HUDSON INSTITUTE

Student Projects

2024

HUDSON
INSTITUTE OF MEDICAL RESEARCH

Welcome to Hudson Institute

Hudson Institute specialises in medical research discoveries in five areas of medical need

- **Inflammation**
- **Cancer**
- **Reproductive health**
- **Newborn health**
- **Hormones and health.**

Our 450+ scientists and students focus on laboratory discovery science and translational research – taking discoveries to patients, clinicians, and industry for real-world impact.

281 STAFF

176 STUDENTS

42 RESEARCH GROUPS

250 RESEARCH PUBLICATIONS

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, industry and clinical research
- Are mentored and trained by highly qualified supervisors and their teams
- Obtain a degree from Monash University – ranked in the top 50 globally
- Have access to world class research facilities
- Publish their research in high impact journals, 41 were first authors in 2022
- Win prestigious prizes and awards
- Join regular networking and learning and development programs, including the off-site Hudson Institute student retreat
- Learn a range of dynamic and transferable skills for careers in the biomedical and clinical research sectors including commercialisation
- Are supported by our culture which embraces equity and diversity, to provide a safe and welcoming environment for all.

Students at a glance 2022

66 POSTGRADUATE AND HONOURS STUDENTS COMPLETED

176 STUDENTS 126 PhD 4 MASTERS 46 HONOURS

47 STUDENTS WITH MEDICAL TRAINING

All work and no play ...

Our students also join a wide range of student networking and social events organised by Hudson Institute Student Society (HISS).

Our precinct

Hudson Institute is 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.

Location | Hudson Institute, Clayton

Our Research Centres

Our five specialist centres bring together the finest professionals in Australian science and medicine to conduct basic and clinical research, and provide hope to the wider community.

Centre for Cancer Research >

Centre for Endocrinology and Metabolism >

Centre for Innate Immunity and Infectious Diseases >

Centre for Reproductive Health >

The Ritchie Centre >

Contact our supervisors >

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.

Contact our supervisors

Students are encouraged to contact supervisors to discuss projects, arrange a time to visit the lab and view our facilities. Simply email the supervisor to arrange a time.

STEP 1: Find a project that you are interested in.

STEP 2: Email the supervisor: *"I am interested in your student project. Could I please arrange a time to visit you in your lab?"*

All the information you need to enrol is on Hudson Institute's website, or the project supervisor can help you enrol.

w: hudson.org.au/students/courses-available/

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HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR CANCER RESEARCH

Centre for Cancer Research

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Centre Head

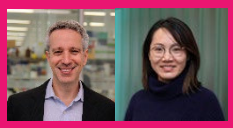
Prof Ron Firestein

Scientists working in the Centre for Cancer Research undertake basic research into the molecular mechanisms underlying the development, growth and metastasis of tumours, as well as the relationship between the innate immune system and cancer. The discovery and development of novel therapies for the treatment of cancers is also an important aspect of the team's work.

Current key areas of interest include:

- Links between innate immunity, inflammatory processes and cancer– Role of embryonic signalling pathways in cancer, and the targeting of these pathways with novel therapies
- Cell signalling pathways involved in tumour survival and growth, and the development of monoclonal antibodies to treat glioma and other cancers
- Role of integrin-linked kinase in cell migration and oncogenesis
- Molecular pathways involved in the metastasis of tumours, including colorectal, ovarian, prostate and bladder cancers
- Role of peptidase activity on inflammatory signalling and tumour microenvironment in ovarian cancer
- Role of the microenvironment in tumour progression, chemoresistance and metastasis
- Cancer precision medicine, including childhood brain cancer and solid tumours

Research Group Heads / Project Supervisors



Next Generation Precision Medicine program >

Program Head
Prof Ron Firestein

Bioinformatician
Dr Claire Sun

Cancer Genetics and Functional Genomics >

Research Group Head
Assoc/Prof Ron Firestein

Postdoctoral Scientist
Dr Marius Dannappel

Postdoctoral Scientist
Dr Chunhua Wan

Developmental and Cancer Biology >

Research Group Head
Dr Jason Cain

STAT Cancer Biology >

Research Group Head
A/Prof Daniel Gough

Ovarian Cancer Biomarkers >

Research Group Head
Dr Andrew Stephens

Research Scientist
Dr Maree Bilandzic

Please note: *All of Dr Stephens and Dr Bilandzic's projects are FULL and not taking on more students.*

Immunohaematology >

Research Group Head
Dr Jim Vadolas

Leukaemia Modelling & Therapeutic Discovery >

Research Group Head
Dr Catherine Carmichael

Structural Biology of Inflammation and Cancer >

Research Group Head
Dr Wilson Wong

Next Generation Precision Medicine Program

Precision Medicine for Childhood Brain Cancer

Keywords: cancer, genetics, paediatrics, brain cancer, CRISPR, drug screens, genomics, personalised medicine, precision therapy

Project leader: Prof Ron Firestein

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Project description: The Next Generation Precision Medicine program marks a significant investment in future clinical management and novel research discovery in childhood cancer. Please see our recent paper in *Cancer Cell* (Sun X., Daniel P., et al Cancer Cell, 2023). The program includes:

The development of a living tumour biobank for paediatric solid tumours

At present, very few reliable patient-derived preclinical models are available to researchers. To bridge this gap, our program will establish and bank organoid, cell lines, and xenograft models directly from childhood tumour tissue. The establishment of a living biobank for paediatric solid tumours will provide a critical renewable resource for local, national and international researchers.

The establishment of a functional genomics pipeline

We capitalise on the living biobank tumour samples to integrate genomic data (next generation sequencing) with functional data obtained from high-throughput genetic (Cas9/CRISPR) and results from global pharmacological drug screens.

Translation of genomic data into targeted therapy

The comprehensive molecular analysis of individual patient tumours will help identify both new and existing therapies that can be rapidly implemented in the clinic. This approach will facilitate clinical implications of data from the functional genomics pipeline for individual paediatric patients.

Unique national and global collaborations

The establishment of a living biobank and functional genomic testing for paediatric solid tumours provides a critical resource for local, national and international researchers. Thus, a key element of the program includes national and international stakeholders' involvement to build expertise, share resources and disseminate results that will advance the field of precision medicine for paediatric cancer patients For more information see the Affiliations and Partners section below.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons)

Allele-specific transcription of tumorigenic mutations in paediatric cancers

Keywords: paediatric cancer, computational biology, bioinformatics, trancriptomics, genomics

Project leader: Dr Claire Sun

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Project description: The VPCC Next Generation Precision Medicine program focuses on utilising genetic profiles of patients' tumour models to identify new therapeutic targets and repurpose existing ones using high-throughput functional CRISPR screens. Advancements in next-generation sequencing and computational biology techniques have facilitated a deeper understanding of the genetic underpinnings of cancers, paving the way for the advent of the next generation of targeted therapy for paediatric tumours. However, less than 15% of paediatric cancer patients harbour actionable mutations, of which fewer respond to targeted therapies. This underscores an urgent need to delve beyond driver mutations to identify biomarker coupled therapies.

Transcriptomics not only enable characterisation of genetic alterations at the RNA level but also quantitatively capture how tumorigenic genotypes are transcribed into the malignant phenotype. It has been shown that allele-specific expression result in preferential expression of mutant or wild-type products. Using best-practice computational pipelines running on high-performance computers, the successful candidate will firstly identify the genetic alterations in a large compendium of patient derived tumour models. Secondly, they will then identify allele-specific expression of these key driver mutations. This project aims to describe whether allele specific expression contributes to tumorigenesis and identify the underlying mechanisms that unbalance transcription between alleles.

Suitability: Honours, BMedSc(Hons)

Identification of tumourigenic RNA splicings in paediatric cancers

Keywords: cancer bioinformatics RNA

Project leader: Dr Claire Sun

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Project description: The VPCC-Next Generation Precision Medicine program focuses on utilising genetic profiles of patients' tumour models to identify new therapeutic targets and repurpose existing ones using high-throughput functional CRISPR screens. Advancements in next-generation sequencing and computational biology techniques have facilitated a deeper understanding of the genetic underpinnings of cancers, paving the way for the advent of the next generation of targeted therapy for paediatric tumours. However, less than 15% of paediatric cancer patients harbour actionable mutations, of which fewer respond to targeted therapies. This underscores an urgent

need to delve beyond driver mutations to identify biomarker coupled therapies.

Aberrant RNA splicing and gene fusions have been shown as recurrent oncogenic drivers in paediatric tumours. Using best-practice computational pipelines running on high-performance computers, the successful candidate will identify the genetic and transcriptional alterations in a large compendium of patient derived tumour models. They will have the opportunity to work in the wet lab to validate the tumourigenic role of the identified targets. They can also work with the bioinformatician team to integrate the results in the public database. This project aims to identify which gene fusions, and how, contribute to tumorigenesis.

Suitability: Honours, BMedSc(Hons)

Cancer Genetics and Functional Genomics

Functional genomic screens to identify new therapeutic targets for bowel cancer

Keywords: genetics, genomics, cancer, screen, personalised medicine

Project leader: Prof Ron Firestein

e: ron.firestein@hudson.org.au

Project description: Bowel/colon cancer is a major cause of cancer related morbidity worldwide. We will use novel genomic technologies (e.g. CRISPR-Cas12) to perform unbiased parallel combinatorial screen to identify synthetic lethality and druggable combinatorial approaches to inhibit colorectal cancer growth and progression.

Suitability: PhD/Doctorate, Masters, Honours

Development of new 3-dimensional models of cancer to model drug resistance and develop new cancer treatment

Keywords: colon cancer, organoids, models

Project leader: Prof Ron Firestein

e: ron.firestein@hudson.org.au

Project description: The development of clinically relevant cancer models that recapitulate human cancer is key to both understanding biological mechanisms of cancer growth as well fine tuning therapeutic cancer treatments. In this project, the student will work with both human tissues and animal models to develop 3-dimensional organotypic culture of genetically defined cancer models. Using CRISPR and other technologies we will genetically manipulate these models, and assess the contribution of new targets in mediating cancer growth. See our recent paper (Dannappel M., Zhu D., et al. *J Clin Inves*. 2022).

Suitability: PhD/Doctorate, Masters, Honours

Transcriptional regulators as cancer targets: new models and therapeutic approaches

Keywords: genetics, genomics, cancer, oncogenes, transcription

Project leader: Prof Ron Firestein

e: ron.firestein@hudson.org.au

Project description: Transcriptional regulators play a key role in activating oncogenic pathways that impinge on tumour growth, invasion and mestasasis. We study the role of Mediator kinases CDK8/19 as transcriptional regulators in normal tissue homeostasis and cancer (Sooraj et al., *Molecular Cell* 2022).

Suitability: PhD/Doctorate, Masters, Honours

KMT2A as a druggable therapeutic target against β-catenin-driven colorectal cancer

Keywords: colorectal cancer, β-catenin, targeted therapy, epigenetics, translational medicine, cancer treatment, KMT2A

Project leader: Dr Chunhua Wan

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Project description: Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death in the world. Australia leads the incidence rates of CRC worldwide that the lifetime risk of developing CRC is 1 in 13 among Australians. What's worse, CRC was ranked the most (2016) and then the second most common (2017-2018) cause of cancer death in Australia, with an estimated death of 5,500 people annually. Unfortunately, due to lack of effective targeted therapy, the 5-year overall survival rate of CRC is limited to roughly 69%, lagging well behind other common cancers such as breast, melanoma and prostate (over 90% survival rate). Hence, there is a critical unmet need to develop new targeted therapies for colorectal cancer.

Over 90% of CRCs arise from genetic mutations that activate a tumour-initiating pathway called Wnt/β-catenin pathway. Abrogating β-catenin function results in the loss of tumorigenic potential of Wnt-active CRC cells. This makes β-catenin a most prominent treatment target in CRC. However, targeting β-catenin so far eludes clinical success, as pharmacologically blocking β-catenin remains technically infeasible. β-catenin mainly promotes the transformation of normal cells into cancer cells through activating the expression of various tumour-initiating genes. This process requires the recruitment of assorted transcriptional co-activators, especially epigenetic enzymes, and these epigenetic enzymes are ideal drug targets. Epigenetic enzymes are responsible for the reading of genetic code via

introducing chemical modifications on DNA and its associated proteins, whose reprograming is indispensable for the initiation and progression of virtually all colorectal tumours. The recruitment of epigenetic enzymes is essential for β-catenin to initiate the expression of tumour-promoting genes and CRC development. Thus, targeting epigenetic enzymes that are essential for β-catenin function is a promising therapeutic strategy against CRC. However, the epigenetic enzymes that are selectively required for β-catenin function remain largely unknown.

Methods and preliminary results: We employed a state-of-the-art gene editing tool (CRISPR-Cas9) to systemically investigate β-catenin-related therapeutic targets on a whole genome scale and validate the results using a confirmatory screen that specifically targeting epigenetic modifiers. Both screenings identified an epigenetic enzyme, namely lysine methyltransferase 2A (KMT2A), as a key player of β-catenin-mediated transcription. We have validated that the impacts of deleting KMT2A on β-catenin targets are almost comparable to deleting β-catenin itself, suggesting that targeting KMT2A can diminish the activity of β-catenin in CRC cells. Furthermore, ablation of KMT2A or pharmacological inhibition of KMT2A led to evidently reduced expression of β-catenin targets and impaired colony and organoid formation in β-catenin-active CRC cells, but not in β-catenin-inactive cells. More importantly, β-catenin-active CRC cells exhibit significantly higher sensitivity towards KMT2A inhibitors that are under clinical development. These findings implicate KMT2A as an epigenetic enzyme highly specifically required for β-catenin function in whole human genome, highlighting the potential of KMT2A therapy as a CRC treatment.

Expected outcomes:

1. The precise mechanisms underlying KMT2A-facilitated β-catenin function.

2. The unique role of KMT2A in the development of CRC.

3. The efficacy of pharmacologically inhibiting KMT2A on CRC treatment.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons), Short Projects

Targeting colorectal cancer stem cells using genome-scale CRISPR screens

Keywords: colorectal cancer, translational medicine, cancer stem cells, CRISPR-Cas9 screen, druggable targets

Project leader: Dr Chunhua Wan

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Project description: Colorectal cancer (CRC) is a most common cancer and the 4th leading cause of cancer-related death worldwide. Australia has one of the highest incidence rates of CRC in the world. According to Australian statistics, the lifetime risk of developing CRC in the general population is 1 in 13. Due to lack of effective targeted therapy, the 5-year overall survival rate of CRC is roughly 69%, lagging well behind other common cancers such as breast, melanoma and prostate (over 90 % survival rate). Thus, the development of novel targeted therapies is a most urgent need in the fight against colorectal cancer.

Colorectal cancer stem cells (CSCs) play a determinant role in colorectal cancer initiation and progression. The presence of LGR5+ CSCs is essential for colon tumors to grow and disseminate remotely. Elimination of CSCs causes colorectal cancer regression and long-term survival in experimental animals. Thus, finding the drug-targetable regulators that are selectively required for CSCs may pave the paths for novel targeted therapy of colorectal cancer. Our recent work has successfully uncovered the key drivers of wnt-initiated colorectal cancer using genome-wide CRISPR screen (Chunhua Wan et al. *Science Advances*. 2021). This powerful strategy may dissect the regulators of CSCs at a whole genome level.

Methods: The present project plans to establish a reporter system of CSCs in colorectal cancer cell lines and organoids (a 3D in vitro tissue culture system), and screen the genes that are selectively required for colorectal cancer stemness at a whole-genome scale. We will build reporter systems using fluorescence proteins (EGFP, RFP) to monitor key markers for cancer stemness (LGR5, ASCL2) and differentiation (KRT20, CEACAM1). A whole genome CRISPR library screen will be performed to identify genes whose knockout may cause the differentiation of CSCs. Following genome-wide screening, we will clarify the key druggable regulators that are required for the maintenance of CSCs using organoid and xenograft studies. The molecular mechanisms underpinning CSCs may also be investigated using biochemical approaches.

Overall Goals:

1. Clarify the regulators of CSCs at a whole genome scale;

2. Identify of druggable targets of CSCs;

3. Investigate the translational merit of pharmaceutical inhibitors in colorectal cancer treatment.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons), Short Projects

Targeting Mediator kinases to improve the efficacy of immunotherapies for treatment of colorectal cancer

Keywords: colorectal cancer, epigenetics, T-cells, immunology, immunotherapy

Project leader: Dr Marius Dannappel

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Project description: Despite the promising results of immunotherapies to treat various cancer (eg melanoma), they have been unsuccessful for the vast majority of colorectal cancer patients. The two major limitations are first, immune evasion, the shaping of

an immunosuppressive tumour microenvironment (TME) by tumour cells to avoid detection by cytotoxic T-cells and second, a concept called T-cell exhaustion, where chronic stimulation of effector T-cells reduce the effectiveness of T-cell mediated immunity. This presents a major problem of immunotherapies to treat bowel cancer and most other solid tumours.

We have recently discovered that two epigenetic regulators called Mediator kinases have so far unappreciated roles to not only control T-cell differentiation, but also their functionality by regulating the secretion of effector cytokines. Deletion or inhibition of Mediator kinases reduced the degree of terminal T-cell differentiation, which resulted in an "improved" effector phenotype known to be more effective attacking and destroying tumour cells. Based on these promising findings, we hypothesize that Mediator kinases can be targeted to improve T-cell responses against colon cancer cells and other solid tumour cells.

Using colorectal cancer as a model, we will use sophisticated genetic mouse models and organoid models combined with state-of-the-art sequencing approaches to investigate whether targeting Mediator kinases in immune cells can reshape the TME and to increase the efficacy of existing immunotherapies for more beneficial patient outcomes.

Suitability: PhD/Doctorate, Masters, Honours, Short Projects

Functions of Mediator in tissue homeostasis and inflammation

Keywords: epigenetics, transcription, cancer, inflammation, homeostasis

Project leader: Dr Marius Dannappel

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Project description: The Mediator complex with its catalytic subunit the Mediator kinase module, composed of CDK8/19 and other members, is multimeric complex regulating the transcription machinery, transcription factor activity at promoter and enhancer regions and the chromatin landscape, thus controlling gene expression and cell lineage differentiation. CDK8 and CDK19 are commonly dysregulated in cancers (eg colorectal cancer, melanoma) and we are evaluating their potential as novel therapeutic targets.

Using a series of genetically modified mouse models, we identified novel functions of Mediator kinases during normal tissue homeostasis in the intestine, liver, lung and the haematopoietic system.

Using innovative cell culture systems and organoid models, combined with state of the art omic approaches and a wide range of molecular approaches, we will investigate the functions of Mediator kinases during tissue homeostasis and diseases, such as cancer, inflammatory bowel disease and non-alcoholic fatty acid liver disease (NAFLD).

Suitability: PhD/Doctorate, Masters, Honours, Short Projects

Developmental and Cancer Biology

Identification of targetable pathway dependenies in childhood sarcoma

Keywords: childhood cancer, sarcoma, cancer biology, osteosarcoma

Project leader: Dr Jason Cain

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Project description: Soft tissue and bone sarcomas represent ~13% of all childhood cancer diagnosis and collectively are the second highest cause of childhood cancer related death, accounting for 20% of all mortalities. Despite the use of neoadjuvant chemotherapy and surgery, survival rates for these patients have remained stagnant for the last four decades. Curative treatment, effective in <70% of all sarcoma patients, leads to lifelong morbidity. For the remaining >30% there is no effective treatment. Whilst molecular markers of disease prognosis at diagnosis are revolutionising the clinical treatment and outcomes of other paediatric cancer types, this approach is largely lacking in childhood sarcoma. This highlights the urgent need for new and improved therapies for these diseases.

In this project, we will utilize comprehensive functional and molecular datasets derived from patient-derived models to identify targetable sarcoma pathways. These pathways will be validated using clinically relevant cell and animal models of disease. The identification of targetable pathways underlying sarcoma growth and therapy resistance would represent a major development in the field and enable the future risk stratification of patients and appropriate application of targeted therapy to minimise side effects and improve overall survival.

Suitability: PhD/Doctorate, Honours

Exploiting Epigenetic Dysregulation in SWI/SNF-Deficient Solid Tumours

Keywords: epigenetics, cancer, peadiatrics, brain, lung

Project leader: Dr Jason Cain

e: jason.cain@hudson.org.au

Project description: Impaired differentiation is a common feature of cancer. We have recently demonstrated the differentiation potential of histone deacetylase inhibitors (HDACi) in paediatric (rhabdoid tumours) and adult (lung adenocarcinoma) solid tumours that are genetically defined by mutations in the SWI/SNF chromatin remodelling complex. Recent genomic studies have shown that mutations in subunits of this complex occur in at least 20% of all cancer. Using preclinical models of SWI/SNF-deficient and intact cancers, the successful candidate

will investigate the mechanisms of epigenetic-mediated differentiation and apply these findings to a broader clinical context.

Suitability: PhD/Doctorate, Honours

Identification of novel combination therapy for diffuse midline glioma

Keywords: DIPG, Histone H3, epigenetics, mouse models

Project leader: Dr Jason Cain

e: jason.cain@hudson.org.au

Project description: Diffuse midline glioma is a highly aggressive cancer that arises in the midline brain structures of children and is universally fatal. Using next-generation sequencing strategies, significant advancement has been made in understanding the genetic profile of these tumours. Mutations in either of two genes encoding the Histone H3 protein converge on a critical lysine residue resulting in substitution with a methionine residue (K27M) have been described in the vast majority of DMG patients, suggesting a pathogenic role in this disease. The purpose of this project is to elucidate potential mechanisms of H3K27M tumorigenesis and likely therapeutic interventions that could be rapidly progressed into the clinic.

Utilizing large functional and molecular datasets we will determine critical pathways required for DMG progression and therapy resistance. A combination approach to targeting selected pathways in clinically relevant DMG cell and animal models will inform on potential new therapeutic approaches that can be rapidly translated into clinical trials to improve patient outcomes.

Suitability: PhD/Doctorate, Honours

Defining the mechanisms of chemotherapy resistance in childhood and adolescent osteosarcoma

Keywords: osteosarcoma, chemotherapy, resistance

Project leader: Dr Jason Cain

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Project description: Osteosarcoma is the most prevalent primary malignant tumour of the bone, mainly affecting teenagers and young adults, particularly during growth spurts. Incorporation of neoadjuvant chemotherapy has increased 5-year survival rates from 10% to ~70% for patients with localised disease. However, ~20% of patients present with metastases at diagnosis and a further 25%-50% will develop metastatic disease during their treatment. Despite aggressive multimodal treatments including polychemotherapy (typically methotrexate, doxorubicin and cisplatin [MAP]), surgery, and radiation therapy (where applicable if complete surgical resection is not possible), cure rates for patients with metastatic or relapsed disease are poor, with a 5-year survival rate of <20% and represent a significant clinical challenge. Alarmingly, these survival rates have remained unchanged for decades highlighting the urgent need for improved therapeutic strategies.

Aside from disease at diagnosis, the histological response to induction chemotherapy is the gold standard indicator for patients with osteosarcoma, assessed by percentage of necrotic tissue using the Huvos grading system. However, individual patients' response to induction chemotherapy is variable suggesting inherent resistance and to date there is no reliable way to predict which patients will respond to therapy. Through direct engagement with sarcoma patients and their families, and via the Australian and New Zealand Sarcoma Association (ANZSA) we have identified two major areas of unmet need and consumer-guided priorities: improved therapeutic strategies to reduce toxicities; and more accurate prognostication to guide individual patient clinical management. This project will work to bridge this gap in translation, by better understanding osteosarcoma biology to identify the mechanisms and molecular signatures of patient response to therapy, and therapeutic strategies to improve response, that will ultimately improve patient survival and survivorship.

Using a functional genomics approach in clinically relevant preclinical models and osteosarcoma patient tissues we will determine the genetic, epigenetic and molecular events underpinning chemo resistance, and identify and validate therapeutic opportunities to overcome resistance.

Suitability: PhD/Doctorate, Honours

STAT Cancer Biology

Teaching an old dog new tricks: STAT3 in health and disease

Keywords: JAK-STAT signalling, biochemistry, cancer, mouse models of disease, functional genomics

Project leader: A/Prof Daniel Gough

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Project description: Signal Transducer and Activator of Transcription 3 (STAT3) is required for diverse biological processes in mammals including cell proliferation, cell death, migration, differentiation, immunity and metabolism. The importance of the fundamental role of STAT3 in mammalian biology is illustrated by the fact that complete genetic loss of STAT3 is lethal in utero. Indeed, subtle gain or loss of function mutations in STAT3 lead to cancer and debilitating immune disorders respectively. These observations make STAT3 an ideal drug target, but to date this has not been possible. It is therefore critical to define the mechanism of STAT3 activity to enable specific targeting of this protein in disease contexts. The current text-book definition of JAK-STAT3 signalling is a vast over-simplification and cannot account for its diverse biological effects. In this project you will combine cutting edge biochemistry, functional genomics and animal models of disease to define critical and draggable targets.

Suitability: PhD/Doctorate, Honours

Leveraging the innate immune system to improve lung cancer treatments

Keywords: lung cancer, immunotherapy, treatment

Project leader: A/Prof Daniel Gough

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Project description: Lung cancer is the leading cause of cancer related deaths worldwide. One of the greatest advances in cancer treatment has been the development of immune augmenting therapies that reactivate the anti-tumour T-cell response. However, despite their promise, around 80% of lung cancer patients do not respond or relapse following immunotherapy. What gets lost, or underappreciated in highlighting these approaches however, it the critical role of the innate immune system in the maturation and activity of the adaptive immune system. In this PhD project you will interrogate the potential of targeting the innate immune system to augment current lung cancer treatments. You will take advantage of sophisticated mouse models of cancer, functional genomics, proteomics, molecular biology and biochemistry to identify novel therapeutic strategies.

Suitability: PhD/Doctorate

Functional genomic screening to identify novel approaches to overcome drug resistance in Small Cell Lung Cancer

Keywords: small cell lung cancer, therapy, platinum resistance, functional genomics, screening, mouse models of cancer

Project leader: A/Prof Daniel Gough

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Project description: Small cell lung cancer is an aggressive and highly metastatic disease that represents around 15% of all lung cancer patients. The majority of patients (70%) present in the clinic with advanced disease that has spread beyond the lung. The treatment options available to these patients are limited to platinum-based chemotherapy. This is effective in the majority of patients, however almost all will rapidly relapse with platinum resistant disease. There is no effective second line therapies which has meant these patients have an appalling overall survival rate of 2-5% which has not improved over the past three decades. Therefore there is an urgent and unmet need to understand the mechanisms of platinum resistance and how to overcome it to provide meaningful improvements in patient outcomes. My laboratory has developed panels of platinum resistant small cell lung cancer cell lines and genetically engineered mouse models. In this project we will use CRISPR/Cas9 technology to perform unbiased pooled screening (whole genome or draggable targets) to identify mechanisms of resistance which will be interrogated in vitro and in vivo.

Suitability: PhD/Doctorate

Ovarian Cancer Biomarkers

Please note: *All of Dr Stephens and Dr Bilandzic's projects are FULL and not taking on more students.*

Identifying New Drug Targets in Ovarian Cancer Stem-Like Cells

Keywords: cancer, stem cell, therapeutic, metastasis, ovarian, translation

Project leader: Dr Andrew Stephens

e: andrew.n.stephens@hudson.org.au

Project description: Ovarian cancers are the most lethal of all gynaecological malignancies, with <30% 5-year survival. Cancer progression requires cells to orchestrate a highly co-ordinated program of attachment, migration and invasion into healthy tissues. We have identified that a specialized subset of stem-like cancer cells, termed "Leader Cells", control these processes in ovarian tumours. Leader cells are also enriched by chemotherapy and exert immune suppressive effects in vivo. Existing therapies do not kill or inhibit the leader cell population, resulting in their enrichment over time and ultimately leading to a poor prognosis for patients.

We hypothesize that therapies targeting leader cells will synergize effectively with standard chemotherapy to achieve stable, long-term disease regression.

This project will use a combination of molecular, biochemical and precision medicine approaches to investigate molecular pathways and identify "druggable" targets in ovarian cancer leader cells, and develop therapeutic strategies for translation into clinical practice.

Suitability: PhD/Doctorate, Honours

STATUS | FULL - no longer accepting students

Novel biomarkers for ovarian cancer diagnosis

Keywords: ovarian cancer, biomarker, proteomic

Project leader: Dr Andrew Stephens

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Project description: Diagnosis of ovarian cancers typically occurs too late for treatment to be effective, resulting a very high mortality rate from this disease. The identification of cancer-specific biomarkers to identify early-stage disease is a crucial and unmet clinical need.

We are exploring the use of additional biomarkers to increase the sensitivity and specificity of our recently commercialised ovarian cancer diagnostic (Cleo Diagnostics Ltd). This project will investigate the utility of protein and peptide biomarkers for use in ovarian cancer diagnostic applications.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons)

STATUS | FULL - no longer accepting students

Mechanisms of ovarian cancer metastasis-characterizing molecules expressed during early cancer invasion

Keywords: cancer, ovarian cancer, metastasis

Project leader: Dr Maree Bilandzic

e: maree.bilandzic@hudson.org.au

Project description: We have identified novel molecules expressed during the early events of ovarian cancer invasion to healthy tissue. We hypothesize that these molecules are key to the metastatic process, and by specifically disrupting their expression we will disrupt the invasion process. This work will seeks to develop new therapeutic strategies to block ovarian cancer metastasis and the formation of metastatic nodules.

Suitability: Honours, BMedSc(Hons)

STATUS | FULL - no longer accepting students

Preventing disease recurrence and increasing disease free survival rates for ovarian cancer patients

Keywords: ovarian cancer, cancer, therapies, treatment, real time modelling, 3D culture

Project leader: Dr Maree Bilandzic

e: maree.bilandzic@hudson.org.au

Project description: The majority of ovarian cancer patients are diagnosed with widespread disease on first clinical presentation. The initial response to chemotherapy and surgery is promising, however close to 90% develop recurrent, resistant disease at which point therapeutic options are limited. This project is focused on finding ways to prevent the spread of tumour cells following initial diagnosis and treatment, with the ultimate aim of increasing disease free lifespan and preventing disease recurrence in ovarian cancer patients. The project utilizes novel models of ovarian cancer metastasis to examine the early interactions between cancer cells and healthy tissue. You will investigate key changes that occur at the earliest point of ovarian cancer spread and devise ways to target molecules that drive the spread of ovarian cancer cells to stabilise disease, prevent tumour spread and recurrence.

Suitability: Honours, BMedSc(Hons)

STATUS | FULL - no longer accepting students

Immunohaematology

Epigenetic modifications of the human β-globin locus: new therapeutic targets for haemoglobin disorders

Keywords: epigenetics, RNA interference, CRISPR/Cas9 genome editing

Project leader: Dr Jim Vadolas

e: jim.vadolas@hudson.org.au

Project description: Haemoglobin disorders, such as sickle cell disease and β-thalassaemia are the result of mutations in the adult β-globin gene. When these disorders are co-inherited with hereditary persistence of fetal haemoglobin, (high levels of γ-globin gene expression in adult life) the disease phenotype is much reduced. Understanding the mechanism of γ-globin globin gene regulation through development has been the subject of intense investigation for many years. These studies led to an appreciation of the role of epigenetic modifications such as DNA methylation and histone acetylation in globin gene expression and regulation. Networks of regulatory proteins interact with epigenetic complexes to regulate DNA accessibility and histone modifications, thereby determining appropriate patterns of globin gene expression, giving rise to several developmental stage-specific hemoglobin variants. This study will investigate the potential impact of epigenetic regulators on globin gene expression. Functional genomic screening strategies will be performed using RNA interference (RNAi) or CRISPR/Cas9 genome editing to either suppress or knockout the expression of specific epigenetic regulators in erythroid cells modified to express fluorescent reporter genes under the control of the γ-globin promoter. Further studies will also be conducted in vivo using unique humanised β-thalassaemia mouse models. Positive outcomes of such studies could pave the way for better treatment strategies for sickle cell anaemia and β-thalassaemia patients by targeting epigenetic regulators to increase fetal globin expression.

Suitability: PhD/Doctorate, Masters, Honours

Harnessing RNA interference in gene therapy vectors for β-thalassaemia

Keywords: gene therapy, RNA interference, anaemia

Project leader: Dr Jim Vadolas

e: jim.vadolas@hudson.org.au

Project description: The β-haemoglobin disorders such as β thalassaemia, haemoglobin E (HbE), and sickle cell disease (SCD) are among the most prevalent inherited disorders worldwide. The conditions are the result of mutations in the adult β-globin gene, leading to production of either aberrant or insufficient β-globin protein. Symptoms appear in the first year of life, the period when fetal haemoglobin (HbF) is replaced by the adult form (HbA), leaving the patient dependent upon the mutated adult β-globin gene. Much of the pathology of this disease is due to excess α-globin chains forming toxic insoluble precipitates in erythroid cells resulting in cell death, ineffective erythropoiesis and severe anaemia. Interestingly, restoration of balanced globin protein synthesis through the reduction of α-globin expression can ameliorate the disease phenotype, exemplified by individuals who co-inherit α- and β-thalassaemia. This definitive observation forms the basis of a novel therapeutic strategy for β-thalassaemia, involving not an elimination but a targeted reduction of complementary α-globin chains, to mimic co-inheritance of α- and β thalassaemia. While the benefits of increased β-globin expression in the context of β-thalassaemia are very clear, decreasing α-globin expression has not yet been extensively investigated. This project aims to develop novel gene therapy strategies harnessing RNAi in gene therapy vectors for β-thalassaemia. Initial studies will be conducted in vitro using both cell lines and primary haematopoietic stem cells. Further studies will also be conducted in vivo using our unique humanised β-thalassaemia mouse models and patient-derived cells.

Suitability: PhD/Doctorate, Masters, Honours

Impact of impaired immune function in haemoglobin disorders

Keywords: thalassaemia, chronic anemia, immune response, iron overload

Project leader: Dr Jim Vadolas

e: jim.vadolas@hudson.org.au

Project description: Haemoglobin disorders, such as sickle cell disease and β-thalassaemia are the result of mutations in the adult β-globin gene. Patients suffering with the most severe form of the disease require chronic blood transfusion for survival. Ongoing transfusion therapy to counteract anaemia exacerbates iron overload, and necessitates iron chelation therapy. One important clinical feature of these conditions is the increased frequency of infectious complications such as pneumonia and sepsis, which are significantly associated with an increased rate of morbidity and mortality. The increased susceptibility to pathogenic organisms has been attributed to multiple deficiencies affecting both innate and adaptive immune systems. What has become apparent, is that iron overload in chronically anaemic patients contributes to aberrant neutrophil effector functions resulting in increased susceptibility to infection and inflammation-related organ damage. This knowledge, combined with the emergence of novel immunomodulatory function and phenotypes for neutrophils has helped to re-invigorate interest in the field. To further understand the clinical significance of aberrant immune function in β-thalassaemia, we will undertake a comprehensive evaluation of the molecular and cellular mechanisms responsible for aberrant innate immune effector functions in β-thalassaemic mice and β-thalassaemia patients. The work proposed in this project will generate a better

understanding of the mechanism underlying aberrant immune functions and provide novel insights into disease progression. Positive outcomes of such studies could pave the way for better treatment strategies for β-thalassaemia and related patients.

Suitability: PhD/Doctorate, Masters, Honours

Leukaemia Modelling and Therapeutic Discovery

Genetic modelling of Acute Erythroleukaemia

Keywords: erythroleukaemia, genetics, therapeutics, red blood cells, disease modelling, leukaemia

Project leader: Dr Catherine Carmichael

e: catherine.carmichael@hudson.org.au

Project description: Acute Erythroleukemia (AEL) is an aggressive and poor outcome subtype of AML that is largely resistant to standard treatments. Unlike other more common AML subtypes, very little is known of the genetic lesions that drive erythroid transformation, and there is a scarcity of in vivo genetic models in which to study AEL pathogenesis.

We have recently contributed to the world's first comprehensive genome wide analysis of the genetic lesions that define AEL (Iacobucci I et al, *Nature Genetics*, 2019), and now have the unique opportunity to generate much needed pre-clinical models that faithfully recapitulate the genetic landscape of the human disease.

Utilising novel genetic models of AEL, this project aims to study the molecular mechanisms driving transformation of the red blood cell lineage. Briefly, CRISPR/Cas9 gene editing approaches will be employed in both mouse and human cells to generate in vitro and in vivo models of AEL that faithfully recapitulate the underlying genetics identified in human AEL patients. Large scale genomic studies will be performed using these models to identify key mechanisms of erythroid transformation and AEL development. Finally, putative drug targets will be identified and tested in these model systems, with the ultimate aim of identifying novel therapeutic approaches for this very poor outcome malignancy.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons)

Therapeutic targeting of EMT modulators in cancer

Keywords: Epithelial to Mesenchymal Transition (EMT), leukaemia, tumour development, cancer metastasis, therapeutic targeting

Project leader: Dr Catherine Carmichael

e: catherine.carmichael@hudson.org.au

Project description: The epithelial-mesenchymal transition (EMT) is a key developmental process that plays an important role during epithelial tumour development and pathogenesis. Activation of EMT in tumour cells contributes to the development of the migratory and invasive phenotype required for effective tumour cell metastasis. Furthermore, expression of EMT modulators has also been linked to the acquisition of cancer stem cell properties and enhanced therapeutic resistance in epithelial tumour cells. Intriguingly, we and others have more recently discovered that altered expression of EMT modulators, such as members of the SNAIL and ZEB families, also plays a role in the development and pathogenesis of haematological malignancies. Broadly targeting EMT processes therefore, is an attractive alternative therapeutic approach for both epithelial and haematopoietic tumours.

In this project, we will screen therapeutic compounds that putatively target regulators of EMT for their ability to inhibit malignant EMT processes, and negatively impact survival and migration capabilities of cancer cells – both epithelial and haematopoietic.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons)

Modelling childhood leukaemia for the development of new and improved therapeutic approaches

Keywords: leukemia, hematology, cancer, blood, childhood cancer

Project leader: Dr Catherine Carmichael

e: catherine.carmichael@hudson.org.au

Project description: Leukaemia accounts for ~30% of all childhood cancers and ~20% of childhood cancer deaths, representing the most common pediatric cancer type and the second highest cause of cancer related death in children. Childhood leukaemia typically presents as either Acute Lymphoblastic Leukaemia (ALL) (80%) or Acute Myeloid Leukaemia (AML) (20%). Significant advances in disease understanding, enhanced prognostic classification and the use of intensive multi-agent chemotherapy in childhood ALL has led to superior 5-year survival rates of >90%. Survival rates in pediatric AML, however, remain significantly lower at only 60-70%, with nearly half of all children experiencing therapeutic refractory disease or relapse. Treatment options for relapsed or refractory AML are limited, with invasive bone marrow transplantation often the only possibility for cure.

The successful candidate will work within the Victorian Pediatric Cancer Consortium (VPCC) (https://vicpcc.org.au) to generate pre-clinical models of pediatric AML that faithfully recapitulate the human disease. These models will then be used to gain a deep understanding of the common mechanisms driving AML development in children, and identify novel therapeutically targetable functional

dependencies in AML cells. Using the knowledge gained from this project, we aim to identify and develop new treatment approaches for childhood AML with reduced toxicity, enhanced efficacy and increased likelihood of long term remission and cure.

Suitability: PhD/Doctorate, Masters, Honours, BMedSc(Hons)

Structural Biology of Inflammation and Cancer

Deciphering the molecular mechanism of the SRSF3 OncomiR-1 Complex in Colorectal Cancer

Keywords: cancer, biochemistry, structural biology

Project leader: Dr Wilson Wong

e: wilson.wong@hudson.org.au

Project description: This project will investigate the role and mechanism of the micro-RNA processing complex (SRSF3 OncomiR-1) in colorectal cancer. Experiemntal approaches will include biochemical, biophysical and structural biology methods to understand how SRSF3 interacts with Drosha and DGCR8 to process the OncomiR-1 RNA substrate. The outcome of this project will provide insights into how SRSF3-OncomiR1 complex contribute to the progression of colorectal cancer.

Suitability: PhD/Doctorate, Master, Honours

HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR ENDOCRINOLOGY AND METABOLISM

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Centre Head

Professor Peter Fuller

The complex endocrine system impacts all aspects of health and disease. As Australia's pre-eminent centre for endocrinology, the Centre for Endocrinology and Metabolism at Hudson Institute of Medical Research undertakes basic and clinical research.

The Centre's goal is to improve the understanding of the role of hormones in human biology and disease to tackle key health challenges facing Australian and global communities, including reproductive health, bone health and cancer metastasis, cardiovascular disease, endocrine cancer and hormone actions, and sex development.

Clinical translation of these findings to improve diagnosis, therapeutic intervention and prevention of disease remains a key focus for the Centre, enabled by the co-location of researchers with clinicians, state-of-the-art technologies and a clinical trials centre.

Research Group Leaders

Clinical Andrology >
Professor Robert McLachlan AM
MBBS PhD FRACP

Endocrine Hypertension >
Associate Professor Jun Yang
MBBS PhD FRACP

Hormone Cancer Therapeutics >
Associate Professor Simon Chu
PhD

Metabolic Bone Research >
Associate Professor Frances Milat
MBBS PhD FRACP

Sex Development >
Professor Vincent Harley
PhD

Steroid Receptor Biology >
Professor Peter Fuller AM
MBBS PhD FRACP

Endocrine Hypertension

Evaluating barriers to the detection of primary aldosteronism

Keywords: primary aldosteronism, hypertension, endocrine hypertension, aldosterone, diagnostic barriers, diagnostic inertia

Project leaders: Associate Professor Jun Yang, Professor Grant Russell

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Project description: Despite growing evidence for the high prevalence of primary aldosteronism in people with hypertension, it remains under-diagnosed. However, it is not clear why clinicians do not screen for this condition. Through surveys and interviews, we will identify the barriers and enablers which can inform the design of interventions to increase the timely detection of primary aldosteronism.

Suitability: Masters by Research, PhD

Evaluation of the cost-effectiveness of different strategies for the diagnosis and management of primary aldosteronism

Keywords: primary aldosteronism, cost-effectiveness, hypertension, endocrine hypertension, aldosterone, health economics

Project leaders: Associate Professor Jun Yang, Associate Professor Gang Chen

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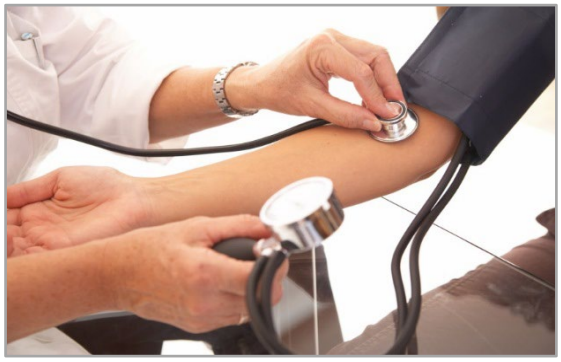
Project description: Primary aldosteronism (PA) is the most common, and a potentially curable, cause of hypertension, estimated to affect 5-10% of all hypertensive patients. It leads to greater cardiovascular injury than hypertension alone. Studies have demonstrated the cost-effectiveness of screening patients with resistant hypertension for PA, but there are no economic modelling studies of screening newly diagnosed hypertensive patients. An early diagnosis is likely to be less complicated for a patient than long-standing disease, and offer greater benefit in reducing cardiovascular risk. Furthermore, there may be strategies to reduce the number of diagnostic tests required prior to the



treatment of PA for these patients. However, without a formal cost analysis, hypertension diagnostic guidelines will remain locked in the past to the detriment of our community. This project will use the cost-utility analysis (CUA) approach to estimate the incremental costs and effectiveness of using various strategies to screen, diagnose and subtype PA. The within-trial analysis will be extrapolated using a Markov model to capture the long-term cost of the various strategies. The estimates of the effect on long-run health outcomes, quality of life and costs (such as cost savings of cardiovascular events averted) will be made from a comprehensive literature review.

Suitability: Masters by Research, PhD

Identification of novel transcriptomic markers of primary aldosteronism

Keywords: primary aldosteronism, biomarker, hypertension, endocrine hypertension, aldosterone

Project leaders: Associate Professor Jun Yang, Professor Peter Fuller

Email: jun.yang@hudson.org.au

Project description: Whilst dichotomous thresholds are currently used to diagnose primary aldosteronism (PA), emerging data support the concept of a continuum of aldosterone excess. A robust cellular marker of aldosterone excess that correlates strongly with clinical outcomes following mineralocorticoid receptor (MR) antagonist treatment or adrenalectomy will complement the aldosterone-renin ratio (ARR) and confirmatory tests in the diagnostic algorithm for PA. As peripheral blood monocytes highly express the MR, they represent an accessible MR-responsive tissue to study aldosterone-induced changes in gene transcription. A number of genes identified by previous students will be characterised *in vitro* using

RT-PCR and cell culture to confirm a change in their expression in response to MR activation or antagonism. These may then be validated in larger patient cohorts as robust biomarkers of aldosterone excess and inappropriate MR activation.

Suitability: Honours, BMedSci, Masters by Research, PhD

Impact of ethnicity on the prevalence and aetiology of hypertension

Keywords: primary aldosteronism, hypertension, endocrine hypertension, ethnicity

Project leaders: Associate Professor Jun Yang, Dr StellaMay Gwini

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Project description: Ethnic differences exist in the pathogenesis, prevalence and complications of hypertension. There is a body of work on the high prevalence of low-renin hypertension in African people, primarily described in Africa and America. What is the prevalence of hypertension in African people living in Australia? What proportion have an identifiable secondary cause for their hypertension, and should their treatment be personalised to reflect the aetiology? Apart from the ethnic difference in blood pressure described in the African population, there is little information about other ethnic groups. The multicultural composition of Australian society will allow us to examine the prevalence and aetiology of hypertension in ethnically diverse groups.

Suitability: Masters by Research, PhD

Exploring endocrine hypertension in Indigenous populations

Keywords: primary aldosteronism, hypertension, endocrine hypertension, Aboriginal patients, Indigenous health

Project leader: Associate Professor Jun Yang, Professor Gurmeet Singh

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Project description: Aboriginal patients experience a disproportionate burden of cardiovascular disease, with hypertension being a key modifiable risk factor. The prevalence of primary aldosteronism, the most common and potentially curable secondary cause of hypertension in non-Indigenous populations, has never been explored in Indigenous populations. We will engage with Indigenous communities to gauge their attitude towards hypertension diagnosis and treatment, and seek their input in exploring primary aldosteronism in their communities.

Suitability: Masters by Research, PhD

Resistant hypertension in primary care – how many patients have primary aldosteronism?

Keywords: primary aldosteronism, hypertension, endocrine hypertension, resistant hypertension, primary care

Project leaders: Associate Professor Jun Yang, Professor Grant Russell

Email: jun.yang@hudson.org.au

Project description: Resistant hypertension is estimated to affect approximately 25% of hypertensive patients on treatment. Screening for a secondary cause such as primary aldosteronism is strongly indicated. However, are patients actually being screened in primary care? If we systematically test for primary aldosteronism in this population, what proportion will be found to have the condition? We will work with research-focussed primary care clinics and general practitioners to co-design a strategy to screen these patients for a potentially curable cause of hypertension.

Suitability: Masters by Research, PhD

Hormone Cancer Therapeutics

Molecular pathogenesis of granulosa cell tumours of the ovary

Keywords: cancer, ovarian cancer, granulosa cell tumour, therapeutics, signalling pathways, transcription factors, nuclear receptors, estrogen

Project leaders: Associate Professor Simon Chu, Professor Peter Fuller

Email: simon.chu@hudson.org.au

Project description: Granulosa cell tumours (GCT) of the ovary are endocrine tumours that both make and respond to hormones. We have recently confirmed a key mutation in the *FOXL2* gene in >90% of adult GCT. We have also found that 40% of GCT contain a mutation in the telomerase gene, *TERT*. Our group seeks to understand the molecular events that lead to the development of advanced and/or aggressive tumours for which there is an 80% mortality. Current studies seek to establish the genomic landscape of these tumours using whole exome sequencing with transcriptomic and microRNA analyses. Other studies explore the role of genes that we have identified as being overexpressed in advanced disease, including *TERT*, with a view to developing novel therapeutic strategies.

Suitability: Honours, Masters by Research, PhD

Role of XIAP in normal ovarian folliculogenesis

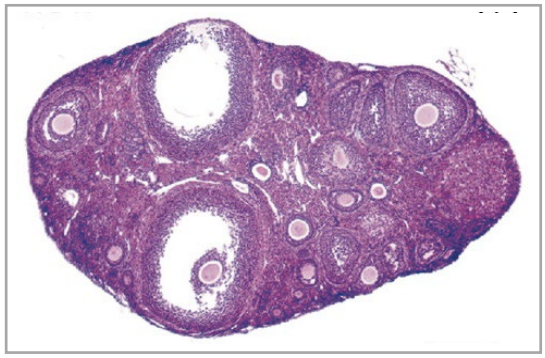
Keywords: ovary, folliculogenesis, ovarian function, apoptosis, XIAP

Project leaders: Associate Professor Simon Chu, Professor Peter Fuller, Professor John Silke

Email: simon.chu@hudson.org.au

Project description: The X-linked inhibitor of apoptosis (XIAP) is a member of the inhibitor of apoptosis (IAP) superfamily, which are endogenous caspase inhibitors that act as anti-apoptotic factors. The expression pattern of XIAP in the ovary suggests it is a critical regulator of follicular atresia. Using single and double *IAP* knockout mice, this project aims to understand the role of XIAP in normal folliculogenesis. This study will involve histological analyses of ovaries at different stages of development and gene expression studies to characterise the ovarian phenotype. We expect these studies will yield novel data regarding ovarian function.

Suitability: Honours, Masters by Research, PhD



Role of XIAP in endocrine cancer (ovarian and thyroid)

Keywords: cancer, ovarian cancer, thyroid cancer, granulosa cell tumour, therapeutics, signalling pathways, transcription factors, nuclear receptors, estrogen, XIAP, apoptosis

Project leaders: Associate Professor Simon Chu, Professor Peter Fuller, Dr Michael Mond

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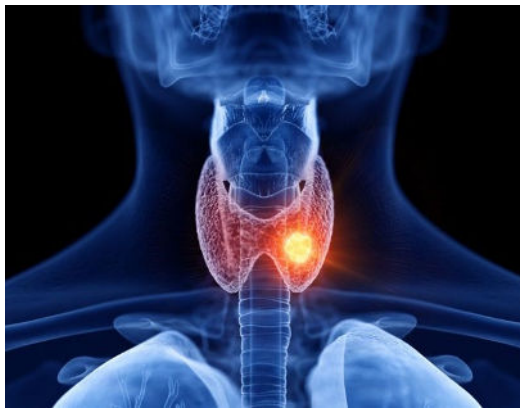
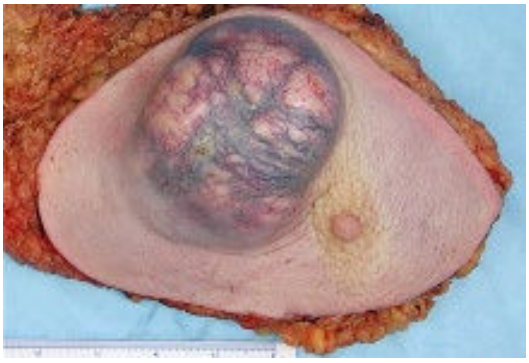
Project description: The X-linked inhibitor of apoptosis (XIAP) is a member of a family of endogenous caspase inhibitors that act as antiapoptotic factors. XIAP is the most potent caspase inhibitor, blocking both intrinsic and extrinsic apoptotic signals through direct caspase binding. Due to its prominent ability to control cell death and its elevated expression in human cancers, XIAP has become an attractive therapeutic target for novel anti-cancer treatment. XIAP has an important role in both ovarian and thyroid cancer. Small-molecule inhibitors are in various stages of development, from preclinical to phase II clinical trials. This



project will explore the efficacy of inhibiting XIAP in combination with targeting a key nuclear receptor in both cancers using unique *in vitro* systems with innovative technology and novel therapeutic compounds, with the ultimate goal of providing an essential pre-clinical, proof-of-concept approach for translation to the clinic.

Suitability: Honours, Masters by Research, PhD



Metabolic Bone Research

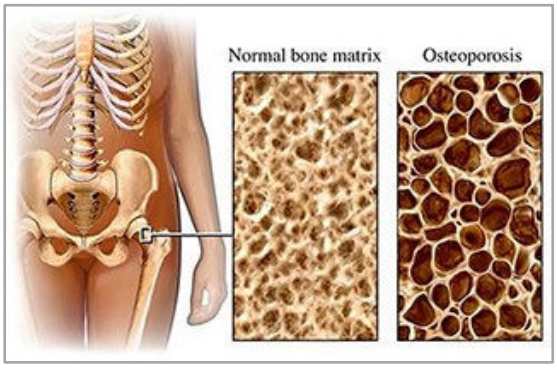
Osteoporosis and metabolic bone disorders

Project leader: Associate Professor Frances Milat

Email: fran.milat@hudson.org.au

Project description: We are currently involved in a variety of projects aimed at improving health outcomes in patients with metabolic bone disorders and osteoporosis. These projects include the optimisation of bone health in adults with neurological disability, understanding osteoporosis in haemoglobinopathies, the evaluation and management of bone disorders in chronic kidney disease, and the management of bone health in premature ovarian insufficiency. Projects are available in all of these areas.

Suitability: BMedSc, PhD



Sex Development

Characterisation of novel gonadal targets of *Sox9*

Keywords: sex determination, *Sox9*, intersex, molecular genetics, sex differences

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: For the majority of intersex cases, the underlying genetic aetiology is unknown. In males, *Sox9* is a critical 'hub' gene involved in sexual development. We hypothesise that *Sox9*'s downstream targets are also essential for gonadal development and are causative variants in intersex patients. By extensive data mining of gonadal microarrays, RNAseq, and *Sox9* ChIPseq, we have identified genes directly regulated by *Sox9*. These candidate genes are up-regulated in XY mouse testes compared to XX ovaries during development and down-regulated in sex-reversed XY ovaries ablated for *Sox9*. We will perform detailed expression profiling in XX and XY embryonic gonads of wild-type mice during the critical sex determination period of E11.5-E13.5, postnatally and at adult stages. We will also perform *Sox9* ChIPseq on gonads and promoter/enhancer analyses, and screen DSD patients towards validation.

Suitability: Honours, Masters by Research, PhD

ATR-X syndrome and gonadal development

Keywords: sex determination, ATRX syndrome, human genetics, intersex

Project leader: Professor Vincent Harley

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Project description: The ATR-X syndrome, an X-linked recessive developmental disorder affecting males, belongs to a growing list of intersex conditions which affect 1% of all

newborns. Clinical features include mental retardation, alpha-thalassemia, and skeletal and genital abnormalities. The focus of our work is to investigate the role of *ATRX* in gonadal development.

Suitability: Honours, Masters by Research, PhD

Identifying the genes responsible for intersex conditions

Keywords: sex determination, genes, human genetics, intersex

Project leader: Professor Vincent Harley

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Project description: Intersex is a term used to describe a variety of congenital conditions where gonadal or anatomical sex is atypical. Intersex conditions encompass a wide range of abnormalities, including hypospadias (abnormal urinary opening in males), gonadal dysgenesis (underdeveloped or imperfectly formed gonads), ambiguous genitalia, and sex reversal (i.e. XX males and XY females). Our aim is to identify genes causing intersex conditions, and the molecular mechanisms underlying testis and ovary formation in the mammalian embryo. This proposal will provide new insights into the molecular control of testis development, and thus offer the potential to improve diagnosis and clinical management of intersex conditions. Approaches include human genetics, as well as molecular, cell and developmental biology. See: Leon NY, Reyes AP and Harley VR (2019) A clinical algorithm to diagnose differences of sex development. *Lancet Diabetes Endocrinol* 7:560-574 or visit the website for the NHMRC research program on intersex conditions: http://dsdgenetics.org/.

Suitability: Honours, PhD

FGF9 signalling and sex reversal

Keywords: *FGFR2/Fgfr2*, sex determination, sex reversal, intersex, mouse models

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: We have identified the first *FGFR2* mutation in an XY female intersex patient. A heterozygous FGFR2c-C342S mutation in a patient with both 46,XY gonadal dysgenesis and Crouzon syndrome, is unusual since gonadal defects have not yet been reported in Crouzon syndrome patients. We now focus on FGF9, the ligand of FGFR2c. We have identified 3 *Fgf9* missense variants affecting sex determination in knock-in mouse models. Analyses of male and female markers will be carried out, as well as markers of FGF signalling. Training includes basic cell and molecular biology as well as: embryonic microdissection, whole mount/section *in situ* hybridisation and immunofluorescence. See: Bagheri-Fam S et al (2015) *FGFR2* mutation in 46,XY sex reversal with craniosynostosis. *Hum Mol Genet* 24:6699-6710.

Suitability: Honours, Masters by Research, PhD

The biological basis of gender identity

Keywords: gender identity, gene associations, sex hormones

Project leader: Professor Vincent Harley

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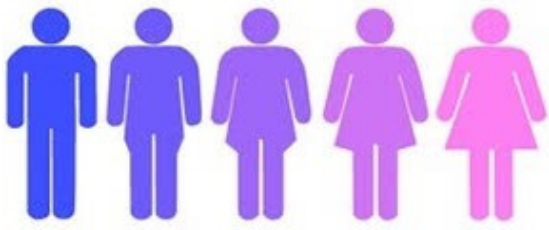
Project description: Gender identity is the gender with which a person identifies. Studies suggest that gender identity is affected by genetic, prenatal hormonal and/or postnatal social determinants. We are investigating the role of genes in people who experience gender incongruence/gender dysphoria. This project involves undertaking a genome-wide association study (GWAS) in the world's largest cohort of transgender women. We have previously identified several gene variants associated with gender dysphoria in transgender women. See: Foreman M et al (2018) A genetic link between gender incongruence and sex hormone signalling. *J Clin Endocrinol Metab* 104:390-396.

Suitability: Honours, PhD



SRY: A risk factor for Parkinson's disease in males

Keywords: Parkinson's disease, brain differences, sex differences, *SRY*

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: Parkinson's disease (PD) is a debilitating neurodegenerative disorder, triggered by the death of dopamine neurons in the brain region known as the substantia nigra. Whilst the mechanisms underlying dopamine cell loss in PD are unclear, it is clear that males are more susceptible to PD than females. We have identified that the male sex-determining gene *SRY* directs a novel genetic mechanism of dopamine cell death in males. Understanding when and how *SRY* increases the vulnerability of male dopamine neurons to injury will help to explain why males are more susceptible to PD and to identify *SRY* as a novel target for neuroprotective therapy in male PD patients.

Suitability: Honours, Masters by Research, PhD

Role of estrogen receptor beta in gonadal development and Parkinson's disease

Keywords: Parkinson's disease, sex reversal, testis, ERβ

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: We have identified a sex-reversed XY female patient with early onset Parkinson's disease (PD). Through whole exome sequencing, it was discovered that this patient harbours a missense mutation in the estrogen receptor beta (ERβ) gene, *ESR2*. Due to estrogen's important functions in both sex determination and in neuroprotection, it is suggested that this mutation might have a function in both aspects of this patient's unusual phenotype. This project will investigate the function of the ERβ variant in *in vitro* models of Parkinson's disease and gonadal development.

Suitability: Honours, Masters by Research, PhD

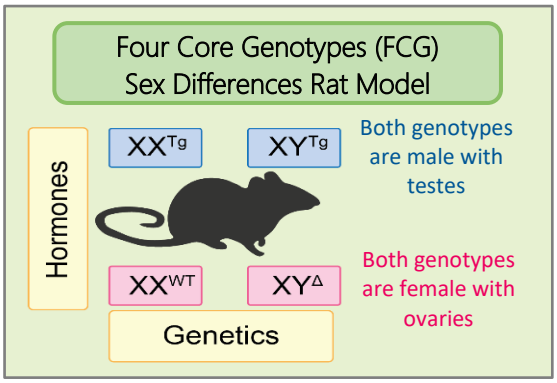
Sex differences in common diseases and drug responses

Keywords: Parkinson's disease, autism, sex differences, animal models, therapeutics
Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: Many diseases show sex differences in incidence, progression or age of onset. Furthermore, treatment of diseases differs between the sexes, with females showing 50-75% more adverse reactions to common medications than males. Despite this, outcomes from research studies are often applied to women based on experimental evidence from men. We have developed a model that determines the basis of sex differences, whether hormonal and/or chromosomal. The so-called 'Four Core Genotypes' (FCG) rat model can be applied to any disease that shows a sex difference in prevalence, severity, susceptibility, or drug efficacy. In collaboration, we will apply this model to several common diseases affecting the developing and ageing brain, including Parkinson's disease and autism, as well as novel therapeutics we have identified to treat these diseases.

Suitability: Honours, Masters by Research, PhD



Investigating the robustness of claims of sex differences in disease

Keywords: sex differences, data analysis, R software, meta-analysis, literature review

Project leaders: Professor Vincent Harley, Dr Shanie Landen

Email: vincent.harley@hudson.org.au

Project description: There are sex differences in the prevalence, onset, and severity of most complex traits and diseases. However, biomedical research has often studied only males or not considered potential sex differences, limiting the rigour and reproducibility of scientific inquiry. In 2016,

the US National Institutes of Health mandated that sex be considered in biomedical research. As such, research including both sexes and accounting for sex differences has increased in recent years. However, studies claiming sex differences in the genetic aetiology of disease, as well as in other disease aspects, are often riddled with poor statistical methodology and study design.

We are interested in assessing claims of sex differences in the literature, specifically, whether sex differences in disease (whether genetic, drug response, or gene regulational) are being appropriately claimed. The last paper of which we are aware that provided this consensus, published in 2007, found that the majority of claims of sex differences in the genetics of disease are not significant when appropriate statistical methods are used.

This project aims to evaluate the literature on sex differences in disease, attributed to genetics, gene regulation or drug response, and whether current claims are methodologically robust. This project will include accessing databases and analysing available data with appropriate statistical methodology using R software. Experience in bioinformatics is preferred but not essential.

Suitability: Honours, Masters by Research, PhD

How are male and female brains different?

Keywords: SRY, brain differences, sex differences

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: Male and female brains differ in anatomy and chemistry. The prevailing dogma that estrogen is the key factor involved in brain sex differentiation was challenged by our discovery of a direct role in the brain for the Y chromosome gene, *SRY*, in the control of voluntary movement, only in males.

This project seeks to identify the target genes that the SRY transcription factor controls in the brain. Approaches include cell and molecular biology techniques (RNAseq, ChIPseq) and rodent dissection of the substantia nigra.

Suitability: Honours, Masters by Research, PhD

Steroid Receptor Biology

Structure-function relationships of the mineralocorticoid receptor

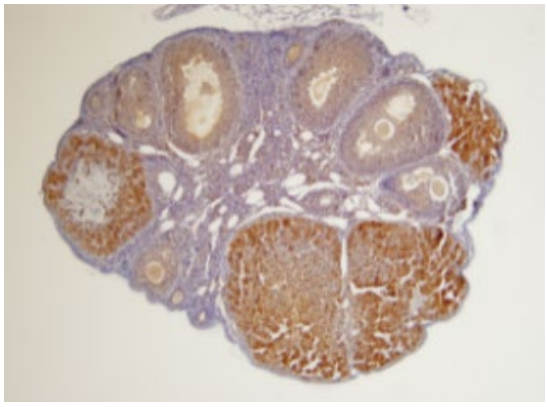
Keywords: aldosterone, mineralocorticoid, receptor, adrenal

Project leader: Professor Peter Fuller

Email: peter.fuller@hudson.org.au

Project description: The mineralocorticoid receptor (MR) is an important therapeutic target in hypertension, cardiovascular disease and mental health. We have identified interactions of the receptor that differ between the physiological hormone ligands, aldosterone, cortisol and progesterone. We also have access to novel therapeutic agents in development. Understanding these interactions and their structural basis will lead to the development of new therapeutic agents. The studies involve the use of transactivation assays, structural analysis, mutation detection, comparative biology and a series of unique transgenic mouse models in which the MR gene has been either mutated or knocked-out. This work is also associated with our clinical program.

Suitability: Honours, Masters by Research, PhD



Mineralocorticoid receptor regulation of gene expression in reproductive tissue

Keywords: mineralocorticoid, mammary tissue, knockout

Project leaders: Professor Peter Fuller, Associate Professor Simon Chu

Email: peter.fuller@hudson.org.au

Project description: The mineralocorticoid receptor (MR) is best known for its involvement in the regulation of salt and water balance. However, non-classical tissues have been identified as expressing MR, giving rise to the hypothesis that the MR also plays a regulatory role in these tissues. We have identified a number of genes that are directly regulated by the MR and are seeking to understand their mechanism of regulation in mammary and ovarian tissue *in vitro* and *in vivo*. The role of this receptor in breast and breast cancer is emerging as a potentially important story, given that MR involvement appears to be linked to differentiation and apoptosis during mammary tissue development. In granulosa cell and breast cancer cell lines, we will manipulate the MR to evaluate the signalling mechanisms involved. Insights gained from these studies may lead to the development of new therapeutic agents for breast cancer treatment and infertility.

Suitability: Honours, Masters by Research, PhD

HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR INNATE IMMUNITY AND INFECTIOUS DISEASES

Centre for Innate Immunity and Infectious Diseases

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Centre Head: Prof Brendan Jenkins

At the Centre for Innate Immunity and Infectious Diseases (CiiiD) we discover and model how the innate immune response regulates disease. We translate our findings into practical outcomes that impact on our health.

The immune response is important in every disease you'll study as a scientist or doctor. A successful early, innate immune response can resolve infectious diseases and eliminate cancer. A poorly regulated immune response causes chronic inflammatory diseases, with multi-organ impact. We:

- Are world-leaders in research on the innate, or first, immune response
- Perform high quality discovery research using the latest technologies
- Translate our research into preventions, diagnostics and treatments
- Publish in the world's top impact journals

CiiiD houses the largest group of inflammation researchers in Australia, bringing in approx. $8M in grant funding per annum and publishing approx. 300 peer-reviewed publications in the past five years, including works in prestigious journals such as *Nat Rev Cancer, Nat Rev Immunol, Nat Rev Biotechnol, Gut, Gastroenterol, Nat Commun, EMBO Mol Med, PNAS USA* and *Clin Cancer Res*.

CiiiD values its students. We offer world-class training in biomedical research and carefully help students find appropriate projects and supervisors. Students receive one-on-one training and mentoring in practical and theoretical aspects and career development.

Staff and students working in CiiiD have collective multidisciplinary expertise in molecular biology, signal transduction, protein interactions, cell biology, immunology, cancer, bacteriology, infectious disease, functional genomics and bioinformatics, as well as clinical research and transgenic techniques for generating and characterising gene knockout and transgenic mouse preclinical models of human disease.

CiiiD students are first authors on scientific papers in prestigious journals

Students were first authors on 37 of Hudson Institute's 257 research publications in 2022. Some examples from our Centre are:

- Sean M Solari, Remy B Young, Vanessa R Marcelino, Samuel C Forster, expam—high-resolution analysis of metagenomes using distance trees, Bioinformatics, Volume 38, Issue 20, 15 October 2022, Pages 4814–4816, https://doi.org/10.1093/bioinformatics/btac591
- Ullah, T. R., Balka, K. R., Ambrose, R. L., Pépin, G., Wilce, M. C. J., Wilce, J. A., Thomas, B. J., De Nardo, D., Williams, B. R. G., & Gantier, M. P. (2022). Genistein Targets STING-Driven Antiviral Responses. MBio, 13(4), e0206422. https://doi.org/10.1128/mbio.02064-22
- Dawson RE, Deswaerte V, West AC, Tang K, West AJ, Balic JJ, Gearing LJ, Saad MI, Yu L, Wu Y, Bhathal PS, Kumar B, Chakrabarti JT, Zavros Y, Oshima H, Klinman DM, Oshima M, Tan P, Jenkins BJ.STAT3-mediated upregulation of the AIM2 DNA sensor links innate immunity with cell migration to promote epithelial tumourigenesis. Gut. 2022 Aug;71(8):1515-1531. doi: 10.1136/gutjnl-2020-323916
- Saad MI, Weng T, Lundy J, Gearing LJ, West AC, Harpur CM, Alanazi M, Hodges C, Croagh D, Kumar B, Sagi I, Rose-John S, Jenkins BJ.Blockade of the protease ADAM17 ameliorates experimental pancreatitis.Natl Acad Sci U S A. 2022 Oct 18;119(42):e2213744119. doi: 10.1073/pnas.2213744119

CiiiD students win prestigious prizes and awards

- Winner Faculty of Medicine, Nursing and Health Sciences '3 Minute Thesis' Competition – Zoe Marks
- Milstein Travel Award for the International Cytokine and Interferon Society – Mohamed Saad
- Travel grant from the Science Mobilisation Program of the Embassy of France in Australia – Kimberley D'Costa
- Winner, PhD Student Prize, Victorian Infection and Immunity Network Young Investigator Symposium – Charlotte Nejad

What we study

Infectious diseases (influenza, HIV, *Helicobacter pylori*, diarrhoeal diseases, Legionnaire's disease, *Shigella*, Respiratory syncytial virus and others)

Cancer (stomach, lung, pancreas, ovary, breast and others)

Inflammatory diseases (inflammatory bowel disease, sepsis, lupus, gastritis, diabetes, COPD)

Research Groups Heads

Cancer and Immune Signalling >
Professor Brendan Jenkins
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Cell Death and Inflammatory Signalling >
Associate Professor Kate Lawlor
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Gastrointestinal Infection and Inflammation >
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Host-Pathogen Interactions >
Associate Professor Jaclyn Pearson

Innate Immune Responses to Infection >
Professor Elizabeth Hartland
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Microbiota and Systems Biology >
Associate Professor Sam Forster
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Pattern Recognition Receptors and Inflammation >
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Nucleic Acids and Innate Immunity >
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Regulation of Interferon and Innate Signalling >
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Structural Biology of Inflammation and Cancer Research >
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Viral Immunity and Immunopathology >
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Cancer and Immune Signalling

Identification of immune system regulators as therapeutic targets in lung cancer

Keywords: cancer, lung cancer, ADAM proteases, innate immunity, pattern recognition receptors, cytokines, signal transduction

Project leader: Prof Brendan Jenkins

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Project description: The cytokine Interleukin-6 (IL-6) has been implicated as a causative factor in lung cancer, the most lethal cancer worldwide, albeit by unknown mechanisms. Since IL-6 is also important for immune system homeostasis, the development of anti-IL-6 therapies requires an intimate knowledge of pathological versus physiological IL-6 signalling pathways. To address this, we are studying the role of the ADAM family of proteases as key upstream oncogenic regulators of pathological IL-6 signalling in the lung. This project aims for the first time to fully elucidate the mechanistic basis by which ADAM family proteases can influence lung carcinogenesis, and in doing so also identify how they potentially impact on innate immune responses triggered by pattern recognition receptors. This project employs a combination of in vivo lung cancer mouse models (genetically engineered, xenograft - including patient-derived), CRISPR gene editing and clinical biopsies to foster translation, as well as a vast range of molecular and cellular biological techniques.

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Identification of novel immune regulators in stomach (gastric) cancer

Keywords: cancer, gastric carcinogenesis, pattern recognition receptors, cytokines, signal transduction, innate immunity

Project leader: Prof Brendan Jenkins

e: brendan.jenkins@hudson.org.au

Project description: Stomach (gastric) cancer is among the most common cancers worldwide, and is strongly linked with a deregulated immune response, leading to chronic inflammation. However, the identity of regulators of the immune system, in particular those of innate immunity, with oncogenic potential in the stomach remains largely unknown. Using preclinical genetically engineered and xenograft mouse models for gastric cancer, our aim is to identify and understand how novel immune regulators (e.g. pattern recognition receptors, inflammasomes, cytokine signal transducers such as STAT3) in the stomach trigger chronic inflammatory and oncogenic responses that lead to gastric cancer. This project encompasses a wide range of molecular and cell biological and genetic approaches (including CRISPR/Cas9).

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Precision medicine for innate immune pattern recognition receptors in pancreatic cancer

Keywords: cancer, pancreatic cancer, innate immunity, patient samples, mouse models, translational studies, biomarkers

Project leader: Prof Brendan Jenkins

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Project description: Pattern recognition receptors (PRRs) are key molecules of the innate immune system that recognise microbial- and/or host-derived products to trigger the inflammatory response. Recently, however, we and others have identified that PRRs, such as toll-like receptors (TLRs) can be involved in non-immune responses, such as driving tumour cell survival and proliferation. In this regard, this project aims to understand the molecular basis by which specific PRRs promote pancreatic cancer, which is one of the most lethal and aggressive cancers in the world that is strongly linked with a dysregulated immune response (albeit ill defined). This research is intimately linked with the use of preclinical genetically engineered and xenograft (including patient-derived) mouse models, as well as translational studies using our large collection of biobanked pancreatic cancer patient samples. Such research will ultimately assist in identifying genes that could be used as biomarkers for screening/early detection of pancreatic cancer, and also targets for the design of therapeutic treatment strategies in the context of precision medicine/targeted therapy.

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Cell Death and Inflammatory Signalling

Defining regulators of cell death and inflammasome activation

Keywords: Cell death, Inflammasomes, Innate immunity, infection, type I IFN, signal transduction

Project leader: Dr Kate Lawlor

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Project description: Pattern recognition receptors, including Toll-like receptors (TLRs) and NOD-like receptors (NLRs) are key components of the innate immune response. They sense microbial, host derived and environmental danger molecules, and induce inflammatory signalling responses, via inflammasomes and other molecular complexes. We recently defined how deficiency in the cell death inhibitory protein XIAP sensitises innate immune cells to TLR-induced NLRP3 inflammasome activation (Lawlor KE et al. Nature Comms 2015, Lawlor KE* et al. Cell Reports 2017). The aim of this project is to further define molecules, like XIAP, that regulate this alternative inflammasome pathway. This project offers the opportunity to be trained in a variety of techniques, including cell culture, Western blotting/immunoprecipitation, proteomics, overexpression/CRISPR Cas9 gene editing, flow cytometry, ELISA and qPCR.

Suitability: PhD/Doctorate, Honours

Identifying mitochondrial factors that activate inflammatory signalling

Keywords: Cell death, Cell signalling pathways, Inflammasomes, Innate immunity, Cancer

Project leader: Dr Kate Lawlor

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Project description: Mitochondrial ("intrinsic" BCL-2 family regulated) apoptosis has long been thought to be immunologically silent. However, using small molecule inhibitors of pro-survival BCL-2 family members, we have recently discovered that mitochondrial apoptosis can induce a cascade of events that culminate in activation of the NOD-like receptor 3 (NLRP3) inflammasome and pro-inflammatory cytokine, IL-1beta (Cell Reports 2018). In this project we will further characterise this pathway and test whether its activation alters cancer progression in vivo. This project will use our novel gene knockout macrophages and specific targeted drugs, plus a range of cell biology, biochemical and molecular approaches (e.g. inflammasome/cell death assays, ELISA, Western blotting, CRISPR Cas9 gene editing screens, proteomics).

Suitability: PhD/Doctorate, Honours

Mitochondrial apoptosis and inflammasome activation

Keywords: Cell death, Cell signalling pathways, Inflammasomes, Innate immunity, Infectious Diseases

Project leader: Dr Kate Lawlor

e: kate.lawlor@hudson.org.au

Project description: Macrophages are innate immune cells that detect environmental, pathogen or host cellular danger molecules, and initiate appropriate immune responses. We have recently discovered that targeting pro-survival proteins BCL-XL and MCL-1 in macrophages induces apoptosis to clear microbial infection (Speir M et al. Nature Microbiology 2016) and also triggers inflammation via activation of the NOD-like receptor 3 (NLRP3) inflammasome and Interleukin-1beta (Cell Reports 2018). This project aims to define novel regulators of this pathway and investigate how these proteins alter pathogen clearance. This project will use our novel gene knockout macrophages and specific targeted drugs, as well as a range of cell biology and biochemical/molecular approaches (e.g. inflammasome/cell death assays, ELISA, Western blotting, Q-PDR, over-expression systems, CRISPR Cas9 gene editing, infectious preclinical models).

Suitability: Honours, PhD/Doctorate

Role of pore forming proteins in Type 2 Diabetes

Keywords: Type 2 Diabetes, Inflammation, IL-1, inflammasomes, immunometabolism, Gasdermins

Project leaders: Dr Kate Lawlor, Dr Hazel Tye

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Project description: Dietary danger molecules, such as the saturated fatty acid palmitate, trigger the activation of the pro-inflammatory cytokine, interleukin-1β (IL-1β), via NLRP3 inflammasome activation. Based on our past work (Lawlor KE Nature Commun 2015 6:282) we recently discovered that extrinsic apoptotic caspase-8 activity in myeloid cells may drive this pathogenic NLRP3 inflammasome activation in a model of Type 2 Diabetes. Gasdermins (GSDMs) are a family of membrane pore-forming proteins that have recently been defined as proteolytic caspase substrates that induce a lytic form of cell death called pyroptosis. Specifically, inflammasome-associated caspase-1 and apoptotic caspase-8 have been shown to cleave GSDMD (Kayagaki N Nature 2015 526:666; Orning P Science 2018 362:1064), and apoptotic effector caspase-3 cleaves GSDME (Wang Y Nature 2017 547:99) to allow the release of inflammatory damage associated molecular patterns (DAMPS). The aim of this project is to define, using our GSDMD-, GSDME- and GSDMD/E-deficient mice, whether GSDM-dependent pyroptotic cell death contributes to NLRP3 inflammasome activation and/or DAMP release to worsen obesity-induced Type 2 Diabetes. This project offers the opportunity to be trained in a variety of techniques,

including cell culture, Western blotting, inflammasome/cell death assays, ELISA, qPCR, tissue analysis-histology, flow cytometry, serum/liver/adipose metabolic assays, Type 2 diabetes preclinical models.

Suitability: PhD/Doctorate

Gastrointestinal Infection and Inflammation

Defining the immunomodulatory and oncogenic properties of bacterial extracellular vesicles

Keywords: Innate immunity, infection, extracellular vesicles, exosomes

Project leaders: Prof Richard Ferrero, Dr Caroline Skene

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Project description: The release of extracellular vesicles (EVs) is a property that has been conserved by both multi- and unicellular organisms during evolution. One of the major functions of these EVs is to facilitate intercellular communication and transport of molecules. The release of EVs by prokaryotes was first described over 50 years ago, yet the biological significance of these structures is only beginning to be appreciated. We have shown that bacterial EVs are potent modulators of host immune responses. The overall aim of the project is to investigate the immunomodulatory and oncogenic properties of bacterial-derived EVs. For this, we will use cell culture and mouse models to elucidate EV interactions with host cells and to characterise the responses induced by these EVs. This project will involve a variety of techniques, including cell culture, mouse models, proteomics, molecular biology, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.

Suitability: Honours

Defining the role of a novel NLR protein in B cell lymphomagenesis associated with chronic *Helicobacter* infection

Keywords: Innate immunity, infection, signal transduction, gastric disease, cancer, MALT lymphoma

Project leaders: Prof Richard Ferrero, Dr Dongmei Tong

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Project description: Our laboratory has for the first time identified a new NOD-like receptor (NLR) protein in the regulation of inflammation in response to chronic *Helicobacter pylori* infection. Specifically, we have shown that conditional knockout mice lacking this NLR exhibit an accelerated formation of gastric B cell mucosa-associated lymphoid tissue (MALT), consistent with the early stages of MALT lymphoma, in response to chronic *Helicobacter* infection. The overall aims of the project are to investigate how this novel NLR prevents B cell lymphomagenesis induced by chronic infection and whether this protein may play much broader functions in the host immune system. These questions will be addressed in both in vitro and in vivo models, including conditional knockout mice. The project will involve various techniques, such as primary cell culture, mouse infection, immunohistochemistry, flow cytometry, cytokine ELISA and qPCR.

Suitability: Honours

The role of the innate immune system in preventing stomach cancer during chronic *Helicobacter pylori* infection

Keywords: innate immunity, infection, signal transduction, gastric disease, cancer

Project leaders: Prof Richard Ferrero, Dr Dongmei Tong

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Project description: During cell division, bacteria remodel their cell walls, resulting in the release of low molecular weight fragments of peptidoglycan, known as muropeptides. The muropeptides from Gram-negative bacteria are recognised by host cells via the actions of the innate immune molecule, NOD1, resulting in the induction of a pro-inflammatory signalling cascade. Preliminary data suggest that *Helicobacter pylori* exploits the NOD1 signalling pathway to maintain tissue homeostasis during chronic infection. This project will test the hypothesis that *H. pylori* can alter its muropeptide composition to actively engage the NOD1 pathway thereby preventing pre-cancerous changes in the stomach and thus favouring its survival in vivo. This project will involve a variety of techniques, including primary cell culture, mouse infection, histology, cytokine ELISA and qPCR.

Suitability: Honours

Host-Pathogen Interactions

Host cell death signalling and susceptibility to *Salmonella* infection

Keywords: Bacterial pathogenesis, necroptosis, cell death signalling, innate immunity.

Project leader: Dr Jaclyn Pearson

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Project description: Enteric bacterial pathogens such as *Salmonella* spp. and enteropathogenic *E. coli* deliver "effector" proteins directly into host cells via specialised secretion systems which exert specific enzymatic activity on host proteins to subvert host responses and prolong infection. Our recent work characterised an effector protein from pathogenic *E. coli* as a cysteine protease that cleaves and inactivates all mammalian RIP homotypic interaction motif (RHIM) proteins including RIPK1, RIPK3, TRIF and DAI. RHIM proteins are key immune signalling factors that mediate inflammation, apoptosis and necroptosis. Dysregulated immune responses and cell death form the basis of much human disease pathogenesis. This study aims to understand the role of RHIM proteins in controlling *Salmonella* and other enteric infections. Research methods will include: cell culture, mouse infection model, molecular biology, protein purification, bacteriology, confocal microscopy, western blot, mass spectrometry.

Suitability: Honours, BMedSci (Hons), PhD

Regulation of TNF signalling in *Salmonella* infection

Keywords: Innate immunity, bacterial pathogenesis, host-pathogen interaction, cell signalling pathways

Project leader: Dr Jaclyn Pearson, Dr Kate Lawlor

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Project description: The regulation of host immune and cell death signalling is central to the pathogenesis of many human diseases. We have recently gained some exciting new preliminary data that suggests *Salmonella enterica* serovar Typhimurium induces the degradation of host proteins that regulate tumour necrosis factor receptor (TNFR1) signalling, thus regulate cell death and innate immune responses. This project aims to understand how the bacterium, *Salmonella* mediates degradation of these critical immune signalling factors and what the implications are for pathogen survival within the host and disease outcomes for the host. Research methods include: molecular biology, protein purification, bacteriology, cell culture, confocal microscopy, western blot, potential mouse experimental work.
Suitability: Honours, PhD

Understanding the biochemical mechanisms of *Salmonella* virulence proteins

Keywords: Bacterial pathogenesis, *Salmonella,* type III effector proteins, innate immunity, cell signalling pathways.

Project leader: Dr Jaclyn Pearson, Prof Elizabeth Hartland

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Project description: Pathogenic serovars of *Salmonella* are the causative agents of a spectrum of disease states, including typhoid fever, self-limiting gastroenteritis, and invasive bacteremia. Australia has one of the highest incidences of Salmonellosis in the developed world. Pathogenesis is dependent on the activity of two distinct type III secretion systems (T3SS), encoded by genetic regions termed Salmonella pathogenicity islands (SPI). The SPI-1 T3SS is associated with bacterial invasion as well as activation of innate immune signalling, and the SPI-2 T3SS is associated with intracellular survival in immune and epithelial cells, replication and systemic infection. While the importance of the SPI-1 T3SS to *Salmonella* pathogenesis is well established, the function of many SPI-2 encoded effectors remains unknown. This project aims to investigate the role of a subset of relatively uncharacterised SPI-2 effectors in *Salmonella* virulence. Overall this project will provide critical insights into the pathogenic mechanisms of an important public health issue and provide the basis for potential future therapeutic development. Research methods will include: molecular biology, protein purification, bacteriology, cell culture, confocal microscopy, western blot, mass spectrometry, protein-protein interactions.

Suitability: Honours, BMedSci (Hons), Short projects, PhD/Doctorate

Understanding the molecular basis of virulence in invasive *Salmonella* lineages

Keywords: Salmonellosis, food borne, invasive bacteria, inflammation, molecular biology, genomics, epidemiology.

Project leader: Dr Jaclyn Pearson

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Project description: Pathogenic enteric bacteria often occupy distinct ecological niches, and have evolved specific genomic characteristics that enable host and environmental adaptation, with resulting changes in virulence (manifested by clinical disease severity) and transmissibility. For example, *Salmonella* is an example of a genus in which there is a genomic signature for either a gastrointestinal or an extra-intestinal lifestyle, whereby functions required for promoting growth in the gastrointestinal tract are lost when the lineage becomes invasive. This project aims

to integrate epidemiological, genomic and molecular microbiological data to understand the host and pathogen factors that result in invasive salmonellosis. This information will inform our understanding of the evolutionary pressures that lead to the emergence of highly adapted clones that persist in the food chain. Using a combination of molecular genetics, cell biology approaches and established infection models, we will test the role of these evolving factors in the initiation of infection and progression of disease. Research methods include: bacteriology, bacterial genomics, cell culture, molecular biology, protein purification, confocal microscopy, western blot, potential mouse infection model.

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons), Short projects

Identifying novel biomarkers of paediatric inflammatory bowel disease

Keywords: Inflammatory Bowel Disease, cell death, microbiome, inflammation

Project leader: Dr Jaclyn Pearson, Dr Edward Giles,

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Project description: Inflammatory bowel disease (IBD) is an incurable lifelong disease for one in 200 Australians, including more than 10,000 children, that causes severe inflammation of the gut. It's often so severe that sufferers need to be hospitalised and may require surgery.

Currently IBD is kept under control using drugs that suppress the immune system, but these become less effective over time and can have significant side effects, leaving patients with an increased risk of colorectal cancer. The ongoing and chronic nature of IBD impacts a young patient's emotional, physical and social wellbeing, causing severe embarrassment and disruption to their education, employment and relationships. Overall, a better understanding of the true causes of IBD are needed to develop new and more effective treatments.

We have strong evidence that disruptions in 'programmed cell death' in the gut plays a major role in the development of IBD. In collaboration with paediatric gastroenterologist, Edward Giles, we aim to specifically identify these cellular disruptions in a cohort of 200 young IBD patients from the IBD clinic at the Monash Medical Centre in Melbourne. This study will be providing a new and specific target for IBD treatments that we hope will be more effective with less side effects.

Suitability: PhD/Doctorate, Honours

Innate Immune Responses to Infection

Intracellular bacterial pathogens and cell intrinsic immunity

Keywords: microbiology, *Legionella*, *Burkholderia*, innate immunity, cell biology

Project leader: Prof Elizabeth Hartland

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Project description: Many bacterial pathogens have acquired the capacity to replicate inside human cells by avoiding cell intrinsic innate immune pathways. Pathogens such as *Legionella* and *Burkholderia* are environmental organisms that cause the life-threatening opportunistic infections known as Legionnaire's Disease and Melioidosis respectively. A feature of both pathogens is the capacity of the bacteria to replicate within human cells through the manipulation of host cell biology. This depends on the ability of the pathogens to inject multiple virulence effector proteins into the host cell during infection. Our goal is to identify and characterize effectors that interact with cell intrinsic innate immune pathways. Bacterial effectors function in diverse ways and some perform unique functions not normally observed in mammalian cells. Ultimately this will allow us to understand the molecular mechanisms by which intracellular bacteria cause disease. The techniques utilised in this project may include bacteriology, cell culture, cloning, qPCR, western blotting, confocal microscopy, flow cytometry and mouse models.

Suitability: PhD/Doctorate, Masters by Research, Honours

Translocated effector proteins of intestinal bacterial pathogens

Keywords: microbiology, inflammation, cellular biology, innate immunity, bacterial diseases

Project leader: Prof Elizabeth Hartland

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Project description: The subversion of host cell processes by microbial pathogens is an intrinsic part of the host-pathogen interaction. Many bacterial pathogens have the ability to transport virulence proteins, termed effector proteins, into host cells via specialized protein secretion systems. We work on a range of effectors from pathogenic *E. coli*, *Shigella* and *Salmonella* that interfere with host innate immune signalling pathways and block inflammation and cell death. The aim of this work is to investigate the manipulation of host cell signalling by effector protein families to understand their influence on host cell function, inflammatory signalling and the innate immune response. The techniques utilised in this project may include bacteriology, cell culture, cloning, qPCR, western blotting, confocal microscopy.

Suitability: PhD/Doctorate, Masters by Research, Honours

Innate immune responses to the human microbiota

Keywords: microbiome, innate immunity, commensal bacteria, intestinal microbiota, mucosal immune responses

Project leader: Prof Elizabeth Hartland

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Project description: The study of host-pathogen interactions has significantly advanced our understanding of bacterial virulence, infection and the host immune response. However, until recently these studies have largely ignored the role of the resident microbiome. Although the commensal microbiome is known to provide some protection against infection by mucosal pathogens, we know little about the interactions between pathogens, the specific elements of the microbiome and the innate immune response at mucosal surfaces. Classical bacterial pathogens have evolved specific virulence factors to compete with resident commensals as well as subvert host immune responses. In addition, many bacterial infections are treated with antibiotics causing further disruption to the microbiome. To understand how the mucosa and microbiome communities respond to disruption by pathogen infection and antibiotic treatment, we will use an iPSC-derived tissue system and defined human microbiome communities to map the mechanisms underlying infection resistance, tissue repair and ongoing inflammation, as well as identify potentially protective human microbiome communities and isolates. The techniques utilised in this project may include bacteriology, stem cell and organoid cell culture, qPCR, western blotting and confocal microscopy.

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Microbiota and Systems Biology

Characterization of microbiota composition in paediatric inflammatory bowel disease

Keywords: microbiota, microbiome, paediatric, inflammatory bowel disease, microbiology, IBD, UC, ulcerative colitis

Project leaders: Assoc Prof Sam Forster, Dr Ed Giles, Dr Michelle Chonwerawong

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Project description: The gastrointestinal microbiota, mediated by complex interactions between the patient's immune system and environment, is now associated with diseases as diverse as infections, inflammatory bowel diseases and cancers. Paediatric Inflammatory bowel disease (PIBD) is a chronic incurable condition, affecting children and teenagers, that is increasing in incidence. Changes in the microbiota reflect the development of IBD and are a potential target for therapy or even cure. We have used our unique technology to establish key patient cohorts and large experimental datasets and discovered novel live biotherapeutic candidates licensed to Biomebank Australia through this work. This project combines our expertise in the culturing and phenotypic analysis of the human gastrointestinal microbiota to discover and characterize the bacterial community present in IBD, specifically ulcerative colitis and Crohn's disease patients. This project represents a close collaboration between clinical and experimental elements with sample collection, world-leading in-vitro culturing, bacterial whole genome sequencing, phylogenetic analysis and metagenomic sequencing. It will focus on further sample collection and analysis of these unique datasets with the capacity to focus the project from clinical sampling to analysis and experimental validation in cell-based model systems. Students interested in experimental or computational biology are encouraged to contact us regarding this project.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons), Masters by Research

Developing methods to disrupt the microbiome for improved therapeutic efficacy

Keywords: computational biology, bioinformatics, metagenomics, microbiota, machine learning, statistics, genomics, phylogeny, ecology, microbiome

Project leaders: Assoc Sam Forster

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Project description: For over 100 years the need to understand specific disease causing bacterial isolates to treat disease has been clearly understood. Importantly, combining genomics and traditional microbiology, it is now clear that different bacterial lineages and even individual isolates may induce vastly different disease outcomes for patients. While these principles are well established for pathogenic organisms it is now evident that the vast majority of bacterial species with which we are associated likely provide beneficial functions. Similar strain and isolate level understanding are limited by our ability to identify, classify and investigate these species. In the human gastrointestinal tract alone, there are 100 trillion bacteria, representing more than 500 species, that are intimately associated with our daily lives. Leveraging our extensive collection of genome sequenced isolates we have developed new methods for high resolution, whole genome shotgun metagenomics sequencing for detailed analysis of host/disease/microbiome relationships. This project is focused on understanding community stability within the human gastrointestinal microbiome and how this may be modified for therapeutic benefit. This project can be undertaken as a pure computational biology or hybrid experimental and computational project. Please contact Assoc Prof Sam Forster (sam.forster@hudson.org.au) for further information on this project.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

Modulating gastrointestinal microbiota stimulation of the innate immune system

Keywords: innate immune response, gastrointestinal microbiota, immunology, microbiology, bioinformatics, genomics, microbiome, metagenomics, microbiota

Project leader: Assoc Prof Sam Forster, Dr Michelle Chonwerawong

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Project description: The innate immune system is capable of intricately detailed detection, differentiation and elimination of pathogenic bacteria. However, the vast majority of bacteria encountered by our innate immune system are beneficial to health. Indeed, over 500 species of these commensal bacteria, containing approximately 10,000-fold more

genes than the human genome exist in the human gastrointestinal tract alone. Emerging research is demonstrating the importance of these bacterial communities in maintaining health and causing or exacerbating disease. We recently developed novel methods to grow the vast majority of bacteria from the gastrointestinal microbiota resulting in the discovery of hundreds of novel species which require further investigation. Combined with the established experimental and computational expertise in the analysis of innate immune signalling pathways, this project will include cutting edge microbial culturing techniques, cell culture assays and advanced computational analysis to identify pro- and anti-inflammatory bacterial species. Please contact Assoc Prof Sam Forster (sam.forster@hudson.org.au) or Dr Michelle Chonwerawong (michelle.chonwerawong@hudson.org.au) for more information.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

Phenotypic characterisation of antimicrobial resistance in the Gastrointestinal Microbiota

Keywords: antibiotic resistance, microbiota, phenotypic, microbiology, molecular biology, genomics, bioinformatics

Project leader: Assoc Prof Sam Forster, Dr Emily Gulliver

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Project description: Antimicrobial resistance (AMR) is emerging at an alarming level, rendering some bacterial infections untreatable and increasing dependence on last line antibiotics. There is an urgent need to provide clinicians with the data to inform antibiotic selection that will optimise treatment success, while minimizing the spread of resistance and dispersal of antibiotic resistance genes. Despite the bacterial diversity within our microbiota, current understandings of the genetic factors that confer resistance are almost exclusively limited to pathogenic or opportunistic organisms. For example, in the human gastrointestinal tract, there are 100 trillion bacteria, representing more than 500 species, which are exposed to antibiotic selection during oral antibiotic treatment. The resistance mechanisms in these commensal bacteria remain largely undefined, despite representing a significant, hidden source of antibiotic resistance genes that could be transferred to pathogenic or other commensal bacterial species. We have recently developed methods to culture the vast majority of the human gastrointestinal microbiota providing an important resource to undertake these studies. This project will combine detailed genomic sequence analysis with microbiology techniques to understand and monitor the diversity and distribution of antibiotic resistance within the human gastrointestinal microbiota. The opportunity also exists to focus the project to experimental or computational biology. The Centre for Innate Immunity and Infectious Diseases is a world leader in infection and inflammation with a strong record of student training and development. Please feel free to contact Assoc Prof Sam Forster (sam.forster@hudson.org.au) or Dr Emily Gulliver (emily.gulliver@hudson.org.au) for further information.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

Nucleic Acids and Innate Immunity

Creating a new generation of adjuvants for vaccine and cancer immunotherapy

Keywords: innate immunity, adjuvants, immune responses, cancer immunotherapy

Project leader: Dr Michael Gantier

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Project description: Our laboratory has recently discovered that select Toll like receptor agonists could be modified to present novel adjuvant properties - with broad implications in vaccine development and cancer treatments. This project will advance our knowledge of the therapeutic applications of our discovery using cutting edge disease models to study immune responses - with a combination of in vitro and in vivo experiments. It has the potential to revolutionise adjuvants (for instance leading to less frequent vaccinations in children), and reignite immune responses against cancer cells within the tumour microenvironment. Importantly, the successful candidate is guaranteed to publish peer-reviewed works related to their studies upon joining our laboratory (with a possible Thesis by publication stream for PhD students).

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Targeting auto-immune sensing of DNA damage

Keywords: innate immunity, inflammation, lupus

Project leader: Dr Michael Gantier

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Project description: We and others have recently discovered that DNA damage can promote inflammation through recruitment of the cGAS-STING pathway (Pepin et al., Nucleic Acids Research 2016 and 2017). In this project we propose to investigate new classes of cGAS and STING inhibitors that have the potential to help curb auto-immune sensing of DNA for instance seen in Cutaneous Lupus Erythematosus.

The successful candidate will gain cutting edge practical knowledge in molecular, cellular and animal biology, working on a project with a strong translational angle.

Suitability: PhD/Doctorate, Masters by Research, Honours

Making better mRNA therapeutics

Keywords: mRNA vaccines, mRNA therapeutics, innate immunity

Project leader: Dr Michael Gantier

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Project description: Despite the huge success of the Pfizer-BioNTech and Moderna mRNA vaccines in the SARS-CoV-2 pandemic, unwanted inflammation due to activation of innate immune sensors remains a major challenge in the manufacture and implementation of mRNA therapeutics.
Our team has recently discovered that select short, synthetic RNA molecules are strong inhibitors of the nucleic acid sensors (TLR3, 7, 9 and cGAS) (Valentin 2021 Nucl. Acids Res.). This project will investigate how our discoveries can be applied to improve the immunogenicity and production of mRNA therapeutics such as mRNA vaccines. This exciting work has the potential to directly impact how mRNA therapeutics are made. Importantly, the successful candidate is guaranteed to publish peer-reviewed works related to their studies upon joining our laboratory (with a possible Thesis by publication stream for PhD students).

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSci (Hons)

Pattern Recognition Receptors and Inflammation

Innate immune immunometabolism: the intersection between metabolism and immunology

Keywords: innate immunity, inflammation toll-like receptors, pattern recognition receptors, cell biology, mitochondria, metabolism

Project leader: A/Prof Ashley Mansell

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Project description: Recent discoveries have positioned mitochondrial reprogramming by Toll-like receptors (TLRs), at the centre of innate immune inflammation. Immunometabolism describes the interplay between immunological and metabolic processes which are not only critical to the immediate innate immune response to infection, but also the new paradigm of innate memory or training, the concept that myeloid lineage cells can respond more strongly to future challenge via epigenetic reprogramming. We have discovered a role for STAT3 in immunometabolism and how this regulates inflammatory gene induction, mitochondrial health, and metabolism. This project offers the opportunity to explore the molecular dynamics and mechanisms of TLR-induced mitochondrial metabolism, and the temporal influence on transcriptional and epigenetic remodelling using advanced genetic sequencing and metabolomic approaches, in conjunction with novel mouse models of dysfunctional STAT3 signalling and inflammatory disease.

Suitability: Honours, PhD

Developing therapies to treat inflammasome-mediated inflammation and disease

Keywords: innate immunity, inflammation, inflammasomes, drug development

Project leader: A/Prof Ashley Mansell

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Project description: Inflammasomes are implicated and associated with nearly every major disease afflicting mankind: cancer; infections, cardiovascular, neurodegenerative and metabolic diseases. There is considerable interest therefore in developing novel therapies to target inflammasome-mediated inflammation. We, and our industrial partner have developed a family of novel multi-NLRP inflammasome inhibitors. This project offers the opportunity to characterise and evaluate the efficacy of these inhibitors in in vivo models of disease, cellular immunological assays and biochemical mechanism of action assays. These projects also offer the opportunity for the biopharma experience of drug development and potential clinical application/trials.

Suitability: Honours, PhD

Regulation of Interferon and Innate Signalling

Characterisation of a novel cytokine in mucosal immune responses to infections

Keywords: women's health, reproductive / sexual health, innate immunity, infectious diseases

Project leaders: Dr Eveline de Geus, Prof Paul Hertzog

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Project description: We have discovered a new cytokine exclusively expressed in the female reproductive tract, which is essential for the optimal response to Sexually Transmitted Infections such as Herpes Simplex Virus (HSV) and Chlamydia and possibly HIV. It is unique for several reasons: unlike conventional cytokines, IFN epsilon (IFNe) is constitutively expressed, especially in the female reproductive tract, is not regulated by pathogens, but is regulated by hormones. This work was recently published in the prestigious journal, Science. 2013 Mar 1;339(6123):1088-92. Current projects involve our unique repertoire of reagents including gene knockout mouse models of the female reproductive tract, as well as recombinant cytokines, antibodies, clinical patient cohorts and primary cell cultures for an ongoing study program that includes the following specific areas to characterise the mechanisms whereby this new cytokine regulates the immune response:

- Molecular Biology – determining the mechanism of regulation of IFNe gene expression,
- Biochemistry – characterising the mechanism of IFNe interaction with receptors and activation of novel signalling pathways,
- Immunology – determining how and which immune cells are regulated in the FRT mucosa during infections and other disease,
- Infectious Diseases (clinical and animal models) – determining whether hormonal regulation of IFNe makes women more susceptible to infection at certain times with pathogens such as HIV, HSV and Chlamydia, and
- Cancer Biology and immunology – characterising the role of IFNe in the development and progression of uterine and ovarian cancer progression of uterine and ovarian cancer.

Suitability: Honours, PhD

Systems biology of innate immune signalling

Keywords: signal transduction, innate immunity, bioinformatics, microRNAs, infectious diseases

Project leader: Prof Paul Hertzog, Dr Jamie Gearing, Dr Sam Forster

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Project description: This project studies the complex regulation of cell signalling in the innate immune response to infection and inflammation. This is performed at the genome, transcriptome, proteome and sometimes metabolome level. The objective is to understand how this immune response is balanced to achieve a protective response, rather than a disease-causing inappropriate response. The systems biology team use a combination of computational and "wet lab" approaches to discover regulatory factors, networks and molecular control pathways involved in disease pathogenesis. In order to help analyse the pathways and how they are integrated, we have a computational biology group working on the generation of methods and databases (e.g. INTERFEROME), whereby we can integrate our data with all published information on this topic. We are developing tools to predict pathways and regulatory networks, including transcription factor binding sites in gene promoters. Specific projects include:

- Analysis of innate immune or inflammatory "signatures" in disease (infections, inflammation, autoimmunity, cancer)
- Discovery of novel signalling pathways by computational predictions and practical experimentation
- Transcriptional regulation of gene expression
- Post-transcriptional regulation of gene expression
- Whole transcriptome (RNA-seq) analysis and integration of interferon signalling across multiple datasets

Suitability: Honours, PhD

Structure-function studies of interferon signalling

Keywords: structural biology, biochemistry, protein chemistry, signal transduction, imaging

Project leaders: Dr Nicole De Weerd, Dr San Lim, Prof Paul Hertzog

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Project description: The type I interferons (IFNs) are important in regulating host defence against cancer infectious and inflammatory disease. However, if signalling occurs at an inappropriate time, place, duration or strength it is extremely toxic or even

lethal. Therefore, it is essential to understand how positive and negative signals are controlled and balanced. This process begins at the cell surface of the responding cell when the IFNs interact with two receptor components that ultimately transmit a signal into the cell. We use structural biology, biochemistry and sophisticated imaging to examine this process. Importantly we also correlate results from these studies with sophisticated systems biology assessments of signalling, biological responses in cells and model systems, ultimately in clinical studies in humans.

Suitability: Honours, PhD, Short projects

Investigation of a novel cytokine in female reproductive tract infections

Keywords: women's health, reproductive / sexual health, immunology, innate immunity, infectious diseases.

Project leader: Prof Paul Hertzog

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Project description: We have discovered a new cytokine, interferon epsilon (IFNe) that is exclusively expressed in the female reproductive tract, which is essential for the optimal response to Sexually Transmitted Infections such as Herpes Simplex Virus and Chlamydia and possibly HIV. IFNe is expressed most abundantly by epithelial cells in the female reproductive tract. Epithelial cells that are the first line of defence against infections and not only provide a protective physical barrier against infections but they also have direct antigen presenting and anti-microbial functions to restrict and block infections with commensals and pathogens. The aim of this project is to understand for the first time the role of IFNe in the modulation of epithelial cell functions in the female reproductive tract. Techniques to be used include in vitro infection studies, primary cell culture and cell line culture, cell proliferations and migration assays, co-culture studies, real-time PCR, cytokine quantification assays.

Suitability: Honours, PhD

Essential virus sensors: investigating RNA receptors in infection

Keywords: virus, infection, innate immunity, RNA, nucleic acid sensors, signalling

Project leaders: Dr Natalia Sampaio, Prof Paul Hertzog

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Project description: The innate immune system is the body's first line of defence against infection, and is necessary for our survival. Our cells have evolved specialized mechanisms for sensing viral infection to kickstart an immune response. Sensors of aberrant nucleic acids play a key role in detection of viruses. Among these, receptors that bind double-stranded RNA, such as MDA5, PKR and OASs can detect a wide array of viruses, including SARS-CoV-2, West Nile virus, and Zika. However, the activation and regulation of these receptor signalling pathways are poorly understood. This project will investigate these receptors in the context of important human pathogens, such as in respiratory infections and mosquito-borne viruses, to gain biologically relevant insight into their role in protection from disease. There will be opportunity to apply cutting-edge methods, including next-generation sequencing, iCLIP (Individual-nucleotide resolution UV crosslinking and immunoprecipitation), CRISPR/Cas9 gene editing, and iPSC (induced pluripotent stem cells).

Suitability: PhD, Honours, BMedSci (Hons), Short projects

Interferon-epsilon: a novel interferon in endometrial function

Keywords: female reproductive tract, FRT, interferon, endometrium, endometriosis.

Project leaders: Dr Fiona Cousins, Prof Paul Hertzog

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Project description: In the female reproductive tract (FRT), homeostasis is maintained to enable embryo implantation and development in parallel with priming of the immune system, which protects against localised infection. Interferon epsilon (IFNε) is a new protein of the Type I Interferon family that are important in the protection of the body from infections. Our group have shown that IFNε is most abundantly expressed in the FRT, in the endometrium, where it has an important role in protection against sexually transmitted infections. However, it is not well understood how IFNε protects the FRT from infections or what endometrial and immune factors regulate its expression. We do know that the levels of IFNε are constantly changing during the menstrual cycle, during which the endometrium is undergoing cycles of breakdown and regeneration. Importantly, factors in menstrual fluid have been shown to influence the repair of the endometrium following menses and we hypothesise that these factors also regulate IFNε expression. Endometrial epithelial cell lines will be treated with menstrual fluid or patient matched peripheral blood plasma and the impact of these fluids in IFNε gene expression determined. Similarly, supernatants from treated cell cultures will be examined for secretion of interferon-epsilon. Cell lines will be treated with IFNε at the same time as treatment with the above fluids to determine how IFNε affects the immune response induced by these fluids. Finally, expression of IFNε within immediately pre-menstrual, menstrual and repair phase human endometrium will be determined.

Suitability: PhD/Doctorate, Masters by research

Transition to adult care in paediatric inflammatory bowel disease

Keywords: inflammatory bowel disease, transition, paediatrics

Project leader: Dr Edward Giles

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Project description: Inflammatory Bowel Disease is an incurable disease that affects approximately 1 in 200 young Australians, with increasing incidence worldwide. Up to 25% of patients are diagnosed <20 years of age, many in the paediatric services. Transition to adult care is a complex and high-risk time for all patients with chronic diseases, and IBD is no exception. Monash has recently established a dedicated young adult IBD clinic under Dr Ed Giles. This unique service in Australia is based on limited overseas models, however the evidence for the success of such clinics remains limited. This project would involve a combined approach of assessing the outcome of the establishment of this service through audit and prospective evaluation of patient outcomes, as well as patient satisfaction data. Please do not hesitate to contact me should you wish further information or preliminary data for this project.

Suitability: Masters, Honours, BMedSci (Hons), Short projects

Mucosal Immunology in Paediatric Inflammatory Bowel Disease

Keywords: paediatric, IBD, immunology, interferon

Project leader: Dr Edward Giles

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Project description: This project involves the translation of findings from mouse models of inflammatory bowel disease (IBD) to human patients, both with IBD and healthy controls. This project explores novel targets for treatment in IBD, as well as exploring possible causes for IBD. By focusing on paediatric patients, we aim to better understand the development of the mucosal immune system and its relationship with the microbiota in early life, and how this can be disrupted in IBD. Currently there are two mouse models of colitis (IBD) with significant results supporting important new pathways for disease in IBD. The project (s) will therefore focus on identifying the importance of these pathways in human patient samples. This project will involve the handling of human samples (ethics already approved and some samples stored), and the use of such techniques as immunohistochemistry, flow cytometry and quantitative real-time PCR, as well as novel microbiome culturing and analysis. The lab has a strong record of training and supporting students regardless of previous laboratory experience.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

A novel protein regulator of host-bacterial interactions in the gut in health and disease

Keywords: interferon, microbiota, IBD, colitis, gastroenteritis, mucosal immunology

Project leaders: Dr Edward Giles, Dr Eveline de Geus

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Project description: The healthy intestine maintains a homeostatic equilibrium between epithelial integrity, a resident immune system and a symbiotic microbiome. Intestinal infections temporarily disrupt this balance, and inflammatory bowel disease (IBD) can be defined as permanent disruption of this homeostasis. Enteric infections are a significant cause of childhood mortality worldwide, and remain a major cause of GP and hospital presentations in Australia. IBD affects 1/200 young Australians, with increasing worldwide incidence. IBD is a life-long disease that often presents in childhood. Treatments are expensive, have serious side effects and lose efficacy over time. There is an urgent need for new therapies for IBD that are effective without systemic immunosuppression.
Type I interferons (T1IFN) are a family of cytokines with a single receptor and pleiotropic functions. Constitutive T1IFN is critical in maintaining intestinal homeostasis and limiting inflammation after infection or injury. We have recently identified IFNε, a novel T1IFN, in mouse and human intestinal epithelium. We propose it plays a crucial role in regulating intestinal immune responses to the microbiome. We have compelling preliminary data to support this idea, as IFNε was protective in a mouse model of IBD and limited an in vitro infection model. Other T1IFNs have been used in both IBD patients and models of infection with conflicting results about their protective effects.

We now hypothesise that IFNε, expressed in the human intestinal epithelium, is an important regulator of responses to the microbiome. To move these findings from murine models to the clinic, we have recently developed a creative technique to simultaneously analyse both host immune responses from patient intestinal biopsies and the bacteria from the same sample. This allows concurrent host-microbiome analysis to tease apart their interactions. From our paediatric (P)IBD cohort (n=150), we have shown a dysregulated T1IFN response in IBD. By using cutting edge bioinformatic analysis of this extremely large dataset (>3000 bacterial isolates), we have identified a candidate Lactobacillus species associated with this T1IFN response. From this same cohort we have grown small intestinal organoids (mini-guts). These will allow us to analyse ex vivo epithelial-microbe interactions in health and IBD with both pathogens and putative commensal organisms. This patient cohort, combined with unique access to in-house IFNε reagents, will allow us to understand the role of this critical cytokine in human intestinal health and disease. We are seeking enthusiastic students to study this novel protein-microbiome interaction with

the aim of developing new therapies for gut diseases in children and adults around the world.

Suitability: PhD, Masters, Honours, BMedSci (Hons), Joint PhD/Exchange Program

Novel bacteriotherapeutics in paediatric inflammatory bowel disease

Keywords: IBD, microbiota, Crohns, colitis, mucosal immunology, clinical trial

Project leaders: Dr Edward Giles

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Project description: Inflammatory Bowel Disease (IBD), predominantly Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic inflammatory condition of unknown aetiology. It is caused by an aberrant immune response to the environment, including the microbiota. IBD is incurable, with debilitating albeit hidden symptoms and an increasing incidence worldwide. The cost to the Australian economy was $2.7 billion in 20123. IBD affects 1 in 250 Australians aged 5-40. Over the last decade, an explosion in microbiome research in IBD has not yet affected diagnostic algorithms or treatments. I have developed a program at Hudson Institute to isolate and mechanistically characterise bacteria while simultaneously measuring host immune response to form a more complete understanding of the host-microbiome in IBD. My preliminary work has shown several exciting novel candidates for bacterial therapeutics and new targets for therapy. The exceptional technical resources and infrastructure that I have established in a world-leading environment will ensure transformational changes from this program, including a clinical trial of bacteriotherapy. I am seeking students to progress this working into Phase I clinical trials.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

Synergy Program

Innate Mucosal Sensing and Shaping of the Human Microbiome

Keywords: signal transduction, innate immunity, bioinformatics, infectious diseases, microbiology, inflammation, cellular biology, microbiome

Project leaders: Prof Elizabeth Hartland, Prof Paul Hertzog, Dr Sam Forster, Prof Christine Wells

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Project description: The reciprocal interactions between mucosal epithelium, innate immune cells and commensal microbial communities across sites including the gastrointestinal and urogenital tract, play an essential role in health and disease. The commensal organisms sculpt the nature and the responses of the local epithelial and immune cells. Conversely, the status of these front-line innate cells influence the composition of the commensal microbiome. However, a deep understanding of these reciprocal interactions is lacking despite it being an important problem that defines the healthy state, modulates the pathogenesis of disease in mucosal sites and potentially in distant organs.
This program offers student projects in multidisciplinary areas including innate immune signalling, commensal and pathogenic microbiology, systems biology and bio-engineering with complementary aims to uncover interactions enabling understanding of the microbe-host interactions that regulate mucosal immunity, define the healthy state and determine disease outcomes. This important problem will be addressed with integrated projects under the umbrella of the three following themes:

1. Characterising the impact of microbiome components on the innate response.

2. How does the host innate immune system influence the microbiome community

3. Model discovery systems for interrogation, biomarker and diagnostic discovery and *in vivo* sensor and delivery.

One example approach will be to use iPSC-derived tissue systems and defined human microbiome communities to map the mechanisms underlying infection resistance, tissue repair and ongoing inflammation, as well as identify potentially protective human microbiome communities and isolates.
The outcomes will be in knowledge gain: to define the microbiome community composition and the host response in the intestine, compared with other sites, to identify organ-specific factors; to distinguish commensal from pathogen and why an organism can be a symbiont at one site and pathogen at another.
This will lead to the development of next generation diagnostics and therapeutics.

Suitability: PhD, Honours, Short projects

Respiratory and Lung Disease

Characterisation of innate immune responses during exacerbation of asthma and COPD

Keywords: asthma, virus, bacteria, innate immunity, mouse models, infection

Project leaders: Dr Belinda Thomas, Prof Phil Bardin

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Project description: Our research is focussed on understanding how viruses and bacteria cause exacerbations of inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Previous studies in our laboratory have demonstrated that reduced innate immune responses contribute to enhanced virus infection in asthmatic persons and in a mouse model of influenza A infection. We have also demonstrated the detrimental effect of glucocorticosteroids on viral infection in these diseases (Thomas et al., Am J Resp Cell Mol Biol, 2009, Thomas et al., Sci Rep, 2014). Further studies using validated primary cell culture models and various mouse models of viral and bacterial infection are examining the mechanisms contributing to reduced host immune responses and potential therapeutic strategies to counter these adverse effects.

Suitability: PhD/Doctorate, Masters by Research, Honours

Improving recovery from acute exacerbations of COPD

Keywords: COPD; acute exacerbations; physiotherapy; rehabilitation; pulmonary rehabilitation; physical activity; phenotyping; eosinophils; personalised medicine; treatable traits; NIV; clinical care; instrument validation; exercise testing

Project leaders: Dr Christian Osadnik, Prof Phil Bardin

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Project description: We are currently undertaking a structured suite of projects targeting improvements in recovery from acute exacerbations of chronic obstructive pulmonary disease. These projects are led by Dr. Osadnik in close collaboration with a team of medical and allied health clinicians and researchers with an interest in the field of respiratory medicine. This includes Prof. Philip Bardin, Director of Respiratory Medicine at Monash Lung and Sleep, and Prof. Terry Haines, Head of Monash University's School of Primary and Allied Health Care.

Individual projects range from small to large scale, with tailoring available to suit rapid publications or PhD candidature. Most projects relate to gaining insight into the ways we can optimise care models to enhance recovery from acute exacerbations of COPD. This currently takes the form of specific cohort studies, clinical trials, systematic reviews, and instrument (outcome tool) validation. We have large data sets suitable for data-mining related to specific research questions, but are also interested in initiating new projects that build upon our team's expertise. This may include research in other chronic lung diseases such as asthma and bronchiectasis.

Data collection is based clinically at Monash Health (predominantly Monash Medical Centre, Clayton), but includes other sites as required. Our team also extends into the basic science laboratory, allowing for human and/or animal tissue sampling to assist scientific research and translation from 'bench to bedside'. We have access to administrative support, IT software and data analysis packages via Monash University, patients via Monash Health, clinical equipment such as lung function testing and exercise testing equipment via Monash Health, and a range of physical activity and muscle testing equipment via the Mobile Movement and Activity Monitoring Laboratory - a joint initiative between Monash University Department of Physiotherapy and our clinical partners.

Please don't hesitate to be in touch to see how we can cater a project to your needs. Small project funding may be possible (on an individual need basis), subject to competitive availability.

Suitability: Honours, PhD/Doctorate, Masters by Research

Structural Biology of Inflammation and Cancer Research

Understanding the mechanisms of SARS-COV-2 mediated inflammation during COVID-19 infection.

Keywords: cryo-EM, structural biology, biochemistry, inflammation, inflammasome, SARS-COV-2, COVID-19, NLRP1

Project leader: Dr Wilson Wong

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Project description: A hallmark of COVID-19 infection is the destructive inflammatory responses triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in tissue damage to the airway of infected patients. Inflammasomes, multi-subunit signalling complexes, have been shown to play a key role in driving this detrimental inflammatory process.

Recent studies have shown that the SARS-COV-2 viral protease NSP5 is an activator of the NLRP1 inflammasome during SARS-COV-2 infection of lung epithelial cells. This project aims to investigate how the viral protease NSP5 interacts and activates the NLRP1 sensor to drive NLRP1-inflammasome formation. Experimental approaches will include biochemical, biophysical and structural biology methods to characterise the NSP5-NLRP1 interaction. This project will provide insights into how SARS-COV-2 triggers the destructive inflammation during COVID-19 infection.

Suitability: Honours, Masters by Research, PhD

Structural and biochemical characterisation of inflammasome signaling

Keywords: cryo-EM, structural biology, biochemistry, inflammation, inflammasome, AIM2

Project leader: Dr Wilson Wong

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Project description: Inflammasomes are key cytoplasmic sensors that detect pathogen components to undergo conversion from inactive to active signalling platforms to drive inflammatory signalling. The activation status of inflammasomes is under tight regulation to maintain healthy homeostasis. However, mutations in inflammasome components can result in imbalance of inflammatory signalling which is the underlying basis of many autoinflammatory diseases.

In this project, we aim to investigate the interactions between AIM2 inflammasome sensor and its binding partners to determine the role of these interactions in AIM2 inflammasome activation. In particular, we will characterise the mechanism of DNA induced AIM2 oligomerisation and recruitment of core components of the inflammasome including ASC and caspase1 to form signalling inflammasome. This project will utilise a variety of techniques that include protein expression and purification, functional biochemistry and structural biology method (cryo-EM) to understand the molecular details of AIM2 inflammasome signalling.

Suitability: Honours, Masters by Research, PhD

Deciphering the molecular mechanism of the SRSF3-OncomiR-1 microRNA processing complex in Colorectal Cancer

Keywords: cryo-EM, structural biology, biochemistry, cancer, microRNA

Project leader: Dr Wilson Wong

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Project description: In colorectal cancer, the microRNA-processing complex (SRSF3-OncomiR-1) plays a key role in tumorigenesis. The biogenesis and maturation of the oncogenic OncomiR-1 miRNA precursor is important for various RNA metabolism within the cancer cell. However, the mechanism of SRSF3 mediated processing of OncomiR-1 RNA is unclear.

This project will use biochemical, biophysical and structural biology methods to characterise how SRSF3 interacts with Drosha and DGCR8 to process the OncomiR-1 RNA substrate. The outcome of this project will provide insights into how SRSF3-OncomiR1 complex contributes to the progression of colorectal cancer.

Suitability: Honours, Masters by Research, PhD

Viral Immunity and Immunopathology

Understanding the role of cell death during severe influenza virus infections

Keywords: influenza, virus, infection, inflammation, cell death, innate immunity, therapies

Project leader: A/Prof Michelle Tate

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Project description: Excessive inflammation, cell death and immunopathology are characteristic features of fatal viral infections of the lung. Experts predict an influenza A virus (IAV) pandemic is inevitable and without safe and effective therapies that protect against damaging host responses, we are ill-prepared.

While the molecular mechanisms involved in the induction of inflammation during IAV infection have been well studied, the pathways involved in IAV-induced cell death and their impact on immunopathology have not been fully elucidated.

This project aims to gain a greater understanding of the role of cell death in modulating inflammation, viral replication and disease severity. It will explore the therapeutic strategy of targeting cell death to limit IAV disease. This project will utilise *in vitro* and *in vivo* pre-clinical infection models. Techniques that will be employed include flow cytometry, microscopy, histology, western blot, ELISA, cytokine bead array, viral plaque assays etc.

This project will provide unique exposure to industry collaborations.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

Novel host-targeted therapies for severe influenza virus infections

Keywords: virus, innate immunity, pulmonary disease, influenza, inflammation, immunotherapies

Project leader: A/Prof Michelle Tate

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Project description: Excessive inflammation and immunopathology are characteristic features of fatal viral infections of the lung. Alarmingly, experts predict an influenza A virus (IAV) pandemic is inevitable. Current antiviral drugs, which target the virus itself, show limited efficacy. Without safe and effective host-directed therapies that promote viral resistance and protect against damaging host responses, pandemic viruses will continue to cause significant mortalities in the future.

This project aims to identify new therapeutic targets and strategies that promote host resistance and dampen damaging inflammation. This project will utilise *in vitro* and *in vivo* pre-clinical influenza infection models. Techniques that will be employed include flow cytometry, histology, microscopy, western blot, ELISA, cytokine bead array, viral plaque assays etc.

This project will provide unique exposure to industry collaborations.

Suitability: PhD/Doctorate, Honours, BMedSci (Hons)

The NLRP3 inflammasome as a therapeutic target and biomarker of silicosis lung disease

Keywords: pulmonary disease, silicosis, inflammation, fibrosis, innate immunity, therapies

Project leader: A/Prof Michelle Tate

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Project description: Silicosis is a debilitating and untreatable lung disease characterised by chronic inflammation and permanent fibrotic scarring. The need for novel treatments of this disease has been emphasised by the recent increase in silicosis cases among workers in the Australian artificial stone benchtop industry. Treating the symptoms and preventing disease progression remains a major challenge.

There is increasing evidence in the literature that the host innate NLRP3 inflammasome promotes damaging inflammatory and fibrotic disease in silicosis.

This project aims to investigate the potential of targeting the host NLRP3 inflammasome to limit disease and identify NLRP3-associated biomarkers of disease severity and risk of progression to severe silicosis. This project will utilise *in vitro*, *in vivo* and ex vivo pre-clinical silicosis models, as well as clinical samples. Techniques that will be employed include flow cytometry, histology, microscopy, western blot, ELISA, cytokine bead array etc.

This project is underpinned by collaborations with clinicians and industry partners.

Suitability: Honours, BMedSci (Hons)

HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR REPRODUCTIVE HEALTH

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Centre Head

Associate Professor Patrick Western

Reproductive health is a key global challenge that affects every individual, as it both reflects and determines the health of present and future generations. Recent breakthroughs in our discipline have provided unequivocal proof that an individual's lifelong health is determined by events which occurred prior to their conception; their effects are transmitted by both mother and father via the placenta, oocyte and sperm. Using basic and translational science, Reproductive Health and Biology researchers are making discoveries about sperm and egg development, formation of the embryo and its implantation into the womb, formation of the placenta and its impact on fetal development. We study how each of these affects human development and health and use animal and cell culture models to reveal the cellular, molecular and biochemical mechanisms involved.

With an increasing number of couples seeking the use of assisted reproductive technologies and the rapidly increasing world population, new approaches are needed in the field of fertility research. Advances in reproductive sciences translate to allied fields: cancer biology, animal food production, and conservation of endangered species. In addition, proteins involved in the regulation of reproduction have wider actions, influencing inflammation and tissue repair in a variety of organs. Due to our focus on clinical problems, we expect our studies to lead to new approaches for improved diagnosis, prevention or treatment of disease.

Research Group Heads

Germ Cell Development and Epigenetics >
Associate Professor Patrick Western

Endocrinology and Immunophysiology >
Professor Mark Hedger

Testis Development and Germ Cell Biology >
Professor Kate Loveland

Germline Stem Cell Biology >
A/Prof Robin Hobbs

Male Reproductive Health

Research Group
Testis Development and Germ Cell Biology

Regulation of the germline and fetal organ growth by environmental cues

Keywords: Cellular stress, infertility, fetal growth, epigenetics

Project leader: Prof Kate Loveland

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Project description: The cells that form into sperm and eggs in adults play a unique and fundamental role in human health and well-being, because they transmit the parent's genes to the next generation. In addition to transmitting DNA, gametes also carry the 'epigenome', chromatin modifications that determine which genes are switched on and off. However, when sperm and egg precursors form during pregnancy, the fetus may be exposed to profound changes in the maternal environment brought on by pre-eclampsia, medications and infection. To understand how fetal exposure to maternal stressors affects the epigenome of sperm and egg precursors and impacts on growth of organs in the fetus, projects will use materials from animal models and human clinical samples. Culture experiments will be conducted using placentas to identify genes that are targets of maternal stress in this organ, and to evaluate their downstream impacts on cellular functions.

Suitability: Masters by Research, Honours

An Importin protein that mediates growth factor signalling and pathway crosstalk: Its roles in spermatogenesis

Keywords: Cell signalling, spermatogenesis, nucleocytoplasmic transport, cell differentiation

Project leader: Prof Kate Loveland

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Project description: Signalling through many distinct pathways drive normal testis development and are essential for normal fertility in males. We are investigating an importin protein, IPO5 (also named importin 5) ,a nucleocytoplasmic transport factor which selectively binds and carries cytoplasmic cargo proteins into the nucleus. In this manner, its actions can control signaling by Transforming Growth Factor-beta superfamily proteins (for example, Bone Morphogenetic Proteins {BMPs} and activins) as well as Wnts. Our published work has demonstrated that IPO5 synthesis is highly regulated during spermatogenesis, both in fetal life and in adulthood, and we have an ongoing research effort to identify what its cargo and functions are during spermatogenesis. We have new evidence that IPO5 also serves as a protein scaffold, to anchor proteins in subcellular regions, including in developing sperm. Goals of this project are to validate potential binding partners we have already identified at different stages of spermatogenesis, though cell culture and knockdown experiments, primarily working with cell lines, but also through interrogation of samples collected from our unique strains of IPO5 KO mice. Knockdown of IPO5 or its cargo in cell lines using siRNA may be performed in conjunction with addition of signalling pathways inhibitors; analyses we generally conduct include measurements of pathway activity using direct reporters of transcriptional activation (eg. luciferase activity), analysis of downstream target gene activity, and evaluation of cell functions (migration, adhesion, proliferation, survival, differentiation).

Suitability: Masters by Research, Honours

Research Group
Endocrinology and Immunophysiology

Discovering therapies to prevent inflammatory diseases of the male reproductive tract and infertility

Keywords: Inflammation, men's health, infertility, testis, epididymis, immunoregulation, infection, interferons, bacteria, viruses, autoimmunity

Project leader: Dr Rukmali Wijayarathna

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Project description: Inflammation in the testis and epididymis can impair male fertility, and epididymal obstruction is a major cause of infertility following infection and inflammation of the male tract. Activin is a cytokine that has both proinflammatory and immunoregulatory functions, but until now, the role of activin in testicular and epididymal inflammation has been very poorly investigated. This project examines activin and its binding protein, follistatin in regulating inflammation and fibrosis caused by infection and autoimmunity in the male tract. These studies will also assess the potential for exogenous follistatin to serve as a therapeutic intervention for these conditions. Futhermore, the unique immune-privileged environment in the testis favours persistent viral infections. Many viruses, including Covid19, can infect the testis. We are using the Zika virus as a model to study what factors increase the susceptibility of the testis to viruses. We are investigating if a novel anti-viral protein Interferon epsilon can be used against viruses in the testes.

Suitability: PhD/Doctorate, Masters by Research, Honours

Exploring the functional regulation of the male reproductive tract in health and disease

Keywords: Inflammation, men's health, fertility, chronic pain, epididymis, immunity, infection, immune privilege, autoimmunity

Project leader: Dr Rukmali Wijayarathna

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Project description: Disorders of the epididymis and vas deferens contribute to infertility, recurrent infections, chronic inflammation and pain. Evidence suggests that interactions between the inflammatory cytokine, activin and its binding protein, follistatin, play fundamental roles in creating the unique functions of the epididymis and vas, and that defects in activin-follistatin interactions underlie disease in these tissues. In this project, the student will investigate activin and its regulation by follistatin in control of the development and mature functions of the epididymis and vas deferens. This project can also involve studies of the role of activin in controlling inflammation, infection and immunity in the male tract.

Suitability: PhD/Doctorate, Masters by Research, Honours

Uncovering the novel phenotype of macrophages in the testis

Keywords: Inflammation, men's health, fertility, testis, immunoregulation, macrophages

Project leader: Dr Rukmali Wijayarathna

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Project description: Mouse testicular macrophages have several unique functional properties associated with testicular immune privilege. These cells have an alternatively activated phenotype that creates an environment whereby cell-mediated immune responses are tightly controlled. The intratesticular mechanisms responsible for directing the maturation of the testicular macrophages, and their functional consequences need to be investigated. In this project, monocytes isolated from blood will be matured in culture in the presence of putative testicular macrophage-regulating factors, such as activin and testosterone, in order to understand the relative importance of the testicular environment in creating the unique testicular macrophage phenotype.

Suitability: PhD/Doctorate, Masters by Research, Honours

Molecular Biology of Reproduction

Research Group
Germ Cell Development and Epigenetics

Defining how epigenetic mechanisms regulate the hypothalamic-pituitary-adrenal axis

Keywords: Epigenetics, hypothalamus, pituitary, adrenal, ovary, testis, endocrinology, developmental origins of disease

Project leader: A/Prof Patrick Western

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Project description: Epigenetics provides an interface between the environment and DNA function through the ability of epigenetic modifications to regulate gene expression. Environmental disruption of epigenetic programming is considered to underlie developmental origins of disease, a process by which early changes in development lead to life-long health consequences. Primary epigenetic modifications involve methylation of the DNA or chemical modifications, such as methylation, acetylation, phosphorylation, of the histones that facilitate DNA organisation and packaging. These modifications regulate the combination of genes that are switched on or off in a cell, and can provide a "long-term memory" of the transcriptional state for that cell and its progeny, substantially contributing to the maintenance of the cell's specialised function. Changes to this long-term memory are thought to underlie developmental origins of disease, but the epigenetic mechanisms involved are poorly understood. Epigenetic modifiers have been widely studied in some somatic tissues, but their roles in regulating endocrine state through the hypothalamic-pituitary-adrenal axis are poorly understood. The Hypothalamic-Pituitary-Adrenal axis (HPA) regulates endocrine homeostasis, controlling reproduction, food intake, blood pressure and a range of other physiological responses. Altered hypothalamic, pituitary, adrenal and/or gonad development and function underlies a wide range of physiological and social sequelae that can threaten life or compromise endocrine homeostasis, leading to multiple impacts, including infertility, ovarian deficiency, altered food intake, altered blood pressure, and increased incidence of bone, metabolic, heart and cardiovascular disease. Eed is an essential component of the highly conserved epigenetic modifier, Polycomb Repressive Complex 2. Previous studies and recent work in our laboratory suggest that PRC2 plays essential roles in regulating hypothalamic, adrenal and ovarian development. However, the role of Eed in regulating development of these organs and

the consequences of epigenetically dysregulating function of these organs remains unknown. We propose Eed regulates formation and function of the hypothalamic-pituitary-adrenal-gonadal axis. This project will delete Eed only in the developing hypothalamus, pituitary, adrenals and gonads (ovaries and testes). A range of state-of-the-art technologies, including immunofluorescence, advanced imaging, genome-wide sequencing, morphological and physiological, will be used to determine the role of Eed in the hypothalamus, pituitary, adrenals and gonads. The data obtained will reveal how epigenetic mechanisms regulate the hypothalamic-pituitary-adrenal-gonadal axis, providing insight into the epigenetic regulation of the primary organs regulating endocrine physiology. The project will address a critical knowledge gap in endocrinology and reproductive health by defining novel epigenetic processes that underpin hypothalamic, pituitary, adrenal and gonad development / function, aspects of which may be altered by lifestyle factors such as diet and drugs. As PRC2 is commonly dysregulated in cancer (including ovarian cancer) and drugs targeting PRC2 have been developed for treatment, this work will also provide essential preclinical insights into the possible impacts of specific cancer therapies on endocrine state and whether patients should undergo fertility preservation.

Suitability: PhD/Doctorate, Masters by research, Honours

Defining the epigenetic origins of maternally inherited disease

Keywords: Epigenetic, offspring health, inherited disease, oocyte, ovary

Project leader: A/Prof Patrick Western

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Project description: The notion that non-genetic factors in oocytes (eggs) and sperm can alter development and postnatal health in offspring is gaining traction with our increased understanding of epigenetic programming in male and female germ cells. Epigenetics provides an interface between the environment and DNA function through the ability of epigenetic modifications to regulate gene expression. Primary epigenetic modifications involve methylation of the DNA or chemical modifications, such as methylation, acetylation, phosphorylation, of the histones that facilitate DNA organisation and packaging. These modifications regulate the combination of genes that are switched on or off in a cell, and can provide a "long-term memory" of the transcriptional state for that cell and its progeny, substantially contributing to the maintenance of the cell's specialized function. Epigenetic modifiers have been widely studied in somatic tissues, but their roles in the germline are poorly understood. Germ cells are unique in that they undergo the most extensive epigenetic reprogramming of any in vivo cell type, a process that ultimately results in establishment of specialized epigenetic information in oocytes and sperm. Some of this information is transmitted via the oocyte and sperm to the next generation, and disruption of this inherited epigenetic information can lead to developmental defects and disease in offspring The Germ Cell Development and Epigenetics group aims to understand how epigenetic modifiers acting in germ cells, alter development and health in offspring. One such modifier is EED which establishes methylation on lysine 27 in histone 3 (H3K27me3), thereby repressing gene expression (turning genes off) in animal cells, including in humans. To understand the role of EED in epigenetic programming of oocytes and in inheritance, we developed a model for deleting Eed only from growing oocytes in mice. This model provides a unique opportunity to study epigenetic inheritance in genetically identical offspring in the absence of maternally contributed confounding factors. Our studies demonstrate that EED-mediated epigenetic programming in oocytes is important for offspring development, but the mechanisms remain unclear. This project will examine: (i) how the loss of EED activity impacts on epigenetic programming in oocytes, and (ii) how EED-mediated programming in oocytes affects development and postnatal health in offspring. (iii) how altered fetal and placental development in offspring affects the mother's physiology This research will involve application of genome-wide sequencing, immunofluorescence and confocal imaging and a range of molecular and cell biological approaches. Determining how epigenetic programming in oocytes and sperm regulates outcomes offspring is highly topical and of direct relevance to understanding the impacts of environmental impacts, such as drugs, diet and toxins, on health and developmental outcomes in humans.

Suitability: PhD/Doctorate, Honours

Impacts of epigenomic drugs on female and male reproductive health

Keywords: Ovary, epigenetics, endocrinology, female health, fertility

Project leader: A/Prof Patrick Western

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Project description: Epigenetics provides an interface between the environment and DNA function through the ability of epigenetic modifications to regulate gene expression. Environmental disruption of epigenetic programming is considered to underlie developmental origins of disease, a process by which early changes in development lead to life-long health consequences. Primary epigenetic modifications involve methylation of the DNA or chemical modifications, such as methylation, acetylation, phosphorylation, of the histones that facilitate DNA organisation and packaging. These modifications regulate the combination of genes that are switched on or off in a cell, and can provide a "long-term memory" of the transcriptional state for that cell and its progeny, substantially contributing to the maintenance of the cell's specialised function. Changes to this long-term memory are thought to underlie developmental origins of disease, but the

epigenetic mechanisms involved are poorly understood. Epigenetic modifiers have been widely studied in some somatic tissues, but their roles in regulating ovarian folliculogenesis, female fertility and female endocrine state are poorly understood.

The follicle encompasses the functional unit of the ovary and regulates endocrine homeostasis, leading to multiple influences, including on infertility, ovarian function and endocrine state. Impacts on ovarian function can compromise female reproductive health, including long term physiological impacts on fertility and endocrine state and consequences including increased incidence of bone, metabolic, heart and cardiovascular disease EED and EZH2 are essential components of the highly conserved epigenetic modifier, Polycomb Repressive Complex 2. PRC2 is also dysregulated in cancer, and drugs have been developed to target PRC2. However, these drugs act systemically, and their potential impacts on the ovary remain unknown.

Recent work in our laboratory demonstrates that PRC2 plays essential roles in ovarian development. However, the role of PRC2 in regulating development of these organs and the consequences of epigenetically dysregulating function of PRC2 as a potential off-target impact of clinical treatment remain unknown, raising the possibility that measures that preserve fertility options and/ovarian function may be beneficial to patients.

This project will use drugs that inhibit PRC2 function to treat ovarian tissue in culture to determine the potential for these drugs to have off-target impacts on folliculogenesis and/or ovarian function. A range of state of the art technologies, including immunofluorescence, advanced imaging, genome-wide sequencing, morphological and physiological, will be used to determine the impacts of PRC2 inhibiting drugs on ovarian cultures. The data obtained will reveal how epigenetic mechanisms regulate the ovarian function, providing insight into the epigenetic regulation of the ovary and processes regulating endocrine physiology.

The project will address a critical knowledge gap in endocrinology and reproductive health by defining novel epigenetic processes that underpin ovarian function, aspects of which may be altered by lifestyle factors such as diet and drugs. Specifically, as PRC2 is commonly dysregulated in cancer (including ovarian cancer) and drugs targeting PRC2 have been developed for treatment, this work will also provide essential preclinical insights into the possible impacts of specific cancer therapies on endocrine state and whether patients should undergo fertility preservation.

Suitability: PhD/Doctorate, Masters by research, Honours

Research Group
Germline Stem Cell Biology

Preservation and regeneration of male fertility by germline stem cells

Keywords: Stem cells, fertility, regeneration

Project leader: A/Prof Robin Hobbs

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Project description: Maintenance of fertility in men is dependent on a population of germline stem cells (known as spermatogonial stem cells or SSCs) within the testis that continually produce maturing germ cells for production of sperm. Male infertility is surprisingly common and disrupted formation or function of SSCs is potentially involved in a large number of these cases. Importantly, germline cells are highly sensitive to many cancer therapies including chemotherapeutic drugs and cancer patients can be at a high risk of permanent infertility. Therapy-resistant SSCs can restore sperm production in individuals but cellular pathways mediating the regenerative response of SSCs following testis damage remain poorly understood. This project aims to study and dissect cellular pathways and mechanisms regulating the SSC regenerative response using mouse models of chemotherapy-induced infertility. The project will involve SSC culture, molecular biology, biochemistry and genomics techniques. Development of therapies capable of promoting SSC regenerative capabilities may ultimately help in the reversal of infertility caused by cancer treatment.

Suitability: PhD/Doctorate, Masters by Research, Honours

Spermatogonial stem cells and male fertility

Keywords: Stem cells, fertility, regeneration, ageing

Project leader: A/Prof Robin Hobbs

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Project Description: The production of sperm and male fertility are dependent on a population of cells found in the testis known as spermatogonial stem cells or SSCs. Despite the importance of SSCs for male fertility, the molecular mechanisms that regulate their function are very poorly understood. SSC function and male fertility can be compromised by multiple factors including ageing or exposure to genotoxic drugs. Increased paternal age is associated with disruption of SSC activity and declining sperm quality, with an elevated risk of genetic diseases in offspring. Infertility can also occur prematurely in men because of genotoxic therapies such as chemotherapy. However, cellular pathways regulating the regenerative response of SSCs following germline damage and loss of SSC function with age are poorly studied. The research in our group focuses on

understanding genetic controls and cellular pathways regulating SSC function and male fertility. We employ a range of in vivo models and in vitro experimental systems allowing dissection of mammalian SSC function. Current research projects are focused on understanding cellular machinery modulating the response of SSCs to stimuli from the testis niche, the impacts of ageing on SSC function and molecular mechanisms supporting the regenerative capacity of SSCs.

Suitability: PhD/Doctorate, Masters by Research, Honours

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Centre Head

Professor Suzanne Miller

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

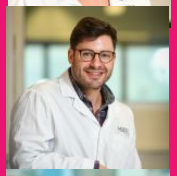
Perinatal Transition >
Prof Graeme Polglase

Fetal and Neonatal Health >
Prof Stuart Hooper AM

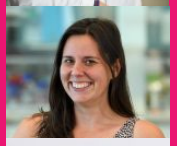
Amnion Cell Biology >
A/Prof Rebecca Lim

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

Characterisation of a novel interferon in the pathogenesis and treatment of endometriosis

Keyword: endometriosis; inflammation; endometrium; women's health

Project Leaders: Dr Fiona Cousins, Prof Paul Hertzog
Email: *fiona.cousins@hudson.org.au*

Project Description: Endometriosis is a chronic disease characterised by growth of cells in ectopic locations and chronic inflammation. This project looks to 1) characterise a novel interferon in the pathogenesis of disease and 2) determine whether IFN can be used as a therapeutic for endometriosis. This project utilises both in vitro and in vivo models of endometriosis and will include techniques such as tissue/cell culture, immunofluorescence, flow cytometry, PCR, bioinformatics. This project can be adapted for BSc Hons, MSc and PhD.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Masters/Honours/BMedSc (Hons), PhD

A novel non-invasive diagnostic for endometriosis/adenomyosis

Keywords: Endometriosis, flow cytometry, stem cells, diagnostics

Project Leader: Prof Caroline Gargett, Dr Shanti Gurung
Email: *caroline.gargett@hudson.org.au*

Project description: Women with endometriosis 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 that grow throughout the pelvic cavity, causing pain, disease and infertility. This project will build upon our novel findings that menstrual fluid may serve as a novel non-invasive diagnostic for endometriosis. The project involves quantitation and functional characterisation of endometrial stem/progenitor cells and proteins found in small extracellular vesicles (sEVs) in menstrual fluid. Techniques include sEV preparation, flow cytometry, proteomics and immunofluorescence. Techniques employed can be tailored to suit the interests of the student.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: PhD/Honours/Masters

Vaginal Stem Cells: the missing link to vaginal reconstruction

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

Project Leaders: Prof Caroline Gargett. Dr Shanti Gurung
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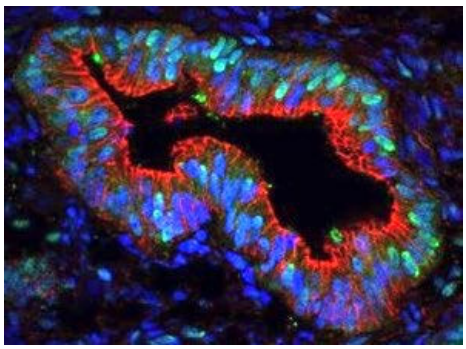
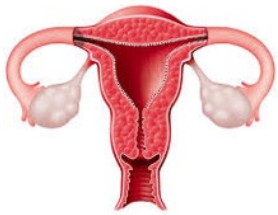
Project description: The vagina is central to a woman's sexuality, her sexual health, body image and sense of wellbeing. Vaginal epithelial stem cells and mesenchymal stem cells are likely responsible for maintaining vaginal tissue and could be harnessed for use as cell therapies for women who have lost 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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Masters/Honours/BMedSc (Hons)





Women's Health

Deciphering Immune Response to Bioengineered Meshes

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

Project Leaders: Dr Shayanti Mukherjee, Prof Caroline Gargett, Dr Saeedeh Darzi
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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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**

Combating Maternal Childbirth Injury with Cellular Therapies

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

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**

Women's Health

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

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

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**

Exploring the morphometric properties and immunobiology of Human Fascia Lata as a biological graft in pelvic reconstruction surgery

Keywords: gynaecology, biomedical engineering, surgery, pelvic organ prolapse, preclinical models

Project Leaders: Dr Shayanti Mukherjee, Prof Anna Rosamilia
Email: shayanti.mukherjee@hudson.org.au

Project description: Pelvic Organ Prolapse (POP) is a disorder with a growing incidence and hidden clinical burden of disease. At present, there are relatively few surgical grafts available to augment POP repair, despite the increasing need as the population ages. This is due to the commercial withdrawal of all transvaginal mesh, and the more recent withdrawal of all mesh for sacrocolpopexy (abdominal correction of usually apical prolapse). Human fascia lata (HFL) grafts have long been used for incontinence procedures, and more recently for sacrocolpopexy or graft augmented vaginal repair where synthetic mesh is contra-indicated or unavailable. However, there is insufficient data pertaining to the durability of HFL grafts when compared with mesh for sacrocolpopexy, which has demonstrated a low recurrence rate with long-term follow-up. Furthermore, the mechanical, morphological, cellular, matrix, and immunological properties of HFL are poorly understood. This project will directly compare the unique properties of fascial grafts with synthetic polypropylene mesh through histology, immunohistochemistry, immunofluorescence, scanning electron microscopy, biomechanical tensile testing and atomic force microscopy. In doing so, we hope to better characterize its long term implications and mechanisms driving its integration in the body, which is necessary before it is more generally adopted. The project involves a large immunology and pathology component. We welcome students from all background with innovative thinking and interest in interdisciplinary research contribute this project.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters/BMedSc (Hons)**

Women's Health

Endometrial organoids: novel tools for precision gynaecological medicine

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

Project Leaders: Prof Caroline Gargett, Dr Harriet Fitzgerald
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, where by 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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters**

Exosomes/small extracellular vesicles (sEVs) as biomarkers of endometriosis

Keywords: Exosomes, endometriosis, biomarkers

Project Leaders: Dr Thomas Tapmeier, Prof Caroline Gargett, Prof Beverley Vollenhoven
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 uterine fluid or 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 uterus and the peritoneum. This project will investigate exosomes in uterine fluid and peritoneal fluid within the same patients in order to determine the potential for substitution of exosomes isolated from one or the other fluid as biomarkers. If available, blood samples will be added to the analysis, to compare exosomes found in circulation to the species found in uterine and peritoneal fluids. Methods: Exosome isolation, ultracentrifugation, nanosight tracking analysis, immunoblotting, RNA extraction, proteomics, a lot of statistics.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters**

Women's Health

Metabolic Imaging to diagnose endometriosis

Keywords: Endometriosis, biomarkers, diagnostics, imaging

Project Leaders: Dr Thomas Tapmeier, Prof Beverley Vollenhoven
Email: *Thomas.tapmeier@monash.edu*

Project Description: The detection of endometriosis is a major challenge that delays diagnosis and appropriate treatment by 8-10 years on average. Addressing the metabolomic adaptations of endometriosis lesions persisting in the peritoneal cavity could provide a means to detect lesions. Low pH sensing peptide probes1 have been used by us2 to detect early lesions in a mouse model of breast cancer by their acidity. The probes can easily be modified by altering the polypeptide sequence, and conjugated to fluorescent or radioactive labels3. This project will investigate the possibility of using pHLIP probes to detect endometriosis.

The first stage will be an investigation into the metabolism of endometriosis lesions, the second stage will try to label these in spheroid/organoid models in vitro, and the third stage will test the probes in animal models in vivo using near infrared or radioactive labels appropriate for clinical detectors (PET/SPECT). Thus, a successful probe could be swiftly translated into clinical trials.

1. Weerakkody, D. et al. Family of pH (low) insertion peptides for tumor targeting. Proc. Natl. Acad. Sci. U. S. A. 110, 5834–9 (2013). 2. Tapmeier, T. T. et al. The pH low insertion peptide pHLIP Variant 3 as a novel marker of acidic malignant lesions. Proc. Natl. Acad. Sci. U. S. A. 112, 9710–5 (2015). 3. Macholl, S. et al. In vivo pH imaging with (99m)Tc-pHLIP. Mol. Imaging Biol. 14, 725–734 (2012).

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters**

Leiomyomata (uterine fibroids) as solid tumour models

Keywords: Tumour angiogenesis, imaging, tissue clearing microscopy, light sheet microscopy, immunofluorescence

Project Leaders: Dr Thomas Tapmeier, Prof Beverley Vollenhoven, Prof Caroline Gargett
Email: *Thomas.tapmeier@monash.edu*

Project Description: Leiomyomata (uterine fibroids) are benign tumours of the myometrium that are extremely common, with ca. 80% of women affected during their lifetime. Interestingly, intramural fibroids form a structure around themselves termed a 'pseudocapsule', which provides blood vessels to sustain tumour growth.

We plan to study the angiogenesis mechanisms at play in uterine fibroids with a view of establishing them as model solid tumours. We use advanced microscopy techniques such as light-sheet fluorescence microscopy on cleared tissues (CUBIC, Susaki 2015), which allows 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.

Methods: tissue preparation, two photon microscopy, light sheet microscopy, immunostainings (immunofluorescence), immunoblotting, tube formation assays, organoid cultures, automated image analysis, lots of statistics.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters**

Women's Health

3D multicellular organoid cultures of endometrium for precision medicine

Keywords: Endometriosis, 3D organoid cultures, drug screening, immunofluorescence, flow cytometry
Project Leaders: Prof Caroline Gargett, Dr Harriet Fitzgerald
Email: caroline.gargett@hudson.org.au

Project Description: Human endometrium is the lining of the uterus that is shed every month during menstruation and regrows nearly a centimetre of tissue. The processes are not well understood in health or diseases such as endometriosis, where endometrium-like tissue grows outside the uterus . New 3D organoid methods have been developed to culture human endometrial epithelium that was not previously possible, generating mini endometrial organs. These can be used for experimental studies and for testing drugs for endometrial disorders such as endometriosis. However, endometrial epithelial cell crosstalk with the stromal cells is critical to epithelial functioning.

This project is to develop 3D co-cultures of endometrial epithelial cells and stromal cells and potentially mesothelial cells that may have a role in endometriosis for drug screening. Techniques include 3D tissue culture, co-culture and drug screening, flow cytometry, immunofluorescence.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: **Honours/PhD/Masters**

Assessing the Beneficial effects of Antioxidants

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

Project leaders: Dr Sarah Marshall, A/Prof Kirsten Palmer
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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc (Hons)

Women's Health

Metformin in women with polycystic ovarian syndrome

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

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.

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **Honours, BMedSc (Hons)**

Usefulness of clinical research in Obstetrics and Gynaecology

Keywords: Obstetrics, Gynaecology, Women's Health

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

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **PhD**

Women's Health

Evidence-based fertility care (including assisted reproduction)

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

Project Leaders: Dr Rui Wang Prof Ben Mol,
Email: *rui.wang@monash.edu*

Project 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

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **PhD**

Women's Health

Optimise the flow of Placental Pathology guidelines

Keywords: pregnancy, fetal growth restriction, histopathology, placenta

Project Leaders: Prof Ben Mol, A/Prof Kirsten Palmer
Email: *ben.mol@monash.edu*

Project Description: Histopathological examination of the placenta may contribute to understanding the aetiology of stillbirth, preterm birth, fetal growth restriction (FGR) and neurological impairment. It may also be possible to identify if the condition of the fetus was caused by chronic or acute pathophysiology. Medical conditions that may reoccur may be able to be recognised, providing information for prevention and/or treatment in subsequent pregnancies.

At Monash, we routinely ask for histopathology and microbiology of the placenta after a range of indications, obviously including stillbirth, but also babies born after asphyxia. There is however limited capacity to investigate, resulting in long wait times.

BMedSc(Hons) Project In this project, you will map the current route that is organised for placenta investigations. You will perform a cohort study that includes all the placentas that have been send for histopathology and/or microbiology in 2023. You will record the clinical information of these cases (course of pregnancy, delivery, outcomes, medical complications) and relate these findings to the placenta findings. You will also study the literature including existing guidelines, meta-analyses and cost-effectiveness analyses. You will compare the pathways deriving from these guidelines/meta-analyses to the current practice at Monash. This is expected to optimise the diagnostic flow and reduce costs. You will work in a dynamic team that publishes on the highest level on this topic. We anticipate you will present the work at conferences and write a first author article about the study. Our group publishes papers on the highest level, for example in the Lancet pubmed.ncbi.nlm.nih.gov/36366885/ & pubmed.ncbi.nlm.nih.gov/34217399/ . As a BMedSc student, you can publish your own project, see pubmed.ncbi.nlm.nih.gov/33258514/

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **BMedSc (Hons)**

Utility of predicting Caesarean section following Induction of Labour

Keywords: Caesarean Section, Induction of labour, pregnancy, mode of delivery

Project Leaders: Prof Ben Mol, A/Prof Daniel Rolnik
Email: *ben.mol@monash.edu*

Project Description: Induction of labour is one of the most common obstetric procedures, performed when the risks of continued pregnancy outweigh benefits. Rates of labour induction have significantly increased up to 35% of Australian pregnancies over the last decade, reflecting increasing acceptability to clinicians and pregnant women. Despite the frequency of induction, clinicians' ability to predict for successful induction, resulting in a vaginal birth, is limited. Several models and calculators used to predict the likelihood of labour induction resulting in Caesarean section have been developed and validated, to be used to assist in shared decision making around mode of delivery.

BMedSc(Hons) Project Incorporating prediction models into routine obstetric practice can provide valuable guidance around difficult decision making. However, the implications of a predicted likelihood of Caesarean delivery may be viewed differently by pregnant women and clinicians. This project would aim to investigate the perspectives of pregnant women undergoing induction of labour, as well as the medical and midwifery clinicians caring for them during the procedure. It would assess the perceived utility and impact of a calculator for Caesarean section following induction of labour, as well as the likelihood at which risk of Caesarean section may indicate a recommendation or preference for elective caesarean section. You will work in a dynamic team that publishes on the highest level on this topic.

We anticipate you will present the work at conferences and write a first author article about the study. Our group publishes papers on the highest level, for example in the Lancet https://pubmed.ncbi.nlm.nih.gov/36366885/. As a BMedSc student, you can publish your own project, for example https://pubmed.ncbi.nlm.nih.gov/33258514/.

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **BMedSc (Hons)**

Women's Health

Pre-conception weight change and health outcomes in women with infertility

Keywords: infertility, epidemiology, obesity, overweight, weight loss, lifestyle, diet, physical activity

Project Leaders: Dr Rui Wang, A/Prof Lisa Moran
Email: rui.wang@monash.edu

Project Description: Various guidelines recommend lifestyle interventions based on dietary and/or physical activity targeting at a 5% to 10% reduction in body weight as an initial step prior to fertility treatment for women with infertility and overweight or obesity. However, evidence supporting such a recommendation is limited. Large randomised controlled trials (RCTs) assessing the effect of lifestyle interventions (diet and physical activity) prior to fertility treatments have not consistently demonstrated an improvement in fertility outcomes. It remains unclear whether weight is a modifiable factor to improve fertility/perinatal outcomes remains unclear in women with infertility. This project will involve a series of epidemiological studies from routinely collected clinical data and registry data, as well as evidence synthesis studies.

The project will be available for PhD students, who will be supported by leading experts in reproductive health, epidemiology, dietitian and implementation sciences during their candidature. The project would allow the candidate to gain experience in women's health research, epidemiological research, and evidence synthesis in a collaborative and supportive environment. 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 Monash Centre for Health Research and Implementation (MCHRI) a collaborative partnership between Monash University and Monash Health. It aims to deliver health impact by parterning with community, clinicians and researchers to co-create knowledge, and use implementation to drive equitable, quality health care and public health.

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **PhD, Masters by Research**

Meiotic Aneuploidy Screening Trial – Economic Analysis

Keywords: IVF, preimplantation genetic testing, aneuploidy, miscarriage, embryo transfer

Project Leaders: Prof Ben Mol, Prof Luk Rombauts
Email: ben.mol@monash.edu

Project Description: Meiotic Aneuploidy Screening Trial – Economic Analysis Background: Preimplantation genetic testing for aneuploidy (PGT-A) has been proposed as a method of improving the time to pregnancy and reducing the miscarriage rate in IVF cycles, by avoiding the transfer of embryos with low potential for ongoing pregnancy. Current NGS-based methods of PGT-A evaluate all chromosomes and have high dynamic range with increased sensitivity for intermediate copy number events (often interpreted as mosaic results).

This has the potential to reduce the cumulative live birth rate of an IVF cycle by excluding embryos with potential for transfer. We aim to evaluate the efficacy of screening for meiotic aneuploidy. Trial Design: Retrospective single-centre cohort study; nested non-selection study for effect of mitotic aneuploidy. Patients: Women aged >35 undertaking a stimulated cycle at Monash IVF, Melbourne, and/or Repromed, South Australia. Intervention: Aneuploidy screening using genome-wide haplotyping and parental samples to identify embryos at high risk of meiotic aneuploidy. Comparison: Patients undertaking a stimulated cycle without PGT-A in the same time period, matched for age and other variables.

Outcome Primary: Cumulative live birth rate over the study period (non-inferiority) Secondary: Number of embryo transfers required to achieve a clinical pregnancy, pregnancy loss due to aneuploidy.

BMedSc(Hons) Project Utilising the trial here, the successful applicant will conduct a financial modelling study of IVF with PGT-A compared to IVF without PGT-A. The successful applicant will also be able to participate in the original trial, thereby enabling the chance of multiple publications. The successful applicant will be supported by multiple senior researchers and clinicians, as well as having the direct support of junior researchers who will assist in the literature review, data analysis, and manuscript preparation. It is anticipated that the above work would be suitable for presentation at suitable scientific meetings as well as publication in a reputable journal. The student will work in a dynamic team supervised by Professor Luk Rombauts and Professor Ben W . Mol.

Location: Department of Obstetrics and Gynaecology, Level 5, Monash Medical Centre, Clayton

Suitability: **BMedSc (Hons)**

Fetal and Neonatal Health: Respiratory and Cardiovascular

Transition to Life After Birth

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

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc (Hons)

Imaging the Entry of Air into The Lungs at Birth

Keywords: birth, newborn, lung aeration

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc (Hons)

Trialling novel glucocorticoids to reduce lung disease in preterm birth

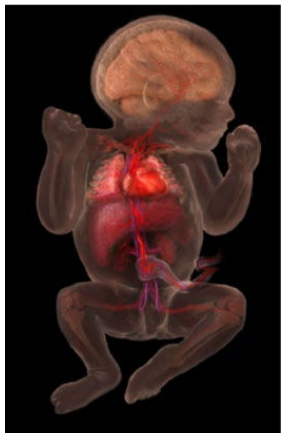
Keywords: preterm birth, preterm babies, glucocorticoids, corticosteroids, respiratory distress, bronchopulmonary dysplasia, ventilation, brain injury

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc (Hons)



Fetal and Neonatal Health: Respiratory and Cardiovascular

Improving breathing of preterm newborns exposed to inflammation during pregnancy

Keywords: chorioamnionitis, neural control of respiration

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD

Improving the transition at birth in asphyxiated infants

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

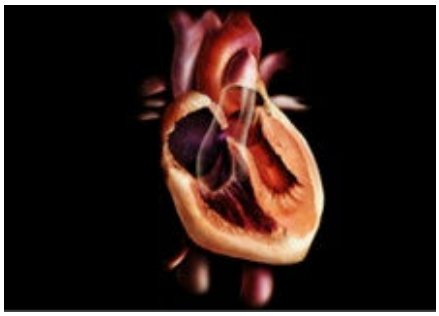
Project Leaders: Prof Graeme Polglase, Prof Stuart Hooper
Email: graeme.polglase@monash.edu
Phone: 03 8572 2822 (Prof Polglase)

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD



Fetal and Neonatal Health: Respiratory and Cardiovascular

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

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

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc (Hons)

NICU emergency frequency, risk factors, causes and potential treatments

Keywords: neonatal resuscitation, NICU emergencies

Project Leaders: Dr Doug Blank, Dr Calum Roberts
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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.

Location: The Ritchie Centre, Department of Paediatrics, Monash Medical Centre, Clayton

Suitability: BMedSci (Hons)

Fetal and Neonatal Health: Brain Injury and Neurodevelopment

Cell therapies for neonatal conditions

Keywords: stem cells, neonatal, brain, lung

Project Leaders: A/Prof Atul Malhotra, Dr Courtney McDonald, Prof Suzie Miller
Email: *atul.malhotra@monash.edu*

Project Description: Opportunities exist to join a world leading team in translational cell therapy research. Projects offered include lab work in cell characterisation, profiling, expansion and related studies. There are also opportunities to be involved in either or both clinical and pre-clinical neonatal cell therapy translational work.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: BMedSc (Hons)

Developing 3D brain organoids to model perinatal brain injury

Project Leaders: Dr Courtney McDonald, Prof Michael Fahey
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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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD

Improving functional deficits associated with fetal growth restriction

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

Project Leaders: Prof Suzie Miller, Dr Amy Sutherland
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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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD

Infant and Child Health

Evaluation of innovative digital monitoring devices in neonates

Project Leaders: A/Prof Atul Malhotra. Dr Faezeh Marzbanrad
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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.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: BMedSc (Hons)

Development of face perception in preterm infants (The BabyFace Study)

Keywords
Preterm infants, brain development, cerebral blood flow, cerebral oxygenation

Project Leaders: A/Prof Flora Wong, Prof David Walker, Dr Robin Laycock
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Project Description: The study aims to better understand how preterm babies develop the ability to recognise and understand faces. Exposure to faces and facial expressions are thought to promote the development of face perception, which has been linked to development of speech and social skills such as cooperative play.

Children born preterm have been reported to have slower development of face perception. We will recruit babies born before 32 weeks and at full-term. We will record their brain response to human faces with and without face-masks using multi-channel NIRS (near infrared spectroscopy). The data will allow understanding of face perception which is critical for play and speech in babies, and how this is affected by mask-wearing (mandatory in hospitals since COVID-19).

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours, BMedSc(Hons)

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

Keywords: preterm infants, developmental outcomes, apnoea, sleep

Project Leaders: Prof Rosemary Horne, A/Prof Flora Wong
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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.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours/PhD/Masters

Infant and Child Health

Obstructive sleep apnoea in children with Down syndrome

Project Leaders: Prof Rosemary Horne, A/Prof Gillian Nixon
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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.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours/Masters by Research, PhD

Understanding excessive daytime sleepiness in children

Keywords: sleep, children, paediatrics,

Project Leaders: Prof Rosemary Horne, A/Prof Gillian Nixon, Dr Lisa Walter
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Project Description: Children who experience excessive daytime sleepiness are referred to the Melbourne Children's Sleep Centre for assessment of idiopathic hypersomnolence or narcolepsy. Narcolepsy is a neurological disorder that affects your ability to wake and sleep. People with narcolepsy have excessive, uncontrollable daytime sleepiness. They may also suddenly fall asleep at any time, during any type of activity. Usually when you fall asleep you go through stages of non rapid eye movement (NREM) sleep, however people with narcolepsy go into REM sleep almost immediately in the sleep cycle and sometimes while they're awake. Idiopathic hypersomnia is similar in presentation to narcolepsy, but patients with this condition have no sleep-onset REM period, and naps are unrefreshing. Children with excessive daytime sleepiness are referred for an overnight sleep study at the Melbourne Children's Sleep centre, the following day children undergo a Multiple Sleep Latency Test where they are given the opportunity to try to nap every two hours throughout the day. There are two things being looked at: how long it takes the child to go to sleep and what type of sleep do they have when they go to sleep. There have been case reports and small studies demonstrating autonomic dysfunction in adults with idiopathic hypersomnolence, there are few studies in children. Narcolepsy is associated with low hypocretin 1 levels. Hypocretins are involved in regulation of heart rate and blood pressure. This study will use heart rate variability as a non invasive measure of autonomic control to examine differences in autonomic control between children diagnosed with narcolepsy, idiopathic hypersomnolence and control children. Students will have the opportunity to be involved in sleep studies and will analyse heart rate data collected from clinically referred children with and without excessive sleepiness.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours/Masters by Research, PhD

Infant and Child Health

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

Keywords: obstructive sleep apnoea, MRI, children Supervisor ref

Project Leaders: Prof Rosemary Horne, Dr Lisa Walter, Dr Brendan Tan
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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.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours/Masters by Research, PhD

Temperature changes during sleep in children with sleep disordered breathing

Keywords: sleep, children, paediatrics

Project Leaders: Prof Rosemary Horne, Dr Lisa Walter
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Phone: 03 8572 2827 (Prof Horne)

Project description: The quality and quantity of sleep are very closely related to variations in body temperature: falling asleep generally occurs in the period when there is a decrease in internal temperature while spontaneous morning awakening is associated with an increase in body temperature. Variations in body temperature are associated with sleep in a causal manner, any practice that generates distal vasodilation, such as thermally by using a hot water bottle, or wearing socks or non-thermally by turning off lights, lying down, physical and/or cognitive relaxation, can promote more rapid sleep onset. Conversely, when distal skin temperatures are reduced , such has being in a cold draft, or having a cold bath, this promotes vigilance and wakefulness. Studies in adults have shown that sleep or alertness could be improved in a non-drug induced manner by simple thermal modifications without any side effects. Sleep, in terms of both quantity and quality, is of paramount importance for a child's neurological development, health and even survival.

This raises the question of whether the relationship between body temperature and sleep is similar in children. Sleep disordered breathing describes a range of severities of breathing disruption which ranges in severity from simple or primary snoring at the mild end to obstructive sleep apnoea (OSA) at the severe end. Primary snoring affects up to 35% of children while OSA occurs in 1-6% of children. OSA results in increased effort of breathing to overcome the partial obstruction of the upper airway and has been demonstrated to be associated with increased metabolic rate and energy expenditure during sleep. This study aims to provide proof-of-concept data that there is a difference in body temperature during sleep in children with more severe forms of OSA. Such data would open opportunities for investigation of easily-obtained temperature data for diagnosis of management alternatives in paediatric OSA. This study will analyse time synchronised temperature recordings made using a small ibutton during sleep to determine the effects of sleep state and stage, sleep disruption and SDB severity on temperature across the night.

Students will have the opportunity to be involved in overnight clinical sleep studies, collecting and analysing the temperature data recorded and matching this to sleep state and sleep disordered breathing severity recorded during the sleep study.

Location: Department of Paediatrics, Level 5 Monash Children's Hospital

Suitability: Honours/Masters by Research, PhD

Infection, Inflammation, and Immunity

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

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

Project Leaders: Dr. Robert Galinsky, Prof Rod Hunt
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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.

Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD

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

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

Project Leaders: Dr. Robert Galinsky, Prof Claudia Nold, Prof Marcel Nold
Email: robert.galinsky@hudson.org.au

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD

Infection, Inflammation, and Immunity

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

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

Project Leaders: Prof Claudia Nold, Dr Ina Rudloff
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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.

Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/BMedSc (Hons)

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

Keywords: inflammation, IL-37, kidney disease

Project Leaders: Dr Malcolm Starkey, Prof Claudia Nold,
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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.

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

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

Suitability: Honours/BMedSci (Hons)

Infection, Inflammation, and Immunity

The Role of IL37 in the pathogenesis of inflammatory bowel disease

Keywords: preclinical study, inflammatory bowel disease, inflammation, immunology, interleukins

Project Leaders: Prof Claudia Nold, Dr Rimma Goldberg, Prof Marcel Nold
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Project description: The Role of IL37 in the pathogenesis of inflammatory bowel disease IL37 is a novel anti-inflammatory cytokine which is reduced in the circulation of patients with auto-immune diseases, including inflammatory bowel disease (1). Human peripheral blood mononuclear cells are capable of producing IL37, and in particular the T cell subset (2). Aberrant helper T cell responses play a key role in the pathogenesis of IBD (3-5). Thus it is of paramount importance to understand the triggers for pro and anti-inflammatory cytokine production by T cell subsets of patients with inflammatory bowel disease. This project will look at characterising IL37 production in different cell subsets in the blood and lamina propria of patients with inflammatory bowel disease. Cells will be isolated from peripheral blood and colonic biopsies. Following appropriate processing or digestion and stimulation, flow cytometry will be used to characterise immune cell subsets and their capacity to produce IL-37. Additionally, colonic biopsy samples will be collected and stored to create frozen sections for immunofluorescent staining. Concurrently, patient data on disease activity, medication use and response will be collected. Disease activity and response to currently available medications will be correlated with IL-37 production to assess whether this cytokine plays a role not only in pathogenesis of disease, but also response to immunomodulating medications.

Location: The Ritchie Centre, Hudson Institute of Medical Research, Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/BMedSc (Hons)

Cell therapy and regenerative medicine

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

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

Project Leaders: Prof Graham Jenkin, Dr Courtney McDonald, Dr Tayla Penny
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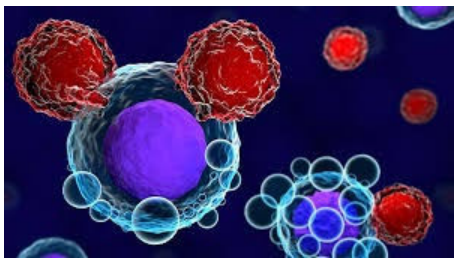
Phone: 0419534101 (Prof Jenkin)

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc/Masters



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

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

Project Leaders: Prof Graham Jenkin, Dr Courtney McDonald, A/Prof Atul Malhotra
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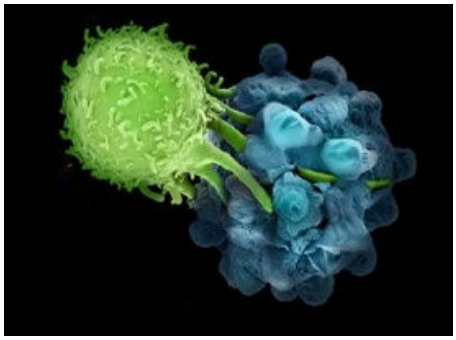
Phone: 0419534101 (Prof Jenkin)

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.

Location: The Ritchie Centre, Hudson Institute of Medical Research; Level 5, Translational Research Facility, Monash Medical Centre, Clayton

Suitability: Honours/PhD/BMedSc/Masters



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