with non-invasive diffusion tensor imaging in non-snoring control children and children with sleep disordered breathing. We have identified that sleep disordered breathing is accompanied by predominantly acute brain changes in areas that regulate autonomic, cognitive, and mood functions, and chronic changes in frontal cortices essential for behavioural control. This is the first time that these changes have been identified in children and likely result from the repetitive hypoxia falls in cerebral oxygenation that we have shown are associated with sleep disordered breathing.

What we need to understand now is if these acute and chronic brain changes can be normalised following treatment and whether these changes are disease severity dependent.

Keywords: obstructive sleep apnoea, MRI, children
Supervisor ref

Understanding ventilatory control in children with Prader Willi Syndrome

Suitability: Honours/Masters by Research, PhD, BMedSc (Hons)
Location: Department of Paediatrics, Level 5 Monash Children's Hospital
Project Leaders: Prof Rosemary Horne, Dr Bradley Edwards
Email: *rosemary.horne@monash.edu*
Phone: 03 8572 2827 (Prof Horne)

Project description: Individuals with Prader Willi Syndrome (PWS) have impairments in ventilatory control and are predisposed toward sleep disordered breathing due to a combination of characteristic craniofacial features, obesity, hypotonia, and hypothalamic dysfunction. In order to understand the underlying causes of ventilatory control instabilities, we typically measure the sensitivity of the negative feedback loop controlling breathing (i.e. loop gain). Interestingly, we have recently completed studies showing increased ventilatory instability (which is often termed a system with a high loop gain) in children with a high number of central apnoea's. However, it is not known if children with PWS have similarly high loop gain or whether the recurrent central apnoea's seen in this condition are a manifestation of depressed ventilatory drive (low loop gain). Understanding this mechanism will allow tailored treatment of central sleep apnoea in children with PWS.

Students will learn how to analyse sleep studies in children with PWS to determine loop gain. They will be involved in data analysis, statistical analysis and preparing the study for publication. Students will also be able to interact with postgraduate research students, attend weekly research meetings and be involved in an active paediatric research group.

Keywords: sleep, children, paediatrics, control of breathing

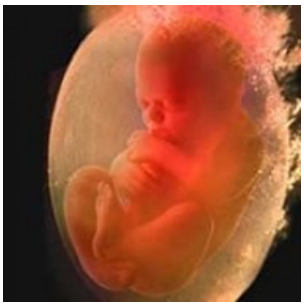
Infection, Inflammation, and Immunity

An anti-inflammatory approach to preterm neuroprotection

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr. Robert Galinsky, Prof Claudia Nold, Prof Marcel Nold
Email: *robert.galinsky@hudson.org.au*
marcel.nold@monash.edu,
claudia.nold@hudson.org.au

Project description: Chronic inflammation after preterm birth is strongly associated with impaired brain development and life-long disability. There is no effective therapy to prevent inflammation-induced impairments in brain developmental after preterm birth. We will assess how effectively two innovative anti-inflammatory mediators, interleukin 1 receptor antagonist (IL-1Ra) and IL-37, protect against inflammation induced impairments in brain development in newborn mice (neurologically similar to preterm infants at ~30 weeks of gestation) exposed to chronic inflammation. We will quantify whether increased levels of IL-1Ra or IL-37 improve brain development, as reflected in biochemical and cellular markers of inflammation, white matter development and neuronal maturation on days 3 and 28 of life.

Research techniques: Various aspects of work with mice, workup of tissues for various downstream applications, flow cytometry, histology, immunohistochemistry, protein detection by ELISA



Closing the gaps – paediatric reference intervals of pro-inflammatory and anti-inflammatory cytokines

Suitability: Honours/BMedSci/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Marcel Nold, Prof Claudia Nold, Dr Stephen Cho
Email: *marcel.nold@monash.edu*,
claudia.nold@hudson.org.au

Project description: Cytokines have attracted substantial attention as diagnostic biomarkers for infectious and inflammatory diseases in recent years. However, understanding of maturation of the immune system and normal ranges for various patient age brackets in health and disease have not been established. Cytokines play an important role in maintaining homeostasis on the one hand, and a wide range of childhood diseases on the other hand. Their potential as diagnostic and prognostic biomarkers that may guide treatment in infectious, autoimmune, allergic, and haematological diseases is beginning to be recognised. Studies have suggested that cytokine production is influenced by age; however, larger datasets on cytokine profiles for healthy neonates, infants and children are lacking.

The aim of this study is to investigate cytokine concentrations in healthy infants and children, and to explore conditions that influence cytokine production in the paediatric age group. For Honours, this project will involve the following approaches and techniques: - Obtaining and working up samples in collaboration with the Department of Paediatrics and Pathology - Clinical data entry in an electronic database - Elisa or multiplex protein quantification assays to measure serum/plasma markers in infants and children. For candidates interested in a PhD, the study's scope is easily expandable to investigate further age groups and diseases.

Keywords: cytokines, inflammation, reference ranges, paediatric, children, infants

Targeting IL-1β for prevention of inflammation-induced brain injury in premature infants

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr. Robert Galinsky, Prof Rod Hunt
Email: *robert.galinsky@hudson.org.au*,
rod.hunt@monash.edu

Project description: Inflammation-induced brain injury remains one of the main causes of disability after premature birth. There is no effective treatment. The pro-inflammatory cytokine interleukin-1β (IL-1β) has been implicated in inflammation –induced brain injury through activation of cerebral microglia (the brain's resident immune cell) however it remains unclear whether this association is causal.

This project is aimed at understanding the role of IL-1β in inflammation-induced preterm brain injury and evaluating whether an FDA approved IL-1 receptor antagonist can improve outcomes.

Research techniques: Fetal surgery, electronic fetal monitoring of brain activity, movement, breathing and cardiovascular function. Neuropathological assessment using immunohistochemistry and molecular biology.

Developing new anti-cytokine therapies for preventing brain injury in the preterm infant

Suitability: Honours/PhD
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Dr. Robert Galinsky, Prof Rod Hunt
Email: *robert.galinsky@hudson.org.au, rod.hunt@monash.edu*

Project description: Inflammation-induced brain injury remains one of the main causes of lifelong disability after birth. There is no effective treatment. Elevated levels of inflammatory proteins (cytokines) are strongly associated with brain inflammation and impaired neurodevelopment in the womb and after preterm birth. Developing therapeutic interventions to target these proteins could provide a new approach for reducing the incidence and severity of disability after preterm birth.

This project aims to improve our understanding of how cytokines disturb healthy brain development and develop new anti-cytokine therapies for inflammation-induced brain injury.

Research techniques: Fetal surgery, electronic fetal monitoring of brain activity, movement, breathing and cardiovascular function. Neuropathological assessment using immunohistochemistry and molecular biology.

Molecular Characterisation of Regulation and Mechanism of Action of the Anti-inflammatory Cytokine Interleukin 37

Suitability: Honours/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Claudia Nold, Dr Ina Rudloff, Prof Marcel Nold
Email: *claudia.nold@monash.edu, ina.rudloff@hudson.org.au*
marcel.nold@hudson.org.au

Project description: Direct clinical relevance: medium/low. Hands-on learning opportunities: Culture of primary human blood cells and cell lines, protein detection by ELISA, RNA detection by real-time PCR, flow cytometry, immunohistochemistry. Interleukin (IL)-37 was discovered in silico in 2000, but it remained a neglected molecule, and nothing at all was known about its function until 2010, when we described the powerful anti-inflammatory properties of this cytokine. IL-37 belongs to the IL-1 family of cytokines and imparts a strong inhibition of the production of pro-inflammatory cytokines. Interestingly, this protection from inflammatory responses is not limited to one or a few triggers but covers a wide spectrum of inflammatory assaults - a rare property, which renders IL-37 a prime candidate for clinical use.

However, further research on the mechanism of action of this unusual cytokine is required before such steps can be taken. In this project, we will characterise several aspects of regulation and function of IL-37, in particular the mRNA and protein expression profile of IL-37 across a spectrum of cell types and the effect of IL-37 one of the key molecular regulators of inflammation, the inflammasome.

Keywords: medicine, immunology, inflammasomes, interleukin1 family, ELISA, PCR, flow cytometry, immunohistochemistry

Novel Anti-inflammatory Approaches for Currently Untreatable Diseases of the Preterm Baby: Human specimen analysis and animal models of bronchopulmonary dysplasia and necrotising enterocolitis

Suitability: Honours/BMedSc (Hons)
Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Claudia Nold, Dr Ina Rudloff
Email: *claudia.nold@monash.edu*, *ina.rudloff@hudson.org.au*

Project description: Direct clinical relevance: high. Hands-on learning opportunities: Various aspects of work with mice, workup of tissues for various downstream applications, flow cytometry, histology, immunohistochemistry, protein detection by ELISA. Established collaboration with the Monash Health department of Paediatric Surgery to collect human specimen including blood, intestinal and stool samples. The severe chronic lung disease bronchopulmonary dysplasia (BPD) causes considerable suffering for premature infants and their families and contributes substantially to health care costs. Necrotising enterocolitis (NEC) is a disease of the premature gut that is poorly understood and carries a high mortality. No effective therapy is known for either devastating disease.

In view of the importance of inflammation for BPD and NEC, we will assess how effectively innovative anti-inflammatory treatments protect against BPD and NEC. In newborn mice with a BPD-like lung disease, we will quantify if treatments protect against the development of lung pathology as reflected in biochemical and cellular markers of inflammation and loss of alveolarisation and vascularisation on day 3 and 28 of life. In a newborn mouse model of NEC, involving formula feeding and brief exposure to cold and hypoxia, we will assess the protective properties of immunotherapies by histology and flow cytometry and by analysis of selected biochemical markers. In human specimen we will assess the underlying mechanism of disease.

Keywords: Paediatrics, preterm infants, inflammation, lung, gut, bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), interleukin, histology, flow cytometry, immunohistochemistry

Baby Microbiome: Investigating the Human Neonatal Lung and Gut Microbiome and its impact on Health Outcome

Suitability: Honours/BMedSci/PhD
Location: H The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Claudia Nold, Prof Marcel Nold, Dr Samuel Forster
Email: *claudia.nold@monash.edu*, marcel.nold@hudson.org.au

Project description: The neonatal microbiome, in healthy full-term infants and in preterm infants presents with a highly dynamic nature. As such, the microbiome is extremely susceptible to external influences that can dramatically affect the short- and long-term health of the infant. In this project we set out to investigate the underlying mechanisms how the intestinal and pulmonary microbiome influences the neonatal immune system and thereby impacts disease outcome. In collaboration with Monash Children's, we collect clinical data and samples from term and preterm infants. This project gives you the opportunity to closely work with clinical collaborators and have the opportunity to gain experience in a diverse set of molecular techniques

Keywords: microbiome, immunology, intestine, lung,

Targeting inflammatory pathways as a novel therapy for kidney stone-induced renal injury

Suitability: Honours/BMedSci (Hons)
Location: Immunology and Regenerative Medicine research Group (Starkey group), Department of Immunology and Pathology, Alfred Hospital Precinct, Level 6 Burnet Institute, 89 Commercial Road, Melbourne
Project Leaders: Dr Malcolm Starkey, Prof Claudia Nold,
Email: malcolm.starkey@monash.edu

Project description: Hypothesis/aim: This project aims to improve our understanding of how our immune system protects against the formation of kidney stones and prevents long-term deleterious consequences such as impaired kidney function and susceptibility to reoccurring stones.

Brief description of project: Kidney stones affect approximately 9% of the population, with rates increasing globally. Whilst the surgical techniques used to remove obstructive stones have improved, few if any advances have been made to prevent stone recurrence. Stones are a significant risk factor for the development of chronic kidney disease, which currently affects 2 million Australians. We believe the solution to curing kidney stones and related kidney diseases is in harnessing the power of our immune system. Our immune system is known to be pivotal in controlling the severity of inflammation and regulating the repair of our organ systems after injury.

However, as our understanding of the immune system grows and becomes more complex, new factors are identified that may hold the key to understanding the "switch" that controls whether an injury is appropriately dealt with or not, and whether the affected organ system is appropriately repaired. Incomplete repair may lead reoccurring injuries and chronic disease. We believe an anti-inflammatory cytokine may be one of the key regulators of that "switch" that controls appropriate repair and regeneration of structural cells in the kidney.

There are multiple components of this inflammation pathway that may be targeted in translational studies using available small molecule inhibitors and blocking monoclonal antibodies that are in clinical use or development for other disease.

This project will involve the following techniques: - In vivo mouse model of kidney stones - In vivo measurement of glomerular filtration rate. This allows real time measurement of kidney function in the same animal over time. - Use of genetically modified mice - In vivo administration of therapeutic small molecule inhibitors or monoclonal antibodies - Histological assessment of kidney stone formation and injury - Multicolour immune cell profiling using flow cytometry - Quantitative real time PCR for assessment of mRNA expression in tissue homogenates - Multiplex protein quantification assays to measure inflammation markers - Blood chemistry analysis used clinically using our IDEXX Catalyst One

Keywords: inflammation, IL-37, kidney disease,

Cell therapy and regenerative medicine

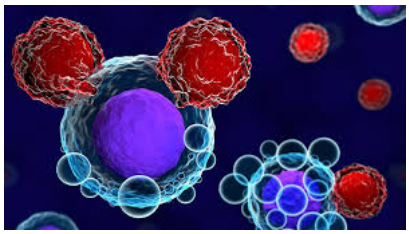
Isolation and Expansion of Umbilical Cord Blood Stem Cells for Regenerative Medicine

Suitability: Honours/PhD/BMedSc/Masters
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Graham Jenkin, Dr Courtney McDonald, Dr Tayla Penny
Email: *graham.jenkin@monash.edu*
Phone: 0419534101 (Prof Jenkin)

Project description: Umbilical cord blood (UCB) is one of the richest sources of "young" haematopoietic stem cells. Currently, more than 3000 UCB stem cell transplants are performed each year. However, these are mostly restricted to children, as UCB samples usually do not contain sufficient stem cells to treat adults. The umbilical cord and cord blood also contains multiple potentially efficacious cell types for a range of diseases. Hence, this research project aims to develop and refine methods for expanding the number of stem cells obtained from human UCB and umbilical cord under laboratory conditions and translation of this research to the clinic.

This stem cell research could help save lives of people suffering from blood disorders, cancers, and auto-immune diseases. The experiments will include cell culture and gene analysis/molecular biology techniques and transplantation of UCB stem cells to determine their efficacy.

Keywords: Umbilical Cord Blood, Cord Blood, Stem Cells, Cord Blood expansion, Regenerative Medicine



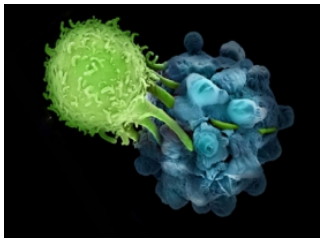
Isolation and Banking of Umbilical Cord Blood Stem Cells and Placental Tissues for Future Clinical Therapies

Suitability: Honours/PhD/BMedSc/Masters
Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Graham Jenkin, Dr Courtney McDonald, A/Prof Atul Malhotra
Email: *graham.jenkin@monash.edu*
Phone: 0419534101 (Prof Jenkin)

Project description: Umbilical cord blood and the umbilical cord are a recognised source of a range of stem cells including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs) which have the potential to differentiate into a wide range of cell types and are also potently neuroprotective, angiogenic, immunomodulatory and anti-inflammatory.

The use of these cells is being explored in a number of therapeutic settings. This project, carried out in collaboration with Cell Care, will validate methods for collection, processing and storage of umbilical cord tissue containing these cells, and their retrieval post-thaw, to enable patients to have the option to store umbilical cord tissue at birth, in addition to cord blood.

Keywords: Umbilical Cord Blood, Cord Blood Stem Cells, inflammation, neuroregeneration, Neuroprotection, Cerebral Palsy



The development of macrophages from iPSC (iMacs) for novel cancer immunotherapy

Suitability: PhD/Honours
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Graham Jenkin
Co-supervisors: Prof Alan Trounson, Dr Frederico Calhabeu. Prof Richard Boyd
Email: *graham.jenkin@monash.edu*

Background: Immunotherapy as a discipline has provided a potentially revolutionary approach to combatting cancer. While CAR technologies have provided unheralded advances in blood cancer treatment, they are currently mono-directional targeting one cancer marker. They also fail to engage the advantages of the patient's "polyvalent" immune system. In this regard, the first line of defence of the immune system centres around more functionally "primitive" but ultimately critical macrophage lineage cells. Macrophages represent a major, underutilized, potential pillar in cancer immunotherapy. Macrophages themselves are heterogenous with two main functionally distinct subsets: M1 (pro-inflammatory) and M2 (anti-inflammatory). M1 are clearly the most important for attacking cancer and are the focus of this project.

However, macrophages have a very short half-life but can be produced effectively and efficiently from haemopoietic stem (HSC) cells. Very recently two groups have addressed the problem of the short half-

life of macrophages by using iPSC technology. iPSCs have effectively limitless capacity for self-renewal. If they can be successfully differentiated into macrophages this could overcome the major shortfall of their life span. Although macrophages have long been impervious to genetic manipulation, researchers have recently discovered a new type of viral vector that allows them to engineer the cells to retain and bolster their cancer-attacking abilities when injected into solid tumours in mice.

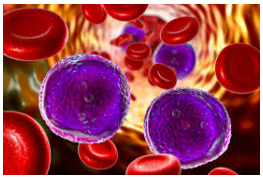
This project takes its lead from the Cartherics platform which uses iPSCs derived from homozygous haplotype donors, to minimise MHC mismatch and immune rejection.

Aims of project:
1. To develop the technology for inducing macrophages from iPSC (iMacs).
2. To preferentially induce M1 macrophages by varying the differentiating conditions to block the M2 pathway or promote the M1 pathway.
3. To characterise these cells phenotypically and functionally (pro- versus anti – inflammatory cytokines; CD surface expression).
4. To endow these cells with a cancer specific CAR such as a TAG-72 CAR.
5. To develop stable TAG-72 Car-expressing iPSC clones.
6. To genetically engineer the IPSC to enhance iMac function and longevity.
7. To show that engineered iMac/CAR-iMac/ gene KO iMac possess essential properties of PBMC-derived macrophages, such as homing capacity and cytotoxity activity (phagocytosis). iPSC-derived macrophages capacity to eliminate human ovarian cancer will be assessed both in vitro and in vivo. An in vivo bioluminescence imaging method will be used to evaluate the capacity of iMacs to kill human ovarian cancer in NSG mice.
8. To explore the additive benefits of iMacs followed by, or coupled with, iNK or iT cells for cancer killing capacity in NSG mice.

Supervision: Main supervisor: Professor Alan Trounson; Co-Supervisors: Dr Frederico Calhabeu, Professor Richard Boyd

Sample References: 1. The Role for Monocyte Chemoattractant Protein-1 in the Generation and Function of Memory CD8+ T Cells. Tao Wang et al J Immunol (2008); 180:2886-2893. 2. Pluripotent stem cell-derived CAR-macrophage cells with antigen-dependent anti-cancer cell functions. Li Zhang et al. J Hematol Oncol (2020) 13:153.

Keywords: Immunotherapy, Cancer Therapy, iPSCs, Chimeric Antigen Receptor Technology, Ovarian Cancer



Novel derivation and gene editing of human haematopoietic stem cells and differentiation to immune cell types. *Not available 2021/2.*

Suitability: Honours/PhD/Masters/BMedSc
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Richard Boyd, Prof Graham Jenkin, Dr Roland Shu, Dr Nicholas Boyd
Email: *graham.jenkin@monash.edu*
Phone: 03 8572 2801 (Prof Jenkin)

Project description: Human hematopoietic stem cells (HSCs) will be isolated from umbilical cord blood and expanded in large numbers for clinical therapies. This project will use novel cutting edge technology to edit the genetic profile of HSCs to enable their universal transplantation across histocompatibility barriers and their differentiation into strategically sculptured cancer fighting immune cells. Multiple samples of human umbilical cord blood are being banked by large private and public banks but are only being used sparingly for treatment of patients receiving chemotherapy for restoration of their bone marrow blood cell populations in a number of cancers. The more widespread use of banked cord blood samples is hampered by the need to partially match the HLA type to the transplant recipient.

This project will involve testing the concept of gene editing the major histocompatibility antigens (type I HLA-A, HLA-B and type II HLA-DR). This would essentially create universal compatibility at the major HLA loci. HLA-C, which exists as two types HLA-C1 and C2, is more easily matched to recipients and the presence of HLA-C prevents destruction of HLA-A and HLA-B null (KO) cell types by Natural Killer (NK) cells, so would not need to be edited out for such cells to act as universal donor cells. In addition, cord blood HSCs can be differentiated into T cells, NK cells, macrophages and other cells of the immune system. The PhD would involve the gene editing of cord blood HSCs and their differentiation, via their transformation into iPSCs, into functional immune cells for assessment of their ability to kill target cancer cells. Their immune compatibility will be tested in vitro and in in vivo models.

Keywords: Haematopoietic Stem Cells,CAR-T, Immunotherapy, Stem Cells, Clinical Translation, Cartherics Commercial Clinical Translation Projects, Regenerative Medicine

Genetically engineered human MSCs as supporting inducers of in vitro t-cell production. *Not available 2021/2.*

Suitability: PhD/Honours/Masters/BMedSc
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton

Project Leaders: Prof Richard Boyd, Prof Alan Trounson, Prof Graham Jenkin, Co-supervisors Dr Roland Shu, Dr Nicholas Boyd
Email: *graham.jenkin@monash.edu*
Phone: 0419534101 (Prof Jenkin)

Project description: Genetically modified chimeric antigen receptor T cells (CAR-T cells) represent a new revolution in anti-cancer immunotherapy. A major problem, however, is that the treatment currently relies on using the cancer patients own blood but they invariable have too few T cells available for genetic enhancement. Furthermore, prior treatment with chemotherapy substantially reduces their function. This study aims to develop a new approach to generating CAR-T cells from stem cells. T cells derived in vitro from both hematopoietic stem/progenitor cells (HSCs) and induced human pluripotent stem cells (iPSC) offer great potential advantages in generating a self-renewing source of T cells that can be readily genetically modified for immunotherapy .

The project aims to generate a genetically modified human stromal cell line from human Mesenchymal Stem Cells (MSC), for supporting the T cell in vitro differentiation. In the thymus, complex interactions between stromal cells, cell-surface ligands, cytokines, chemokines, and extracellular matrix create a microenvironment that guides T-lymphocyte differentiation from bone-marrow-derived progenitors . The OP9-DL culture system permits the generation of HSC-derived T cells in vitro, serving both as a means to facilitate the study of T-cell differentiation, as well as the potential to produce large numbers of cells for adoptive transfer. OP9-DL1 cells provide Notch signalling, which is a crucial mediator of T-cell development. The mouse bone marrow (BM)-derived stromal cell line, called OP9, is engineered to overexpress the Notch ligand, Delta-like ligand 1 (Dll-1); hence the line is termed OP9-DL1 .

Optimising the function of anti-cancer killer T cells: the role of endogenous TCR in CAR-T function and overcoming exhaustion to supercharge CAR-T cells. *Not available 2021/2.*

Suitability: Honours/PhD/Masters
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Richard Boyd, Prof Graham Jenkin, Co-supervisor: Dr Vera Evtimov
Email: *graham.jenkin@monash.edu*
Phone: 03 8572 2801 (Prof Jenkin)

Project description: Chimeric Antigen Receptor T cells are providing extraordinary results in the clinic, particularly for haematological malignancies. As exciting and tantalising as this immunotherapy revolution is, there are still major hurdles to be overcome in optimising their clinical utility. This project will apply the rules that govern normal endogenous T cell function to CAR-T cells, to help their functional impact across a range of cancers and to increase their longevity after transplantation. Recent studies have shown that T cell exhaustion significantly impacts the ability for chimeric antigen receptor (CAR-) T cells to remain potent killers.

Overall, this project will aim to characterise how T cell receptor (TCR) mediated activation and ultimately modulation of T cell exhaustion will enhance CAR-T potency in vitro and in vivo. Pre-clinical studies conducted by Cartherics to date have demonstrated that T cell hyper-activation leads to the potent, indiscriminate elimination of target cells induced by both CAR-T and non-transduced T cells. Through real-time cell monitoring we have identified a collection of culture conditions which have the ability to augment CAR-T function in vitro. Importantly, manipulation of exogenous growth factors and cytokines significantly enhances target cell elimination to the detriment of target-antigen specificity.

This project would use these findings as a springboard to further explore activation/exhaustion and how we could manipulate these elements to generate CAR-T cells that can reduce tumour burden AND persist indefinitely to ultimately improve the efficacy of CAR-T treatment.

Keywords: CAR-T, Immunotherapy, Stem Cells, Clinical Translation, Cartherics Commercial Clinical Translation Projects, Regenerative Medicine

Elimination of cancer stem cells using chimeric antigen receptor T cells. *Not available 2021/2.*

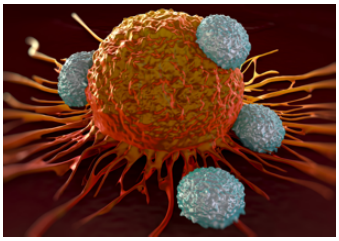
Suitability: PhD/Honours/BMedSc
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Richard Boyd, Prof Alan Trounson, Prof Graham Jenkin, Co-supervisor: Dr Vera Evtimov
Email: *graham.jenkin@monash.edu*
Phone: 0419534101 (Prof Jenkin)

Project description: Disease relapse in CAR-T therapies of solid tumours suggests that current treatments lack the ability to eliminate the small subset of cells known as cancer initiating cells or cancer stem cells (CSCs). We propose to use the sophisticated specificity of immunotherapy to target surface membrane antigens present on the CSC, negating the current need for the cancer cell to be proliferating for killing efficacy of CAR-T therapies.

This project will aim to phenotypically and functionally characterise CSCs from multiple cancer indications including ovarian, gastric and cutaneous T cell lymphoma and demonstrate the ability of CAR-T cells to effectively eliminate these cells in vitro and in vivo. At the conclusion of this project, you will have successfully characterised the CSC subpopulation in select cancer indications

and demonstrated that CAR-Ts are able to completely eliminate these cells both in vitro and in vivo.

Keywords: Cancer Therapy, CAR-T Therapies, T-cell generation, Clinical Translation, Immunotherapy, Cancer Stem Cells, Cartherics



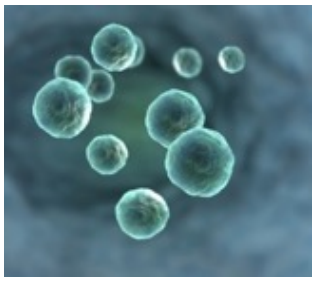
Re-engineering the function of natural killer cell receptors via CRISPR/Cas9: a new approach for 'off-the-shelf' immunotherapy. *Not available 2021/2.*

Suitability: PhD/Masters
Location: The Ritchie Centre / Cartherics, Hudson Institute of Medical Research; Translational Research Facility, Monash Medical Centre, Clayton
Project Leaders: Prof Richard Boyd, Prof Graham Jenkin, Co-supervisors: Dr Roland Shu, Dr Vera Evtimov, Dr Nicholas Boyd
Email: graham.jenkin@monash.edu
Phone: 0419534101 (Prof Jenkin)

Project description: Cellular immunotherapy with chimeric antigen receptors (CARs) have provided unprecedented results in treatment of liquid cancers. However, inherently, these treatments face major challenges to reach mass adoption. Furthermore, autologous CAR-T treatments can require ~2 months to manufacture (often time patients don't have) and produce variable (often insufficient) cell numbers as a result of poor immune systems hampered by chemotherapy. An on-demand, highly defined, universal product, which is compatible with multiple patients is required to unlock cellular immunotherapy therapy for the public. The answer lies in the utilisation of stem cells. Cartherics is focused on developing a scalable, clinically applicable manufacture system to differentiate induced pluripotent stem cells (iPSC) to CAR+ cytotoxic cells: T-cells and Natural killer (NK) cells.

To enhance the potency and longevity of NK immune-therapeutics, this PhD will investigate a new alternative to inserting an entire synthetic CAR signalling system into the NK cells. Via CRISPR/Cas9 gene-editing, the terminal binding domain of NK surface receptors will be replaced with single chain variable fragments (scFV) that work as targets for cancer cells. Upon binding, all the natural activation and killing mechanisms related to that NK surface receptor will be engaged, giving the NK cell the potential to alleviate short-falls of CAR-triggered cytotoxicity and enhance the effect of tumour specific NK cell killing.

The project will involve CRISPR-Cas9 and scFv-R gene editing of iPS cells and, upon successful conversion to mature NK cells characterised via flow cytometry, the in vitro and in vivo activity of iPSC derived scFv-R-NKs will be compared with PBMC scFv-R NKs in vitro and in vivo in animal models. giving the NK cell the potential to alleviate short-falls of CAR-triggered cytotoxicity and enhance the effect of tumour specific NK cell killing.



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27-31 Wright Street
Clayton VIC 3168
Australia
t: +61 3 8572 2700
w: hudson.org.au
e: info@hudson.org.au